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A Longitudinal Study of the Evolution of Neuropsychological Change in Amyotrophic Lateral Sclerosis: The Incidence, Nature and Progression of Language Impairment.

A dissertation submitted to Trinity College Dublin for the degree of

Doctor of Philosophy (PhD)

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Summary

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that involves the progressive degeneration of upper and lower motor neurons, leading to wasting and weakness of limb, bulbar and respiratory muscles. ALS is now recognised as a multisystem disease that also affects cognition and behaviour. Cognitive change in ALS manifests most commonly as executive dysfunction. Although changes in language function have been described, these have not been investigated within a large population-based sample of incident cases.

The primary objective of this thesis was to investigate the existence of different neuropsychological phenotypes within the ALS disease spectrum, with a special focus on language function. To this aim, a large incident population-based ALS sample (n = 135) was recruited. This project employed an observational, prospective, case-control design with complementary cross-sectional and longitudinal analyses.

The findings presented support the theory that the neuropsychological profile in ALS falls along a spectrum of frontotemporal involvement. Accordingly, 9% of ALS patients presented with cognitive impairment alone, single behavioural change was characteristic of 18% of newly diagnosed ALS patients, and 15% met criteria for both cognitive and behavioural impairment. Moreover, 13% of newly diagnosed ALS cases met criteria for comorbid Frontotemporal Dementia (FTD) and 33% had preserved cognitive function and behaviour.

Incident language deficits in ALS were confined to the domains of word retrieval, orthographic lexical processing and syntactic/grammatical processing, whereas phonological lexical processing and semantic processing were spared at early stages in the disease. Language change in ALS was associated with executive dysfunction to a degree, although pure deficits of linguistic nature were also observed. Nevertheless, the presence of language impairment alone was not frequent, and this most likely indicated the presence of a more widespread frontotemporal disease extending beyond those areas involved in executive control.

Our results support the theory that different patterns of disease spread are likely to determine the presence of distinct disease phenotypes in ALS. Thus, we identified a subgroup of ALS patients that presented with a more aggressive form of the disease characterised by higher functional disability scores and bulbar involvement, a more rapid progression in motor symptoms with a shorter survival, and a more generalised cognitive presentation with executive and language impairment along with behavioural change. In contrast, a more pure motor phenotype characterised by slower functional decline and no behavioural or cognitive deficits was also identified, which suggests a more contained pathological spread.

The links between the C9orf72 ALS genotype and particular neuropsychological phenotypes were also confirmed by our results. Thus, C9orf72 positive patients and familial ALS cases with an unidentified genetic mutation were characterised by cognitive and behavioural impairment that suggests a more extensive propagation of ALS pathology. On the contrary, sporadic ALS patients more frequently presented with spared cognition and behaviour, which suggests less aggressive forms of disease spread.

Longitudinal analyses indicated that there was no significant decline on cognitive measures overall, but a significant increase in behavioural impairment was observed over time. These results, however, must be interpreted with caution given that cognitively impaired patients at baseline discontinued with the research participation more frequently and therefore these were underrepresented at longitudinal follow-ups. The underrepresentation of ALS patients with more marked forms of cognitive as well as motor impairment at follow-up is a challenge inherent to longitudinal ALS research.

In conclusion, this study contributes to the characterisation of different disease phenotypes within the ALS spectrum. Neuropsychological status in ALS has been proven to be an important disease marker with significant implications for disease management and prognosis.

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Glossary of Terms

ALS – Amyotrophic Lateral Sclerosis

ALSbi – ALS with Behavioural Impairment

ALSci – ALS with Cognitive Impairment

ALScbi – ALS with Cognitive and Behavioural Impairment

ALSei – ALS with Executive Impairment

ALSli – ALS with Language Impairment

ALSeli – ALS with Executive and Language Impairment

ALSn – ALS Normal

ALS-FTD – ALS with Frontotemporal Dementia

ALS-FTSD – ALS Frontotemporal Spectrum Disorder

ALS-PDC – ALS-Parkinsonism-Dementia Complex

ALS-LAUS – ALS with Laboratory Abnormalities of Uncertain Significance

ALSFRS-R – ALS Functional Rating Scale Revised

ANT – Action Naming Test

BBI – Beaumont Behavioural Inventory

BMAA – β-Methylamino-L-Alanine

BNT – Boston Naming Test

bvFTD – Behavioural-Variant Frontotemporal Dementia

CBD – Corticobasal Degeneration

CNS – Central Nervous System

COI – Cut-Off Index

CWIT – Colour-Word Interference Test

D-KEFS – Delis-Kaplan Executive Function System

DTI – Diffusion Tensor Imaging

EMF – Electromagnetic Fields

EMG – Electromyography

FAB – Florida Affect Battery

FALS – Familial ALS

FSIQ – Full Scale Intellectual Quotient

FTD – Frontotemporal Dementia

FTLD – Frontotemporal Lobar Degeneration

FVC – Forced Vital Capacity

HADS – Hospital Anxiety and Depression Scale

HALS/GALS – Hereditary or Primary Genetic ALS

ICC – Intra-Class Correlation

IMV – Invasive Mechanical Ventilation

IQ – Intellectual Quotient

IQR – Interquartile Range

LMN – Lower Motor Neurons

MND – Motor Neurone Disease

MRI – Magnetic Resonance Imaging

NCS – Nerve Conduction Studies

NIV – Non-Invasive Ventilation

NMR – Nuclear Magnetic Resonance

NPV – Negative Predictive Value

$PaC0_2$ – Carbon Dioxide Partial Pressure

PALPA – Psycholinguistic Assessments of Language Processing in Aphasia

PB – Pseudobulbar Palsy

PBP – Progressive Bulbar Palsy

PEG – Percutaneous Endoscopic Gastrostomy

PET – Positron Emission Tomography

PLS – Primary Lateral Sclerosis

PMA – Progressive Muscular Atrophy

PPA – Primary Progressive Aphasia

PPT – Pyramids and Palm Trees Test

PPV – Positive Predictive Value

RCI – Reliable Change Index

RIG – Radiologically Inserted Gastrostomy

RMET – Reading the Mind in the Eyes Test

SBM – Surface-Based Morphometry

SEE – Standard Error of the Estimate

SEM – Standard Error of Measurement

SNIP – Sniff Nasal Respiratory Pressure

SPB – Self-Perceived Burden

SPECT – Single Photon Emission Computed Tomography

$Sp0_2$ – Peripheral Capillary Oxygen Saturation

SRB – Standardized Regression-Based methods

TDP-43 – TAR DNA-Binding Protein 43

TIP – Time Increase Proportion

TOPF – Test of Premorbid Function

UNM – Upper Motor Neurons

VBM – Voxel-Based Morphometry

VFI – Verbal Fluency Index

VIF – Variance Inflator Factor

VWFA – Visual Word Form Area

WAIS-IV – Wechsler Adult Intelligence Scale Version IV

Thesis Outline

This thesis is concerned with the evaluation of cognitive phenotypes within the Amyotrophic Lateral Sclerosis spectrum, with a special emphasis on language.

The thesis is structured around ten different chapters. Three introductory chapters are included, the first one presenting background information on what Motor Neurone Disease is and, more specifically, it introduces relevant terminology and knowledge relating to Amyotrophic Lateral Sclerosis. This chapter sets the context for the interpretation of findings presented in subsequent chapters. Chapter two presents an overview of the language processing system, given that the evaluation of language skills in patients diagnosed with ALS is a core part of this work. Moreover, an overview of language dysfunction in neurodegeneration and what assessments are usually employed to evaluate the same are included. Again, the concepts presented in this chapter serve as background information that is used in subsequent chapters to discuss our findings. The third and last introductory chapter presents current knowledge on cognition in ALS, including a systematic review of studies investigating language change. A brief overview on neuroimaging and genetic findings in regards to cognition in ALS is also included.

Chapter four specifies the thesis primary objective and details explicit aims and hypotheses. Chapter five comprehensively describes the study methodology.

Four results chapters are included, from chapter six to chapter nine, each one analysing distinct aspects of the project. Accordingly, chapter six presents an initial examination of healthy control data, chapter seven looks at the incidence of neuropsychological change in ALS, chapter eight analyses the longitudinal evolution of such neuropsychological change, and chapter nine determines the clinical and genetic characteristics of frontotemporal dysfunction in ALS.

Finally, chapter ten provides a summary and general discussion of findings as well as implications of the same. Study limitations are also stated, and perspectives for future research are presented.

CHAPTER 1 Outline.

An introduction to Motor Neurone Disease and Amyotrophic Lateral Sclerosis

1.1. The Motor Neurone Diseases: An Overview

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CHAPTER 1.

An introduction to Motor Neurone Disease and Amyotrophic Lateral Sclerosis

1.1. The Motor Neurone Diseases: An overview

Motor Neurone Disease (MND) is a fatal neurodegenerative disease that involves progressive muscle atrophy and paralysis caused by the degeneration of corticospinal upper motor neurons (UMNs) and/or brainstem and spinal cord lower motor neurons (LMNs) in the motor system (Figure 1.1). Depending on the pattern of motor neuron degeneration, MND can be classified into four main clinical phenotypes: Amyotrophic Lateral Sclerosis, Primary Lateral Sclerosis, Progressive Muscular Atrophy, and Progressive Bulbar Palsy.

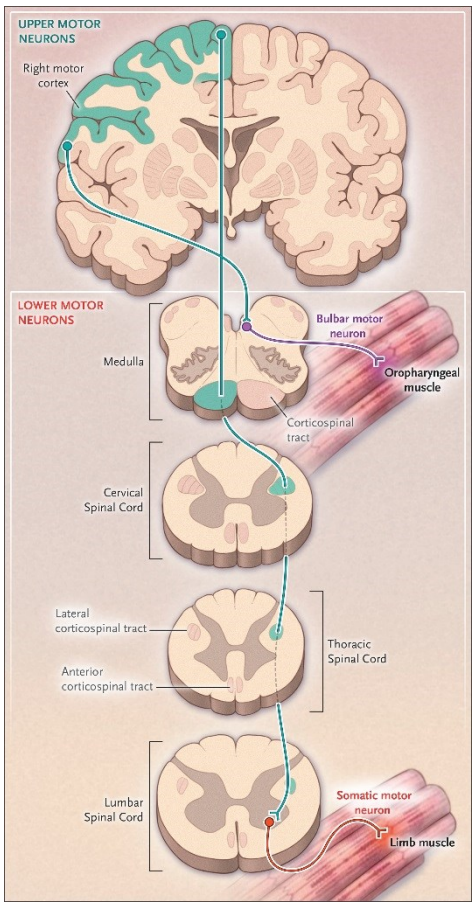

Figure 1.1. The motor system. From Brown and Al-Chalabi (2017)

Amyotrophic Lateral Sclerosis (ALS) is the most severe form of MND and is characterised by a combination of UMN and LMN signs and symptoms. This form of MND is the most common,

representing 75% of all cases (Moore, McDermott, & Shaw, 2008). A detailed description of ALS is provided in Section 1.2.

Primary Lateral Sclerosis (PLS) is characterised by evidence of pure UMN degeneration and therefore no muscle atrophy (or amyotrophy) caused by lower/spinal motor neuron degeneration is observed. The first signs of degeneration are often seen at a lower limb level in PLS (Moore et al., 2008). This form of MND is approximately 0.5% as prevalent as ALS (Saberi, Stauffer, Schulte, & Ravits, 2015); median age at onset is 50 years old and it has a better prognosis than ALS, with survival of more than 10 years (Moore et al., 2008). Some ALS cases only present initially with UMN signs (i.e. UMN-dominant ALS), and approximately 50% of PLS cases progress to ALS with time (Moore et al., 2008). Thus, absence of LMN signs for 3/4 years is now recommended as diagnostic criteria to confidently diagnose PLS (Al-Chalabi & Hardiman, 2013; Wijesekera & Leigh, 2009).

Progressive Muscular Atrophy (PMA) represents the MND phenotype with LMN involvement occurring in isolation. Five to ten percent of MND cases suffer from PMA (Wijesekera & Leigh, 2009). This form of MND is most common in men (M:F ration 5:1) and age of onset is usually 50+ years (Moore et al., 2008). About 30% of PMA cases can develop UMN signs and progress to ALS (Hardiman, Van Den Berg, & Kiernan, 2011).

Progressive Bulbar Palsy (PBP) is characterised by articulation, swallowing and chewing difficulties, which are caused by specific degeneration of the lower brainstem muscles that control bulbar function (i.e. speech and swallowing). PBP represents 20% of MND diagnoses and is most common in elderly women (Moore et al., 2008). In the majority of cases, patients with PBP subsequently develop widespread signs and symptoms of ALS, representing an extension of the pattern of motor neuron degeneration. This leads some clinicians to consider PBP a clinical presentation of ALS (i.e. bulbar onset ALS).

When MND commences with symmetrical LMN signs localised in the upper or lower limbs, **segmental variants of MND** are diagnosed. Thus, **Flail arm syndrome** (also Vulpian-Bernhardt syndrome or brachial amyotrophic diplegia) is characterised by symmetrical, predominantly proximal LMN involvement affecting both upper limbs, leading to wasting of shoulder muscles and flaccid arms hanging at each side (Wijesekera & Leigh, 2009). This segmental variant is more frequent in men (Al-Chalabi & Hardiman, 2013). **Flail leg syndrome** (or Pseudopolyneuritic form of ALS) is a symmetrical, predominantly distal LMN disease that affects both lower limbs (Al-Chalabi et al., 2012). These MND variants are rare and have a slower progression, with median survival of 8 years or more (Al-Chalabi & Hardiman, 2013). All MND variants share similar pathological abnormalities, although differences remain in the anatomical distribution of such neuropathology (Saberi et al., 2015).

1.2. Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) involves the progressive degeneration of motor neurons in the primary motor cortex, brainstem and spinal cord, leading to progressive wasting and weakness of limb, bulbar and respiratory muscles. ALS receives its name from its involvement of both upper and lower motor neurons. 'Amyotrophy' denotes muscle atrophy that occurs as a result of degeneration of lower or spinal motor neurons, and 'lateral sclerosis' refers to stiffening of the anterior and lateral corticospinal tracts.

1.2.1. Clinical Presentation

The first symptoms of ALS are varied among patients (Figure 1.2). Depending on the site where the first motor symptoms present, there are different forms of onset.

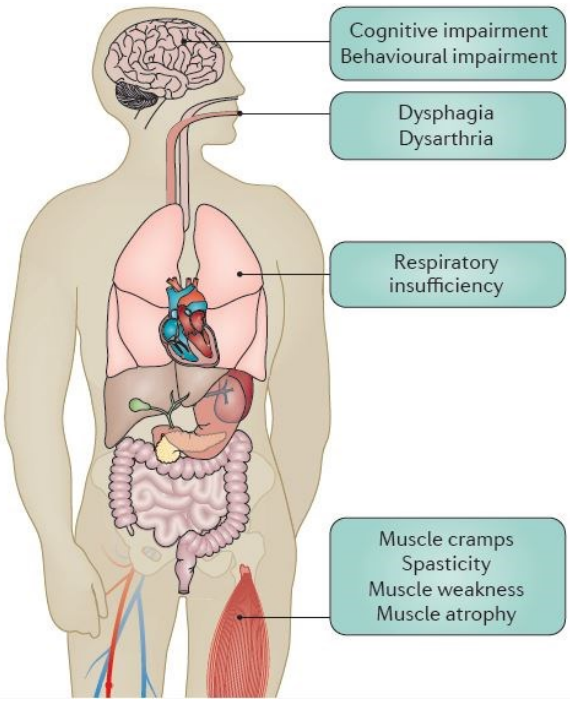

Figure 1.2. ALS clinical manifestations. From Hardiman et al. (2017)

Spinal onset ALS consists of insidious weakness or wasting of limb muscles as the starting symptom. When these signs are noticed at a lower limb level, the patient may experience a foot drop, unsteadiness, a tendency to trip or fall, or stiffness of the leg/s, which progressively leads to difficulty walking. Alternatively, these symptoms may be first noted on the upper limb/s, in which case the first symptoms may consist of a weakness in the arm or hand, poor grip or difficulty with hand dexterity. This form of onset is the most common and represents 65% of all ALS cases (Hardiman et al., 2011).

Bulbar onset ALS is characterised by wasting and weakness of muscles in the mouth, tongue and throat as starting signs. The characteristic symptoms of this form of onset are dysarthria (i.e. a disorder of speech articulation) or dysphonia (i.e. hoarseness and tightness of the voice). Dysphagia (i.e. difficulty in swallowing) is also observed and is initially more prominent for liquids than solids. Sialorrhoea (i.e. saliva drooling) is also present due to difficulty swallowing. Around 30% of ALS cases experience this form on onset (Hardiman et al., 2011). A higher proportion of bulbar onset ALS is observed in older women (Chiò et al., 2009), whereas men are more prone to spinal–onset ALS (Hardiman et al., 2017). Bulbar-onset ALS is generally under-represented in young patients (Turner et al., 2013).

Finally, **respiratory onset ALS** is diagnosed when the first signs of ALS consist of weakness and wasting of breathing muscles. Respiratory symptoms in ALS include dyspnoea (i.e. shortness of breath) and orthopnoea (i.e. a discomfort in breathing when lying flat). Respiratory onset ALS is the least frequent, with only 5% of patients experiencing breathing difficulties as the initial symptom (Hardiman et al., 2011). This form of ALS is also more prevalent in men (Turner et al., 2013).

Fasciculations (i.e. involuntary muscle twitching) and cramps are also common in ALS and can precede the onset of muscle wasting and weakness (Wijesekera & Leigh, 2009). These are present throughout the extremities in spinal presentations and in the tongue in bulbar patients.

Cognitive dysfunction is now also recognised as a significant characteristic of ALS. Up to 40% of patients develop mild to moderate cognitive abnormalities, and an estimated 10-15% of cases develop comorbid Frontotemporal Dementia (FTD: Phukan et al., 2012). In some cases, cognitive symptoms may precede the onset of the motor symptoms, and this known as **cognitive onset ALS**. Chapter 3 incorporates a detailed review on cognition in ALS.

Pseudobulbar palsy (PB), an inability to control the muscles in the face, mouth and throat, can also contribute to dysarthria and dysphagia in ALS, similar to PBP. Unlike PBP, PB is caused by bilateral involvement of UMN of the corticobulbar tracts. One of the most common symptoms of PB is emotional lability or pseudobulbar affect, present in approximately 25% to 50% of ALS patients (Oskarsson, Gendron, & Staff, 2018). Emotional lability is characterised by episodes of involuntary crying, laughing or other emotional presentations which are not always accompanied by the underlying feeling and which can be inadequate for the specific circumstance. Excessive yawning is also common in pseudobulbar affect.

Motor neurons in the oculomotor nuclei and Onuf's nucleus, which regulate micturition and fecal continence, are unaffected, therefore eye movement and sphincter control are preserved (van Es et al., 2017). Functions regulated by the autonomic nervous system such as the heart rate, digestion or sexual arousal are also preserved in most cases (Hardiman et al., 2017).

1.2.2. Epidemiology

ALS is a rare disease with an overall incidence in Europe of 2-3 people per 100,000 inhabitants over the age of 15 per year (Al-Chalabi & Hardiman, 2013; van Es et al., 2017), and a prevalence of 5.2 people per 100,000 inhabitants (Wijesekera & Leigh, 2009). In Ireland, the annual incidence of ALS is 2.5 cases per 100,000 inhabitants over the age of 15 and the prevalence is 6.8 people per 100,000 inhabitants (O'Toole et al., 2007; Rooney, Byrne, et al., 2015). This translates into approximately 110 new diagnoses per year and 300 diagnosed ALS cases at a time. The incidence and prevalence of ALS is higher in European populations compared to populations with mixed ancestral origins (van Es et al., 2017).

ALS is slightly more prevalent in men (M:F ratio~1.5:1; Oskarsson et al., 2018). Possible explanations for this include increased exposure to risk factors in men, protective hormonal factors in females, or under ascertainment of elderly females; however, recent data suggest that this ratio is currently reaching parity (Wijesekera & Leigh, 2009). At present, the overall lifetime risk for men developing ALS is 1:350, whereas for women is 1:400 (Al-Chalabi & Hardiman, 2013).

Although ALS can develop at any age, increasing age is a risk factor and there is a peak between the age of 50 and 75 which plateaus thereafter (Hardiman et al., 2011). In genetically mixed populations, age of onset is around 10 years earlier (van Es et al., 2017). Onset of ALS before the age of 30, although possible, is rare, and these cases represent only 5% of all ALS cases (Wijesekera & Leigh, 2009).

A geographic focus of ALS in the Western Pacific was identified, which included the Chamorro tribe from Guam island in the Northern Mariana islands, the Kii Peninsula of Honshu island in Japan, and the Auyu and Jakai people of south west New Guinea. In these areas, the prevalence of ALS was about 50-100 times higher (Wijesekera & Leigh, 2009) and it was also associated with Parkinsonism and dementia (ALS-Parkinsonism-Dementia Complex; ALS-PDC). This higher incidence in Guam was initially related to exposure to β-methylamino-L-alanine (BMAA), an atypical amino acid believed to be toxic for the central nervous system. BMAA originates from cyanobacteria and is contained in the cycad nut, eaten by fruit bats, which are part of the diet of the indigenous inhabitants in Guam. However, the hypothesis of cyanotoxic BMAA-induced ALS in Guam has yet to be proven by detailed epidemiological and toxicological studies, leaving uncertainty as to the exact cause (Al-Chalabi & Hardiman, 2013). Moreover, incidence rates in Guam have decreased in the last 40 years (Wijesekera & Leigh, 2009). Regarding higher prevalence of ALS in the Kii Peninsula in Japan, this is thought to be caused by a local genetic founder effect (i.e. C9orf72 repeat expansion within the chromosome 9; Al-Chalabi & Hardiman, 2013).

1.2.3. Diagnosis

The diagnosis of ALS is purely clinical, with relevant investigations being carried out to rule out the presence of other diseases that mimic the symptoms (Hardiman et al., 2011). Thus, careful history taking and comprehensive physical and neurological examination are the first steps in making a diagnosis of ALS. On neurological examination, evidence of concurrent UMN and LMN signs in four designated regions of the central nervous system (CNS: brainstem/bulbar, cervical, thoracic, or lumbosacral) is sought to consider a diagnosis of ALS (Brooks, Miller, Swash, & Munsat, 2000). Signs of UMN degeneration include hypertonicity, spasticity, brisk reflexes and extensor plantar responses, slowness of movement, pseudobulbar features and nasal slow speech. Differentially, LMN signs include muscle wasting and atrophy, weakness, reduced or absent reflexes, fasciculations and cramps. The presence and spread of UMN or LMN signs through the four regions of the CNS are considered regardless of the side of involvement (right or left), but the side where the signs are present provides information on the direction of involvement along the neuraxis (Brooks et al., 2000; Hardiman et al., 2011). The neurological signs on examination are commonly more extensive than the clinical symptoms (Moore et al., 2008).

The lack of a biological diagnostic marker in ALS along with the heterogeneity of the presenting symptoms at onset make the diagnosis of ALS challenging and compromise its certainty. Diagnostic delay (i.e. time from symptom onset to diagnosis) is generally 9 to 12 months (Al-Chalabi & Hardiman, 2013). In Ireland, a population-based study showed that the mean time from onset to diagnosis is 15 months, the median being 11 months (Galvin et al., 2017).

El Escorial Criteria (Brooks, 1994; Brooks et al., 2000) is a diagnostic criteria that categorises the diagnosis of ALS into various degrees of certainty, based on the presence of UMN and LMN signs in the same anatomic region on clinical assessment. Thus, considering El Escorial Criteria, the diagnosis of ALS can be classified as:

1. **Clinically Definite:** clinical evidence of UMN and LMN signs in the bulbar and at least two spinal regions, or in three spinal regions.

2. **Clinically Probable:** clinical evidence of UMN and LMN signs in at least two regions, with some UMN signs being rostral to the LMN signs.

3. **Clinically Possible:** clinical evidence of UMN and LMN signs in only one region; or UMN signs alone in two or more regions; or evidence of LMN signs rostral to UMN signs.

4. **Clinically Suspected:** when the diagnosis of ALS may be suspected but not enough certain evidence exists. This last category has been eliminated from the revised El Escorial criteria, or Airlie House criteria (Brooks et al., 2000).

When a diagnosis of ALS is considered at a clinical level, electrophysiological studies are recommended to increase diagnostic certainty. Electrodiagnostic examinations in ALS include needle Electromyography (EMG) and peripheral Nerve Conduction Studies (NCS). These electrophysiological evaluations help in confirming LMN involvement in clinically affected areas, in detecting LMN signs in regions where there is yet no clinical symptoms, as well as in excluding other pathophysiological conditions. When electrophysiological studies confirm that there is a sufficient number of regions involved, other conditions with similar electrophysiological abnormalities can be outruled and the diagnosis of ALS is more reliable. Thus, complementing El Escorial classifications previously described, electrophysiological evidence supports the diagnosis of **Clinically Probable – Laboratory-supported ALS**. This is defined when there is clinical evidence of UMN and LMN signs in only one region, or UMN signs alone in one region, and evidence of LMN signs defined by EMG criteria in at least two of the four CNS regions (and appropriate investigations to rule out other conditions have been carried out). Neurophysiological findings cannot determine the diagnosis of ALS in the absence of clinical support (Wijesekera & Leigh, 2009).

El Escorial criteria provides a useful standardised framework for the diagnosis of ALS and is advantageous in the selection criteria for clinical trials or other research fields, although the value of such criteria in clinical practice has been argued (Agosta et al., 2015). Research into the utility of the El Escorial criteria has shown that such classification does not clearly improve diagnosis accuracy (Mitchell et al., 2010) and does not account for the recent description of ALS as a spectrum disease with specific phenotypes reflecting distinct neuropathological processes (e.g. the presence of cognitive and behavioural changes, or the presence of family history; Agosta et al., 2015).

In 2008, the Awaji recommendations (de Carvalho et al., 2008) were published, which advocate the use of electrodiagnostic studies when considering criteria for the clinical diagnosis of ALS in order to increase diagnostic sensitivity and reduce diagnostic delay. Results from a systematic review and meta-analysis assessing the potential of the Awaji criteria (Costa, Swash, & de Carvalho, 2012) showed an increase in diagnosis sensitivity, especially in bulbar onset ALS, and maintained specificity when compared to the El Escorial criteria. Although it has been suggested that the Awaji criteria should be considered as complementary to the main clinical diagnostic criteria, arguments exist regarding the universal availability of required equipment (Agosta et al., 2015).

Recently, El Escorial criteria has been revisited to discuss how to better address the aforementioned limitations (Ludolph et al., 2015). Accordingly, this now requires progressive UMN and LMN signs in at least one region (previously Possible ALS), or LMN signs in one region

on clinical examination and/or in two regions as per EMG. This revision aims to increase sensitivity at early stages of the disease and facilitate prompt enrolment in therapeutic trials.

The differential diagnosis with other diseases that masquerade as ALS but which are not caused by ALS pathogenic processes (i.e. **ALS-Mimic Syndromes**) is crucial. Thus, the X-linked disorder of Kennedy's syndrome or spinobulbar muscular atrophy, a genetic syndrome caused by a CAG trinucleotide repeat expansion in the androgen receptor gene which presents with LMN and bulbar signs, needs to be ruled out. Among conditions that present with LMN signs, multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, spinal muscular atrophy, post-poliomyelitis syndrome, mononeuritis multiplex, nerve entrapment disorders, and myopathies need to be highlighted. The presence of isolated fasciculations and cramps also need the pursuit of a differential diagnosis with a non-progressive benign cramps and fasciculations syndrome. UMN signs can also be observed in conditions such as hereditary spastic paraparesis and inflammatory myelopathies. Similarly, cervical radiculomyelopathy and syringomyelia present with both UMN and LMN signs. Finally, in bulbar presentations, myasthenia gravis, brainstem or oropharyngeal lesion and oculopharyngeal muscular dystrophy need to be considered. Other conditions such as endocrinopathies (i.e. hyperparathyroid and hyperthyroid states), paraneoplastic syndrome, lead intoxication, or other infections are also considered ALS-mimic syndromes. Diagnostic errors of ALS-mimics occur in 5-10% of cases (Wijesekera & Leigh, 2009).

Among the appropriate investigations used to rule out ALS mimics, EMG is helpful in excluding peripheral neuropathies and myopathies. Genetic testing is available to rule out Kennedy's syndrome, and lumbar puncture is useful to exclude inflammatory diseases. Laboratory tests routinely recommended for the differential diagnosis of ALS include: cerebrospinal fluid analysis, measurements of serum calcium and phosphate, serum and urine protein electrophoresis and erythrocyte sedimentation rate, as well as thyroid function tests (Hardiman et al., 2011). Regarding neuroimaging, there is currently no method that provides positive support for the diagnosis of ALS. Neuroimaging techniques are mainly used at present to exclude structural lesions that can cause UMN or LMN signs. Signal changes in the corticospinal tract or the primary motor cortex in conventional structural MRI can support a suspected diagnosis, but these signs are not ALS-sensitive nor ALS-specific (Chiò et al., 2014). Current research is working on identifying potential ALS neuroimaging diagnostic markers (van Es et al., 2017).

Clinical and neurophysiological evidence of ALS can sometimes be observed in the presence of signs and symptoms of other neurological conditions. **ALS-Plus Syndrome** is diagnosed when ALS is present in association with clinical signs and symptoms of other neurological diseases which are not a consequence of ALS pathogenic processes. To consider a diagnosis of ALS-Plus

Syndrome, criteria for clinically Possible, Probable or Definite ALS need to be met. Likewise, when non-ALS pathogenic, laboratory-defined abnormalities are observed in conjunction to a confirmed diagnosis of Probable or Definite ALS, a diagnosis of **ALS with Laboratory Abnormalities of Uncertain Significance (ALS-LAUS)** is considered. These non-ALS pathogenic laboratory-defined abnormalities observed in ALS-LAUS can be associated with monoclonal gammopathy, non-malignant endocrine abnormalities, antibodies diseases, lymphoma, infections or exogenous toxins.

When the diagnosis of ALS is still unclear despite appropriate diagnostic methods and procedures, repeat clinical examinations and electrophysiological studies at least six months apart are recommended to examine progression. Neuroimaging evaluations as well as laboratory examinations may also need to be repeated.

Neuropathological studies can definitively prove or reject the diagnosis of ALS (Brooks et al., 2000). In the living patient, muscle biopsies can be used to prove LMN involvement in a region that may not have shown to be involved using other techniques. Other biopsies (e.g. skeletal muscle, peripheral nerve or other tissues) are not helpful in diagnosing ALS but can rule out the presence of non-ALS pathological changes. Autopsy examination can conclusively prove the diagnosis of ALS.

Criteria required to make a diagnosis of ALS are summarised in Table 1.1.

Table 1.1. Requirements for the diagnosis of ALS.

The presence of:	✓ Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination; ✓ Evidence of UMN degeneration by clinical examination; and ✓ Progressive spread of symptoms and signs within a region or to other regions, as determined by history or examination.
The absence of:	× Electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN degeneration; and × Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

From Brooks et al. (2000)

1.2.4. Disease Progression

The progression of ALS is variable and difficult to predict, although it is generally a disease of rapid progression. Despite the fact that ALS is a disease of focal onset, it progressively extends throughout the motor system, gradually spreading in distribution as well as in severity (Moore et al., 2008). Thus, limb-onset patients also develop bulbar symptoms, and vice versa. Spinal

signs progressively exacerbate, leading to total loss of functional hand dexterity and non-purposeful leg movement. Bulbar symptoms also progress to inability to communicate verbally or swallow safely. Ultimately, patients require the use of communication aids and parenteral or enteral feeding. In due course, all patients develop symptoms of respiratory insufficiency (i.e. dyspnoea and orthopnoea), which progressively become more prominent. These symptoms cause hypoventilation or insufficient ventilation, which lead to alterations in arterial blood gases (i.e. hypercarbia or CO_2 retention) and reduced oxygen levels (i.e. hypoxemia). These breathing deficits lead to other symptoms such as disturbed sleep, fatigue, excessive daytime sleepiness, early morning headaches, irritability, decreased concentration, and reduced exercise tolerance. The cause of death in ALS is an eventual passing from hypercarbia or other pulmonary complications.

The ALS Functional Rating Scale (ALSFRS: CNTF, 1996) was introduced in 1996 as a measure of physical functional decline in ALS and it was revised and revalidated in 1999 to improve assessment of respiratory function (Cedarbaum et al., 1999). The ALSFRS-R includes three items assessing bulbar function (i.e. speech, salivation and swallowing), six items assessing spinal function (i.e. fine motor tasks: handwriting, and cutting food and handling utensils; and gross motor tasks: dressing and hygiene, turning in bed and adjusting bedclothes, walking, and climbing stairs), and three items assessing respiratory function (i.e. dyspnoea, orthopnoea, and need for ventilation support). The ALSFRS-R score ranges from 0 (maximum disability) to 48 (no disability) points. Bulbar, limb function and respiratory sub-scores can also be obtained considering the aforementioned categories.

Although the ALSFRS-R is a useful tool to assess functional decline which can be related to disease severity, this tool has some shortfalls such as the lack of established thresholds to interpret transitions into different functional statuses as well as its difficulty in capturing ALS late-stage functional characteristics (Chiò, Hammond, Mora, Bonito, & Filippini, 2013). Thus, the need for a staging system in ALS was stated, to define clinical milestones that inform about disease severity, treatment options and prognosis (Chiò et al., 2013; Roche et al., 2012). Two main ALS staging systems have been developed and are used in clinical practice: King's Staging (Roche et al., 2012) and ALS Milano-Torino Staging (ALS-MITOS: Chiò et al., 2013).

On the one hand, the King's staging system (Table 1.2) was developed in 2012 with a cohort of 1,459 ALS patients diagnosed between 1993 and 2007.

On the other hand, the ALS-MITOS staging system (Table 1.3) is a more recently developed and validated system based on loss of function in four domains assessed by the ALSFRS-R, that define 5 stages of clinical milestones in ALS.

Table 1.2. King's staging system.

	STAGE	Description	% of disease progression when milestone occurs	Resources required
Stage 1	**Symptom onset (involvement of first region)**	Functional involvement by weakness, wasting, spasticity, dysarthria or dysphagia of one CNS region defined by bulbar, upper limb, lower limb or diaphragmatic.		Access to healthcare diagnostic services
Stage 2A[a]	**Diagnosis**	Confirmed diagnosis of ALS made either by the referring neurologist or at the tertiary centre, as recorded in the case records.	35%	Use of the multidisciplinary team
Stage 2B[a]	**Involvement of a second region**	Involvement of a second CNS region, defined by bulbar, upper limb, lower limb or diaphragmatic.	40%	
Stage 3	**Involvement of a third region**	Involvement of a third CNS region, defined by bulbar, upper limb, lower limb or diaphragmatic.	60%	
Stage 4A[b]	**Need for gastrostomy**	Time gastrostomy or nasogastric feeding was provided or refused.	80%	Palliative and end of life care
Stage 4B[b]	**Need for respiratory support (non-invasive ventilation)**	Time non-invasive ventilation was provided, trialled or refused.		

[a] Need for having two alternatives for Stage 2: time to diagnosis may differ depending on health system or clinician, but time to second region involvement is more likely to be consistent across centres. Moreover, time to diagnosis tends to be close to time of involvement of a second region.

[b] Need to consider both gastrostomy and non-invasive ventilation as Stage 4: the order in which they are needed frequently depends on onset (bulbar onset patients require gastrostomy before non-invasive ventilation, and vice versa for spinal onset patients). Thus, including one of them as Stage 5 would not lead to consistent staging.

Adapted from Roche et al. (2012)

Table 1.3. ALS-MITOS staging system.

Stage	Functional domains lost	
Stage 0	None	Functional involvement, but no loss of independence on any domain
Stage 1	1 domain	Refer to domains below
Stage 2	2 domains	
Stage 3	3 domains	
Stage 4	4 domains	
Stage 5	Death	

Domains	ALSFRS-R items	ALSFRS-R Response considered as loss of function
Movement (walking / self-care)	Walking	▪ Non-ambulatory functional movement only ▪ No purposeful leg movement
	Dressing and hygiene	▪ Needs attendance for self-care ▪ Total dependence for self-care
Swallowing	Swallowing	▪ Needs supplemental tube feeding ▪ Exclusively parenteral of enteral tube feeding
Communicating	Speech	▪ Speech combined with non-vocal communication ▪ Loss of useful speech
	Writing	▪ Able to grip pen but unable to write ▪ Unable to grip pen
Breathing	Dyspnoea	▪ Occurs at rest, difficulty breathing when either sitting or lying ▪ Significant difficulty, considering using mechanical respiratory support
	Need for ventilation support	▪ Continuous use of non-invasive ventilation during the night ▪ Continuous use of non-invasive ventilation during the night and day ▪ Invasive mechanical ventilation by intubation or tracheostomy

Adapted from Chiò et al. (2013)

The average life expectancy in ALS is generally 3 to 5 years from symptom onset (Chiò et al., 2009). Nevertheless, considerable variability is observed in survival and some slower progressing cases exist. Indeed, 25% of people with ALS are still alive after 5 years and 5 -10% survive for 10 years or more (Andersen et al., 2012; *Motor Neurone Disease: assessment and management. NICE guideline*, 2016). An ALS survival analysis of a period of 15 years from 1995 in Ireland showed a mean survival of 2.39 years from symptom onset and 1.27 years from diagnosis date (Rooney et al., 2013).

Although this high variability in survival is not fully explained, some prognostic factors have been investigated. While gender does not appear to be a prognostic indicator in ALS, age is a strong one, with older age at symptom onset negatively correlating with survival time (Chiò et al., 2009). Patients with symptom onset before the age of 40 have a higher survival time, which can exceed 10 years, while patients who develop symptoms at the age of 80 or older normally live less than 2 years (Chiò et al., 2009). A longer diagnostic delay in ALS has also been associated with a better prognosis (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). Other prognostic factors associated with decreased survival are bulbar onset

ALS (2-3 years of overall median survival; Wijesekera & Leigh, 2009), weight loss, poor respiratory function (especially at diagnosis), low ALSFRS-R score, fulfilling EL Escorial diagnostic criteria for Definite ALS, and the presence of cognitive impairment (Chiò et al., 2009; *Motor Neurone Disease: assessment and management. NICE guideline*, 2016). Some psychosocial factors such as psychological distress or living alone are also thought to be negative prognostic factors in ALS (Chiò et al., 2009). Evidence also suggests that high triglyceride and cholesterol levels improve survival (Hardiman et al., 2011).

1.2.5. Neuropathology

The neuropathological hallmark of ALS, like in most neurodegenerative diseases, is protein aggregates or inclusions, which are encoded by mutated genes (Al-Chalabi et al., 2012). In most ALS cases, such pathological features consist of cytoplasmic ubiquitin-positive inclusions, primarily comprised of TAR DNA-binding protein 43 (TDP-43), encoded by the TARDBP gene (Saberi et al., 2015). However, specific genetic mutations cause distinctive neuropathological processes in ALS. For instance, TDP-43 inclusions are not present in SOD1-related ALS, a gene mutation attributed to a high proportion of ALS cases, the neuropathological mechanisms of which are not fully understood (Turner et al., 2013).

The main pathological process in ALS is axonopathy (i.e. defects of the axons of the corticospinal tract and peripheral nerve fibres) resulting in axonal retraction and consequent loss of cell bodies in both lower and upper motor neurons (Al-Chalabi et al., 2012). Although the pathophysiology of ALS is not fully understood, pathogenic mechanisms known to contribute to the degeneration of motor neurons have been described (Hardiman et al., 2017; Van Damme, Van Den Bosch, & Robberecht, 2016):

a) Impaired protein homeostasis or proteostasis;
b) Disturbed RNA metabolism and RNA-binding proteins (RBPs);
c) Nuclocytoplasmic transport defects;
d) Cytoskeletal and axon-transport defects;
e) Impaired DNA repair;
f) Vesicle-transport defects;
g) Glutamate excitotoxicity;
h) Mitochondrial dysfunction;
i) Neuroinflammation and reactive astrogliosis; and
j) Oligodendrocyte dysfunction.

Figure 1.3 displays the main pathophysiological mechanisms involved in ALS, the interactions between these and the genetic mutations implicated in them. Proteostasis and disturbed RNA metabolism are predominant mechanisms, linked to various ALS causative genetic mutations.

The exact role of some of these molecular pathways as disease-causing pathogenic mechanisms or as secondary to disease process still needs to be established (Van Damme et al., 2016).

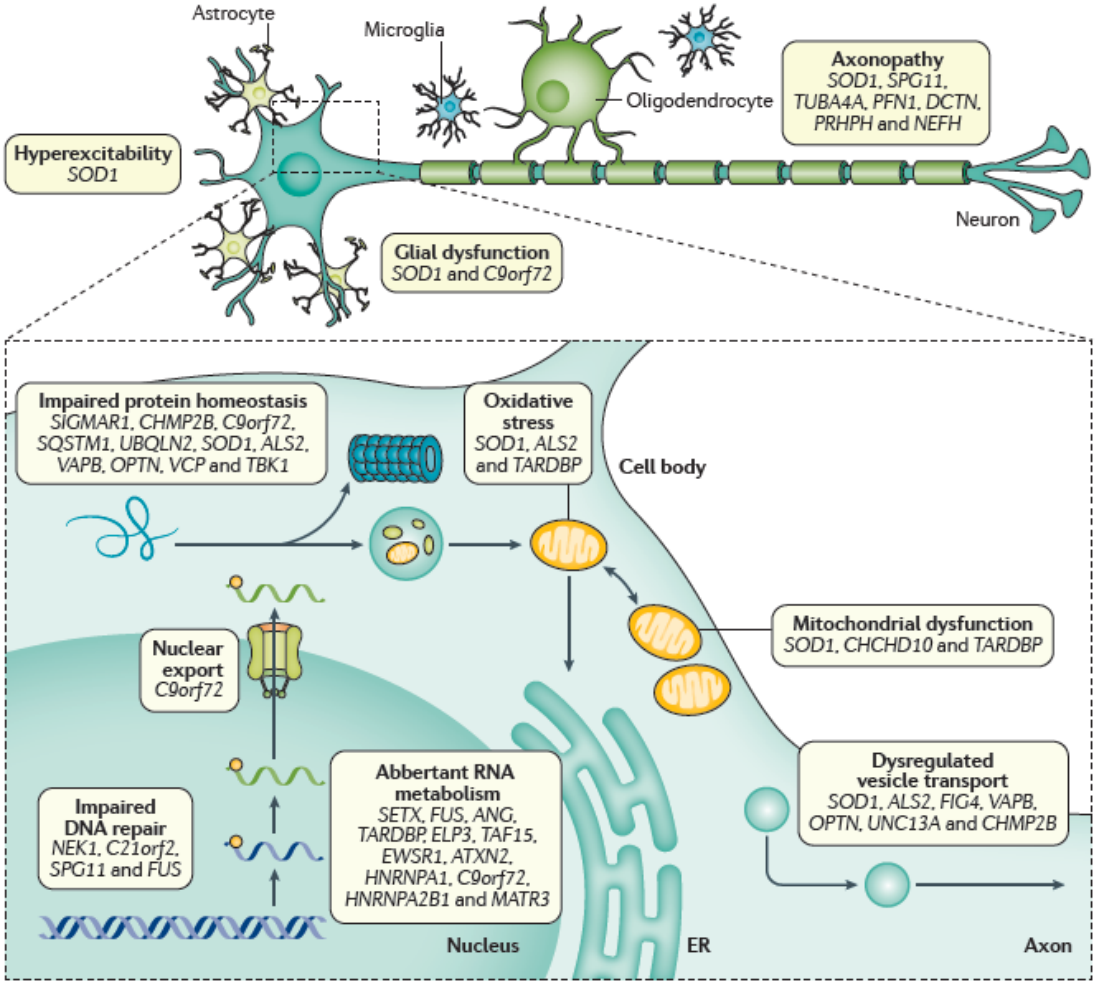

Figure 1.3. Pathophysiology of ALS. From Hardiman et al. (2017)

In terms of microscopic changes in the motor system, degeneration of motor neurons in the lateral and anterior columns of the spinal cord and the lower motor cranial nerve nuclei of the brainstem, as well as loss of Betz cells in the motor cortex are described (Saberi et al., 2015). Considering macroscopic changes, these include atrophy of the anterior nerve roots in the spinal cord and white matter reduction in the corticospinal tract (Saberi et al., 2015). Atrophy of the precentral gyrus can be seen, although generally no gross changes at brain level are observed (Saberi et al., 2015).

1.2.6. Aetiology

The aetiology of ALS, and MND in general, is not completely understood, although a complex genetic-environment interaction is believed to underlie the disease. It is thought that approximately 60% of the risk of developing ALS is genetically driven, and the other 40% is determined by the environment (Al-Chalabi & Hardiman, 2013).

1.2.6.1. Genetics

ALS is a disease of significant genetic variability. Up to date, it has been associated with mutations in more than 20 genes (Van Damme et al., 2016). Particular involvement of such genes trigger specific pathogenic pathways which cause selective motor neuron degeneration.

Table 1.4 displays genes associated with ALS, protein aggregates encoded by each gene mutation and pathogenic mechanisms triggered. These genetic mutations and associated neuropathological protein aggregates also map onto the degree of UMN, LMN and cognitive involvement (Figure 1.4).

Table 1.4. ALS-associated genes, related neuropathological protein aggregates and pathogenic mechanisms triggered.

Gene	Neuropathological protein aggregates	Pathogenic Mechanism
Most frequent		
C9orf72: Hexanucleotide repeat expansion GGGGCC (G_4C_2) in the C9orf72 gene (chromosome 9). Whereas normal individuals have up to 23 repeats, those with pathological expansion can range from hundreds to thousands.	TDP-43 aggregates * Most of the ubiquitinated inclusions in C9orf72-ALS are p62-positive, but TDP-43-negative. Deposited in frontal regions and CA4 region of the hippocampus.	▪ Impaired proteostasis ▪ Disturbed RNA metabolism and RBPs ▪ Nuclocytoplasmic transport defects ▪ Vesicle-transport defects ▪ Glutamate excitotoxicity
TARDBP: TAR DNA-binding protein gene (chromosome 1), which encodes TDP-43 or transactive response DNA binding protein 43 kDa.	TDP-43 aggregates	▪ Impaired proteostasis ▪ Disturbed RNA metabolism and RBPs ▪ Mitochondrial dysfunction
SOD1: Coding for cooper/zinc (Cu/Zn) superoxide dismutase type -1 gene, an enzyme related to cellular antioxidant defence mechanisms.	Cytoplasmatic inclusions of SOD1. Usually no TDP-43 aggregates.	▪ Impaired proteostasis ▪ Cytoskeletal and axon-transport defects ▪ Glutamate excitotoxicity ▪ Mitochondrial dysfunction ▪ Neuroinflammation and reactive astrogliosis ▪ Oligodendrocyte dysfunction
FUS: RNA Binding Protein FUS, a Protein Coding gene.	FUS aggregates. No TDP-43 aggregates.	▪ Impaired proteostasis ▪ Disturbed RNA metabolism and RBPs ▪ Impaired DNA repair ▪ Glutamate excitotoxicity

Table 1.4 (continued). ALS-associated genes, related neuropathological protein aggregates and pathogenic mechanisms triggered.

Gene	Neuropathological protein aggregates	Pathogenic Mechanism
Less frequent, or associated with atypical ALS		
ALS2, CHMP2B, UNC13A, VAPB	**VAPB*: probable TDP-43 aggregates	▪ Vesicle-transport defects
ANG, ATXN2, SETX, ELP3, HNRNPA1/A2/B1, MATR3	**ANG*: TDP-43 aggregates	▪ Disturbed RNA metabolism and RBPs
C21ORF2, NEK1		▪ Impaired DNA repair
CCNF, FIG4, OPTN, SIGMAR1, SQSTM1, UBQLN2, TBK1, VCP	**FIG4*: not known **OPTN*: TDP-43 aggregation (Glu478Gly) **UBQLN2*: Ubiquitin-2, also TDP-43-positive and FUS-positive	▪ Impaired proteostasis
CHCHD10		▪ Mitochondrial dysfunction
DAO		▪ Glutamate excitotoxicity
DCTN1, NEFH, PRPH, TUBA4A, SPG11, PFN1		▪ Cytoskeletal and axon-transport defects
GLE1		▪ Nuclocytoplasmic transport defects

Adapted from: Al-Chalabi et al. (2012), Al-Chalabi and Hardiman (2013), Saberi et al. (2015), Turner et al. (2013) and Van Damme et al. (2016)

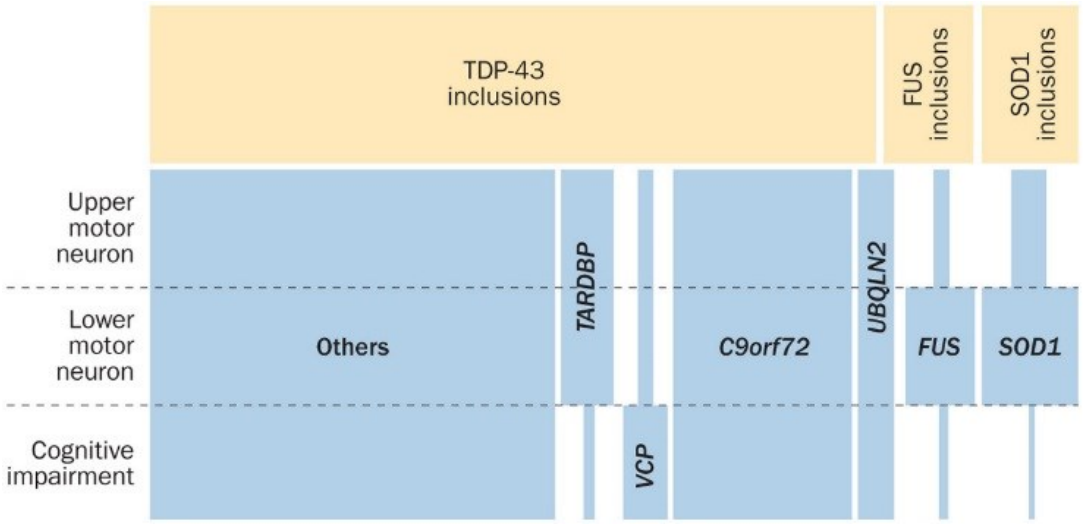

Figure 1.4. Pathological, phenotypic and genetic groupings of ALS. From Al-Chalabi and Hardiman (2013)

Genotype-phenotype studies have described particular clinical phenotypes for specific gene mutations. For instance, patients with the SOD1 mutation show more severe upper motor

neuron than lower motor neuron degeneration (Saberi et al., 2015). Specifically, mutations in the Ala4Valvariant of the SOD1 gene causes a rapid, primarily lower motor neuron syndrome, and the Asp90Ala recessive variant is associated with a slow progressive form that sometimes presents with sensory involvement (Al-Chalabi & Hardiman, 2013). TARDBP gene mutations have been related to a more rapid disease progression (Al-Chalabi et al., 2012), and FUS mutations, specifically p.P525L FUS mutation, is associated with a very aggressive juvenile-onset ALS (Turner et al., 2013). Patients with the C9orf72 hexanucleotide repeat expansion express a disease characterised by an earlier age of onset, decreased survival, increased incidence of cognitive and behavioural changes, as well as higher degree of family history of neurodegenerative and neuropsychiatric conditions (Turner et al., 2013). Finally, males with the UBQLN2 mutation frequently develop the disease at a younger age compared to females, as the mutation of this gene is X-linked and females are heterozygous for the mutation, thus being more likely protected (Al-Chalabi et al., 2012).

When the presence of ALS is associated with defined pathogenic mutations (i.e. Mendelian forms), and the disease is present in one or more generations in the family, this is considered familial/genetic ALS. Thus, the diagnosis of **Familial ALS** (FALS) is considered if at least one relative within three generations also suffers from ALS and/or FTD. FALS represents 10% of ALS cases worldwide (Saberi et al., 2015), although the rate of FALS in Ireland seems to be 16% (Byrne et al., 2013). **Hereditary** or **Primary Genetic ALS** (HALS/GALS) is diagnosed if a pathogenic mutation in a known ALS-causing gene is encountered in the patient (Ludolph et al., 2015). If such pathogenic mutation segregates within the family, such diagnosis is classified as **Clinically Definite Familial ALS – Laboratory-supported** (Brooks et al., 2000). In the context of a positive genetic test, the presence of only UMN or LMN signs in one body region is sufficient to make a diagnosis of ALS (Ludolph et al., 2015). Considering the most common mutations reported in ALS, SOD1 mutations are responsible for 20% of FALS cases, TARDBP gene mutations explain 2 to 5% of FALS cases, FUS mutations explicate 5% of FALS cases, and 50% of ALS patients with family history of ALS or FTD carry a C9orf72 repeat expansion (Byrne et al., 2013; Saberi et al., 2015; van Es et al., 2017).

Alternatively, when there is no presence of relevant family history, the occurrence of ALS is considered sporadic (i.e. **Sporadic ALS),** which represents 90% of all diagnoses of ALS (Saberi et al., 2015). Notwithstanding, genetic factors also contribute to the development of apparently sporadic ALS. Thus, a specific genetic constitution plays a part in the susceptibility to develop the disease. More than 80 candidate susceptibility genes have been related to a risk of developing ALS (Kenna et al., 2013), and disease-causing genetic mutations have been characterised in about 10% of sporadic ALS cases (Van Damme et al., 2016). Most of the gene mutations commonly associated with FALS are also discovered at a low level in sporadic ALS

cases (Figure 1.5). The C9orf72 repeat expansion is more frequently characterised as a cause of sporadic ALS, representing 10% of the cases (Al-Chalabi et al., 2012). Nevertheless, the presence of family history could have been misidentified in some cases. Therefore, when evaluating the presence of family history in ALS, it is worth considering that unknown or incomplete family history, small family sizes or early deaths prior to the development of ALS could underestimate the presence of family history. Moreover, the presence of FTD in such families only recently denotes a positive family history (Turner et al., 2013).

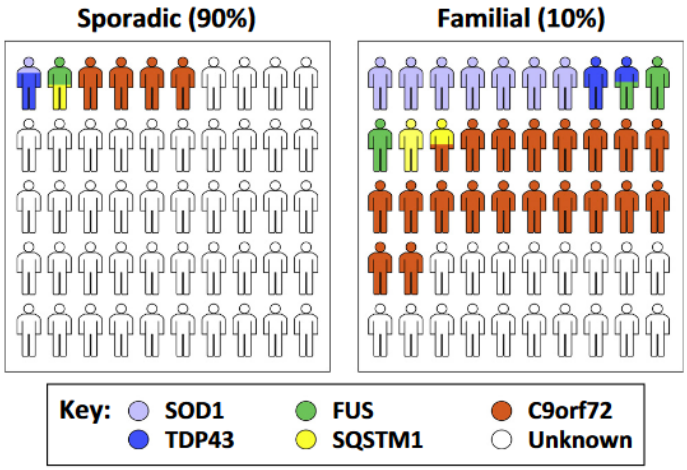

Figure 1.5. Major genetic causes in familial and sporadic ALS. From Lattante, Ciura, Rouleau, and Kabashi (2015)

In Ireland, SOD1 and UBQLN2 mutations have not been recognised as a cause of ALS (Kenna et al., 2013; McLaughlin et al., 2014); and in a population-based study of 444 Irish ALS cases only a few number of cases of TARDBP and FUS mutations were identified (0.45% of the total population for each mutation; Kenna et al., 2013). However, the C9orf72 repeat expansion was identified in almost 10% of the Irish sample, and this seems to be an important contributor to FALS and apparently sporadic ALS cases in Ireland (Byrne et al., 2013; Kenna et al., 2013). Regardless, a high proportion of genetic contribution to ALS in Irish population still remains undetermined (McLaughlin et al., 2014).

In conclusion, while it was previously suspected that major single genes were responsible for cases of FALS, evidence of incomplete penetrance of various genes in FALS as well as the presence of apparently 90% of sporadic cases suggest that some forms of ALS are more likely caused by an interplay of multiple genetic variants that co-occur with major frequency than the expected by chance, in combination with not yet fully understood environmental factors and stochastic events (Turner et al., 2013). Therefore, ALS is understood as an oligogenic disease, being an intermediate between monogenic (i.e. inheritance determined by a single causative gene) and polygenic diseases (i.e. inheritance determined by the additive effect of many genetic polymorphisms plus environmental contributors). This is concordant with findings such as an incomplete penetrance in many ALS pedigrees as previously mentioned,

and also with the consegregation of multiple ALS-associated genes in some kindreds and the decreased rate of ALS in genetically mixed populations (van Es et al., 2017). In this context, the dichotomisation familial/sporadic ALS is considered simplistic (Hardiman et al., 2017).

1.2.6.2. Environmental Factors

Some environmental and lifestyle factors have been investigated as potential risk factors for the development of ALS. Nevertheless, the influence of these factors is not yet fully elucidated due to the challenges of researching environmental causes. These challenges include the high cost of prospective, case-control longitudinal epidemiological studies, the fact that such risk factors are continuously changing in space and time, and that they act on specific genetic backgrounds (Al-Chalabi & Hardiman, 2013). The most studied environmental factors in ALS are described below.

Smoking has been identified as a risk factor for ALS, although some studies have suggested an increased risk only in female smokers, specifically at the menopausal stage (Ingre, Roos, Piehl, Kamel, & Fang, 2015). Results in this field appear inconsistent and the role of smoking in ALS warrants further investigation (Factor-Litvak et al., 2013; Ingre et al., 2015). Evidence of the role of alcohol and coffee consumption as risk factors for ALS is limited (Ingre et al., 2015). History of traumatic brain injury also seems to be linked with an increased risk of developing ALS (Pupillo et al., 2018).

Evidence that vigorous physical activity is associated with a higher risk of ALS also exists, although the nature of this relationship is not fully understood. Recent evidence suggests that physical activity as such does not increase the risk of ALS (Bozzoni et al., 2016), and alternative explanations exist. For instance, the existence of a specific genetic profile in some people that affects metabolic response to intense exercise levels, or that ALS in people with a predilection to physical activity reflects a set of predisposing genetic determinants to both athletic prowess and risk for neurodegeneration (Turner et al., 2013).

Independently, low body-mass index (BMI) has been linked to a higher risk of developing ALS (Ingre et al., 2015), and while the biological cause of this relationship is not fully understood, it is probably related to hypermetabolism, which is highly characteristic of ALS (Turner et al., 2013).

Pesticides (i.e. herbicides, insecticides, fungicides and rodenticides) are known to be neurotoxic, and its exposure has been strongly associated with an increased risk of developing ALS (Ingre et al., 2015). This is one of the most reliable risk factors described to date (Bozzoni et al., 2016). Two recent meta-analyses have described a male-specific connection between pesticides and ALS (Bozzoni et al., 2016).

Heavy metals exposure as an ALS risk factor has been broadly studied, with inconsistent results. As such, a cautious approach to interpretation is required. Exposure to lead has been related to the development of ALS (Factor-Litvak et al., 2013) and manganese, another metal with neurotoxic properties, has also been found to accumulate in the CNS of ALS patients (Ingre et al., 2015). Elevated concentrations of iron in the motor cortex and ventral spinal cord of ALS patients has also been described (Ingre et al., 2015). The role of metalloid selenium in the development of ALS in some regions of South Dakota and Northern Italy has been investigated, driven by the elevated presence of selenium in drinking water in these regions (Bozzoni et al., 2016). Increased selenite concentrations have been found in the cerebrospinal fluid of ALS patients in Italy (Ingre et al., 2015). Other metals that have been found in high amounts in the cerebrospinal fluid of ALS patients include: aluminium, coper, cobalt, zinc, arsenic, uranium, cadmium and vanadium (Ingre et al., 2015). A relationship between ALS and exposure to extremely low-frequency electromagnetic fields (EMF) and electric shocks, both perceptible and imperceptible, was also suggested, although recent findings advise that this evidence is inconclusive (Bozzoni et al., 2016).

Finally, the neurotoxin BMAA, although not concluded as the cause of ALS-PDC in Guam, has also been found at increased levels in the brain in populations other than Guam, while at lower levels, suggesting that this neurotoxic amino acid is likely to be a risk factor for ALS (Bozzoni et al., 2016).

Some occupations, with the common denominator of long-term exposures to previously mentioned environmental risk factors, have been related to a higher risk of ALS. Among these, professional football players or other athletes, military personnel, precision metal workers, construction workers, farmers, carpenters, painters, hairdressers, laboratory technicians, nurses, programmers and electrical occupations stand out.

Considering football players, an increased risk of ALS has been demonstrated in professional footballers, but not within recreational players (Ingre et al., 2015). Among the various possible explanations of this phenomenon are: repeated experience of head trauma (i.e. Chronic Traumatic Encephalopathy), exposure to pesticides used in football fields, or exposure to illegal performance-enhancing substances such as growth hormone, creatine monohydrate and branched-chain amino acids (BCAAs: Bozzoni et al., 2016). For military personnel, the hypotheses attempting to explain the association between this occupation and ALS include: exposure to heavy metals and chemicals, involvement in psychological trauma, intensive physical activity, and vaccines and viral infections, all of which have already been related to increased risk of ALS (Ingre et al., 2015). Finally, although an increased risk of ALS in occupations that require exposure to EMFs has been suggested, no increased risk of ALS in people living near EMFs has been reported (Bozzoni et al., 2016).

Some protective factors, such as increased antioxidants intake, particularly Vitamin E and polyunsaturated fatty acids, have been related to a lower risk of developing ALS (Ingre et al., 2015). Diabetes Mellitus type 2, hyperlipidaemia and exposure to hormonal contraception also seem to be protective (Hardiman et al., 2017).

In Ireland, spatial analyses aiming to identify environmental risk factors in ALS have been performed (Rooney et al., 2014; Rooney, Vajda, et al., 2015). This has been possible due to the small dimension of the country, which allows to perform population-based studies, and the existence of the Irish ALS Register, a database including all diagnosed cases in Ireland since 1993 (Rooney et al., 2013; Traynor, Alexander, Corr, Frost, & Hardiman, 2003; Traynor et al., 1999). Two studies have looked at high risk areas for ALS in Ireland, including all diagnosed cases in the country from January 1995 to July 2013 (a total of 1,684). The first study used Bayesian risk mapping analysis based on standardised incidence rates (Rooney et al., 2014), and the second used spatial cluster analyses, which allows for cluster identification using hypothesis testing (Rooney, Vajda, et al., 2015). Bayesian analysis showed some regions of slightly higher risk for ALS including Cork city, the Dingle peninsula in Kerry, West Donegal, and the north-east coast (Co. Louth, Meath and North-Dublin), and two areas of significantly steady low incidence for ALS, one in the Carlow-Kilkenny region and the other in the Clare-Galway area (Rooney et al., 2014). Nevertheless, when using more sophisticated cluster analysis, only the two areas of reduced ALS incidence remained as a significant finding (Rooney, Vajda, et al., 2015). Hypothetical explanations of such findings lie within a high genetic mixture due to a complex historical settlement in Carlow/Kilkenny which diverges from other areas, and complex, not fully explored environmental circumstances in the Clare/Galway region.

1.2.7. Management

There are currently no existing treatments to stop the course of ALS. However, several pharmacological and multidisciplinary therapies are available which help in managing the symptoms of the disease and maintaining quality of life.

1.2.7.1. Pharmacotherapy

Up to date, Riluzole is the only drug licensed/approved specifically for the treatment of ALS worldwide. The precise mechanism of action of Riluzole is still not fully understood, although it is believed to be a neuroprotective agent which presumably blocks the neurotransmission of glutamate in the CNS (Ingre et al., 2015). The administration of 100mg of Riluzole a day improves survival by 15%, and following 18 months of treatment, survival is increased by 3 months (in patients younger than 75 years of age, symptoms onset < 5 years, and forced vital capacity > 60%), therefore having a modest effect with limited survival benefit (Miller, Mitchell,

Lyon, & Moore, 2007). Riluzole is normally prescribed as early as possible at an initial dose of 100mg (50mg twice daily) by a consultant neurologist with specialist expertise in ALS (Moore et al., 2008). Riluzole is generally safe, although it can have some minor side effects such as fatigue, nausea, gastrointestinal issues and abnormal liver function, which should be regularly checked up (Wijesekera & Leigh, 2009). This drug is not recommended in cases of liver or renal dysfunction, pregnancy or if the patient is breast-feeding (Moore et al., 2008).

Another compound, Edaravone, which acts as a free radical scavenger potentially reducing oxidative stress, has recently been approved in the US, South Korea and Japan for the treatment of ALS. This occurred following results of a randomised, double-blind, placebo controlled trial which proved that Edaravone slowed functional decline over a period of 24 weeks (Abe et al., 2017). However, this study presented with important limitations that can question the efficacy of Edaravone for all ALS clinical presentations (Hardiman & van den Berg, 2017).

Other medications are prescribed in ALS for symptom management (Table 1.5).

Table 1.5. Pharmacological therapies for the management of ALS symptoms.

Symptom	Pharmacological Therapy	
Muscle cramps	▪ Quinine ▪ Tizanidine, *muscle relaxant* ▪ Dantrolene, *muscle relaxant* ▪ Mexiletine, *anti-arrhythmic* ▪ Diazepam, *benzodiazepine* ▪ Baclofen, *muscle relaxant and antispastic agent*	▪ Carbamazepine, *anticonvulsant* ▪ Gabapentin, *anticonvulsant* ▪ Phenytoin, *anticonvulsant* ▪ Levetiracetam, *anticonvulsant*
Spasticity	▪ Baclofen, *muscle relaxant and antispastic agent* ▪ Tizanidine, *muscle relaxant*	▪ Dantrolene, *muscle relaxant* ▪ Gabapentin, *anticonvulsant* ▪ Botulin toxin type A injections
Drooling / Sialorrhoea	▪ Amitriptyline, *tricyclic antidepressant* ▪ Atropine, *anticholinergic muscarinic antagonist* (if alternates with dry mouth) ▪ Glycopyrrolate, *anticholinergic muscarinic antagonist* * if cognitive impairment ▪ Socopolamine patches, *anticholinergic muscarinic antagonist* ▪ Botulin toxin type A injections ▪ Salivary gland irradiation	
Tenacious saliva and bronchial secretions	▪ Carbocisteine, *mucolytic* ▪ Propranolol, *beta-blocker* ▪ Metoprolol, *beta-blocker* Nebulised saline	
Laryngospasms	▪ Lorazepam sublingual, *benzodiazepine*	
Emotional lability	▪ Amitriptyline, *tricyclic antidepressant* ▪ Citalopram, *selective serotonin reuptake inhibitors (SSRIs) antidepressant* ▪ Levodopa, *dopamine agonist* ▪ Dextromethorphan, *opioid analgesic* ▪ Quinidine, *anti-arrhythmic*	
Excessive yawning	▪ Baclofen, *muscle relaxant and antispastic agent*	

Table 1.5 (continued). Pharmacological therapies for the management of ALS symptoms.

Symptom	Pharmacological Therapy
Pain	▪ Analgesics ▪ Non-steroidal anti-inflammatory drugs (NSAIDs) ▪ Gabapentin and Pregabalin, *anticonvulsants* ▪ Tricyclic antidepressants (for neuropathic pain) ▪ Opioids
Constipation	▪ Lactulose, *laxative* ▪ Movicol, *laxative* ▪ Docusate, *laxative* ▪ Senna, *laxative*
Fatigue	▪ Modafinil, *wakefulness promoting agent*
Insomnia	▪ Amitriptyline, *tricyclic antidepressant* ▪ Zolpidem, *imidazopyridine hypnotic*
Anxiety	▪ Lorazepam, *benzodiazepine*
Depression	▪ Amitriptyline, *tricyclic antidepressant* ▪ Citalopram, *selective serotonin reuptake inhibitors (SSRIs) antidepressant*
Terminal restlessness and confusion	▪ Chlorpromazine, *neuroleptic*

Adapted from Andersen et al. (2012),Hardiman et al. (2017), Moore et al. (2008), *Motor Neurone Disease: assessment and management. NICE guideline* 2016), and Wijesekera and Leigh (2009)

Pharmacological treatments always need to be combined with a multidisciplinary team care, as these are complementary. The input from multidisciplinary therapies sometimes reduces the need for medication, which can be challenging, especially when swallowing problems are present.

1.2.7.2. Multidisciplinary Team

The treatment for ALS currently consists of a holistic multidisciplinary care approach, mainly focused on symptom management. This multidisciplinary team is ideally clinic-based and MND specialist, and it includes a neurologist, nurse specialist, physiotherapy, occupational therapy (OT), dietetics, and speech and language therapy (SALT). Co-ordinated assessments at the specialist MND clinic by the multidisciplinary team should be carried out every 2 to 3 months, this being tailored to the person's needs (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016).

Physiotherapy manages symptoms related to movement and function, such as balance problems, difficulty walking or with transfers, weakness, spasticity or pain in the joints, as well as difficulty with Activities of Daily Living (ADLs). Physiotherapists undertake mobility assessments to evaluate transfers, risk of falls and manual handling risks, as well as assessments for the need of equipment to help with mobility, such as ankle-foot orthoses, mobile arm supports or neck supports. Regular review of such appliances is necessary. Respiratory symptoms and cough effectiveness are also monitored by physiotherapy.

Movement, posture and positioning as well as passive limb and cardiopulmonary exercises can be taught to better manage symptoms such as spasticity, abnormal muscle tone, contractures, pain and respiratory insufficiency. Fall prevention is also an important task for physiotherapists which is done by working with the patient on maximizing balance and safety.

OT assesses ADLs and provides compensatory strategies and environmental changes to improve function. OTs assess and anticipate changes in needs in activities such as dressing, showering, eating and drinking, which are a result of loss of dexterity and reduced mobility. They also provide assistive equipment and adaptations when necessary. Some of the appliances that are supplied by OT include button and zipper aids, shoe horns, sock aides, palmar cuffs (to hold cutlery), pen holders, and key turners, among others. Regular and ongoing OT assessments are required.

Dietitian's input is required when there are concerns regarding dysphagia or weight loss. Advice on diet and nutrition, swallowing techniques and fluid intake, and weight control is provided to prevent malnutrition and dehydration, which impact survival. Moreover, ALS patients suffer from a hypermetabolic state which requires a higher intake of calories (Wijesekera & Leigh, 2009). Risk of aspiration and/or choking and the need to modify food and liquids' consistency is also assessed. Recommendations on posture, positioning, suctioning and oral care in the presence of salivation problems such as sialorrhoea and viscous saliva are also offered to prevent aspiration.

SALT assesses speech and communication needs and provides augmentative or alternative communication (AAC) aids when necessary. AAC supports can be classified as 'low-level' technologies, which include alphabet, word or picture panels, and 'high-level technologies', comprising of tablets or other computerised devices, including eye-gaze communication systems. These support systems need to be adapted to the ability of the person to use it, and adequate training and support needs to be provided. SALTs can also provide valuable instruction on swallowing techniques.

A healthcare professional with expertise in palliative care is also required within the multidisciplinary team, this usually being the MND nurse specialist. Respiratory function also needs to be monitored by a trained healthcare professional (usually a physiotherapist), ideally at each clinic visit using tests such as forced vital capacity (FVC) or sniff nasal respiratory pressure (SNIP: Andersen et al., 2012). Respiratory muscle weakness is considered at FVC ≤ 80% of the predicted value, or SNIP ≤ 40cmH2O (Wijesekera & Leigh, 2009).

Although clinical psychology and neuropsychology are not considered part of the core MND specialist multidisciplinary team (*Motor Neurone Disease: assessment and management. NICE*

guideline, 2016), this expertise is increasingly recognised as part of the fundamental MND clinical care. Thus, routine neuropsychological screenings are administered at clinic visits, usually performed every four months, and this can inform medical care and indicate if further comprehensive assessment or support is required (Strong et al., 2017). For this purpose, two assessment tools are recommended: the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), a short screening test developed specifically for use in ALS which has been validated against comprehensive neuropsychological examinations (Abrahams, Newton, Niven, Foley, & Bak, 2014; Pinto-Grau, Burke, et al., 2017), and the Beaumont Behavioural Inventory (Elamin et al., 2017; Pinto-Grau, Costello, et al., 2017), a validated behavioural proxy-report measure for caregivers. The psychological and emotional impact of the disease also needs to be discussed with the patient as well as with family members and carer/s at routine clinic appointments; a referral to clinical psychology services or counselling may be required. Other sources of emotional support such as support groups may also be available.

Input from other medical professionals such as a respiratory physiologist, a gastroenterologist or an orthotist may also be required. Social workers may also need to be involved to assist with social care needs.

Multidisciplinary care improves survival, reduces number and length of hospital admissions and improves quality of life (Chiò, Bottacchi, Buffa, Mutani, & Mora, 2006; Chiò et al., 2009; Rooney, Byrne, et al., 2015; Van den Berg et al., 2005). Patients attending clinic are more likely to use Riluzole and non-invasive ventilation, and are referred earlier to palliative care (Andersen et al., 2012). A study investigating the effect of the multidisciplinary specialist ALS team on survival in Ireland over a five year period showed that survival was increased by 7.5 months in patients who attended the clinic (Traynor et al., 2003).

1.2.7.3. Palliative Care

Palliative care is specialised medical care for people facing an illness of incurable nature. In ALS, palliative care aims to treat the symptoms of the disease to better manage them and maintain quality of life, to enhance communication between the patient, family and healthcare professionals to better guide them through the process of advanced care planning and end-of-life decision making, and to provide support for patients and family members throughout the disease process, especially for those under emotional distress. At every stage, palliative care assesses the needs of patients and families and provides appropriate care. Although palliative care can be involved at any stage during the course of the disease, early referral to palliative care services is recommended (Andersen et al., 2012). Obstacles to accessing palliative care can include limited resources and professional care provider's lack of familiarity with the disease trajectory or fear of decreasing hope (Connolly, Galvin, & Hardiman, 2015). Effective

communication between the hospital-based multidisciplinary team, community-based services and the palliative care team is crucial to provide adequate healthcare support.

Among the treatments offered to palliate ALS symptoms, respiratory and nutrition support need to be highlighted. Non-Invasive Ventilation (NIV), specifically Bi-level Positive Airway Pressure device (BiPAP), is the treatment of choice to reduce symptoms of hypoventilation. Continuous Positive Pressure (CPAP) ventilation does not appear helpful in ALS (Wijesekera & Leigh, 2009). NIV in ALS prolongs survival and improves quality of life, especially for patients who are able to tolerate it for 5 hours or more per day (Hardiman et al., 2011). The American Academy of Neurology suggests the criterion to start NIV is when FVC is less than 50% of the predicted value (Wijesekera & Leigh, 2009), although sometimes earlier intervention is applied as it has shown to improve survival (Moore et al., 2008). Currently, a more appropriate guideline seems to be FVC of 75% or less, as respiratory failure can develop at FVC above 70% (Wijesekera & Leigh, 2009). NIV is usually intermittently initiated at night to ease the symptoms of nocturnal hypoventilation, although the advancing nature of the disease progressively requires continuous nocturnal support and intermittent daytime use, to eventually oblige day and night continuous support. NIV has positive effects on survival but it does not stop the progression of the disease (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). The effectiveness in patients with bulbar onset is controversial (Andersen et al., 2012), as although it improves sleep-related complications, it does not benefit survival (Wijesekera & Leigh, 2009).

To relieve the symptoms of respiratory insufficiency, Invasive Mechanical Ventilation (IMV) via tracheostomy can also be used. IMV can prolong survival for many years, although there is no established evidence of improved quality of life and there is also a risk of developing a 'totally locked-in state' (TLS) with various degrees of oculomotor paralysis (Andersen et al., 2012; Wijesekera & Leigh, 2009). The use of IMV in ALS is not recommended in all countries due to its high cost, as well as the social and emotional implications it has on patients and relatives.

Cough augmentation techniques, such as manual assisted cough, unassisted breath stacking or assisted breath stacking (for bulbar patients who don't find the unassisted breath stacking effective) are also prescribed to ALS patients with ineffective cough (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). Mechanical cough assist is also considered if none of the aforementioned techniques is effective and/or in case of respiratory tract infection (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). The use of caught-assist devices improves the effectiveness of assisted ventilation (Andersen et al., 2012).

In the face of effortful feeding, distressing risk of choking, symptoms of aspiration and continued weight loss, the need for enteral feeding is discussed. Guidelines to consider tube insertion recommend to discuss it when the premorbid weight has fallen by more than 10% (Wijesekera & Leigh, 2009), although a 5% weight loss can be sufficient to consider early intervention (Hardiman et al., 2017). Two types of gastrostomies are applied in ALS: Percutaneous Endoscopic Gastrostomy (PEG) and Radiologically Inserted Gastrostomy (RIG). Although PEG improves nutrition, evidence about improved survival and quality of life and reduced risk of aspiration is not definite (Andersen et al., 2012). RIG is more recommended at advanced stages or when respiratory function is poor, as it can be inserted without sedation (Moore et al., 2008). However, both procedures are invasive and not always tolerated. Early insertion of gastrostomy is recommended, considering the possible risks of complications of a late placement, such as low critical body mass, risk of dehydration and respiratory difficulties, which are more likely to cause procedural complications and are associated with a higher risk of mortality (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). Nasogastric tube (NGT) feeding can also be used and is safe to apply on most patients, although downsides to consider are nasopharyngeal discomfort, increased secretions and, in some cases, ulceration (Andersen et al., 2012). NGT is usually considered for patients who cannot undertake enteral tube insertion (Wijesekera & Leigh, 2009). Home parenteral nutrition administered through an intravenous catheter can be an option in patients with severe respiratory dysfunction and advanced disease status (Andersen et al., 2012).

When supporting patients and families through the process of advanced care planning and end-of-life decision making, advance care directives (i.e. patient's outline of his/her desires regarding life-sustaining treatments in anticipation of a circumstance whereby ability to make an informed decision may be compromised) need to be considered, preferably in a formal written format. This is especially relevant where IMV is used as an emergency treatment after an acute respiratory failure. It is imperative that breathing management and the availability of treatments is discussed with the patient and family members as soon as it is believed appropriate, to allow for advanced care planning decision making to be made informatively. The introduction of respiratory or nutritional support are sometimes seen as anchor points to initiate formal discussions regarding end-of-life decisions (Connolly et al., 2015). Furthermore, appointing a surrogate decision maker early in the course of the disease may also be relevant for patients experiencing cognitive decline (Connolly et al., 2015).

Palliative care services also support end of life care needs by providing terminal symptom control and hospice care, as well as subsequently comforting bereaved families. Referral to hospice care optimises symptom control and can increase the likelihood of dying peacefully (Connolly et al., 2015).

1.2.8. Disclosing the Diagnosis of ALS

The manner in which the diagnosis of ALS is disclosed influences patients' perceptions of their quality of life and determines their engagement in support seeking during the course of the disease (Aoun et al., 2016; Hardiman et al., 2017). When giving a diagnosis of ALS, many aspects need to be considered (Andersen et al., 2012; Fallowfield & Jenkins, 2004; *Motor Neurone Disease: assessment and management. NICE guideline*, 2016). A private setting is necessary to ensure confidentiality. It is recommended that the patient has the support of a relative at the time of diagnosis, whilst always respecting the person's right to decide who should be present. Professional support also needs to be present when delivering the diagnosis. Thus, the lead consultant should be the person giving the diagnosis, but the presence of another member of the multidisciplinary team, ideally the nurse specialist, is also recommended. The person needs to be informed in an honest and factual but sensitive and compassionate manner of the incurable nature of the disease and the unpredictable prognosis, but again, always respecting the person's right to decide how much information he or she wants to receive. It is recommended to explore the level of knowledge about the disease and the understanding of the situation the person has when giving such a diagnosis. It is important to acknowledge the person's immediate reaction and allow time and space for an initial shock. Sometimes it can be difficult for the person to take in information immediately after the diagnosis has been given. The clinician should listen to the person's concerns and acknowledge their emotions. When they are ready, treatment and supports available need to be discussed, including the role of the multidisciplinary team as well as psychological support that may be accessible. This discussion should always reflect the needs of the person at that time. Enough time for the person to ask questions has to be allowed before they are let go. A prompt (4 weeks since diagnosis; *Motor Neurone Disease: assessment and management. NICE guideline*, 2016) and ongoing follow-up is crucial after this first interaction.

A study investigating the factors that determined satisfaction with the delivery of the diagnosis from the patient's perspective showed that among the most valued determinants were: perceiving an empathic response towards their feelings and those of their families, receiving accurate information about all aspects of the disease and being suggested realistic goals, being asked how much they already knew about the condition and how much they wished to know, and being offered a plan which was followed-through (Aoun et al., 2016).

1.2.9. Emotional Impact of the Diagnosis of ALS

ALS is a devastating disease that involves the progressive loss of independence, with the inevitable outcome of death. When a person receives a diagnosis of ALS, there are many changes to expect, not only for the patient but also for the family members and other relations. This is accompanied by a unique set of emotions which may require time to process and may

necessitate professional support. This emotional experience will most likely influence the way patients and families face the various stages of the disease and losses associated with it.

The most evident loss that ALS patients have to face is the loss of functional status and becoming progressively dependent on others. Accompanying this loss of independence, other losses include not being able to fulfil certain roles and responsibilities (e.g. being able to work) or the changes in the nature of relationships (e.g. changes in intimate relationship between spouses). The concept of self-perceived burden (SPB) or 'feeling of being a burden to others' is also gaining interest in research, as this feeling can cause significant distress and feelings of guilt in the patient, and can affect their decisions regarding medical care (McPherson, Wilson, & Murray, 2007). Moreover, patients also have to face preoccupations about the impact that the disease and their inevitable death will have on others. A recent systematic review on psychological morbidity in ALS reported the prevalence of depression ranging from 20% to 60%, and that of anxiety from 20% to 70% (Carvalho et al., 2016). Depression, hopelessness and anxiety have been proven to negatively impact overall quality of life (Hardiman et al., 2017; see Figure 1.6). Therefore, it is important to address psychological distress in ALS.

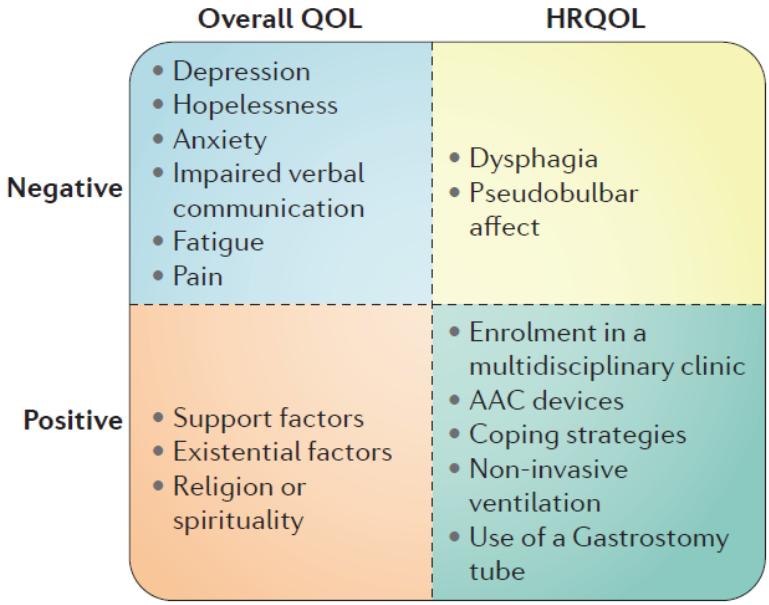

Figure 1.6. Factors affecting overall and health-related quality of life in ALS patients. From Hardiman et al. (2017)

The experience of caring for a loved one diagnosed with ALS can also cause remarkable strain due to the rapid progressive nature of the disease (Aoun et al., 2013). The level of dependence of the person with ALS increases rapidly and caregiving can become a very time consuming activity, causing personal and social restrictions. Moreover, ALS caregivers experience daily changes and long-term adjustments, changes in family roles and dynamics, worries about the progression of the disease and anticipation of forthcoming loss, and a sense of fear and uncertainty about the future. In most cases, there is also a changing nature of the reciprocal

relationship between the caregiver and the patient, especially in the case of spouses. Thus, the experience of caregiving in ALS can cause physical exhaustion and can be emotionally overwhelming, which can lead to caregiver burden. Caregiver burden is relatively common within ALS caregivers; among 81 informal caregivers attending the National Irish Specialist MND Clinic, 52% reported substantial levels of caregiver burden shortly after diagnosis (Galvin et al., 2016). Signs and symptoms of caregiver burden include: experiencing negative emotions such as anger, frustration, dissatisfaction, anxiety or low mood, feelings of guilt when taking a break from caregiving, decreased efficiency due to a lack of enthusiasm, inability to concentrate or boredom, decreased self-confidence, conflicts with others, social isolation, and health problems such as headaches, fatigue or insomnia (*Caring and MND: support for you guide*, 2016). Long hours of care provision, psychological distress and lower quality of life have proven to be significant predictors of caregiver burden (Galvin et al., 2016). Among other factors that increase the levels of burden in the caregivers are the need for assisted ventilation, the presence of cognitive and behavioural deficits, and end-of-life caregiving (Aoun et al., 2013; Caga, Hsieh, Lillo, Dudley, & Mioshi, 2019; de Wit et al., 2018). Moreover, some interventions used to palliate the symptoms of the disease may not be suitable for ALS patients with severe cognitive or behavioural impairment (e.g. learning how to use of communication aids, use of enteral feeding, or tolerating NIV), and compliance is also generally affected in these cases (Caga et al., 2019). This presents with a unique set of challenges and can increase frustration in the caregiver.

Assessment of caregiver distress and burden and provision of adequate practical and emotional support should be part of the core management of ALS (Aoun et al., 2013). Thus, when supporting ALS carers, it is important to help them acknowledge that their own personal needs also have to be addressed. It is important that they take time away from caregiving to dedicate to themselves, and that they maintain good social supports and connections with informal networks to avoid social isolation. To be able to achieve this, access to external supports and assistance are valuable, including home help services and respite care, as well as adequate information on how to reach and navigate the health-care services (Galvin et al., 2018). Healthcare professionals should also undergo continued educational and training programmes to improve communication and provide useful and updated information to the person with ALS and his/her family. ALS caregivers also value emotional support (Galvin et al., 2018). Thus, in cases where patients and/or caregivers are under substantial distress, these may benefit from community support groups or individual psychological support. Separately, psycho-educational programmes for family members around behavioural and cognitive deficits in ALS can raise awareness and help in understanding and managing them better. Moreover, caregiver burden can continue after the patient passes away and bereavement support in such families is strongly recommended.

CHAPTER 2 Outline.

The Language-Processing System

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CHAPTER 2.

The Language-Processing System

2.1. Introduction

"Language performance - the perception and production of written and spoken language - is mediated by an internal information-processing system, the language-processing system, which acts to form and to transform various types of linguistic representations" (Coltheart, Sartori, & Job, 2013, p. 1). The language-processing system is a complex structure that requires the interaction of a set of functions with underlying complex cognitive and neural mechanisms. This second introductory chapter presents an overview of the language-processing system, given that the study of language dysfunction in ALS is a primary component of this research. The chapter is structured around the main communication components, which include the comprehension of auditory input and the production of spoken output, as well as reading and writing. Moreover, the last two sections of this chapter offer an overview of language dysfunction in neurodegenerative diseases and the assessments that are usually used to evaluate these.

In this chapter, each of the language components mentioned above is broken down into different levels of processing, including phonological, orthographic, lexical, semantic, grammatical, and discourse processing. Regarding auditory language comprehension, phonological lexical processing (i.e. identification of single words) and access to semantics (i.e. association of specific lexical representations into meaningful concepts) are considered at a single-word level. At a sentence level, grammatical processing, including morphology (i.e. analysis of the internal structure of words) and syntax (i.e. analysis of rules that govern sentence structure), are covered, as well as semantic processing. Finally, regarding discourse processing, elements such as cohesion (i.e. connection of grammatical and lexical aspects within and between sentences) and coherence (i.e. semantic connections between and within sentences) are described. Regarding language expression, the processes of translating mental lexical representations into meaningful words, followed by syntactic and grammatical organisation of phonological output are considered. Reading and writing abilities are also core components of the language system, which in addition to phonological processes, also involve orthographic processing.

The neuroanatomical correlates of each of the above language processes are also discussed in this chapter. A range of brain networks have been associated with specific language functions based on neuroimaging and lesion studies, although we are still far from having the language

system completely mapped. Regardless, initial evidence suggests that inferior parietal and posterior superior temporal areas are implicated in the processing of phonological input, whereas anterior inferior temporal regions play a role in semantic processing (Démonet, Thierry, & Cardebat, 2005). Inferior and lateral prefrontal areas seem to be involved in syntactic and grammatical processing, and posterior inferior frontal and insular regions in the processing of phonological output (Ochsner & Kosslyn, 2017). The left posterior inferior frontal gyrus (or Broca's area) has been associated with language production including fluency and word retrieval, but also with aspects of language comprehension such as lexical processing, semantic access and syntactic comprehension (Ochsner & Kosslyn, 2017). Functional imaging studies have mapped discourse processing to anterior superior temporal, medial parietal and posterior cingulate areas (Démonet et al., 2005). Processing of reading and writing involves complex interactions between temporo-parieto-occipital areas, reflecting the interaction of visual and auditory perceptual, graphomotor and linguistic processes, as well as posterior inferior fontal and insular regions (Ochsner & Kosslyn, 2017). The main brain regions that have been related to the processing of language and that are going to be referred to in this chapter are depicted in Figure 2.1.

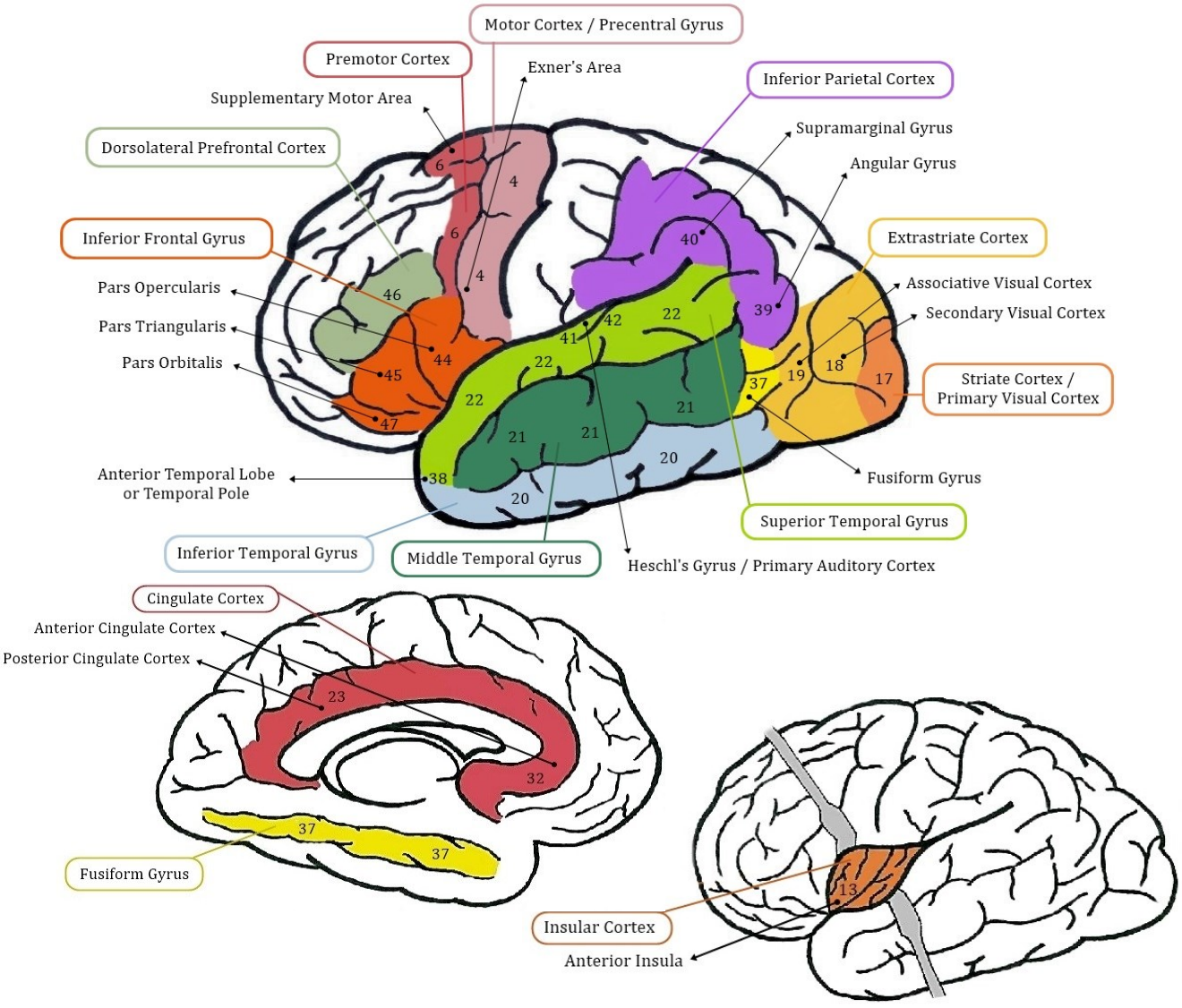

Figure 2.1. Anatomical substrates related to language processing and corresponding Brodmann Areas (BA)

The dominant hemisphere, which is the left in about 90% of right-handed and 70-80% of left-handed people, is where the language is mainly lateralised (Papadatou-Pastou, 2011). However, this lateralisation is not absolute and there is considerable individual variation in brain lateralisation. Moreover, the right hemisphere has also been related to important linguistic tasks, including lexico-semantic processing, context processing (e.g. understanding inferences, metaphors, irony/sarcasm, humour, or indirect requests), discourse planning (i.e. coherence), and comprehension and generation of emotional prosody (Barroso & Nieto, 2009).

Evidence from neurological patient populations has been used to derive the various cognitive sub-components forming the language-processing system, which seem to be relatively independent from each other. This chapter aims to describe the cognitive processes underlying these sub-components and to identify the association between such cognitive processes and specific neural networks, based on existing evidence.

In psycholinguistics, a debate exists between *connectionist/interactive* versus *modular* models. Broadly, modular approaches assume a serial processing from lower to higher sequential levels of processing or modules (i.e. bottom-up processing), whereas interactive models assume parallel processing which permits feedback activations from higher levels to lower levels of processing (i.e. top-down processing). No approach will be preferred here, but instead the most popular models for each stage of processing will be described.

2.2. Auditory Language Comprehension

This section is concerned with the perception and comprehension of spoken language. The mental processes that take place during the interpretation of speech input require the integration of different types of knowledge regarding the utterance properties, including lexical, semantic, syntactic and pragmatic information. The processing and integration of this information allows to transform the speech input into a meaningful representation to the listener.

The following sub-sections are organised around the main processes involved in receptive language, which are of growing complexity. These start with the analysis of basic speech units (*phonemes* and *morphemes*) and the identification of words formed by these (*lexicons*), followed by the association of words to symbolic meanings (*semantics*), to finally process compositions of words or sentences (*syntax*) and connected speech (*discourse*).

2.2.1. Auditory Word Recognition

The recognition of a single-word involves the mapping of an acoustic signal onto a specific word. Spoken words are composed of strings of phonemes (i.e. distinct units of sound). The

first stage of this process involves an *auditory phonological analysis* or *acoustic analysis*, which consists of identifying single sounds for each phoneme to subsequently match this phoneme-string to the pronunciation of a known word. Such information is retrieved from the *phonological input lexicon*, where phonological knowledge (i.e. knowledge of the auditory form of words) is stored. Every word is stored in this mental inventory as a separate entry. The process of word recognition is carried out on-line while the auditory information flows into the system. Therefore, a type of buffer system of temporary storage is needed, which keeps the phoneme-string temporarily available while the task of auditory word recognition is carried out by accessing the phonological input lexicon. This system is known as *phonologic input buffer*.

Different psycholinguistic models exist that attempt to explain how the process of mapping acoustic signals onto word representations in the phonological input lexicon is carried out. Three of the most popular ones are briefly described here. These models mainly differ on the patterns of activation that occur resulting from the perception of a spoken word. For instance, according to the **Cohort Model** (Marslen-Wilson & Welsh, 1978), the initial phoneme of a word activates a cohort of word candidates for which the first phoneme is the same, and as the succeeding phonemes are being processed, the various candidates are ruled out until there is only one last and unique candidate that matches the whole phoneme-string. Updated versions of this model, like the Revised Cohort Model (Marslen-Wilson, 1987) and the Distributed Cohort Model (Gaskell & Marslen-Wilson, 1997) abandon the restricted view of cohort candidates activating based on the very first phoneme, but still place an important focus on the word's initial phonemes. Alternatively, the **Neighbourhood Activation Model** (Luce & Pisoni, 1998) suggests that the activation of words in the lexicon is based on their global similarity to the spoken word. Thus, words that differ by one phoneme in any position (i.e. neighbours) are activated. Neighbour words may differ from the target one in terms of substitution, addition or deletion of one phoneme. Finally, the **TRACE Model** (McClelland & Elman, 1986) presents an intermediate view between the two previous models. It argues that similar words that do not match from the beginning are activated, but that words with the same initial phonemes, as they will be activated earlier, will have an advantage. These three models described are *interactive*; they assume that higher levels of processing (i.e. lexical knowledge) influence lower levels of processing (i.e. acoustic analysis of phonemes). Modular models also exist (e.g. the Race Model; Cutler & Norris, 1979), but it is beyond the scope of this overview of the language processing system to review all spoken word recognition models.

The representation of polymorphemic words within the lexicons is a matter of investigation. A morpheme is a minimum meaningful speech unit with grammatical meaning, which complements lexemes or speech units with lexical meaning (e.g. the morphemes *un-* and *-ness*

plus the lexeme *happy* form the polymorphemic word *unhappiness*). Although it seems that word representations within the lexicon are decomposed in morphemes to some degree, polymorphemic words that are commonly used or those called semantically opaque (i.e. whose meaning cannot be easily discerned by analysing its morphemes) appear to be represented and processed as monomorphemic (Marslen-Wilson, Tyler, Waksler, & Older, 1994; Schreuder & Baayen, 1995).

Auditory lexical decision tasks are usually used to assess auditory word recognition. Some properties of words such as frequency or imageability (i.e. ease with which a word can evoke mental imagery) affect performance on such tasks, with a disadvantage for low frequent and abstract (i.e. low imaginable) words (Patterson & Shewell, 2013).

Regarding neuroanatomy, the processing of auditory input starts at the primary auditory cortex, in the posterior superior temporal gyrus (BA 41, 42; or Heschl's gyrus) and extends to the superior temporal gyrus and sulcus, where acoustic signals of speech are processed (Blumstein & Myers, 2017). Both hemispheres are related to the processing of auditory representations of speech components, although a slight left dominance has been observed for those representations specific to the human voice. Thus, while the left superior temporal gyrus seems to be more specialised in the processing of verbal input, the right homolog seems to be specialised in the processing of non-verbal stimuli such as environmental sounds (Démonet et al., 2005). The neural pathway conveying phonological information goes from caudal (i.e. temporal and parietal) to rostral (i.e. frontal) regions. Thus, the left posterior superior temporal gyrus (BA 22 or Wernicke's area) and parietal areas including the angular (BA 39) and supramarginal (BA 40) gyri are related to phonological processing and lexical access, and the inferior frontal gyrus, which activates with the presence of competing phonological alternatives, is involved in lexical selection (Blumstein & Myers, 2017). The phonological buffer which temporarily stores the sequence of speech units to be transformed into lexical representations seems to be situated at the junction between the posterior part of the superior temporal sulcus and the inferior part of the supramarginal gyrus (Démonet et al., 2005).

2.2.2. Auditory Word Comprehension: The Semantic System

The translation of lexical representations into meaningful concepts occurs in the *semantic system*. This system stores the meanings of all the concepts known to a person, ranging from concrete objects to abstract ideas. The different concepts stored in the semantic system also go from generic categories (e.g. animal) to more concrete concepts (e.g. dog).

A central debate in semantic processing is the existence of a unitary versus multiple semantic systems. In this regard, the view of a *single modality-independent semantic system* which processes the meaning of all types of semantic representations (i.e. spoken words, written

words, and pictures or seen objects) is assumed by some authors (Caramazza, Hillis, Rapp, & Romani, 1990; Rapp, Hillis, & Caramazza, 1993). Other theorists however postulate the existence of *multiple semantic representation systems* with separate conceptual representations for each input modality (Shallice, 1993; Warrington & Shallice, 1984). Case reports of modality-specific deficits exist (Hart Jr, Berndt, & Caramazza, 1985; Hart Jr & Gordon, 1992; McCarthy & Warrington, 1988). The multiple semantic systems approach interprets modality-specific deficits as a result of confined impairments within the semantic system for that modality. Contrastingly, the single modality-independent semantic system approach interprets such deficits as a difficulty of access to the semantic system from preceding processing systems (i.e. phonological, orthographic or visual).

Category-specific impairments which cause disproportionate difficulties for specific semantic categories while sparing others also exist. These include selective deficits for living-things (Warrington & Shallice, 1984), animals (Caramazza & Shelton, 1998), fruits/vegetables (Hart Jr et al., 1985) or man-made objects (Warrington & McCarthy, 1983), among others (McKenna & Warrington, 2000). Since these initial case reports of category-specific deficits, some models have been developed that attempt to provide insight into how semantic representations are organised in the brain. Two broad approaches exist: those based on the *neural structure principle*, according to which distinct neural networks represent different semantic categories that can be selectively damaged causing category-specific deficits; and those based on the *correlated structure principle*, according to which conceptual knowledge associated with categories or domains is not organised in different functional networks of the brain, but these representations are instead based on correlations between features across semantic categories (Mahon & Caramazza, 2017).

Within the first group, the **Sensory-Functional Theory** (Warrington & McCarthy, 1987) proposes that semantic concepts are organised into different types of knowledge (i.e. visual/perceptual and functional/associative), and that the attributes of such concepts are represented in distinct modality-specific semantic systems. Considering the category-specific deficits for living-things and inanimate objects described by Warrington and colleagues (1983, 1984), these authors hypothesised that the semantic processing of living things is more based on visual information, whereas for objects it depends more on functional knowledge. These authors predicted that category-specific deficits for a certain category (e.g. living-tings) will also be accompanied by impairment in the modality of knowledge that the specific category is more dependent on (e.g. visual-perceptual deficits). However, it has now been shown that category-specific deficits can be associated with impairment in all types of knowledge (i.e. perceptual and functional) for that specific category (Mahon & Caramazza, 2017). Contrary to this view, the **Domain-Specific Hypothesis** (Caramazza & Mahon, 2003) postulates the

existence of category-specific brain systems which allow for selective deficits in a conceptual category, but which are not necessarily associated with a modality-specific deficit. H. Damasio, Grabowski, Tranel, Hichwa, and Damasio (1996) postulated an anterior-to-posterior organisation of category-specific information (specifically for the categories *persons*, *animals* and *tools*) along the inferior temporal pole. Although the role of the inferior temporal lobe (also known as the basal temporal language area; BA 19, 20, 37) in semantic processes is widely recognised, the neural network underlying semantic processing is now thought to be much more complex, extending beyond this region (Démonet et al., 2005). Another theory also concordant with the existence of a unitary semantic system, the **Sensory-Motor Theory** (Martin, Ungerleider, & Haxby, 2000), assumes that modality-specific representations of concepts within the semantic system are in the form of features that define such concepts, and retrieval of a feature associated with a concept activates brain regions that mediate such feature (i.e. retrieval of colour activates primary sensory areas, whereas retrieval of the action associated with an object activates primary motor areas).

Alternatively, Tyler and Moss (2001) created a connectionist model of semantic knowledge, the **Conceptual Structure Theory**, based on the postulate that conceptual knowledge is represented within a single semantic system in a distributed manner, not organised a priori by category or modality. Category-specific and modality-specific deficits occur as a result of random damage to specific connections. Finally, the **Conceptual Topography Theory** (Simmons & Barsalou, 2003) integrates aspects from three of the previously mentioned theories (sensory-functional theory, domain-specific theory, and conceptual structure theory) to explain how conceptual knowledge is organised. This approach is based on the similarity-in-topography principle (CIT), according to which features that form properties and categories of concepts are hierarchically organised with convergence zones based on their similarity, and are therefore topographically organised. Category-specific deficits, ranging from deficits into single to multiple domains, will depend on the level and location of the disturbance in this system.

Despite the efforts of existing theories to discern how conceptual knowledge is organised in the brain, important questions remain to be answered regarding the functional unification of the different types of information that make up a concept, as well as regarding the principles of neural organisation of distinct semantic categories, whose breakdowns cause modality-specific and category-specific deficits, respectively (Mahon & Caramazza, 2017).

Irrespective of how semantic information is represented in the brain, which seems to be in a widely distributed manner throughout the cortex, the association between phonological information from the superior temporal sulcus to semantic representations seem to occur in the temporal lobe, specifically in middle posterior regions bilaterally (Hickok & Poeppel, 2007).

The anterior temporal lobe also seems to be crucial in semantic processing, given evidence that bilateral atrophy in the temporal pole has been long associated with impaired semantic processing (Harciarek & Kertesz, 2011). The role of the inferior frontal gyrus in semantic processing has also been investigated. This area, as mentioned earlier, has been related to lexical selection between competing phonological representations. Evidence suggests that while the posterior part (BA 44 or *pars opercularis*) could be involved in phonological/lexical aspects, more anterior parts (BA 45, 47; *pars triangularis* and *pars orbitalis*, respectively) seem to processes semantic features from these competing alternatives (Démonet et al., 2005).

Importantly, when assessing semantic processing, it is essential to test for modality effects using tests that include visual (i.e. written words and pictures/objects) and verbal representations. Moreover, when testing for category-specific deficits, the effect that some variables such as word frequency, familiarity or visual complexity have on performance must be controlled for by using tests with selected stimuli that control for such artefacts (Mahon & Caramazza, 2017). Finally, it is also important to consider that imageability is related to the richness of a word's semantic representation, and therefore an effect of imageability on lexical decision tasks may indicate that performance is supported by access to the semantic system (Kay, Lesser, & Coltheart, 1992).

2.2.3. Sentence Processing

The ability to understand sentences depends on a series of processes, the first being to understand the words that are contained in them. Other linguistic information that is not present when processing single words but that is embedded in sentences is grammar. Grammatical processing includes the processing of morphological (i.e. word type) and syntactic (i.e. sentence structure) information. Thus, inability to comprehend sentences can be observed in the context of spared single word comprehension. The interpretation of sentences involves the interaction of a range of information coming from lexico-semantic, grammatical and contextual systems.

Grammar is concerned with the identification of sentence constituents and their relationship, which is informed by morphological and syntactical analyses. **Morphology** is interested in the type of word (i.e. *content wo*rds, which carry meaning: verbs, substantives, adjectives and adverbs; versus *function words*, which inform syntax: prepositions, conjunctions, auxiliary verbs, pronouns, grammatical articles and particles) and its relationship to other words in the sentence. **Syntax**, on the other hand, is defined as the ability to assess the rules that govern sentence structure, including word order and punctuation. Syntactic analysis or *parsing* consists of identifying the role that each sentence part plays in the larger structure. Five different syntactic functions can be fulfilled within a sentence: subject, predicator, object, complement or adverbial. These are known as clause structure elements.

Verbs are content words used to describe an action within a sentence and therefore their syntactic function is that of predicator. Two different kinds of information are embedded in verbs: lexical information (i.e. word's meaning and phonological form) and syntactic information (i.e. grammatical class). Whereas the first is necessary for the retrieval of an action word from the lexicon, discrepancy exists among psycholinguistic models regarding to at what stage of processing grammatical class information becomes available. *Lexicalist approaches* (R. M. Kaplan & Bresnan, 1982) argue that this information is available at the same time that phonological and lexico-semantic information is retrieved, whereas other approaches such as *combinatorial* or *emergentist* (Vigliocco, Vinson, Druks, Barber, & Cappa, 2011) argue that grammatical class is not lexically specified but it is only available when verbs are processed at a sentence level.

One of the main questions investigated in grammatical representation is whether words from different grammatical classes are represented by different neural networks. In comparison to nouns, verbs are more complex syntactically and require greater processing demands, as they are directly related to the other clauses of the sentence and therefore are responsible for assigning thematic roles (i.e. who the subject and the object are within a sentence). Moreover, verbs are morphologically more complex than nouns. Some evidence suggest that nouns and verbs are represented by separate neural networks with left inferior frontal areas processing verbs and left temporal areas processing nouns (A. R. Damasio & Tranel, 1993; Lubrano, Filleron, Démonet, & Roux, 2014), others suggest that are their morpho-syntactic properties that are rather represented in different neural networks compared to their lexical characteristics, with left prefrontal and posterior inferior frontal areas processing grammatical properties and left posterior temporal regions processing lexico-semantic characteristics (Perani et al., 1999; Shapiro, Pascual-Leone, Mottaghy, Gangitano, & Caramazza, 2001). A systematic review of evidence from neuropsychological, behavioural, electrophysiological and imaging studies suggested that neural segregation exists for semantic knowledge of words from different grammatical classes (i.e. object knowledge is processed by the left inferior temporal cortex, and action knowledge by the prefrontal cortex), but a common neural system involving the left inferior frontal gyrus processes all words from a morpho-syntactic perspective (Vigliocco et al., 2011). This region, along with other frontal regions such as the dorsolateral prefrontal cortex bilaterally, has shown to be related to verb inflection, which is based on the rules of grammatical morphology (Kielar, Milman, Bonakdarpour, & Thompson, 2011). The work from Vigliocco et al. (2011) also provided evidence against lexicalist approaches and confirmed that grammatical class information is not automatically retrieved with lexico-semantic information when a word is retrieved in isolation, but that this information only becomes available when verbs are processed in a more complex sentence context.

An association between action or verb processing and primary motor and premotor areas has been proposed in healthy samples on both neuroimaging (Hauk, Johnsrude, & Pulvermuller, 2004; Pulvermuller, Hauk, Nikulin, & Ilmoniemi, 2005) and neurophysiological studies (Pulvermuller, Lutzenberger, & Preissl, 1999), suggesting that brain areas involved in action processing extend beyond language centres to areas considered part of the motor system. In fact, the premotor cortex has been linked to action semantics and it seems to be where representations of the motor features of action words are characterised, although this is part of a more complex representation system and therefore retrieval of such features is not always a requisite to process the word semantically (Kemmerer, 2015).

Both morphology and syntax play a crucial role in determining aspects of sentence meaning. Two sentences differing in one function word (e.g. *He started to scratch / He started from scratch*) or in the order of two words (e.g. *She told her baby the story / She told her the baby story*) can have very different meanings. We can even construct syntactically well-formed sentences that make no sense semantically (e.g. *Non-shaped square approaches walked swiftly*). Some principles have been defined that describe how sentences are processed based on syntactic rules, from a structure-based heuristic point of view (Frazier & Rayner, 1982). According to this view, initial processing is thought to be guided by the **minimal attachment principle**, which states that the simplest syntactic structure consistent with the available information guides initial interpretation. For instance, take the sentence '*The defending attorney will prove the story is not true*'. According to this principle, initially '*the story*' will be interpreted as the direct object of the sentence '*The defending attorney will prove the story*'. However, as new information becomes available, this interpretation is updated. Thus, with the full sentence being available, '*the story*' will then be understood as the subject of the sentence '*The story is not true*', a subordinate clause which is the direct object in the main sentence. Another principle that guides grammatical sentence interpretation is the **late closure principle**, according to which incoming information tends to be related to the clause being processed rather than to clauses that may appear after. For instance, when processing the sentence '*While Sue was reading the book broke*', '*the book*' is taken as the direct object of the sentence '*While Sue was reading the book*', but when further information in the sentence is presented, this interpretation then needs to be updated to understand '*the book*' as the subject of '*broke*'.

A third principle applied in sentence interpretation, which questions the former, is the **Argument Preference Strategy** (Abney, 1989). According to this strategy, if ambiguity exists in prepositional phrase attachment, syntactico-semantic properties of the relationship between sentence constituents is considered, rather than structural properties alone. For instance, in the sentence '*I appreciate his interest in the movie*', '*in the movie*' will be attached to

'*his interest*' because its relation is lexically specified, rather than to '*I appreciate*', even though the latter would be simpler structurally and preferred by the minimal attachment principle. In fact, syntactic theory has moved from a structural configuration view of sentence interpretation to a view that also highlights the importance of lexico-semantics and context (Altmann & Steedman, 1988; Spivey-Knowlton & Sedivy, 1995). Interactive sentence processing models, developed on the basis of **competitive constraint-based theories** (MacDonald, Pearlmutter, & Seidenberg, 1994; McRae, Spivey-Knowlton, & Tanenhaus, 1998; Trueswell, Tanenhaus, & Garnsey, 1994), assume that different sources of information are available and used during sentence processing. Thus, initial processing activates all possible interpretations in parallel, and depending on the support these receive, they will keep activated or will be inhibited, until a single interpretation will dominate among all. According to this connectionist view, frequent constructions will be easily activated when they receive the appropriate support than less common ones.

The importance of lexico-semantic and contextual information to sentence processing in addition to syntactic information can be seen in the processing of active vs passive sentences. Active sentences are those where the subject is the agent of the action (e.g. *Adam reads the book*), whereas in passive sentences the subject is not the agent of the action, but it is the object (e.g. *The book is read by Adam*). Syntactic processing impairment can complicate interpretation of passive sentences given that they don't follow the basic canonical *Agent (Noun) + Action (Verb) + Object (Noun)* structure. Thus, if the morphological markers of passive sentences (i.e. *object + auxiliary verb + past participle + by + agent*) are not correctly interpreted due to syntactic processing deficits, the first element of a passive sentence can be interpreted as the agent of the sentence. For instance, in the sentence '*The boy is kissed by the girl*', '*the boy*' may be interpreted as agent giving the kiss because it appears first. This is an example of a reversible sentence (i.e. sentences where it is plausible to reverse the agent and the object because the resultant sentence is semantically and pragmatically acceptable). However, semantic and pragmatic constraints can help determining thematic roles in passive sentences when these are non-reversible. For instance, in the sentence '*the baby is carried by her father*', the baby cannot be assumed as the agent of the sentence as this would not be plausible, therefore the only semantic and pragmatic possible interpretation is to consider the father as the agent. In sentence-picture matching tasks, usually employed to assess syntactic processing, performance on reversible sentences will be poorer in the context of deficits (Kay, Lesser, & Coltheart, 1996).

On a different note, the effect that executive dysfunction has on the processing of linguistic input must be considered in terms of being able to focus our attention, and monitor and update this information. This becomes increasingly relevant as the complexity of the language input

increments. The executive skill that allows us to temporarily hold the incoming auditory information while being processed is working memory, also named acoustic or phonological input buffer store in the context of language comprehension. Deficits in working memory can confound the interpretation of patients who show deficits on sentence comprehension tasks but in reality have intact syntactic processing (McKenna & Bonham, 2013).

Finally, regarding neuroanatomical substrates, grammatical and syntactical processing have been linked to left inferior frontal cortex (and their right counterpart to a lesser degree) and dorsolateral prefrontal areas (BA 46) for both language production and language comprehension (Démonet et al., 2005; Thompson & Kielar, 2014). However, the extent that working memory involvement has on the recruitment of these brain areas remains unclear. Some evidence suggests that the pars opercularis (BA 44) of the inferior frontal gyrus seems to support syntactic processing, whilst the pars triangularis (BA 45) could be involved in memory buffer functions. More anterior parts of the inferior frontal gyrus, as discussed earlier, are associated with semantic processing (Démonet et al., 2005). A recent neuroimaging study suggests that grammatical processing deficits in patients with aphasia seem to be caused by a disconnection between posterior inferior frontal and superior temporal regions (Fridriksson et al., 2018). Anterior regions of the brain seem to be more involved in building a syntactic structure, in comparison to posterior regions, which work on syntactic and semantic integration (Thompson & Kielar, 2014). Both substrates are crucial to achieve adequate sentence processing

2.2.4. Discourse Processing

Joint sentences make up discourses, which need to be interpreted as unified messages. To process discourse, two elements are necessary to ensure its meaningfulness and adequate organisation: coherence and cohesion. **Coherence** refers to discourse unity and continuity of thematic content, whereas **cohesion** aims to ensure that sentences are adequately linked from a grammatical and lexical perspective. Discourse markers (i.e. addition markers: e.g. *moreover*; contrast markers: e.g. *however*; cause/effect markers: e.g. *therefore;* time markers: e.g. *meanwhile*; and sequence markers: e.g. *firstly*) are lexical cues used as sentence connectors to inform about the relationship between discourse units and ensure coherence and cohesion in connected speech.

Other lexical cues used in discourse processing are **anaphors**, which are words that denote a previously mentioned referent. For instance, in the fragment '*Maria told her grandfather that she was tired of his old-timer stories. After saying it, the young lady wondered if that had offended him*', '*she*' and '*the young lady*' are anaphors of *Maria*, and '*his*' and '*him*' are anaphors of *grandfather*. As seen in the previous example, anaphors can take the form of pronoun referents or synonyms. Resolving anaphors (i.e. determining the referent of a specific anaphor) involves

the constant integration of new incoming information and existing representations in memory, which is crucial in discourse comprehension.

Syntactic and macro-structural cues are also important in discourse comprehension. A strategy used in discourse processing is the **given-new strategy** (Haviland & Clark, 1974), according to which the listener syntactically divides the incoming information into 'already known/given' and 'new', and then integrates the new information into the existing one. Associating new information to existing knowledge enhances comprehension. In fact, coherence is based on the degree to which new information can be connected to previously processed information. At a macro-structural level, an introductory statement on the information to be covered also enriches comprehension. Finally, all these previous processes occur conditioned by a specific context and the listener's background knowledge of the world.

In discourse processing, another key element is prosody, or the pattern of intonation, stress, tone, and rhythm of utterances. Prosody guides parsing and interpretation, and can help resolve ambiguities related to meaning and support content memory. Another key aspect of discourse processing which goes beyond the basic prosody aspects of speech is pragmatics. Pragmatics is a branch of psycholinguistics interested in the social use of language and how the context contributes to the understanding of a situation. Non-verbal communication considered in pragmatics focuses on more complex aspects of linguistic social interactions such as non-literal use of language (i.e. metaphors, irony/sarcasm, humour) or the emotional state of the speaker (i.e. emotional prosody).

According to a review of the neuroanatomical substrates of language processing (Démonet et al., 2005), various brain regions are involved in connected speech processing: the anterior superior temporal gyrus and the right middle temporal sulcus are related to global discourse coherence processing, medial parietal and posterior cingulate areas are linked to the connexion between new incoming information to prior knowledge, and the superior medial frontal cortex appear to be involved in the processing of discourse meaning to achieve an overall comprehension of the message. Concerning emotional prosody, Ross and Monnot (2008) suggested that its anatomo-functional organisation in the right hemisphere is equivalent to the organisation of linguistic prosody in the left counterpart. According to the authors, emotional prosody in production speech is mediated by right posterior inferior frontal regions, whereas its comprehension is also processed by posterior superior temporal areas.

2.3. Auditory Language Production

In spoken language production, the aforementioned processes involved in auditory language comprehension are carried out in the reverse way, aiming to transform conceptual

representations into speech outputs. This section reviews different aspects of language production, first focusing on single-word production, to then discuss the generation of longer utterances.

2.3.1. Single-Word Generation

According to the **Model of Lexical Access** in speech production by Levelt, Roelofs, and Meyer (1999), there are three steps to single-word generation: *conceptualisation* (i.e. determining what concept to express), *formulation* (i.e. retrieving its word form) and *articulation* (i.e. expressing it). At the conceptualisation stage, semantic and pragmatic specifications of the concept to be expressed will be determined, to successively, at the formulation stage, select a word (or *lemma*) from the *phonological output lexicon* (i.e. mental inventory of output phonological representations of spoken words) that matches the target concept. Investigations into the organisation of the content within the phonological output lexicon suggest that its representations are organised distinguishing grammatical category, which may explain dissociations in noun/verb naming performance, as well as differentiating between lexical categories (e.g. abstract/concrete, proper/common nouns); these representations also seem to be morphologically decomposed to some degree (Rapp & Goldrick, 2006).

At the formulation stage, morpho-phonological encoding occurs, which consists of selecting the morphemes and phonemes for that specific word. In speech production, careful selection of the accurate pronunciation of each phoneme depending on its position within the word is essential. This is known as **allophone** (e.g. the phoneme /a/ has two different allophones: it is pronounced [æ] in *Map*, but [eɪ] in *May*). Phonological processing at an output level not only requires the selection of the appropriate phonemes, but also being able to arrange them in the correct order. *Neologisms* (i.e. new made-up words) are caused by impairments at this stage; for instance, 'taple' and 'tabel' for *table* would be neologisms caused by impairments in phoneme selection and ordering, respectively (McKenna & Bonham, 2013).

At the last stage, articulation, a pre-articulatory code is sent to the *phonological output buffer* or *response buffer* (i.e. temporary storage system where the string of sounds forming a word retrieved from the phonological output lexicon are assembled and maintained), while the speech motor response is programmed and executed. This response buffer, also known as *phonological loop* (Baddeley, 2003a), is composed of two subcomponents: a temporary phonological storage system, which holds memory traces but is subject to rapid decay, and a subvocal rehearsal system, the articulatory loop, which keeps actively retrieving such memory traces and is independent of the capacity for overt articulation.

Word production involves an extensive network implicating right and left-hemispheric regions. The conceptually driven process of lemma selection seems to involve the left middle

temporal gyrus, and subsequent phonological code retrieval recruits the left posterior superior and middle temporal gyri as well as the left anterior insula and right supplementary motor area (Indefrey & Levelt, 2004). Regarding the phonological loop, there are two independent substrates for the storage and rehearsal components. Thus, while the storage system is associated with temporoparietal areas (supramarginal gyrus, BA 40), subvocal rehearsal appears to be mediated by premotor and inferior frontal regions (BA 6, 44) mainly on the left hemisphere but also recruiting their right homologous in the context of higher demands (Baddeley, 2003b).

2.3.2. Verbal Fluency

Reduced verbal productivity, which can affect the speed and ease of verbal production, is a very common consequence of brain damage. The ability to access a word representation from the phonological output lexicon is known as *word retrieval*, and this ability is more sensitive to brain pathology than word comprehension (McKenna & Bonham, 2013). Word generation (i.e. verbal fluency) and picture naming (i.e. confrontation naming) are the most frequently used tasks to assess word retrieval in clinical populations.

Generative verbal fluency tests are characterised by rapid intrinsic word generation processes that require the use of effective retrieval strategies and continuous monitoring to select words that meet the constraints of the task and avoid repetition (Abrahams et al., 2003). Two types of verbal fluency paradigms exist: *phonemic/letter* (i.e. generation of words beginning with a certain letter) and *semantic* (i.e. generation of words belonging to a certain category) paradigms. These tasks place important demands on executively-mediated processes aimed at goal-directed behaviour (i.e. selective attention, strategy generation, response selection, initiation and self-monitoring of conflicting responses, error detection, and inhibition of repeated words). However, in order to retrieve words, access to mental lexicons is required. Therefore, a pure linguistic impairment can also affect performance on verbal fluency tasks.

Word fluency tasks involve many different processes and therefore they require the recruitment of various brain substrates. Phonemic verbal fluency paradigms activate left anterior structures including the left inferior frontal gyrus (BA 44, 47), the dorsolateral prefrontal cortex (specifically BA 46), the anterior cingulate (BA 32) and the left insular cortex, as well as parietal areas (i.e. angular and supramarginal gyri), and the anterior temporal cortex (BA 38; Baldo, Schwartz, Wilkins, & Dronkers, 2006; Rodríguez-Aranda et al., 2016; Weiss et al., 2003). Activation of the left inferior frontal gyrus is associated with linguistics aspects of the task, including lexico-phonological and semantic processing, and dorsolateral prefrontal and anterior cingulate areas are related to executive processes (Weiss et al., 2003). Both phonemic and semantic verbal fluency paradigms are mediated by executive and linguistic processes, although semantic verbal fluency relies more heavily on aspects of language and

semantic memory compared to phonemic fluency (Strauss, Sherman, & Spreen, 2006). Thus, temporal areas including the left superior temporal gyrus (BA 22), the fusiform gyrus (BA 37) and the temporal pole (BA 38) have been more frequently related to semantic verbal fluency (Baldo et al., 2006).

2.3.3. Word Naming

Word naming abilities are generally assessed by means of confrontation naming. Perceiving pictures or seen objects is not a purely linguistic process, but being able to recognise them, know what they are and name them, is. To recognise and understand what a picture or object is, its meaning needs to be accessed form the semantic system. Prior to that, a *visual recognition system* that identifies the visual characteristics of the item and matches it to a stored generic image/description of the item is needed. This occurs at the conceptualisation stage of word generation described earlier, where the concept to express, in this case visually perceived, is determined. Then, once the concept is made available by selecting the target semantic representation from the semantic system, the lexical word form or lemma can be retrieved from the phonological output lexicon.

When using confrontation naming tasks to assess naming abilities, there is two types of difficulties that can be observed: difficulties of access/retrieval and difficulties of degradation of semantic knowledge. Accordingly, impairments in confrontation naming tasks require interpretation on the nature of deficits.

When deficits are of access nature, the difficulty is at the stage of retrieving the word form from the phonological output lexicon. This deficit is also known as anomia, word retrieval or word finding difficulty, and it is characterised by intact storage of semantic knowledge. Characteristic of this syndrome are semantically related responses (i.e. semantic paraphasias; e.g. *duck* instead of *pelican*), words phonetically close to the word target (i.e. phonemic paraphasias; e.g. *yokel* instead of *yoke*), or gibberish words or pseudowords which are recognised as distortions of the target word (i.e. neologisms; e.g. *prolector* instead of *protractor*). Moreover, in the context of word retrieval deficits, where access to the semantic system is spared but access to the output phonological representations is challenging, presentation of phonemic cues (i.e. initial phonemes of the word) boosts connections from the semantic system to the phonological output lexicon, which may enhance performance.

If deficits observed are a consequence of degradation of the semantic knowledge, not only a difficulty in naming the item is observed, but familiarity with the concept itself is vague. Loss of semantic knowledge, especially in neurodegenerative conditions, does not happen at once but it rather occurs progressively. This may cause performance dissociations on semantic processing tasks, as sometimes remaining unaffected knowledge can enhance performance.

How the degradation of semantic knowledge progresses is not certainly known. The ***"bottom-up"*** **or "attribute-first"** ***loss of semantic*** **information** approach (Glosser, Friedman, Grugan, Lee, & Grossman, 1998; Martin & Fedio, 1983) supports the idea that specific semantic features, which enable to distinguish similar concepts pertaining to the same superordinate category (e.g. *cat* and *dog*), degrade first and that superordinate category knowledge stays relatively preserved in comparison to knowledge of specific concepts. A different approach understands it as a random gradual loss that increases over time (Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Farah & McClelland, 1991; Tippett & Farah, 1994).

Warrington and Shallice (1979; cited in Shallice, 2013) defined performance criteria to distinguish between semantic access deficits versus semantic loss. These criteria were based on observation of single cases rather than on an underlying theory of semantic memory processes. According to this criteria, if the difficulties are of access nature: 1) no consistency across occasions is observed in the stimuli that can be understood, but this is rather subject to temporary local factors; 2) priming may prompt comprehension; 3) no difference is observed in accessing specific semantic attributes or more general semantic information, such as the superordinate category of a stimulus; 4) stimulus frequency have no effect on the capability of comprehending it; and 5) slower rate of presentation enhances performance. In contrast, if the deficit is of degradation nature, consistency within stimuli is observed occasion to occasion, priming does not elicit comprehension as the representation no longer exists, superordinate category knowledge is more relatively preserved than knowledge about more specific semantic attributes, performance is better for more frequent stimuli, and rate of presentation has no effect on performance. Rapp and Caramazza (1993) questioned the validity of these criteria and argued that the evidence provided was not compelling. This was especially relevant for the statement that semantic priming effects cannot exist in the case of semantic loss because such semantic representations do not exist anymore (i.e. 'all-or-none loss' view of semantic degradation), as evidence suggests that partial degradation of semantic memory occurs, which can permit semantic priming effects in some cases.

In the context of confrontation naming, provision of semantic cue (i.e. information related to the meaning of the word, such as its function or superordinate category) can help discern if an inability to name a picture spontaneously is due to a visuo-perceptual deficit or if a semantic deficit underlies such difficulty. Linguistic characteristics such as word frequency also affect performance on confrontation naming, with higher accuracy and lower response latencies for high-frequent words (Randolph, Lansing, Ivnik, Cullum, & Hermann, 1999). Other semantic tasks like picture-word matching tasks, in which a set of pictures is presented and the correct one needs to be matched to a word (which can be presented verbally or written), can help

discern if deficits in confrontation naming are of access or due to semantic degradation, as deficits of access would not interfere with performance on receptive semantic tasks.

While performance difficulties associated with semantic deficits are a consequence of degradation of those specific representations throughout the cortex, difficulties with word retrieval are associated with damage to the superior temporal and angular gyri (Fridriksson et al., 2018). Other areas related to confrontation naming performance include visual-perceptual centres such as occipital areas bilaterally and the left mid and right posterior fusiform gyrus, semantic centres such as the inferior frontal gyrus, and also the right posterior inferior frontal gyrus (Indefrey & Levelt, 2004).

2.3.4. Sentence and Discourse Organisation

In sentence and discourse production, the complexity of organizing speech output as a meaningful utterance following the rules of grammar and guarantying speech cohesion and coherence is added to the sophistication of semantic access, phonological conversion and articulatory planning of speech output required to produce single-words.

Serial and parallel models have been created to characterise sentence production. These models agree on assuming that speech production processing breaks down from larger or global units (i.e. discourse and sentences) to smaller units (i.e. words, morphemes and phonemes). Thus, three stages very similar to those described for single-word generation are hypothesised: 1) *conceptualisation* of the message to be conveyed; 2) *formation* of phrases, first selecting the appropriate lemmas, which contain specific semantic and syntactic properties (i.e. word class, which determines its functional role within the sentence), and then structuring these following grammatical rules; and 3) *articulation* of the message, which previously requires phonetic encoding. The main difference between these two approaches lies in whether the various stages of speech production occur sequentially or if feedback is available from any level to any level of processing.

Among the most popular serial approaches are **Garret's Model** (Garrett, 1975) and **Bock-Levelt Model** (Bock & Levelt, 1994). According to the former, the formation phase, called *sentence level* by the author, is a two-stage phase, first involving a *functional planning process* where the lexical content is selected (i.e. lexicalisation), the sentence structure/frame is planned (i.e. syntactic planning) and the lexical items are assigned to grammatical roles, followed by a *positional planning process*, where phonemically interpreted lexical items are inserted into the sentence frame, and supporting syntactic elements or morphemes are also phonetically encoded. Based on this model, *paragrammatism* (i.e. the substitution or deletion of grammatical morphemes in spontaneous speech) could be partially explained by a difficulty in specifying morphemes at a positional level, whereas *agrammatism* (i.e. difficulty in

assembling the morphosyntactic fragments that constitute a sentence) could be more related to a deficit at a functional planning level (Schwartz, 2013).

2.3.5. Motor Speech Disorders

Difficulties at a speech output level that are independent from linguistic processes can also be observed. One of the most common motor speech disorders is dysarthria, which, as discussed in chapter 1, it is one of the most common symptoms of ALS. Dysarthria consists of a disruption of the motor control of the musculature required for speech causing articulation, phonation, resonance, prosody and respiration deficits, thus affecting speech intelligibility. Dysarthria can be caused by lesions in the central or peripheral nervous system. Depending on the involved structure, different forms of dysarthria exist (Darley, Aronson, & Brown, 1969). Flaccid dysarthria (i.e. wasted and weak tongue, defective articulation, dysphonia, and nasal emission of air during speech) is observed with lower motor neuron dysfunction; spastic dysarthria (i.e. non-wasted tongue, slurred and slow laborious speech) is caused by upper motor neuron dysfunction; ataxic dysarthria (i.e. irregular articulation, poor voice volume, poor breathing control) is characteristic of cerebellum involvement; and hypokinetic dysarthria (i.e. difficulty with initiation, hoarseness, hypophonia, pallilalia, festination of speech or words getting shorter) and hyperkinetic dysarthria (i.e. harsh vocal quality, super-imposition of bulbar involuntary movements, poor coordination with breathing) are both seen after basal ganglia lesions (substantia nigra and caudate/putamen, respectively). ALS patients usually present with mixed flaccid-spastic dysarthria (Tomik & Guiloff, 2010).

Another motor speech disorder is apraxia of speech, characterised by an inability to plan and coordinate articulatory movements necessary to produce speech. Unlike dysarthria, the problem in apraxia of speech is not of motor control of the muscles involved in speech, but it is a problem of speech motor programming. Therefore, in apraxia of speech there is no slowness, weakness or restriction in the range of movements. The speech characteristic of this disorder is halting, groping to achieve accurate articulatory postures, with moments of silence, awareness of errors and attempts at self-correction. Unlike dysarthria, in apraxia of speech errors committed are inconsistent, highly variable and unpredictable, and include different articulatory errors such as substitutions, repetitions, additions, transpositions, prolongations, omissions or distortions. Some of these errors sound like phonologic errors. Prosody is also altered. Apraxia of speech is caused by damage to the left posterior inferior frontal lobe (Rohrer, Rossor, & Warren, 2010).

A different type of apraxia affecting the buccofacial apparatus is orofacial/buccofacial apraxia, which involves a difficulty coordinating the muscles to perform facial and lip movements causing an inability to carry out non-speech voluntary movements such as whistling, blowing or clicking the tongue. Buccofacial apraxia seems to be related to dysfunction in the left middle

frontal gyrus (BA 46) and prefrontal regions such as the premotor and supplementary motor area (Rohrer et al., 2010). Although buccofacial apraxia can also be present in apraxia of speech, these two disorders are not always associated (Whiteside, Dyson, Cowell, & Varley, 2015).

2.4. Reading and Writing

Reading and writing skills (also known as literacy) are evolutionary skills where the input code differs from the output one, and therefore they involve transcoding or conversion from a type of coded representation to a different one. In reading, written input is decoded into spoken output, and when spelling to dictation, spoken input is encoded into written output based on a conventionalised writing code. Beyond transcoding, reading and writing also require other cognitive mechanisms involved in the broader language and cognitive system. These include mapping the word spellings to their meaning (semantics) as well as working memory and long-term memory aspects that support these processes.

2.4.1. Written Word Recognition

At a single-word level, when writing to dictation, the auditory input (a spoken word) is recognised through the same auditory word recognition system described in section 2.2.1. However, when reading, the input stimuli is a written word and the initial lexical processing of printed words must be mediated by word-recognition devices for written words. The very first step of such process is called *abstract letter identification* or *orthographic analysis*, and it consists of the recognition of individual graphemes (i.e. single letters or letter sequences which represent a single phoneme) that constitute a word.

Various theories exist to explain the complex process of orthographic analysis. The **single route to word recognition** (Henderson, 1982) is a hierarchical linear theory which affirms that the first step to word recognition is letter identification, achieved through the extraction of visual features from each grapheme, which then allows for the recognition of words through the identification of the letter-string that composes a specific word. This theory asserts that the only information required to recognise a word are the identities of the specific letters composing a word arranged in a specific order, and does not take into account other information such as word shape. Complementing this theory, the **ALI model of word recognition** (Evett & Humphreys, 1981) introduces the concept of abstract letter identification (ALI) unit, which is a unit of information of a specific grapheme, independent of characteristics such as the typography (i.e. font, case, etc.) or size of this representation. Thus, for a specific grapheme, say *m,* all possible visual representations (e.g. M, m, m*, m,* **m**, m) will activate the same ALI unit. Tasks such as selecting which of the printed letters B, K, D, P

corresponds to the printed target 'b' are usually used to assess whether the abstract letter identifiers are functioning normally. Nevertheless, visual format distortions, for instance presenting words in aLtErNaTiNgcAsE, can affect the recognition of words in terms of latency but not in error rates (Besner, 1983; cited in Howard, 2013). This phenomena introduced the concept of 'interfacilitation at the level of the ALIs', based on the idea of expectation of a consistent format of words (i.e. whatever typography and size is identified for the first letter of a word, this will also be assumed for the rest of the string). Accordingly, if this interfacilitation or consistency is not present, the time needed to recognise a word is delayed although accuracy of recognition is not affected (Howard, 2013).

The simplicity of the ALI model of word recognition is not universally accepted. The opinion that other sources of information apart from linear letter string are necessary to recognise and differentiate words is also expressed. Among these multiple sources needed for word recognition are word shape or word contour (only relevant for lower case and hand-written words as they have a distinctive contour, but not for upper-case words), and 'transletter features' or features that go beyond single letters, which refer to the visual relation between adjacent letters or graphemic units that normally present together (e.g. *ght*). Supporting this view are examples of cases that took longer to read upper-case in comparison to lower-case words (Baron & Strawson, 1976; cited in Howard, 2013), which likely indicates that word shape characteristics were used to help word recognition. Case reports of patients who made more errors or had longer latency times when reading case alternated words in comparison to upper-case words also exist, and this is likely explained by the fact that case alternation disrupts transletter features and therefore this strategy could not be used to help word recognition (Baron & Strawson, 1976; and Coltheart & Freeman, 1974; cited in Howard, 2013).

The existence of a single route to word recognition based on ALI units and complemented by other sources of information such as word shape and transletter features is not always satisfactory to support neuropsychological evidence provided by some case reports. Howard (2013) described a case of a patient with a history of right posterior parietal ischaemic stroke who presented with severe difficulties with the recognition of distorted words but unaffected performance on the recognition of non-distorted words, irrespective of the case, typeface or if they were print or hand-written. This patient presented with difficulties with all type of distorted words, including case alternations, size alternation, words with the presence of plus signs between letters (e.g. p+l+u+s) or words written diagonally, but the ability to recognise words when letters were separated by spaces was spared. These deficits are not satisfactorily explained by the ACIs model; if a problem with abstract letter identification would have been present, all types of words, including non-distorted ones, should have been impaired. Word shape could have not been used in this case as this patient performed at the same level of ability

for both upper- and lower-case words. Transeletter features were unlikely used either as even though most distorted words were affected, spacing would have been expected to be impaired too. This case and others highlighted by the author raised the need for a complementary method that can also be used in word recognition: the **global route to word recognition**. This method uses a 'global' strategy for identifying words and treats them as idiosyncratic shapes, perceived as a whole, like if they are pictures composed by parts that are meaningless on their own. This global or feature-based input, which is not very precise, can be useful for high frequency words and when abundant and strong contextual information is available. Thus, words that have a familiar form will be readable through this method but distorted words will be unrecognizable, except for simple distortions such as words with spaced letters, which leave the word interpretable in the same way stretched out pictures can be recognised. This makes the written word recognition system a two-route system.

Once this first process of letter-string identification has been completed, these identities are then transferred to the *orthographic input lexicon* (i.e. a mental inventory of orthographic knowledge or knowledge of the written form of words), where the processes of lexical identification are carried out. Like in the phonological input lexicon, in the orthographic input lexicon each representation is stored as a separate entry and no information about meaning or output written form is contained in it. A temporary storage system exists between the process of letter-string identification and lexical recognition, the *graphemic buffer* or *orthographic input buffer*, in which the grapheme-string is held available while the task of written word recognition is carried out.

Written word recognition tasks (i.e. visual lexical decision tasks) are used to assess access to the orthographic input lexicon. Likewise with auditory lexical decision, some properties of the words influence performance on visual tasks, including word frequency or familiarity, word imageability and word consistency (i.e. degree to which a word is pronounced like similarly spelled words; for instance, *mind* is consistent as its pronunciation is similar to *kind* and *find*, but *pint* is inconsistent given that it is pronounced differently than *hint* or *mint*). High frequent, concrete and consistent words are easier recognised (Yap & Balota, 2014).

Mental lexicons only contain words (i.e. grapheme or phoneme strings that are part of the vocabulary of a language), but they do not contain letter-strings or sound-strings that do not form real words (i.e. pseudowords). When trying to read a pseudoword, as this is not found in the orthographic input lexicon, no communication will happen between this lexicon and further language-processing components. Thus, the reading process described above, which is lexical, cannot be used in this case. This suggests the need for an alternative reading mechanism to the one that has been described. The existence of two alternate routes to achieve the reading process is conceived in the **Dual-Route Model** (Coltheart, 2005).

2.4.2. Dual-Route Model of Reading

According to the Dual-Route Model of reading, two different routes exist to complete the process of reading: a lexical reading and a non-lexical reading route. The lexical reading route achieves the process of lexical identification following the processes described in Section 2.4.1. Once the processes of lexical identification through the orthographic input lexicon are achieved, the output phonological information (i.e. pronunciation of the word to be read) is addressed in the phonological output lexicon, and it is subsequently sent to the response buffer, where the speech output is programmed and produced.

In the lexical reading route, lexical input-output connections from the orthographic input lexicon to the phonological output lexicon can go through the semantic system or can bypass it. Evidence of a lexical non-semantic orthographic input – phonological output pathway is given by case reports of patients that are able to read words but are unable to retrieve its meaning (Coltheart, Masterson, Byng, Prior & Riddoch, 1983; Funnell, 1983; Schwartz, Saffran & Marin, 1980; cited in Sartori, Masterson, & Job, 2013).

In the English language two different types of words exist: regular and irregular words. Regular words are those that follow the grapheme-to-phoneme conversion rules when reading or the phoneme-to-grapheme conversion rues when writing (e.g. *plant*). Irregular words, conversely, do not follow the spelling-sound correspondence (e.g. *yacht*). Irregular words are incorporated to one's vocabulary through a learned association between the visual form of the word, its meaning and its pronunciation. Both types of words can be read through the lexical reading route. However, as mentioned earlier, pseudowords cannot be read through this route as these are not contained in the lexicons.

The non-lexical reading route, on the other hand, reads through *orthographic-to-phonological conversion processes* that follow letter-to-sound rules. Thus, the processing of reading through this route also starts with the abstract letter identification system. Although the grapheme-string identification process for real words can be achieved through the abstract letter identification system or by a more global or feature-based analysis, the latter would not be accurate for the identification of pseudowords. Once this information is processed, it is also sent to the graphemic buffer, but in this case, instead of accessing the orthographic input lexicon to carry out word recognition processes, the grapheme-string is deconstructed into orthographic segments and following orthographic-to-phonological conversion rules, these orthographic segments are linked to their corresponding phonological segments. Subsequently, this string of phonological segments which make up an allied phonological representation is sent to the phonological output buffer, where it is being held while the motor articulation of the word is planned and executed.

Regular words, given that they follow grapheme-to-phoneme conversion rules, can also be read through the non-lexical reading route. However, this route cannot read irregular words as these disobey such rules.

2.4.3. Dual-Route Model of Writing

Writing to dictation can also be achieved through the two different routes defined by the Dual-Route Model. Accordingly, a lexical writing route and a non-lexical writing route exist.

For both routes, initial acoustic analysis or auditory phonological analysis is undertaken to identify the phonemes forming a word. This phoneme-string identification system then sends the information to the phonological input buffer, where it is held while the succeeding processes are carried out. At this stage is where one of the other route will play a role, depending on the nature of the word.

If the lexical reading route is used, the information from the phonological input buffer is sent to the phonological input lexicon, where the process of auditory word recognition occurs. After, the information is sent to the semantic system, where the meaning is retrieved, and then to the *orthographic output lexicon* (i.e. the mental inventory of written forms of words), where the specific written form of the word is retrieved. However, like reading, there is also evidence of a non-semantic lexical spelling route which proceeds from phonological input to orthographic output bypassing the semantic system. Patient evidence in support of this lexical non-semantic spelling route exists (Kremin, 2013). Either way, the final stage occurs at the orthographic output buffer. Once a word is retrieved from the orthographic output lexicon to be written down, it may take a few seconds before all the letters are down on paper. The specific spelling retrieved from the lexicon will have to remain available for a few seconds. The orthographic output buffer allows for information to be kept active while writing it down, so it avoids continuously going back to the lexicon and searching for the word all over again.

When the non-lexical writing route is used, the information received at the phonological input buffer following the initial acoustic analysis undergoes a process of *acoustic-to-phonological conversion*, the result of which is sent to the *phonological output* or *response buffer*. This temporary storage system keeps the information active while the *phonological-to-orthographic conversion* processes are carried out, following sound-to-letter rules. The last stage also occurs at the orthographic output buffer and the process is of the same nature as the above-described for the lexical writing route.

The same types of words described earlier are also selectively processed by the two writing routes. Thus, the lexical writing route is used to write real words regardless of these being regular or irregular, but pseudowords cannot be spelled through this route. Contrarily, the

non-lexical writing route can be employed to write down pseudowords and regular words, as they follow the phoneme-to-grapheme conversion rules, but not to spell irregular words.

Although both reading and writing processes can be theorised using the Dual-Route Model, controversy exists on whether the phonological and orthographic lexicons involved in reading are the same of those involved in writing. The **shared-components account** argues that these are the same, whether the **independent-components account** claims that the lexicons involved in reading are independent from those involved in writing, and that these processes only share the semantic system. The existence of case reports with both associations and dissociations between reading and spelling deficits contributes to such controversy (Hillis & Rapp, 2004; Rapp & Lipka, 2011). A schematic representation of the Dual-Route of reading and writing is depicted in Figure 2.2. In this case, an independent-components architecture has been used, as it allows for a greater interpretation of dissociated deficits between reading and writing skills. Separately, single case studies have also provided convincing evidence to indicate separate phonological output processes for reading and speaking (Warrington & Crutch, 2005; cited in McKenna & Bonham, 2013).

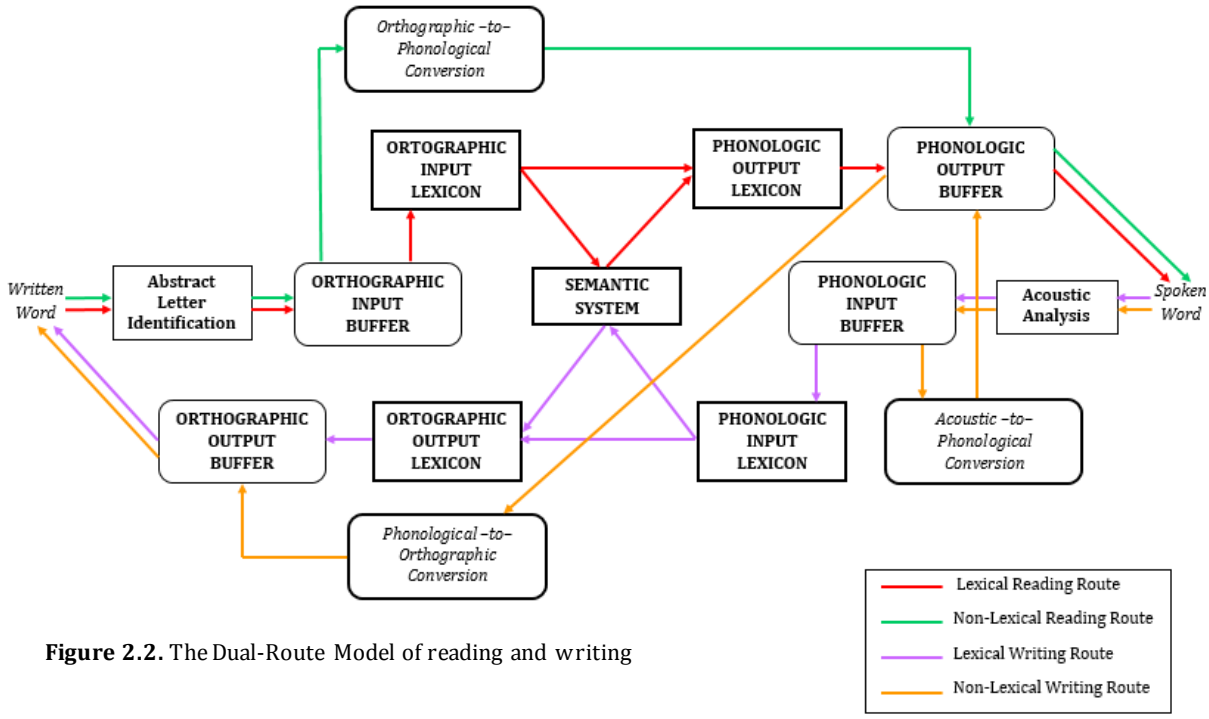

Figure 2.2. The Dual-Route Model of reading and writing

2.4.4. Types of Reading and Writing Impairments

The Dual-Route Model was built on the basis of case reports of patients with a brain injury who showed confined deficits to certain types of words, suggesting impairments on selective psycholinguistic mechanisms. This section reviews the different reading and writing disorders that have been described based on this evidence. While the terms dyslexia/dysgraphia are

typically used by psycholinguists, the terms alexia/agraphia are used here to highlight the acquired (not developmental) nature of such disorders.

Three types of literacy impairments caused by damage to central linguistic mechanisms exist:

- **Surface alexia/agraphia** are caused by an impairment to the lexical reading/writing route, respectively. A specific deficit to process irregular words is observed, while regular and pseudowords can be processed through the non-lexical route.

  A characteristic error of these syndromes are *regularisation errors*, consequence of processing irregular words through the non-lexical route. For instance, if the word *yacht* is read through the non-lexical route, it would sound as /'jækt/, and if it is written through this route, the spelling would appear as '*yot*'. Other errors committed if the lexical reading route is impaired include the confusion of homophones (e.g. retrieving the meaning of *steel* when reading *steal*) or the acceptance of a pseudoword homophone as the correct form of that word (e.g. accepting 'greit' for *great*).

  Lexical processing in surface syndromes can be defective at an input or output stage. If the problem is at an input stage, irregular words cannot get access to the input lexical system, so these words cannot be recognised as words and therefore they cannot be understood nor read/written. If the problem is that the words are not accessible at an output stage, these can be recognised and understood as they will have normal access to the input lexicons and semantic system, but they will be misread/miswritten, most likely produced based on non-lexical rules. Lexical decision tasks (auditory and written, to assess both phonological and orthographic input lexicons) assist in distinguishing if the problem is at an input level, also affecting output performance, or if it is confined to output stages.
- ***Phonological alexia/agraphia*** are caused by a defect to the non-lexical reading/writing route, respectively. These syndromes are characterised by an inability to apply the grapheme-to-phoneme/phoneme-to-grapheme conversion rules, and thus pseudowords cannot be processed. The ability to process real words (regular and irregular) is relatively spared as this can be achieved through the lexical route.

  A type of error characteristic of impaired non-lexical routes are *lexicalisations*. This error occurs when pseudowords are attempted to be processed through the lexical route, and consist of a guess of the reading/writing of the pseudoword based on its resemblance to a real word stored in the lexicons. For instance, if the pseudoword 'teble' was read through the lexical reading route, it would probably be read as /'teɪb(ə)l/, and if it was written through the lexical writing route, the output given would appear as *table*. Impaired non-lexical reading route also causes problems in processing any type of word (regular or irregular) that has not been previously associated with a pronunciation or a written word form and therefore it is not part of the subject's lexicon.

- ***Deep alexia/agraphia*** are observed when both the lexical and non-lexical routes for reading or writing (respectively) are impaired, and the ability to read/write is severely affected for all types of words. In this case, the words are recognised by sight, this means that the subject is only able to process words that are part of his/her sight vocabulary (i.e. words that the person recognises immediately with no need to decode them). It is typical of this syndrome to observe semantic paralexias/paragraphias (i.e. substitutions of a word for a semantically related one, which can be a synonyms, an antonyms, or a superordinate or subordinate concept; e.g. *cop* for *police*). In this type of error, it seems that the accurate semantic representation is retrieved from the semantic system but the wrong output representation is accessed in the phonologic/orthographic output lexicon. In fact, word recognition is relatively preserved in deep syndromes. Visual paralexias/paragraphias (i.e. substitution of a word for a visually similar one; e.g. *cat* for *car*) can also be observed.

In all three types of agraphias described above, difficulties are observed for all kinds of writing output: handwriting, oral spelling, typing, or with the use of letter-response cards.

Other disorders of reading and writing have been described when peripheral rather than central stages of literacy processing are affected. **Neglect alexia** is caused by visual field loss as a result to damage to the right primary visual cortex causing the omission of the beginning of the sentence or part of the word in the left visual field, **Letter-by-letter** or **pure alexia** involves an inability to perceive the word as a whole which is caused by a disconnection between the posterior and the mid-fusiform gyrus, breaking the connection between the initial visual processing of letters and the subsequent abstract orthographic processing of word forms. **Attentional alexia** is characterised by an inability to perceive individual letters caused by an attentional deficit which prevents the subject from focusing the attention to a specific part of the word and only allows for the word to be perceived as a whole. In terms of peripheral agraphias, **spatial agraphia** is caused by visuospatial deficits that impair correct orientation and consecutiveness of the written output, and **apraxic agraphia** is caused by graphomotor planning problems that affect the quality and legibility of the written output, causing a distortion of the letter-shape in the context of correct spelling.

2.4.5. Considerations from the Connectionist Approach

Connectionist models of reading/writing (Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989), contrarily to serial/representational models (Dual-Route), assume that the processing of regular, irregular and pseudowords is achieved through a single processing system. According to connectionism, reading and writing abilities are based on algorithms of interaction between phonological, semantic and orthographic units. Accordingly, phonological units are activated by specific clusters of phonemes and orthographic units are activated by particular clusters of graphemes. There is a third type of units, hidden units, which

work as mediators between phonological and orthographic representations. Connections between these units increase or decrease depending on the frequency with what they activate together, so these connections are modified through repeat exposure.

Three main differences exist between serial and connectionist approaches (Coltheart, 2006):

1) Local vs distributed representations: while the Dual-Route model considers that each word is represented by a single unit in the lexicon, connectionist models assume that each word can be represented by the activation of numerous units.
2) Serial vs parallel processing: while the Dual-Route model postulates a serial processing, connectionist models assume that such processes operate in parallel (e.g. all letters from a pseudoword are processed simultaneously).
3) Learning vs repeat exposure: while the Dual-Route model understands the acquisition of literacy skills as an acquired learning process through education, connectionist models propose that this acquisition occurs through repeated exposure of specific spellings and pronunciations that will activate together, which will increase the strengths between them and progressively adjust the algorithms.

There is an aspect of connectionist models that is worth considering even from a representational perspective, the **principle of parallel distributed processing (PDP)**, according to which the different units or representations are distributed across a network and their processing occurs in parallel rather than serially. Although some aspects of literacy processing have been proven to be performed in a serial manner (e.g. letter-by-letter phonological processing; Rastle & Coltheart, 2006), there is growing evidence that (1) in reality the component processes in these systems interact and thus they operate in parallel instead of strictly sequentially, and that (2) the different representations are actually distributed and overlap with similar phonological or orthographic representations (e.g. the phonological representation 'here' significantly overlaps with 'fear' and 'heap', and completely with 'hear'; Tsapkini & Hillis, 2017). Evidence in support of the latter is provided by *facilitatory effects of neighbourhood sizes* on word recognition tasks (i.e. words with more phonological or orthographic similar representations have lower response latencies), which indicate that these words receive additional activation from similar representations and this facilitates performance (Yap & Balota, 2014). Parallel processing of linguistic information is supported by evidence of *semantic richness effects* on word recognition tasks (i.e. words associated with more semantic information are easier to recognise). This implicates the system to have access to some aspects of meaning while lexical processing is occurring, suggesting some kind of feedback message from semantic processing to the input lexicons (Yap & Balota, 2014). New computational models based on both serial and connectionist approaches have been developed, i.e. the Connectionist Dual Process model (CDP: Perry, Ziegler, & Zorzi, 2007, 2010).

The Dual-Route Model (also converted into a computational model, the Dual-Route Cascaded [DCR] model: Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001) has been chosen as the model that will be used to assess and interpret literacy skills in this work. The reason behind this is that this model is considered more applicable to the interpretation of specific reading and writing impairments described based on cognitive neuropsychology case reports (Coltheart, 2005). However, connectionist approaches have also attempted this. The **Primary Systems Hypothesis** (Patterson & Lambon-Ralph, 1999) interprets selective disorders of reading on the basis of single-word processing connectionist models referenced above. According to this approach, surface alexia is caused by reduced strengths of activation from semantic to phonological units, impairing the reading of irregular words, which benefit from activation of semantic representations that provide additional support for the activation of the correct pronunciation. This is especially relevant for low-frequent words. Phonological alexia is caused by reduced strengths of activation from orthographic to phonological units, impairing pseudoword reading as feedback from phonologically similar units and semantic units can only boost activation for familiar words. Finally, deep alexia is considered a more severe form of phonological alexia.

2.4.6. Neural Substrates of Reading and Writing

Reading and writing are complex processes underlain by distinct but overlapping brain networks. When reading, the processing of visual input starts at the primary visual cortex, in the occipital lobe (striate cortex, BA 17), where the low-level perceptual analysis of the written code takes place, and this information is then sent to the secondary visual cortex (BA 18) and associative visual cortex (BA 19), in the extrastriate cortex, where an early processing of graphic stimuli occurs in ventral and medial areas bilaterally (Démonet et al., 2005). The left medial extrastriate cortex (BA 19), which comprises the lingual gyrus, has been linked to the processing of written letters and it is proven to be important for reading words and pseudowords (Petersen, Fox, Snyder, & Raichle, 1990; Philipose et al., 2007).

The fusiform gyrus (BA 37), specifically the left mid-fusiform gyrus, at the margin of the occipito-temporal sulcus, is known as the 'visual word form area' (VWFA: L. Cohen et al., 2000). Although the specificity of this area for the processing of written input is not fully understood, it is hypothesised that it is involved in the identification of letters and words from low-level perceptual analysis of shapes to provide further access to areas of phonological, lexical and semantic associations (Démonet et al., 2005). Thus, it has been suggested that the VWFA is likely involved in the process of abstract letter identification (Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002), but also in the segmenting and classification of familiar groupings of letters (Jobard, Crivello, & Tzourio-Mazoyer, 2003). Accordingly, it seems to be the first step to the processing of the representations of orthographic word forms (Rapp & Lipka, 2011).

Jobard et al. (2003) published a meta-analysis of neuroimaging studies of reading to investigate if the two routes of reading could be associated with distinct patterns of brain activation. One of the main findings of these authors was that the first steps to word and pseudoword processing are shared and take place in the left mid-fusiform gyrus or VWFA, consistent with what has been reported in the previous paragraph. It is likely that the two different reading routes segregate after this first pre-lexical analysis. In fact, Jobard et al. (2003) showed the predominance of certain brain regions for one or the other reading route. Regarding the lexical reading route, the visual word lexicon or orthographic lexicon, responsible for lexical processing, is thought to be located in the left posterior middle temporal gyrus, very close to the most posterior part of the superior temporal sulcus. This area, however, has also been linked to semantic access and it is therefore postulated as a multimodal integration area that also receives information from other modalities and works as a node for language comprehension. The right counterpart of this area has been linked to the perception of one's own voice when reading aloud (Démonet et al., 2005). Other areas identified as semantic centres for reading include the left inferior temporal gyrus, involved in the semantic processing of words and objects, and the left inferior frontal gyrus, specifically the pars triangularis (BA 45), which is implicated in the monitoring of semantic attributes. Concerning the non-lexical reading route, the left middle temporal gyrus, at the margin of the middle part of the superior temporal sulcus, and the left superior temporal gyrus, especially the left posterior superior temporal gyrus, have been related to phonological processing or orthographic-to-phonological conversions. Buffer areas responsible for temporarily holding these aforementioned conversions have been shown to be located in the left supramarginal gyrus and the left inferior frontal gyrus, particularly in the pars opercularis (BA 44). The latter, apart from temporary phonological store tasks prior to articulation, has also been linked to subvocal rehearsal. In fact, this area not only activates when reading aloud, but also in silent or implicit reading, suggesting that phonological retrieval occurs even when there is no speech output (Démonet et al., 2005). Brain regions involved in speech production described in section 2.3.1 are also involved in reading.

Regarding spelling to dictation, the first stages involve the same anatomical regions for the processing of auditory input that have been described in section 2.2.1. Neural substrates of spelling have been less studied using functional neuroimaging than those involved in reading, although lesion studies suggest that those areas associated with reading deficits are also commonly linked to impaired spelling (Rapp & Lipka, 2011).

The left mid-fusiform gyrus or VWFA is one of the brain regions that has most undoubtedly proven to be involved in both reading and writing (Rapp & Lipka, 2011). In fact, lesions on this 'word form' area also cause impairment in written output (Philipose et al., 2007), and it is

thought to be involved in the retrieval of orthographic lexical representations of words (Rapp & Lipka, 2011). While the mid-fusiform gyrus has been related to the processing of orthographic word form (i.e. visual form of the word, which are case-, font- and orientation-independent), the lateral part of this area has been linked to the processing of lexical attributes, also modality-independent (Tsapkini & Hillis, 2017). Thus, this area has been linked to surface agraphia or lexical spelling (Luzzatti, 2008).

Although some studies have shown that inferior frontal lesions can cause deficits in spelling, the role of the inferior frontal cortex in writing is less clear than its role in reading (Rapp & Lipka, 2011). Evidence show that this area could be implicated in sublexical phoneme-to-grapheme conversion mechanisms along with subjacent areas such as the superior temporal gyrus, precentral gyrus and the insula (Tsapkini & Hillis, 2017). Other cognitive functions that are associated with this region and that are required when writing include working memory and cognitive control (specifically updating task representations), semantic and syntactic processing (Tsapkini & Hillis, 2017).

The premotor cortex and supplementary motor area (BA 6) control the last stages of writing, converting specific graphemes into letter shapes and executing the motor plan to write this down (Tsapkini & Hillis, 2017). The Exner's area, situated in the precentral gyrus close to the junction with the middle frontal gyrus, is a graphemic/motor centre where the motor programmes of the sequence of gestures required to produce each character are contained, and thus lesions on this area cause apraxic agraphia (Longcamp, Velay, Berninger, & Richards, 2016).

Finally, it is important to allude to the involvement of the angular gyrus in reading and writing, which is ambiguous. Although lesion studies suggest that injuries affecting this area are associated with reading and writing impairments, evidence from neuroimaging studies in healthy populations does not indicate such a strong association, which could be due to a higher inter-individual variability for the recruitment of regions within this area to process reading and writing (Rapp & Lipka, 2011). This region has been linked to orthographic/phonological conversion mechanisms (i.e. orthographic to phonological in reading and phonological to orthographic in wring), as well as to lexical processing or access to lexical representations form the orthographic lexicons (Tsapkini & Hillis, 2017). The supramarginal gyrus, which has also been implicated in the reading and writing of both words and pseudowords, seems to be closely related to other reading/writing processing areas such as the fusiform gyrus, and therefore lesions solely confined to this region are unlikely to cause deficits of literacy (Tsapkini & Hillis, 2017).

2.5. Language Dysfunction in Neurodegenerative Diseases

Language dysfunction is characteristic of several neurodegenerative diseases. In some instances, language impairment is the selective and most marked presentation, whereas in other cases language dysfunction is part of a broader presentation of cognitive symptoms. Primary Progressive Aphasia (PPA) is a neurodegenerative disease characterised primarily by a progressive disorder of language function (Gorno-Tempini et al., 2011). PPA is one of the clinical entities comprised within the umbrella term FTD, along with behavioural variant FTD (bvFTD), a dementia-type characterised by changes in personality and social interpersonal comportment (Rascovsky et al., 2011). Diagnostic criteria for bvFTD is detailed in Appendix A (page 344). FTD clinical syndromes, associated with the degeneration of the frontal and temporal lobes, are also referred to as Frontotemporal Lobar Degeneration (FTLD) syndromes, commonly associated with TDP-43 ubiquitin-positive inclusions and tau-positive pathology (Henri-Bhargava & Freedman, 2012).

Depending on the clinical pattern of language impairment observed, PPA can be sub-classified into nonfluent/agrammatic, semantic, or logopenic (Gorno-Tempini et al., 2011). Nonfluent/agrammatic variant PPA (nfvPPA) is characterized by effortful and halting speech with a reduced length of sentences and a gradual increase in phonological, grammatical and syntactic errors (i.e. phonemic paraphasias and agrammatism). Anomia is also present, but semantic knowledge is spared. Reading and verbal comprehension abilities also remain relatively spared, except for complex grammatical constructions, and writing is prominently impaired. Semantic variant PPA (svPPA) is a fluent aphasia characterised by progressive loss of semantic knowledge, causing reduced single word comprehension and impaired confrontation naming. Speech is fluent though impoverished due to the semantic disorder, while phonology, syntax and repetition remain relatively preserved. Surface dyslexia and dysgraphia are also present, with preserved phonological reading and spelling. Finally, Logopenic variant PPA (lvPPA) is characterized by selective anomia with preserved semantics. Single word repetition and comprehension remain intact, but sentence repetition and comprehension are impaired. Diagnostic criteria for each PPA variant are detailed in Appendix B (pages 345-346). Clinical criteria for the diagnosis of Frontotemporal Lobar Degeneration are detailed in Appendix C (pages 347-349).

Each PPA presentation is associated with a particular pattern of brain damage (Gorno-Tempini et al., 2011; Harciarek & Kertesz, 2011). Specifically, nfvPPA is associated with atrophy in left frontal regions, specifically the left posterior inferior frontal gyrus and left insula, as well as the left supplementary motor area, areas implicated in language production and syntax. SvPPA involves the ventral and lateral portions of the anterior temporal lobes bilaterally, with greater atrophy on the left side, regions known to be involved in the processing of semantics. Lastly,

lvPPA is associated with atrophy in the left posterior superior temporal lobe, middle temporal gyri and inferior parietal lobe, areas related to phonological loop functions.

Language impairments also occur in other neurodegenerative conditions, but in the context of a broader presentation of cognitive symptoms. Cortical features of aphasia are also seen in Alzheimer's Disease (AD) and Corticobasal Degeneration (CBD).

Alzheimer's Disease (AD) is mainly characterised by progressive impairment of episodic memory, although language impairment is also observed, with the most prominent deficit being word finding difficulties (McKhann et al., 2011). Diagnostic criteria for AD are detailed in Appendix D (pages 350-351). As the AD pathology spreads from medial to lateral temporal areas, AD patients develop a semantic memory deficit characterised by semantically-based errors on confrontation naming and a more pronounced impairment on semantic fluency compared to phonemic fluency tasks. This is consistent with a disruption of the structure and organisation of semantic knowledge which disturbs accurate access to sematic information (Smith & Bondi, 2013). Language deficits in AD are not confined to spoken language, with difficulties in spelling and reading also being observed (Snowden, 2012).

LvPPA is usually considered within non-amnestic AD presentations as AD pathology, specifically neurofibrillary tangles and neuritic plaques, are the neuropathological abnormality most commonly found in this presentation (M. Grossman, 2010).

Finally, Corticobasal Degeneration (CBD) is a neurodegenerative disease characterised by asymmetrical motor and sensory cortical and extrapyramidal dysfunction (Elamin, Omer, Hutchinson, Doherty, & Bak, 2016). CBD presents with a prominent dementia syndrome, one of its main symptoms is a severe nonfluent progressive aphasia characterised by impaired expressive language, anomia and agrammatism, and relative sparing of receptive language and semantics (Salmon, 2013), a pattern similar to that observed for nfvPPA. In fact, CBD overlaps with FTLD not only clinically but also at a pathological level, with many CBD cases being characterised by tau-positive pathology (Henri-Bhargava & Freedman, 2012).

Neurodegeneration is understood as a network disease, and the selective patterns of language dysfunction observed in different neurodegenerative conditions are thought to represent specific disturbances of the language network (Mesulam et al., 2014). The study of language in neurodegeneration hence allows us to interrogate and map the language processing network.

2.6. The Assessment of Language in Neurodegenerative Diseases

Comprehensive batteries of language assessment exist which are employed for diagnostic purposes, as well as to guide the planning of individually-tailored interventions. Three

commonly used language assessment batteries are described here: the Boston Diagnostic Aphasia Examination (BDAE: Goodglass & Kaplan, 1983; Goodglass, Kaplan, & Barresi, 2000), the Western Aphasia Battery (WAB: Kertesz, 1982, 2007), and the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA: Kay et al., 1992).

The BDAE-III (Goodglass et al., 2000) is one of the most popular language assessment batteries used to characterise aphasia syndromes and their severity. It also provides a profile of language dysfunction that can guide the development of interventions. The BDAE divides language function into five domains: conversational and expository speech, auditory comprehension, oral expression, reading, and writing, each one of these being assessed by a number of subtests (see Table 2.1 for a list of the same). Three kinds of measures are obtained: an *Aphasia Severity Rating Scale*, a *Subtest Summary Profile*, which describes the pattern of deficits observed, and a *Rating Scale Profile*, a qualitative description of the characteristics of the patient's speech.

The WAB-R (Kertesz, 2007) is another of the most frequently used batteries to assess and determine the presence, type and severity of aphasia. The WAB assesses language function by considering six language components: spontaneous speech, auditory verbal comprehension, repetition, naming and word finding, reading, and writing. Each one of these components is assessed through a range of individual tasks, specified in Table 2.1. Three quotient scores can be obtained: the *Aphasia Quotient*, a measure of the severity of the aphasia considering the language domains of spontaneous speech, auditory verbal comprehension, repetition, and naming/word finding; the *Language Quotient*, a measure of combined performance considering previous oral language components plus writing and reading scores; and the *Cortical Quotient*, which also considers other non-linguistic assessments of apraxia, visuospatial and constructional abilities, and calculation.

The PALPA is a comprehensive battery that assesses language processing in the areas of language recognition, comprehension and production. Four language components are considered: auditory processing, reading and writing, word picture and semantics, and sentence processing. The overall battery is comprised of 60 subtests (Table 2.1). The PALPA has been described as the most comprehensive available battery of language-processing (Bate, Kay, Code, Haslam, & Hallowell, 2010). This battery was developed from a cognitive model of language function, the PALPA Transcoding Model (Figure 2.3: Kay et al., 1996), which organises the language system into distinct modules of processing that can be independently damaged and cause specific language impairments. Accordingly, the PALPA battery allows for the investigation of these specific processing components of the language system.

These three language batteries, originally developed to assess aphasia poststroke or following other acquired brain injuries, are also currently used to assess language dysfunction in neurodegeneration (Bate et al., 2010; Kertesz, 2007; Strauss et al., 2006).

Table 2.1. Language domains and subtests assessed on the BDAE, the WAB and the PALPA.

The Boston Diagnostic Aphasia Examination (BDAE)	
Conversational and expository speech ▪ Simple Social Responses ▪ Free Conversation ▪ Picture Description	**Auditory comprehension** ▪ Basic Word Discrimination ▪ Commands ▪ Complex Ideational Material
Oral expression ▪ Nonverbal Agility ▪ Verbal Agility ▪ Automatized Sequences ▪ Recitation ▪ Melody ▪ Rhythm ▪ Single Word Repetition ▪ Repletion of Sentences ▪ Responsive Naming ▪ Boston Naming Test ▪ Screening for Naming of Special Categories	**Reading** ▪ Matching Across Cases and Scripts ▪ Number Matching ▪ Picture-Word Match ▪ Lexical Decision ▪ Homophone Matching ▪ Free Grammatical Morphemes ▪ Basic Oral Word Reading ▪ Oral Reading of Sentences with Comprehension ▪ Reading Comprehension – Sentences and Paragraphs **Writing** ▪ Mechanics of Writing ▪ Primer Word Vocabulary ▪ Regular Phonics ▪ Common Irregular Forms ▪ Written Picture Naming ▪ Narrative Writing
The Western Aphasia Battery (WAB)	
Spontaneous Speech ▪ Conversational Questions ▪ Picture Description	**Auditory Verbal Comprehension** ▪ Yes/No Questions ▪ Auditory Word Recognition ▪ Sequential Commands
Repetition	**Naming and Word Finding** ▪ Object Naming ▪ Word Fluency ▪ Sentence Completion ▪ Responsive Speech
Reading ▪ Comprehension of Sentences ▪ Reading Commands ▪ Written Word – Object Choice Matching ▪ Written Word – Picture Choice Matching ▪ Picture – Written Word Choice Matching ▪ Spoken Word – Written Word Choice Matching ▪ Letter Discrimination ▪ Spelled Word Recognition ▪ Spelling	**Writing** ▪ Writing Upon Request ▪ Writing Output ▪ Writing to Dictation ▪ Writing Dictated Words ▪ Alphabet and Numbers ▪ Dictated Letters and Numbers ▪ Copying a Sentence
The Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)	
Auditory Processing ▪ Nonword Minimal Pairs ▪ Word Minimal Pairs ▪ Word Minimal Pairs Requiring Written Selection ▪ Word Minimal Pairs Requiring Picture Selection ▪ Auditory Lexical Decision: Imageability x Frequency ▪ Auditory Lexical Decision: Morphological Endings ▪ Repetition: Syllable Length	**Reading and Spelling** ▪ Letter Discrimination: Mirror Reversal ▪ Letter Discrimination: Upper – Lower Case Matching ▪ Letter Discrimination: Lower – Upper Case Matching ▪ Letter Discrimination: Words & Nonwords ▪ Letter Naming & Sounding ▪ Spoken Letter – Written Letter Matching ▪ Visual Lexical Decision: Legality

Table 2.1 (continued). Language domains and subtests assessed on the BDAE, the WAB and the PALPA.

The Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)	
Auditory Processing ▪ Repetition: Nonwords ▪ Repetition: Imageability x Frequency ▪ Repetition: Grammatical Class ▪ Repetition: Morphological Endings ▪ Repetition: Sentences ▪ Digit Production/Matching Span ▪ Rhyme Judgements x Pictures ▪ Rhyme Judgements x Words ▪ Phonological Segmentation: Initial Sounds ▪ Phonological Segmentation: Final Sounds	**Reading and Spelling** ▪ Visual Lexical Decision: Imageability x Frequency ▪ Visual Lexical Decision: Morphological Endings ▪ Visual Lexical Decision: Regularity ▪ Homophone Decision ▪ Oral Reading: Letter Length ▪ Oral Reading: Syllable Length ▪ Oral Reading: Imageability x Frequency ▪ Oral Reading: Grammatical Class ▪ Oral Reading: Grammatical Class x Imageability ▪ Morphological Ending ▪ Oral Reading: Regularity ▪ Oral Reading: Nonwords ▪ Oral Reading: Sentences ▪ Homophone Definition x Regularity ▪ Spelling to Dictation: Letter Length ▪ Spelling to Dictation: Imageability x Frequency ▪ Spelling to Dictation: Grammatical Class ▪ Spelling to Dictation: Grammatical Class x Imageability ▪ Spelling to Dictation: Morphological Endings ▪ Spelling to Dictation: Regularity ▪ Spelling to Dictation: Nonwords ▪ Spelling to Dictation: Disambiguated Homophones
Picture and Word Semantics ▪ Spoken Word – Picture Matching ▪ Written Word – Picture Matching ▪ Auditory Synonym Judgements ▪ Written Synonym Judgements ▪ Word Semantic Association ▪ Spoken Word – Written Word Matching ▪ Picture Matching x Written Naming/Repetition/Oral Reading/Written Spelling ▪ Picture Naming x Frequency	**Sentence Comprehension** ▪ Auditory Sentence Comprehension ▪ Written Sentence Comprehension ▪ Auditory Comprehension of Verbs & Adjectives from the Sentence Set ▪ Auditory Comprehension of Locative Relations ▪ Written Comprehension of Locative Relations ▪ Pointing Span for Noun – Verb Sequences

The BDAE and the WAB follow the classic anatomically-based conceptualisation of poststroke aphasia syndromes (i.e. Broca's, Wernicke's, anomic, conduction, transcortical motor, transcortical sensory and global aphasia). The revised version of the WAB has also been standardised to assess language deterioration in patients with neurodegenerative conditions (Kertesz, 2007), and clinical studies have also proven the sensitivity of the BDAE-III to detect language change in patients with dementia (Strauss et al., 2006). Both the WAB and the BDAE provide a general measure of aphasia and are built to characterise an individual's overall language profile based on broad language domains. However, little is known about the usefulness of their individual subtests to assess specific language processes. Moreover, even

though they integrate the neurological model with psycholinguistic principles (e.g. the revised version of the WAB includes supplemental spelling and reading tasks to assess irregular and nonword processing), they don't offer a psycholinguistic approach, based on cognitive neuropsychology principles, to understanding language deficits.

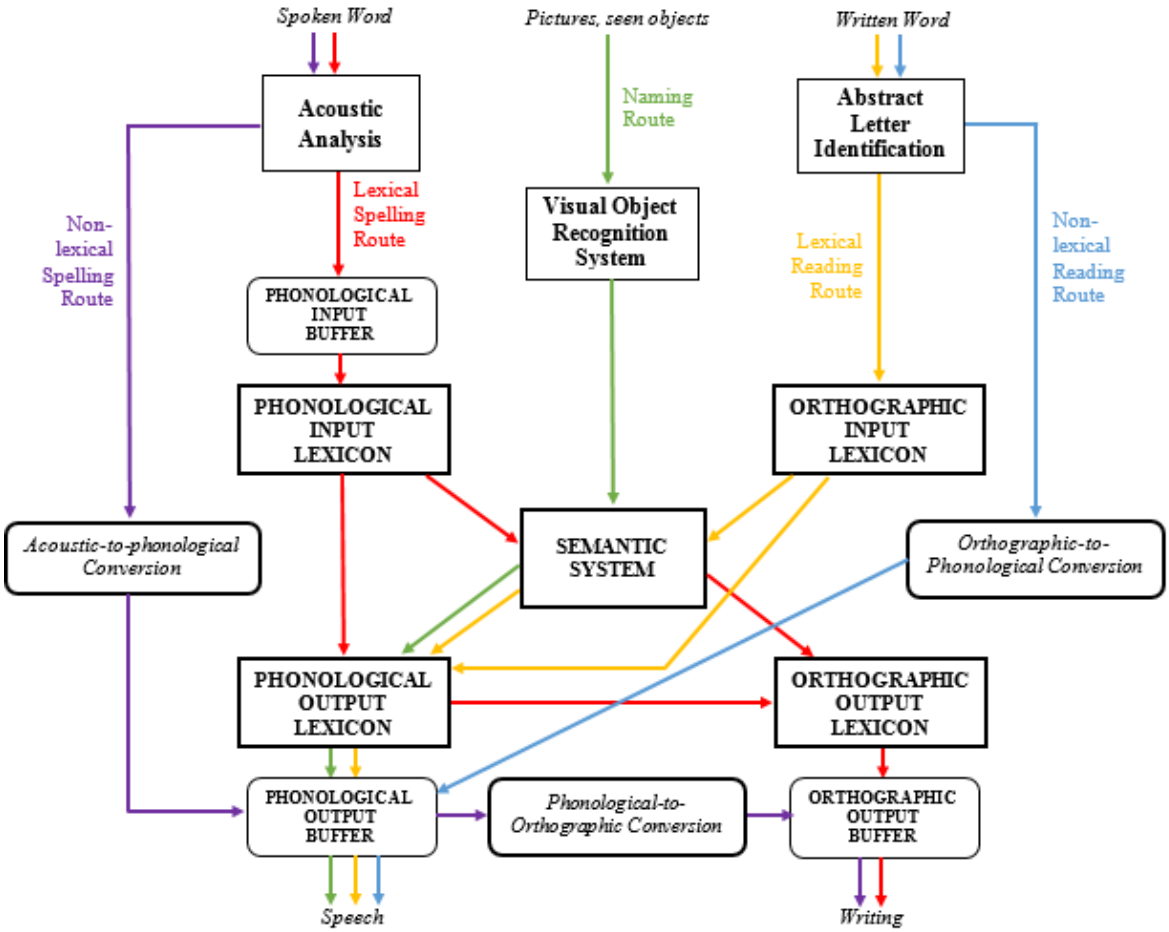

Figure 2.3. The PALPA Transcoding Model. Adapted from Kay et al. (1996)

The PALPA, on the other hand, is based on an underlying model of language processing which, although not universally accepted (A. Ferguson & Armstrong, 1996), achieves its aim of allowing for the identification of different processes which underlie language impairment (Wertz, 1996). Performance on particular tests are interpreted in relation to specific language processing stages, which provides an understanding of selective language dysfunctions at different levels of processing (i.e. phonological, orthographic, lexical, semantic, or syntactic and grammatical). Moreover, the PALPA Transcoding Model is underpinned by the dual-route theory of reading and writing (Coltheart, 2006), and therefore it allows for the differential diagnosis of different types of alexia and agraphia. Another strength of the PALPA is that it was developed to control for linguistic parameters such as word frequency, imageability or regularity (Basso, 1996).

CHAPTER 3 Outline.

Cognition and Behaviour in Amyotrophic Lateral Sclerosis

CHAPTER 3.

Cognition and Behaviour in Amyotrophic Lateral Sclerosis

3.1. The Incidence and Nature of Cognitive Impairment in ALS

ALS is a disease that primarily affects the motor system. Nevertheless, extensive clinical, imaging and neuropathological evidence of extramotor involvement exists, particularly of frontotemporal and frontostriatal areas (Tsermentseli, Leigh, & Goldstein, 2012). Accordingly, ALS is now recognised as a multisystem disease that also affects cognition and behaviour, with evolving evidence for heterogeneity in both disease pathogenesis and clinical presentation (van Es et al., 2017).

Descriptions of a clinical picture of ALS in combination with cognitive, psychiatric and dementia symptoms date back to the late 19th century (Bak & Hodges, 2001), although the first large scale study investigating the prevalence and nature of cognitive changes in ALS was not published until 2005 (Ringholz et al., 2005). This study reported that 51% of the patients had evidence of cognitive impairment and 15% met criteria for the diagnosis of Frontotemporal Dementia (FTD). These conclusions were however drawn from a clinic-based prevalent sample, liable to selection bias, thus questioning the generalizability of the results.

The first large population-based study of cognitive impairment in incident ALS cases was published in Ireland in 2012 (Phukan et al., 2012). In this study, 35% of incident ALS patients showed mild to moderate cognitive impairment and co-morbid dementia occurred in approximately 14% of patients, the majority of these meeting diagnostic criteria for FTD, while at least 45% of ALS patients were cognitively intact. The incidence of cognitive impairment in ALS described in this population-based study has been since replicated in a second population-based study with Italian population (Montuschi et al., 2015) and in a large cross-sectional study of cognitive functioning in Korean ALS patients (Oh et al., 2014).

The profile of cognitive and behavioural impairment in ALS is greatly heterogeneous in terms of both the nature and severity of the deficits. Cognitive change in ALS manifests most commonly as executive dysfunction. Thus, phonemic verbal fluency deficits reflect dorsolateral prefrontal dysfunction (Goldstein & Abrahams, 2013; Phukan et al., 2012; Phukan, Pender, & Hardiman, 2007), and other deficits in dorsolateral and orbitomedial prefrontal functions such as cognitive flexibility, abstract reasoning, working memory and inhibitory control have also been described (Strong et al., 2017). Social cognitive deficits such as difficulties in recognition and processing of emotions and social-cues are also recognised as an integral part of the

orbitofrontal profile of ALS (Beeldman et al., 2016). The presence of behavioural impairment including disinhibition, loss of sympathy and empathy, stereotyped behaviours and dietary changes has also been reported (Strong et al., 2017), and apathy is reported in up to 50% of ALS cases, suggesting anterior cingulate dysfunction (Burke et al., 2017; Woolley, Zhang, Schuff, Weiner, & Katz, 2011). Language changes have also been described, although its study has received less attention than other cognitive domains (Beeldman et al., 2016).

This neuropsychological profile characteristic of ALS is indicative of frontostriatal and temporal involvement of varying severity and it clinically overlaps with an FTD presentation. ALS and FTD have not only been linked at a clinical but also at a genetic and pathological level, and these two conditions are now considered overlapping disease phenotypes representing two extremes of a continuum (i.e. the ALS-FTD continuum). At a neuropathological level, TDP-43 ubiquitin-positive inclusions are one of the most common pathology found in FTD and also in ALS (see Ling et al., 2013 for a review). ALS and FTD also share genetic markers (Figure 3.1). The C9orf72 repeat expansion is the most common cause of FTD and of ALS with cognitive and behavioural changes. Thus, it explains 25% of familial FTD, 6% of sporadic FTD, 5-20% of sporadic ALS, 20-50% of familial ALS, 50-80% of familial ALS-FTD and around 15-20% of apparently sporadic ALS-FTD (Burrell et al., 2016; Lattante et al., 2015; Ling et al., 2013).

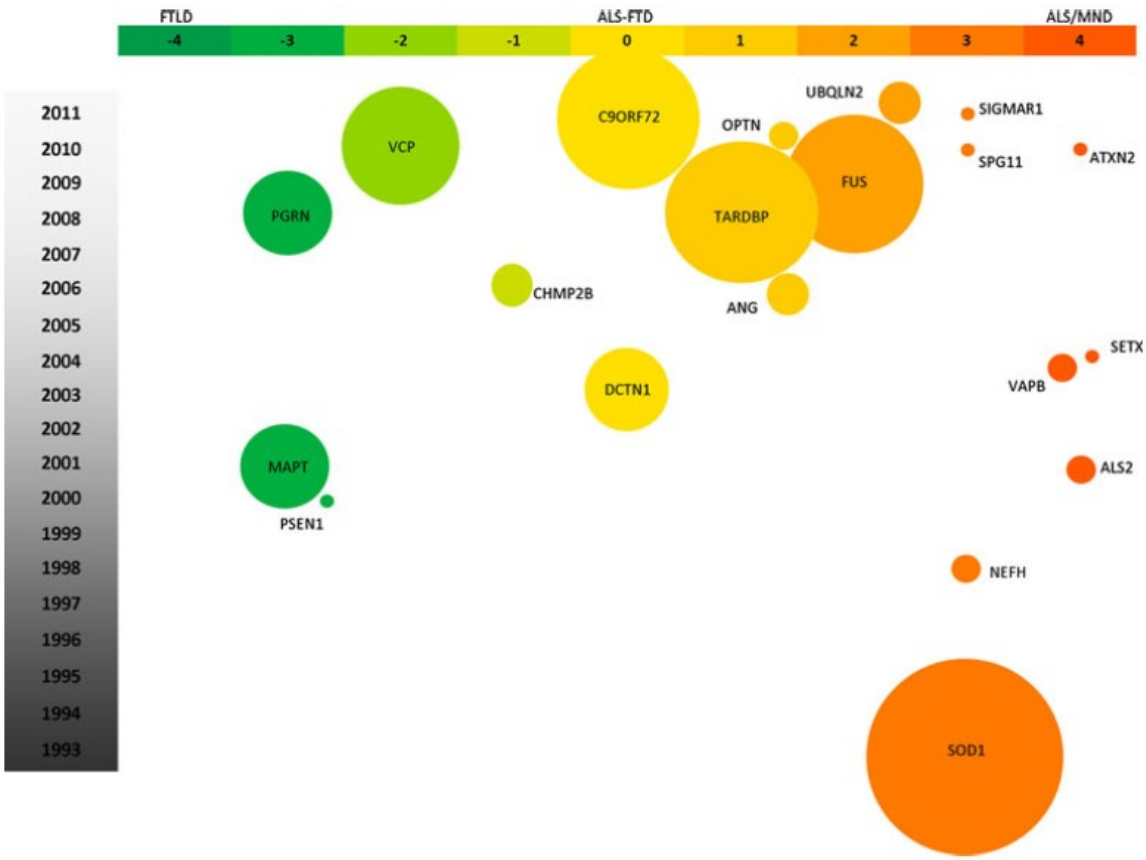

Figure 3.1. Genes involved in the ALS-FTD continuum (X axis), year of discovery (Y axis) and level of research done on each gene (circle size). From Al-Chalabi et al. (2012)

Other rarer genetic mutations have also been related to the ALS-FTD continuum (see Figure 3.1), and some genetic variations (i.e. UNC13A, SIGMAR1) have been found to increase the risk for ALS and FTD or act as disease modifiers (Lattante et al., 2015). Nevertheless, a significant proportion of familial ALS-FTD cases have not yet been linked to any known genetic mutation, suggesting that there are still other unknown genes linked to this disease spectrum (Burrell et al., 2016). In fact, this clinic-pathological disease continuum is more complex than it seems. Some genetic mutations exist which cause ALS or FTD, but rarely ALS-FTD (e.g. the MAPT gene is related to FTD but not to ALS, and ALS genes such as SOD1 and FUS are rarely linked to FTD), and some mutations that cause TDP-43 pathology are not common in the ALS-FTD presentation (Burrell et al., 2016). The complexity of the ALS-FTD continuum is represented in Figure 3.2.

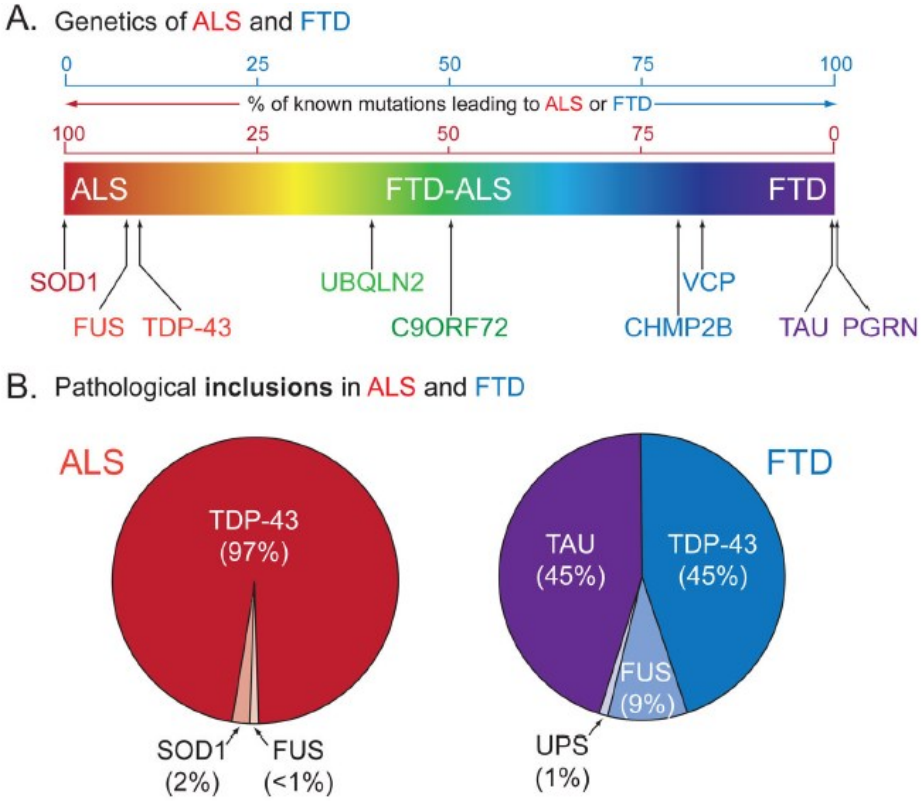

Figure 3.2. Clinical, genetic and pathological overlap between ALS and FTD. From Ling, Polymenidou, and Cleveland (2013)

Cognitive and behavioural symptoms in ALS may precede, co-appear or follow the onset of the motor symptoms. These different clinical phenotypes within the ALS-FTD continuum are explained by different patterns of progression of TDP-43 depositions in the brain, first affecting the motor neurons in the spinal cord and brainstem in ALS, and frontotemporal structures in FTLD (Burrell et al., 2016; van Es et al., 2017). The diagnosis of ALS-FTD as well as the presence of executive dysfunction in ALS patients have been associated with shorter survival (Elamin et al., 2011). In fact, the median survival of ALS-FTD have been described as shorter by approximately a year than the median survival of ALS (Tsermentseli et al., 2012).

3.1.1. Revised Diagnostic Criteria of Frontotemporal Syndromes in ALS

Given the broad range of deficits of varying severity resulting from frontotemporal dysfunction that can be associated with ALS, this disease is now considered a frontotemporal spectrum disorder, namely ALS-FTSD. In this context, revised criteria for the diagnosis of frontotemporal syndromes in ALS have been recently published (Strong et al., 2017). This international guideline, which is a revision of a previously published one (Strong et al., 2009), was formulated by members of a panel of experts following a consensus conference where international content specialists were invited to discuss areas of relevance.

This revised guideline includes three diagnostic axes to define the diagnosis of ALS-FTSD: Axis I defines the motor neuron disease variant, Axis II defines cognitive/behavioural dysfunction, and Axis III defines the existence of extra non-motor manifestations. Table 3.1 displays diagnostic criteria for cognitive and behavioural syndromes (Axis II). Memory dysfunction is excluded as this rarely occurs in isolation in ALS and there is a lack of consensus about its nature, strongly believed to be related to executive dysfunction (Strong et al., 2017). These revised criteria also include three levels of complexity or depth in the assessment of cognition and behaviour, ranging from clinic-based screens to in-depth neuropsychological evaluations, and recommendations on testing paradigms are provided.

A main difference between this revised diagnostic criteria and previous consensus criteria is the inclusion of language impairment for the diagnosis of cognitive impairment in ALS, even though it is acknowledged that the study of language in ALS is work in progress (Strong et al., 2017). Also, the presence of language impairment that meets criteria for PPA in conjunction with ALS is regarded as ALS-FTD. It is currently proposed that language profiles in ALS-FTD, in several instances, resemble the linguistic phenotypes represented by the PPA subtypes, mainly nfvPPA (Bak, O'Donovan, Xuereb, Boniface, & Hodges, 2001; Catani et al., 2004; Coon, Sorenson, Whitwell, Knopman, & Josephs, 2011; Lomen-Hoerth, 2004; Oh et al., 2014) and svPPA (Coon et al., 2011; S. H. Kim et al., 2009; Lomen-Hoerth, 2004; Oh et al., 2014). Since PPA is one of the clinical entities of FTD, it is not unexpected that this presentation is also observed in combination with ALS. Ubiquitin inclusions are the most frequent pathology in svPPA, and have also been observed in nfvPPA and, to a lesser degree, in lvPPA (M. Grossman, 2010).

A recent study highlights, however, that language-variants of FTD have been rarely linked with ALS (Saxon, Harris, et al., 2017), and that ALS-FTD patients are actually characterised by a mixed neuropsychological presentation of behavioural and language decline, with the presence of grammatical processing and sentence comprehension deficits (Saxon, Thompson, et al., 2017). These language deficits correlate with inferior frontal gyrus and anterior insula atrophy (Kamminga et al., 2016). Either way, the presence of language impairment seems to be a significant characteristic of the neuropsychological presentation of ALS.

Table 3.1. Diagnostic classification of frontotemporal syndromes in ALS. From Strong et al. (2017).

Frontotemporal Syndrome	Diagnostic Criteria
ALSci (ALS with cognitive impairment)	A diagnosis of ALSci depends on evidence of either executive dysfunction or language dysfunction, or a combination of the two. *Executive Impairment* [a] ▪ Impairment on phonemic verbal fluency (after controlling for motor/speech impairment) OR ▪ Impairment on two other non-overlapping tests of executive function (may include social cognition) *Language Impairment* [a] ▪ Impairment on two non-overlapping language tests (which could include pragmatic function)
ALSbi (ALS with behavioural impairment)	A diagnosis of ALSbi depends on informant collateral and clinical observation, and requires: [b] ▪ Identification of apathy (with or without other behaviour change) OR ▪ Meeting at least two non-overlapping supportive diagnostic features from bvFTD diagnostic criteria (Appendix A, page 344; Rascovsky et al., 2011).
ALScbi (ALS with cognitive and behavioural impairment)	A diagnosis of ALScbi requires fulfilling diagnostic criteria for: ▪ ALSci AND ▪ ALSbi
ALS-FTD	A diagnosis of ALS-FTD requires: ▪ Evidence of progressive deterioration of behaviour and/or cognition by observation or history, AND ▪ The presence of at least three of the behavioural/cognitive symptoms outlined by Rascovsky et al. (2011). OR ▪ The presence of at least two of those behavioural/cognitive symptoms, together with loss of insight [c] and/or psychotic symptoms, OR ▪ The presence of language impairment meeting criteria for semantic variant or nonfluent variant PPA, as defined by Neary et al. (1998; Appendix C, pages 347-349) or Gorno-Tempini et al. (2011; Appendix B, pages 345-346). This may co-exist with behavioural/cognitive symptoms as outlined above.

[a] Impairment on individual measures is defined as a score falling below the 5th percentile compared to age- and education-matched norms. Deficits must not be accounted for by premorbid intellectual function or native language. Selected measures must control for the effect of bulbar and motor dysfunction. On longitudinal follow-ups, a decline from baseline of at least 1.5 standard deviations is considered to indicate new impairment, but the effect of repeated testing on performance that may mask cognitive decline must be evaluated.

[b] Behavioural impairment must not be accounted for by the motor limitations of ALS, a psychological reaction to the diagnosis, a premorbid personality disorder or comorbid psychiatric disorder (e.g. anxiety or depression), or pseudobulbar affect.

[c] Loss of insight must be established by comparing patients' and informants' reports, which may require clinical opinion.

3.2. The Study of Language in ALS: A Systematic Review

In ALS, the study of language was initially confined to the use of non-standardised tasks, based on performance on the Verbal IQ from Wechsler Adult Intelligence Scales (WAIS), or based on the language sections from quick cognitive screens (See Strong, Grace, Orange, & Leeper, 1996 for a review). As per above-described Strong criteria, language dysfunction is now recognised as one of the features that defines ALSci, and this is based on the recent observation of ALS patients who exhibit language impairment but have intact executive function (Ash et al., 2015; Consonni et al., 2016; Taylor et al., 2013). Notwithstanding these studies, the impairment of language in ALS seem to remain under-investigated (Abrahams, 2013).

The purpose of this section is to generate a systematic review of extant neuropsychological findings of language disturbance in ALS, to analyse the findings in the context of relevant methodological factors, and to identify new perspectives required to fully explore this neglected area of cognition in ALS.

While it is acknowledged that language dysfunction is relevant throughout ALS-FTSDs, this review aims to investigate language findings in ALS patients not meeting criteria for dementia. The rationale for keeping this review confined to this particular population within ALS-FTSDs is that this is the population of interest of this work. The main aim of this project is to characterise language dysfunction in ALS patients not meeting criteria for dementia. By keeping this review constrained to this population, we aim to give a more concise account of the language impairments that are characteristic of the non-demented end of the frontotemporal spectrum of presentations in ALS. However, the need to explore language dysfunction within ALS-FTD patients is acknowledged as a natural continuation of the characterisation of language dysfunction in the ALS-FTSD.

For the purposes of clarity, from now on the term ALS is used to refer to ALS patients not meeting criteria for the diagnosis of FTD, and the term ALS-FTD designates those ALS patients meeting such criteria.

3.2.1. Methods

MEDLINE, PsychINFO and Science Direct databases were searched in order to identify articles of language function in ALS published in English in the period from January 1975 to August 2017. Search terms used were “Amyotrophic Lateral Sclerosis” or “Motor Neurone Disease” in the title, in combination with “neuropsycho*”, “cogniti*”, “language” or “aphasia” in the title or abstract. Relevant references in revised papers (i.e. hand search) were also considered for inclusion.

Quantitative observational studies evaluating language as the outcome measure using standardised measures of cognitive performance in an ALS sample or a combined ALS and ALS-FTD sample were included. Both cross-sectional and longitudinal studies were considered. Included studies measured the outcome of interest 'language' by means of (a) verbal expressive language, (b) verbal fluency, (c) confrontation naming, (d) semantic processing, (e) auditory comprehension, (f) action verb processing vs object noun processing, and (g) reading and writing. Studies were excluded if they assessed a linguistic aspect not outlined above, if these solely assessed an ALS-FTD sample, or if these were other reviews or meta-analysis. Studies employing non-standardised measures were only considered if they presented relevant new information, and studies restricted to the use of screening tools were not included. Conference abstracts and reports from meetings were included only if they presented new relevant information.

Study selection process, including the three stages of screening, eligibility and inclusion, is detailed in the systematic review flow diagram (Figure 3.3). The following information was extracted from studies meeting inclusion criteria: (a) authors, (b) title, (c) year, (d) study design, (e) patient sample size, (f) incident vs prevalent sample, (g) clinic-based vs population-based sample, (h) inclusion of control group and sample size of the same where appropriate, (i) number of language tests included and details of the same, and (j) utilisation of corrections for motor disability. Risk of bias was evaluated considering relevant methodological factors, summarised in Table 3.2. Data is presented here by means of a systematic narrative synthesis of findings.

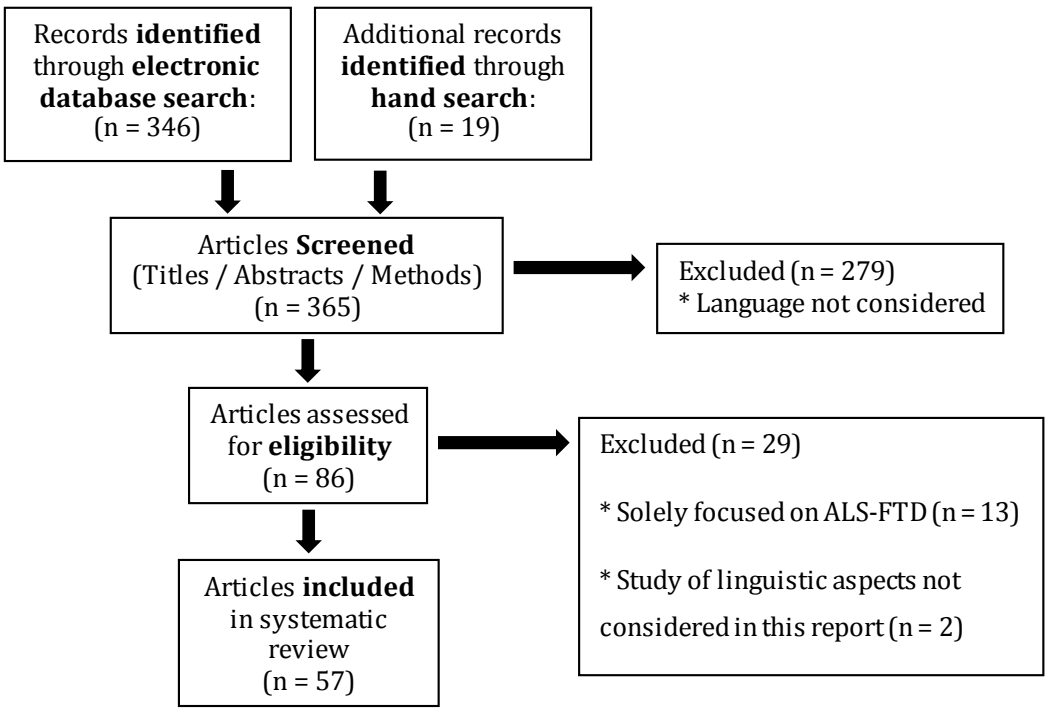

Figure 3.3. Flow diagram of systematic review of language studies in ALS

Table 3.2. Methodological characteristics of the research papers included in the systematic review.

	ALS Patients (n)	Incident vs Prevalent sample	Clinic-based vs Population-based sample	Control Group	Number of language tests included[a]	Corrections for motor disability applied
Abe et al. 1997	26	NS	Clinic-based	Yes (n=26)	2	No
Abrahams et al. 1995, 1996	12	NS	Clinic-based	Yes (n=6)	1	Yes
Abrahams et al. 1997	52	NS	Clinic-based	Yes (n=28)	1	Yes
Abrahams et al. 2000	22	NS	Clinic-based	Yes (n=25)	5	Yes
Abrahams et al. 2004	28	NS	Clinic-based	Yes (n=18)	3	Yes
Abrahams, Goldstein et al. 2005	20	NS	Clinic-based	Yes (n=18)	2	Yes
Abrahams, Leigh & Goldstein, 2005	23	NS	Clinic-based	Yes (n=20)	3	Yes
Ash et al. 2014, 2015	26	NS	Clinic-based	Yes (n=19)	1	Yes
Bak et al. 2001	6	NS	Clinic-based	Yes (n=20)	3	N/A
Cobble et al. 1998	9	NS	Clinic-based	Yes (n=9)	6	No
Consonni et al. 2013	23	NS	Clinic-based	Yes (n=29)	2	Yes
Consonni et al. 2016	71	NS	Clinic-based	No	3	No
Cousins et al. 2017	28	NS	Clinic-based	Yes (n=36)	4	Yes
Donaghy et al. 2009	44	NS	Clinic-based	Yes (n=45)	2	Yes
Elamin et al. 2013	186	Incident	Population-based	Yes (n=110)	2	Yes
Frank et al. 1997	74	NS	Clinic-based	Yes (n=56)	1	No
Gallassi et al. 1985	22	NS	Clinic-based	Yes (n=36)	3	No
Gordon et al. 2010	50	NS	Clinic-based	No	2	No
Grossman et al. 2008	34	NS	Clinic-based	No	4	No
Hanagasi et al. 2002	20	NS	Clinic-based	Yes (n=13)	2	No
Hartikainen et al. 1993	24	NS	Clinic-based	Yes (n=26)	1	No
Ichikawa et al. 2008	19	NS	Clinic-based	No	1	N/A
Kamminga et al. 2016	20	NS	Clinic-based	Yes (n=23)	1	N/A

[a] Verbal fluency paradigms are considered as one test.

Abbreviations: Not Specified (NS)

Table 3.2 (continued). Methodological characteristics of the research papers included in the systematic review.

	ALS Patients (n)	Incident vs Prevalent sample	Clinic-based vs Population-based sample	Control Group	Number of language tests included[a]	Corrections for motor disability applied
Kew et al. 1993	16	NS	Clinic-based	Yes (n=16)	2	Yes
Kilani et al. 2004	19	NS	Clinic-based	Yes (n=19)	1	N/A
Lepow et al. 2010	49	NS	Clinic-based	Yes (n=25)	2	No
Leslie et al. 2015	17	NS	Clinic-based	Yes (n=26)	2	N/A
Lomen-Hoerth et al. 2003	100	NS	Clinic-based	No	1	No
Ludolph et al. 1992	17	NS	Clinic-based	Yes (n=17)	1	Yes
Mantovan et al. 2003	12	NS	Clinic-based	Yes (n=20)	3	Yes
Massman et al. 1996	146	NS	Clinic-based	No	2	Yes
Montuschi et al. 2015	183	Incident	Population-based	Yes (n=127)	2	No
Moretti et al. 2002	14	NS	Clinic-based	Yes (n=15)	4	N/A
Oh et al. 2014	318	Prevalent	Population-based	No	3	No
Papeo et al. 2015	21	NS	Clinic-based	Yes (n=14)	1	N/A
Pettit et al. 2013	30	NS	Clinic-based	Yes (n=30)	1	Yes
Phukan et al. 2012	160	Incident	Population-based	Yes (n=110)	2	Yes
Rakowicz & Hodges 1998	18	Incident	Population-based	Yes (n=24)	6	No
Ringholz et al. 2005	279	NS	Clinic-based	Yes (n=129)	6	No
Rippon et al. 2006	31	NS	Clinic-based	Yes (n=80)	4	No
Roberts-South et al. 2012	16	NS	Clinic-based	Yes (n=12)	6	No
Robinson et al. 2006	19	Incident	Clinic-based	Yes (n=8)	1	N/A
Sarro et al. 2011	16	NS	Clinic-based	No	1	No
Satoh et al. 2009	16	NS	Clinic-based	No	3	No
Schreiber et al. 2005	52	NS	Clinic-based	No	1	Yes
Strong et al. 1999	13	NS	Clinic-based	Yes (n=5)	13	No
Talbot et al. 1995	19	NS	Clinic-based	Yes (n=10)	3	No

[a] Verbal fluency paradigms are considered as one test.

Abbreviations: Not Specified (NS)

Table 3.2 (continued). Methodological characteristics of the research papers included in the systematic review.

	ALS Patients (n)	Incident vs Prevalent sample	Clinic-based vs Population-based sample	Control Group	Number of language tests included[a]	Corrections for motor disability applied
Taylor et al. 2013	51	Prevalent	Clinic-based	Yes (n=35)	12	Yes
Tsermentseli et al. 2015	26	Prevalent	Clinic-based	Yes (n=26)	9	Yes
Tsuji-Akimoto et al. 2010	18	NS	Clinic-based	Yes (n=16)	5	N/A
Van Der Hulst et al. 2010	21	NS	Clinic-based	Yes (n=17)	2	N/A
Wicks et al. 2008	12	NS	Clinic-based	No	2	Yes
Yabe et al. 2012	10	NS	Clinic-based	Yes (n=14)	2	N/A
York et al. 2014	36	NS	Clinic-based	Yes (n=13)	5	N/A
Yoshizawa et al. 2014	25	NS	Clinic-based	No	1	N/A

[a] Verbal fluency paradigms are considered as one test.
Abbreviations: Not Specified (NS)

PRISMA Reporting Guidelines (Liberati et al., 2009) were consulted to complete this systematic review. Detailed systematic review protocol based on the PRISMA-P guideline (Moher et al., 2015) is available in Appendix E (pages 352-355).

3.2.2. Results

From the 365 studies assessing cognition in ALS identified through the systematic search, 279 were excluded as language was not assessed (Figure 3.3). Sample sizes of the 57 studies included on the systematic review (Table 3.2) ranged from 6 to 279 patients (mean = 46.61; median = 23). 19 studies (33%) had a sample size of n ≥ 30. Although the type of sample was unspecified in the majority of studies, only five studies (9%) explicitly specified that incident samples were included. Most studies recruited clinic-based samples (n=52, 91%) and only five (9%) were population-based. The majority of studies (n=45, 79%) included a control group and 21 studies (37%) stated the use of adaptations to control for motor disability. Eight studies (14%) assessed language longitudinally, with durations from baseline to follow-up assessments ranging from 4 to 15 months. It is important to consider that a number of studies consist of overlapping samples.

Neuropsychological findings regarding language changes in ALS extracted from articles included in this systematic review are described below. Results are structured around the seven subdomains considered as outcomes of interest. Subsequently, results across studies are integrated and analysed.

Verbal Expressive Language

Communication deficits in ALS have frequently been attributed to motor speech disability. Although rare, apraxia of speech has been reported in ALS (Duffy, Peach, & Strand, 2007). Changes in expressive language have seldom been investigated.

Strong et al. (1999) analysed discourse samples of spoken (and written) outputs on protocols of topic-directed interviews and on the Cookie Theft picture description task from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983) and reported that ALS patients produced significantly fewer self-corrected utterances in comparison to healthy controls at a six-month follow-up assessment. Semantic paraphasias, substitutions of free grammatical morphemes and semantically deviant sentences were observed.

Roberts-South, Findlater, Strong, and Orange (2012) used the Cookie Theft picture description task to assess discourse production in ALS. They included measures of both discourse productivity (i.e. length of utterances, total words and total utterances) and discourse content (i.e. accuracy and relevance to topic or picture). In comparison to controls, measures of discourse content (i.e. percent of total correct information units) were significantly lower for ALS patients and this pattern was maintained longitudinally. Although ALS participants, as a group, performed similarly to controls on measures of discourse productivity, a subgroup of patients may exist with discourse productivity deficits. A decline over time on mean length of utterances was also observed for some participants. No differences were observed in the total of words produced between patients and controls, suggesting that this deficit was due to reduced language complexity rather than a speech disturbance. The number of total words and utterances varied within patients and across time points, with some patients producing significantly fewer words and utterances than controls and others producing significantly more words, the latter probably reflecting tangential, empty discourse or phrase reformulations.

Ash et al. (2015) used a relatively unknown story from a word-less children's picture book to assess sentence production in ALS. In comparison to controls, patients produced fewer words and utterances and fewer grammatically well-formed sentences, with 42% of the sample scoring two standard deviations below the control mean on percentage of grammatically well-formed sentences. Errors such as incomplete sentences, missing determiners or verb phrase errors were observed in all but one patient. Grammatical impairment was observed in patients without executive deficits, suggesting that this was likely to be independent from frontal-executive dysfunction. These deficits significantly correlated with grey matter atrophy in inferior frontal, anterior temporal and left striatal regions. The same group (Ash et al., 2014) also reported discourse adequacy deficits, assessed in terms of ability to organise narrative discourse, accuracy of the content, connectedness, and theme maintenance, which was related

to executive dysfunction and was correlated with grey matter atrophy in the right dorsolateral prefrontal and bilateral interior frontal cortex. Gallassi et al. (1985) assessed grammatical skills in ALS using a sentence construction task from the Mental Deterioration Battery (Caltagirone, Gainotti, Masullo, & Miceli, 1979) and described significantly poorer performance on the ALS sample in comparison to healthy controls. Tsermentseli et al. (2015) corroborated the relationship between syntactic processing deficits and impaired connected speech production. Compared to controls, ALS patients with syntactic processing deficits produced significant lower mean number of words and length of utterances, higher number of distortions, incomplete sentences and semantic errors, and lower mean duration of the narrative on the Cookie Theft picture description task.

A minority of studies have evaluated repetition in ALS, reporting preserved abilities in the patient group compared to healthy controls (Rippon et al., 2006; Tsuji-Akimoto et al., 2010).

Verbal Fluency

Verbal fluency deficits have been reported in most cognitive studies in ALS, mainly using phonemic paradigms (Abe et al., 1997; Abrahams et al., 1997; Abrahams et al., 2004; Ash et al., 2014; Ash et al., 2015; Consonni et al., 2016; Donaghy et al., 2009; Frank, Haas, Heinze, Stark, & Munte, 1997; Gallassi et al., 1985; Gordon et al., 2010; Hanagasi et al., 2002; Kew et al., 1993; Lepow et al., 2010; Lomen-Hoerth et al., 2003; Ludolph et al., 1992; Mantovan et al., 2003; Massman et al., 1996; Oh et al., 2014; Phukan et al., 2012; Ringholz et al., 2005; Schreiber et al., 2005; Taylor et al., 2013; York et al., 2014). In the first population-based study of cognition in ALS (Phukan et al., 2012), phonemic verbal fluency was abnormal in 94% of patients with executive dysfunction, in 30% of patients with cognitive impairment but no executive dysfunction, and in 10% of patients with no other cognitive abnormality.

Various paradigms have been used to assess phonemic verbal fluency in ALS, including the FAS test (Benton, 1967), the Controlled Oral Word Association Test (Lezak, 2004), or written fluency tasks applied in case of severe dysarthria or anarthria. However, when assessing verbal fluency in ALS, the different nature of spoken versus written paradigms must be considered. While spoken verbal fluency paradigms are carried out through phonological processes, written verbal fluency tasks also involve orthographic processing.

Studies have used different methods to control for the effect of motor disturbances in verbal fluency measures. For example, by checking that other tests affected by bulbar function yield normal results (Ludolph et al., 1992) or that motor speed does not correlate with the number of words produced (Kew et al., 1993). The Verbal Fluency Index (VFI) was introduced by Abrahams et al. (1995) as a standardised method to accommodate for motor disability. The VFI is defined as: [(*time given to generate as many words as possible - time taken to read or copy all*

generated words) ÷ total number of correct words given]. This equation calculates the average time taken to generate a new word. The utility of the VFI was demonstrated in a subsequent study, in which significant differences between patients and controls were identified in a written verbal fluency task when considering total number of words generated but not when using the VFI (Abrahams et al., 2000). These results indicate the value of accommodating for motor disability when assessing verbal fluency in ALS. Abrahams et al. (2000) also introduced a new phonemic verbal fluency condition (restricted to four-letter long words) and demonstrated that after correcting for motor disability using the VFI, this restricted condition was more sensitive than the standard condition to verbal fluency deficits. The four-letter long condition, which also relies on strategic search in input lexicons, requires extra executive-mediated processes such as continuous monitoring that the words meet the length constrain, and the frequency of four-letter long words starting with a specific letter is also lower.

The nature of verbal fluency deficits in ALS was also explored by assessing intrinsic response generation, phonological loop function and simple word retrieval abilities (Abrahams et al., 2000). Because ALS patients performed at similar levels to healthy controls on other tasks assessing these last two abilities, the authors concluded that verbal fluency deficits are a result of higher order executive dysfunction of intrinsic word generation rather than a dysfunction of the phonological loop or a simple word retrieval deficit.

Category fluency tasks have been less frequently used in the study of cognition in ALS. Although some studies have demonstrated normal performance on semantic verbal fluency paradigms (Abrahams et al., 2004; Ash et al., 2014; Ash et al., 2015; Hartikainen, Helkala, Soininen, & Riekkinen, 1993), most studies have reported significantly lower performance of ALS patients compared to controls (Abe et al., 1997; Abrahams, Goldstein, et al., 2005; Abrahams et al., 2000; Consonni et al., 2013; Gordon et al., 2010; Hanagasi et al., 2002; Lepow et al., 2010; Oh et al., 2014; Rippon et al., 2006; Taylor et al., 2013). These results have been observed for the category animals, although not for other semantic categories such as colours, fruits or towns (Abrahams et al., 2000). A further study divided ALS patients into two subgroups (impaired vs unimpaired) based on performance on a letter fluency task. Those with letter fluency deficits performed significantly poorer on a measure of category verbal fluency (Abrahams, Goldstein, et al., 2005).

Lepow et al. (2010) analysed two component processes in verbal fluency, namely semantic clustering and switching. Clusters are sets of words related by meaning, stored and accessed through the left anterior temporal cortex. Switching consists of swapping from cluster to cluster, which is an executively-mediated ability supported by lateral prefrontal regions. For phonemic and semantic verbal fluency conditions, cognitively intact ALS patients generated fewer number of clusters and fewer words per cluster compared to healthy controls, which

indicates temporal lobe involvement. In comparison to healthy controls and cognitively intact ALS patients, cognitively impaired ALS patients and ALS-FTD patients generated a fewer number of clusters and switches. These results were interpreted by the authors as involvement of anterior temporal areas in ALS, with increasing involvement of frontal areas as patients' overall cognitive function decreases.

Verbal Fluency - Longitudinal Findings

The first longitudinal study assessing verbal fluency in ALS showed evidence of deficits on the Controlled Oral Word Association Test in a small cohort of patients which developed after a 6-month interval (Strong et al., 1999). In this study, impaired scores on the Thurstone Written Word Fluency (Thurstone, 1938) were already present on the first assessment period. While some studies failed to detect deterioration on verbal fluency scores assessed longitudinally (Abrahams, Leigh, & Goldstein, 2005; Schreiber et al., 2005) a significant deterioration of semantic verbal fluency (animals) on a longitudinal study of a 6-month period has been reported (Gordon et al., 2010).

Verbal Fluency - Functional Neuroimaging

Functional neuroimaging has been used to investigate anatomical changes in verbal fluency deficits in ALS. Ludolph et al. (1992) investigated brain metabolism using positron emission tomography (PET) and observed decreased cerebral glucose utilisation in frontal, fronto-basal and superior parieto-occipital regions compared to controls, which correlated with performance on a letter fluency task. Kew et al. (1993) used a PET activation motor paradigm which contrasted patterns of activation during freely selected versus stereotyped joystick movements with the right hand. They reported decreased cerebral blood flow responses in the medial prefrontal cortex, anterior cingulate cortex, right parahippocampal gyrus and the anterior thalamic nuclear complex in patients compared to controls, with significant and extensive involvement in patients who were impaired on a written fluency test. Moreover, abnormal activation in the anterior thalamic nuclear complex was significantly correlated with verbal fluency scores. Reduced cerebral blood flow at rest in the anterior cingulate cortex of patients was also described. These two studies speculated that verbal fluency deficits in ALS involve subcortical circuits. Abrahams et al. (1996) investigated abnormalities of frontal activation previously reported in PET studies using a verbal fluency activation paradigm, based on the assumption that verbal fluency paradigms produce relative activation of the left dorsolateral prefrontal cortex, the anterior cingulate gyrus and Broca's area in healthy subjects (Abrahams et al., 1996; Abrahams et al., 1995). These authors divided the ALS sample into two groups (impaired vs unimpaired verbal fluency). The activation paradigm used contrasted cerebral blood flow during a word generation and a word repetition condition to ensure that speech components involved in these two conditions were matched. When performance of ALS

patients with verbal fluency deficits was compared to controls, impaired cerebral blood flow activation was observed bilaterally in the dorsolateral prefrontal cortex, lateral and medial premotor cortex, insular cortex and the thalamus. In ALS patients with no evidence of verbal fluency impairment, the areas of reduced activation in comparison to controls were less extensive and included the right dorsal prefrontal cortex, the left middle and superior temporal gyrus and the inferior parietal lobe. These results confirmed the involvement of the dorsolateral prefrontal cortex in verbal fluency deficits in ALS. The same group explored the pattern of anatomical changes in ALS patients with verbal fluency deficits using automated volumetric voxel-based analysis of grey and white matter densities of Magnetic Resonance Imaging (MRI: Abrahams, Goldstein, et al., 2005). Changes in extra-motor white matter volumes were described in regions that connect the frontal and temporal lobes to other cortical regions, specifically the occipito-frontal fasciculus, the cingulum, the superior longitudinal fasciculus and regions of the anterior commissure. ALS patients who did not present with verbal fluency deficits also showed significant changes in white matter volumes, although these were less extensive. Grey matter changes were not significant in this sample, suggesting that white matter changes can also contribute to cognitive deficits in ALS. Diffusion Tensor (DT) tractography has also been used to reconstruct in vivo white matter tracts in ALS and investigate its association with cognitive changes (Sarro et al., 2011). A significant correlation between verbal fluency deficits and left cingulum fractional anisotropy was reported. Reduced white matter adjacent to Broca's area and the anterior prefrontal cortex which significantly correlated to verbal fluency deficits in ALS has also been described (Pettit, Bastin, & Abrahams, 2013).

Confrontation Naming

Confrontation naming tasks such as the Boston Naming Test (BNT: E. Kaplan, Goodglass, & Weintraub, 1983) or the Graded Naming Test (GNT: McKenna & Warrington, 1983) have also been widely used in ALS to assess word retrieval abilities. Most studies assessing confrontation naming have shown decreased abilities in ALS (Abrahams et al., 2004; Abrahams, Goldstein, et al., 2005; Cobble, 1998; Consonni et al., 2016; Donaghy et al., 2009; Gordon et al., 2010; Hanagasi et al., 2002; Kilani et al., 2004; Leslie et al., 2015; Mantovan et al., 2003; Massman et al., 1996; Oh et al., 2014; Rakowicz & Hodges, 1998; Ringholz et al., 2005; Rippon et al., 2006; Strong et al., 1999; Taylor et al., 2013; York et al., 2014). The presence of phonemic and semantic paraphasias has also been reported (Mantovan et al., 2003; Strong et al., 1999). Donaghy et al. (2009) used a test of premorbid intellectual functioning, the National Adult Reading Test (Nelson & Willison, 1991), as a covariate and showed that this impairment persisted when corrected for premorbid ability. However, it must also be noted that a number of studies have shown no differences between ALS and controls using confrontation naming

tasks (Abe et al., 1997; Abrahams, Leigh, et al., 2005; Abrahams et al., 2000; Ash et al., 2014; Kew et al., 1993; Talbot et al., 1995), while naming from auditory description has not been assessed in ALS.

Confrontation Naming - Longitudinal Findings

Elamin et al. (2013) reported emerging word retrieval deficits at follow-up testing using the Boston Naming Test on initially cognitively intact ALS patients and a significant deterioration in patients who had previously presented with cognitive difficulties. Abrahams, Leigh, et al. (2005) showed evidence of slower word retrieval times over a 6-month period on a sentence completion task accommodated for bulbar disability, although this same cohort showed no deficits on a confrontation naming task and there was no evidence of deterioration on verbal fluency measures at follow-up. Gordon et al. (2010) did not find significant deterioration on the Boston Naming Test over a six-month period, although as previously described this cohort showed significant deterioration on semantic verbal fluency (animals). Another report failed to report significant lower scores at 6 and 12 months follow-up on the Boston Naming Test (Kilani et al., 2004).

Confrontation Naming - Functional Neuroimaging

Functional imaging studies have included confrontation naming paradigms in addition to verbal fluency. Abrahams et al. (2004) carried out a functional MRI (fMRI) study with ALS participants using two overt word retrieval activation paradigms, a verbal fluency paradigm and a conformation naming paradigm. These authors had previously described the pattern of activation in fMRI in healthy subjects while performing these two word retrieval tasks (Abrahams et al., 2003). The verbal fluency paradigm activated the left middle frontal gyrus, inferior frontal gyrus, anterior cingulate gyrus and medial prefrontal cortex. Activation of the middle prefrontal gyrus, anterior cingulate gyrus and prefrontal cortex was related to executive and attentional demands of the task, while the inferior frontal gyrus was involved in the language components of the task, including production, word retrieval and phonological processing. Confrontation naming activated the left inferior frontal gyrus (related to articulatory, phonological and semantic processing of the task), inferior temporal gyrus, and middle and inferior occipital gyrus (related to the occipito-temporal ventral pathway of visual information processing) in healthy controls. Using this fMRI paradigm in ALS patients, Abrahams et al. (2004) demonstrated that abnormal cerebral activation was not specific to the letter fluency paradigm. ALS patients also presented with significantly decreased activation on the confrontation naming paradigm. In the verbal fluency task, reduced activation in ALS patients was observed in the middle and left inferior frontal gyrus, the right anterior cingulate gyrus, the left middle temporal gyrus, precuneus and left interior parietal lobe. Impaired activation in the confrontation naming paradigm was reported in the inferior frontal gyrus,

right cingulate gyrus, left middle and superior temporal gyrus, left middle occipital lobes and cuneus. This pattern of decreased activation (involving the inferior frontal gyrus and temporal and parietal association areas) is likely to represent a pure language rather than an executive impairment in ALS. This pattern of abnormal activation was observed in the context of normal performance on the same task in neuropsychological testing, suggesting that the cerebral structures may be affected before deficits are observed clinically. [11C]-flumazenil PET has been used to identify regions of neuronal dysfunction in ALS and to correlate with performance on word retrieval tasks (Wicks et al., 2008). Poorer performance on a letter verbal fluency task significantly correlated with reduced [11C]-flumazenil binding in the right inferior frontal gyrus, superior temporal gyrus and anterior insula. In the case of the GNT, this reduction was observed in the left inferior and middle frontal gyrus, as well as the left cuneus, related to basic visual processing abilities required to perform such task.

Semantic Processing

Very few studies have investigated semantic processing in ALS. Rakowicz and Hodges (1998) reported significantly lower performance of ALS patients in comparison to healthy controls on the Pyramids and Palm-trees Test (Howard & Patterson, 1992), although no patient was impaired on the task. ALS patients were unimpaired on the word-picture matching task from the Hodges' semantic battery (Hodges, Salmon, & Butters, 1991). Conversely, Cobble (1998) reported impaired performance on a subgroup of ALS patients with severe language deficits on measures of semantic processing such as the Auditory Synonym Judgement, the Written Synonym Judgement and the Word Semantic Association subtests from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA: Kay et al., 1996). Taylor et al. (2013) included various tests assessing semantics in a large clinic-based study of cognition in ALS and showed that a proportion of ALS patients were impaired in such tasks. Specifically, 14% were impaired on the Pyramids and Palm-trees Test, 23% on the Category Specific Names Test (McKenna, 1998) and 19% on Judgement of Synonyms. Contrary to these results, Mantovan et al. (2003) used a 10-question semantic anomalies detection task and reported no impairment in the ALS group.

The Peabody Picture Vocabulary (Dunn & Dunn, 1997) and the British Picture Vocabulary Scale II (Dunn, Dunn, Whetton, & Burley, 1997) have also been used to assess single word comprehension in ALS, with mixed results (Roberts-South et al., 2012; Robinson et al., 2006; Strong et al., 1999; Taylor et al., 2013).

Leslie et al. (2015) specifically investigated semantic processing in ALS using the Sydney Battery (Savage et al., 2013). These authors demonstrated that ALS patients were significantly impaired in comparison to healthy controls on naming and comprehension subtests, but not on the semantic association task, although 17.6% of the ALS sample was impaired on the

semantic task. The authors also created a Semantic Knowledge Composite score using the subtests Word Comprehension and Semantic Knowledge from the Sydney Battery, and word comprehension from the Addenbrooke's Cognitive Examination-Revised (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). Thirty-three percent of the ALS sample was impaired on this composite score. A Naming Composite Score significantly correlated with right temporal and right frontal atrophy. Right lateralisation of semantic deficits in ALS in this study is explained by the use of visual stimuli as the right temporal lobe is crucial for non-verbal semantic storage.

Auditory Comprehension

Tests of language comprehension have not been systematically included in neuropsychological batteries in ALS studies. However, the Token Test (De Renzi & Vignolo, 1962), which assesses verbal comprehension of commands of increasing complexity also requiring preserved phonological working memory and syntactical abilities, has been used by some authors. Talbot et al. (1995) compared performance on the Token Test between ALS patients and healthy controls and described a ceiling in performance in the control group in comparison to occasional errors in the ALS sample. However, these authors observed that patients with poorer performance on the Token Test, with mostly perseverative and inattentive errors, also performed poorly on a test of executive functioning assessing abstract reasoning and mental flexibility. They concluded that difficulties observed on the Token Test were likely due to executive impairment rather than a pure linguistic deficit. Mantovan et al. (2003) reported that 25% of their ALS sample showed impairment on the Token Test, and Tsermentseli et al. (2015) reported significantly poorer performance of ALS patients in comparison to controls. Finally, the Token Test was also used on a population-based study of cognition in ALS to classify patients in the domain of 'non-executive impairment'. Within this cohort, 5.5% of the sample met criteria for 'non-executive impairment' (Montuschi et al., 2015).

Other tests of auditory comprehension have been used to assess receptive language in ALS. Oh et al. (2014) carried out a large study of cognition in Korean population and reported that 7.9% of the sample who presented with cognitive impairment were impaired on the Korean version of the auditory comprehension task from the Western Aphasia Battery (Kertesz, 1982). A Japanese study reported similar findings (Tsuji-Akimoto et al., 2010). However, non-significant differences between ALS and healthy controls on a comprehension task from the Boston Diagnostic Aphasia Examination have also been reported (Rippon et al., 2006).

Auditory comprehension tasks have also been used to evaluate grammatical and syntactic comprehension in ALS. Rakowicz and Hodges (1998) reported lower performance of ALS patients compared to controls on a syntactic comprehension task, the Test of Reception of Grammar (Bishop, 1982). Impairments on this task were also observed on 35% of ALS patients by Taylor et al. (2013), on 25% by Kamminga et al. (2016), and significantly lower scores,

higher number of errors and fewer blocks completed by ALS patients were reported by Tsermentseli et al. (2015). In a study with Japanese population, 72% ALS patients were impaired on a similar auditory comprehension task (Yoshizawa et al., 2014). In comparison to non-reversible sentences, a higher number of errors were detected for reversible sentences, and for passive compared to active sentences. Cobble (1998) had also reported impaired sentence comprehension on the Auditory Sentence to Picture Matching task from the PALPA on three ALS patients with severe language deficits.

Moretti et al. (2002) described severe impairment in complex commands and syntactic comprehension tasks from the Bilingual Aphasia Test (Paradis & Canzanella, 1990) at a fifteen month follow-up assessment in an ALS sample with signs of bulbar palsy. This pattern of impairment was not observed in ALS patients without evidence of bulbar palsy.

Action Verb Processing vs Object Noun Processing

Selective deficits in processing of verbs in comparison to nouns have been shown in ALS on both comprehension and production tasks (Bak & Hodges, 2004; M. Grossman et al., 2008; Taylor et al., 2013; Tsermentseli et al., 2015; York et al., 2014). Taylor et al. (2013) used two picture-matching semantic tasks, the Pyramids and Palm-trees Test, limited to nouns and objects, and a parallel form developed to assess action verb processing, the Kissing and Dancing Test (Bak & Hodges, 2003). These authors demonstrated that 17% of ALS patients showed impairment in the verb-processing task in comparison of 13% of patients impaired on the noun-processing task. Tsermentseli et al. (2015) also showed significantly poorer performance of ALS patients in comparison to healthy controls on the Kissing and Dancing Test. M. Grossman et al. (2008) reported a specific action knowledge deficit in comparison to object knowledge in 72% of their sample. Significantly poorer performance on the action naming subtest from the Italian Battery for the Assessment of Aphasic Disorders (Miceli, Laudanna, Burani, & Capasso, 1994) was noted in ALSci compared to healthy controls, and in patients with lower motor neuron disease (Consonni et al., 2013). By contrast, some reports on action naming are reported to be unimpaired in ALS (Papeo et al., 2015; Roberts-South et al., 2012).

Impairment in action verb processing has been related to involvement of the motor cortex in ALS. Action and object knowledge were assessed using structural MRI in ALS (M. Grossman et al., 2008). Patients exhibited poorer performance on measures of action knowledge, and this correlated with motor and premotor cortex atrophy as well as with non-motor atrophy bilaterally in the dorsolateral prefrontal cortex and the inferior frontal cortex. Although atrophy in non-motor areas also correlated with measures of object knowledge, no correlation with motor areas was observed. The action knowledge deficit observed may relate to degeneration of the neural network that represents motor features of action concepts, which involve motor-related cortical areas named neocortical motor-associated regions.

While studying action verb processing, it is important to consider that verbs are syntactically complex and more abstract than nouns, relying more on grammatical and executive processes (Vigliocco et al., 2011). Impairments in processing of verbs in comparison to nouns could be driven by complexity rather than by the active content of verbs. To explore this, York et al. (2014) investigated three possible explanations for impaired verb processing in ALS, including (1) that verbs are grammatical anchors of sentences (and there is evidence of grammatical deficits in ALS), (2) that these are secondary to executive dysfunction as verb processing is highly executively-mediated due to the multiple grammatical and semantic components involved, or (3) that this is due to the involvement of motor-associated areas in ALS, which contain representations of motor-action words. Performance on measures of action knowledge has been previously correlated with performance on executive function tasks (Bak & Chandran, 2012), supporting that processing of verbs require greater executive demands. Grammatical comprehension measured using the Test of Reception of Grammar correlated with both action and object knowledge, suggesting that grammatical deficits may not account for such greater difficulties in action knowledge compared to object knowledge. York et al. (2014) sought to elaborate on each of these hypotheses by using different types of verbs (action verbs, e.g. walk; vs cognitive verbs, e.g. want; the last ones with higher grammatical and executive demands) in conjunction with two different types of nouns (concrete vs abstract) and two control groups, a disease control group (Parkinson Disease - PD spectrum disorder, an extrapyramidal motor disease with minimal motor cortex involvement) and a healthy control group. They found a specific deficit for action verbs in ALS which was related to motor-associated areas. By contrast, action verb processing in PD did not seem to relate to motor cortical areas, but was supported by cortical-subcortical connections, specifically with the basal ganglia (Cardona et al., 2013).

Cousins, Ash, and Grossman (2017) investigated verb production in ALS using the Cookie Theft picture description task. The authors differentiated between motor verbs (e.g. fall) and non-motor verbs (e.g. think), and within motor verbs, between verbs where the body is the agent (e.g. 'the boy grabs the cookie') or the recipient of the action (e.g. 'the boy is falling'). They hypothesised that motor verbs are associated with the motor system, especially those where the body is the active executor of the action (agent). Results indicated that ALS patients with a greater degree of motor impairment produced fewer agent verbs and more verbs where the body was the object of the action, compared to ALS patients with milder motor impairment. These results were associated with grey matter atrophy in premotor areas, which supports the involvement of the premotor cortex in action verb processing. An association between mild semantic or executive dysfunction and decreased recipient verb production was also observed, possibly due to the grammatical complexity of such verbs, where the identification of the agent is more difficult. In this paradigm, deficits with motor verbs in ALS are likely due to degradation

of motor areas for agent verbs and to cognitive dysfunction for recipient verbs. Finally, against the authors' expectations, the ALS patients with severe motor impairment produced a larger number of motor verbs than non-motor or stative verbs. The authors associated this to a concreteness effect as stative verbs, being more abstract, require more complex cognitive resources than motor verbs, which are more concrete.

Papeo et al. (2015) have pointed out that studies assessing the processing of nouns and verbs in ALS have used tests that do not differentiate between the semantic component (object vs actions) and the syntactic component (nouns vs verbs) of the words. The authors argued that if an impaired semantic-motor representation of an action is the cause of verb processing deficits in ALS, no difference between verb and noun processing should be observed if the two words are semantically related to a same motor representation. The authors used both object-nouns and action-verbs semantically related to the same motor representations (for instance, the object *pen* which is related to the action *writing*) and found that the ALS group performed better on naming and picture matching tasks for objects in comparison to actions. Poorer performance on processing of verbs versus nouns was equally observed for both patients and controls, suggesting that better performance on noun over verb processing is also characteristic of the normal population. Papeo et al. (2015) also evaluated the relationship between action processing and executive dysfunction, as executive function has been related to organisation of motor actions in a logical sequence of events. For this purpose, they used an action sequencing task and showed that patients performed significantly poorer than healthy controls. The authors speculated on a possible role of the precentral cortex in motor executive control system, related to performance on action sequencing.

Reading and Writing

The first evidence of writing errors in ALS was published in 1977 (J. H. Ferguson & Boller, 1977). Two patients with bulbar-onset ALS were reported with evidence agraphia, manifested by errors in spelling and syntactic writing. Cobble (1998) also reported impaired performance of a subgroup of ALS patients on a spelling subtest from the PALPA. Recently, Taylor et al. (2013) reported that 16% of their ALS patients were impaired on a spelling task, the Graded Difficulty Spelling Test (Baxter & Warrington, 1994).

A series of Japanese reports have described writing errors in ALS patients who did not fulfil criteria for the diagnosis of dementia, and who had no other language deficits and preserved reading abilities (Ichikawa, Takahashi, Hieda, Ohno, & Kawamura, 2008; Satoh, Takeda, & Kuzuhara, 2009; Tsuji-Akimoto et al., 2010). The written language in Japanese includes two types of characters. It is composed of *kana characters*, which represent a spoken syllable with one-to-one correspondence between sound and script. These type of characters are seen as equivalent to regular words in European languages. The *kanji characters*, which do not exist in

oral language, are a complex morphogram with different pronunciations, each one of these attached to a specific meaning which is learned during years of formal education. Kanji characters are comparable to irregular words in European languages. Impairments in kanji characters have been related to deficits in visual graphic image recall (Ichikawa et al., 2008; Satoh et al., 2009). The processing of Kanji characters has been related to the left inferior temporal and inferior frontal gyrus, in addition to occipito-temporal visual processing areas (Higuchi et al., 2015). The most common writing error reported by Japanese studies is omission of kana characters, related to difficulties of processing of phonological units (Satoh et al., 2009). Omission of kana characters, among other errors, were also reported by Ichikawa et al. (2008), who reviewed writing samples from the medical records of 19 patients with bulbar-onset ALS. They described writing errors in 15 out of 19 patients including both phonologic and morphologic errors in both kana and kanji characters. No semantic, apraxic or spatial deficits of writing were observed. It must be noted that most participants in this study (10 out of 15) subsequently developed dementia. Of the remainder, two maintained their feature of pure agraphia, suggesting that writing deficits in ALS can precede the development of dementia or can also exist as an exclusive deficit. These authors also reported reduced uptake of isotope, predominately in the left frontal and temporal lobes, using single photon emission computed tomography (SPECT). Further evidence of writing deficits in Japanese ALS patients was presented by Tsuji-Akimoto et al. (2010). Using a picture written description task, these authors developed the Writing Error Index [*WEI = (number of errors ÷ total number of written words) x 100*] and reported significantly poorer performance of ALS patients in comparison to controls. Significant impaired performance in the ALS sample was also reported on dictation of kanji characters but not on kana dictation, although errors such as omissions, substitutions, displacements, incorrect phonetic marks and imperfect characters were observed in kana on a picture written description task. Moreover, syntactic analysis also revealed errors such as missing subjects, unfinished sentences, mismatches between subject and verb and inappropriate use of conjunctions. This group subsequently correlated performance on the WEI with [11C]-flumazenil PET measures, showing a correlation between WEI and binding potential in the anterior cingulate gyrus bilaterally, with mild right predominance (Yabe et al., 2012). The authors speculated that attention errors played a role in the errors observed, which included substitutions, omissions, displacements and incorrect placement of kana characters.

Although reading abilities per se have not been explored in ALS, written lexical decision has been assessed in one report (Taylor et al., 2013). Using the Spot the Word Test (Baddeley, Emslie, & Nimmo-Smith, 1993), these authors reported 23% of the sample as being impaired on this task. 16% of patients were also impaired on a test of spelling, but written lexical decision was not studied in relation to the aforementioned spelling deficits in this sample.

3.2.3. Data Integration and Analysis

A number of key findings emerge from the extant literature on language in ALS. Word retrieval has been assessed in ALS using the two most frequently employed tasks in clinical populations, generative verbal fluency paradigms and confrontation naming tests, with evidence of deficits using both methods. Verbal fluency deficits have been consistently reported in ALS and phonemic paradigms have shown to be a very sensitive marker of cognitive dysfunction even after correcting for the effect of motor disability. The influence of executive-mediated processes in verbal fluency deficits is evident if we consider that phonemic paradigms are more sensitive to such deficits than semantic paradigms, and that restricted phonemic tasks are more sensitive than standard phonemic conditions in ALS. However, current evidence indicates that linguistic processes also play a role in such deficits. In a large population based-study of cognition in ALS, 40% of ALS patients who did not present with executive dysfunction were impaired on verbal fluency, 30% of those being impaired in other non-executive tasks such as confrontation naming (Phukan et al., 2012). Moreover, evidence of decreased activation not only in prefrontal and cingulate areas, which are related to executive processes, but also in inferior frontal, temporal and parietal areas in ALS for both verbal fluency and confrontation naming deficits exists (Abrahams et al., 2004). Lepow et al. (2010) also hypothesised anterior temporal involvement in verbal fluency performance in ALS, which spreads out to frontal areas on patients with increasing cognitive decline. These results suggest that a linguistic, rather than executive impairment alone, contributes to such deficits. However, not all evidence points in this direction. Abrahams et al. (2000) did not find evidence of the influence of word retrieval deficits on verbal fluency performance in ALS. Verbal fluency paradigms are complex tasks that require the involvement of a set of complex functions, and both executive dysfunction and a pure linguistic deficit (i.e. impaired access to the mental lexicons) can affect performance on this task. Considering the current evidence, it is likely that executive and linguistic deficits can contribute to impaired performance on verbal fluency in ALS. This inference suggests the presence of abnormalities in dorsolateral prefrontal areas but also in inferior frontal and posterior superior temporal regions in ALS, which have a deleterious effect on linguistic and executive processes and lead to a gradual breakdown of expressive language over the course of the disease.

Although usually interpreted as word retrieval deficits, difficulties in confrontation naming tasks can also be observed in the context of semantic deficits. In the case of ALS, semantic processing has been seldom assessed and, although significantly lower performance of patients in comparison to healthy controls has been reported, most studies indicate either no impairment, or impairment in a small proportion of patients. This observation suggests that semantic processes remain relatively spared in the majority of patients with ALS, and implies

the presence of genuine word retrieval deficits. However, semantic processing has not yet been studied longitudinally, and the emergence of deficits as disease progresses cannot be excluded.

Discourse productivity in ALS can be strongly restricted by speech disturbances such as dysarthria or apraxia of speech, and its assessment can be challenging in patients with bulbar involvement. Regardless, current evidence suggest that discourse productivity deficits in ALS can be due to syntactic processing deficits which affect the ability to construct long and meaningful sentences. Significant changes in discourse content have been reported in ALS, including fewer grammatically well-formed sentences and discourse adequacy deficits (Ash et al., 2014; Ash et al., 2015; Gallassi et al., 1985; Roberts-South et al., 2012; Strong et al., 1999; Tsermentseli et al., 2015). However, the influence that executive dysfunction can have on syntactic processing cannot be dismissed. Only one group has assessed the influence of executive dysfunction on language production in ALS, showing that while discourse adequacy deficits seem to be related in part to executive dysfunction (Ash et al., 2014), grammatical deficits can also be observed in the absence of executive dysfunction (Ash et al., 2015). Further indications in favour of this conclusion were provided by neuroimaging findings, which have shown significant correlations between impaired grammatical constructs in discourse processing and inferior frontal and anterior temporal atrophy (Ash et al., 2015). Thus, available evidence suggests that, although executive dysfunction can influence grammatical and syntactic processing in ALS, this can also represent a pure linguistic deficit.

Syntactic processing has also been studied in ALS in the context of comprehension abilities. A few reports exist outlining grammatical and syntactic comprehension deficits in ALS (Cobble, 1998; Kamminga et al., 2016; Rakowicz & Hodges, 1998; Taylor et al., 2013; Tsermentseli et al., 2015; Yoshizawa et al., 2014). If syntactic processing deficits have been observed in ALS in the context of spared executive function on language production, it is likely that such deficits also affect language comprehension. However, none of the above reports has assessed syntactic and grammatical comprehension deficits in relation to executive dysfunction. One report exists which relates deficits on the Token Test to executive dysfunction rather than a language deficit, based on the observation that patients with deficits in this task also present with deficits on executive tasks (Talbot et al., 1995). Conversely, in a population-based study using a large incident sample the Token test classified patients in the domain of 'non-executive impairment' (Montuschi et al., 2015). The use of the Token Test to purely assess language comprehension should be interpreted with caution. Its use as an instrument to classify patients as non-executively impaired could be challenged by considering the involvement of the buffer components of working memory that are required to complete the task. Although the influence of executive dysfunction in comprehension deficits in not fully understood, such deficits seem

to be relatively independent of executive impairment when considering language production abilities, and therefore these may also have a pervasive impact on comprehension abilities.

The finding of significant difficulties in processing of verbs in comparison to the processing of nous in ALS, which is observed for both expressive and receptive tasks, can also be linked to syntactic processing deficits. Although the degradation of motor-related areas in ALS contributes to such action verb processing deficits (Cousins et al., 2017; M. Grossman et al., 2008; York et al., 2014), the higher syntactical complexity of verbs in comparison to nouns can also contribute to this, and there is evidence that actually points in this direction (Cousins et al., 2017; Papeo et al., 2015). This observation further supports the presence of pure syntactic and grammatical processing deficits in ALS.

Spelling deficits in English have been reported in some Western ALS patients and richer evidence is available from Japanese populations (Cobble, 1998; J. H. Ferguson & Boller, 1977; Ichikawa et al., 2008; Satoh et al., 2009; Taylor et al., 2013; Tsuji-Akimoto et al., 2010). Impairments on both types of Japanese characters (kana and kanji) have been reported in ALS. Thus, difficulties on the processing of phonological units which impair performance on spelling of words that follow phoneme-to-grapheme rules, as well as difficulties in processing learned visual characters seem to be characteristic of ALS. However, the more common types of impairment seem to involve those characters which are irregular in nature and assimilated through a process of formal learning, comparable to irregular words in English. This evidence further supports the involvement of inferior temporal and inferior frontal regions in ALS.

The available data on language dysfunction in ALS reveals the involvement of a wide network of language anatomical substrates that overlap with executive and behaviourally mediating areas, along with pure motor circuits. Verbal fluency and confrontation naming deficits in ALS, although primarily mediated by dorsolateral prefrontal functions, can also reflect lexical retrieval deficits of posterior superior temporal dysfunction nature. Inferior frontal and anterior temporal dysfunction also contribute to such deficits, and the former is also involved in syntactic and grammatical processing difficulties, and most likely contributes to the selective deficit in processing action verb words. Although no anatomical correlations exist for the spelling deficits in ALS, there is evidence of inferior posterior parietal dysfunction, specifically in the angular and supramarginal gyrus (Tsermentseli et al., 2012). Moreover, superior temporal and posterior inferior frontal areas have also been related to the processing of irregular spelling characters that do not follow the grapheme-to-phoneme conversion rules, which seem to be affected in ALS. Thus, in addition to dorsolateral prefrontal, orbitofrontal and anterior cingulate dysfunction, anatomical dysfunction in ALS also spreads to posterior inferior frontal and superior temporal areas. Semantic and conceptual knowledge seem to remain

relatively spared, suggesting that this pattern of anatomical dysfunction does not spread to anterior inferior temporal areas, at least in early stages of the disease.

3.2.4. Discussion

The study of language in the ALS-FTSD is a natural continuation of the cognitive phenotyping in ALS, which assists in identifying disease markers and helps inform clinical and care management. However, cognitive studies in ALS have been biased towards the study of executive functioning (Beeldman et al., 2016; Raaphorst, de Visser, Linssen, de Haan, & Schmand, 2010). Evidence of the lack of systematic study of language in ALS is provided in this review by the fact that 76% of the cognitive studies identified through the systematic search were excluded because language function was not assessed.

This systematic review has confirmed the presence of language dysfunction in ALS. Word retrieval deficits have been described in ALS using both generative verbal fluency and confrontation naming paradigms. Semantic components do not seem to have an influence on such difficulties, but rather represent a genuine impaired ability to access to the mental lexicons. Verbal fluency is a sensitive marker of early cognitive decline in ALS and has been used as an indicator of executive impairment in ALS. However, executive and linguistic processes can affect performance on this task. It is therefore important to clarify the extent by which this impairment is executive or linguistic. Direct comparisons with performance on other less executively-mediated word retrieval tasks requiring access to the output lexicons are necessary, while correcting for the effect of executive dysfunction. In addition to word retrieval deficits, and also related to posterior inferior frontal as well as to anterior superior temporal regions, grammatical and syntactic processing deficits are reported in ALS. Both expressive and receptive language tasks have demonstrated such deficits, although only one report assessing expressive language has assessed the influence of executive dysfunction on syntactic processing. Evidence from this report (Ash et al., 2015) suggests that syntactic and grammatical processing deficits in ALS can be independent of executive dysfunction. However, the specific contribution of executive impairment to grammatical and syntactic processing in ALS needs careful determination, with a specific emphasis on the role of working memory. Also, the influence that apathy may have on discourse production needs to be considered. Spelling deficits have also been reported in ALS. Japanese studies have capitalised on the different processing systems for kana and kanji characters, and have suggested that spelling errors relate to different underlying processes depending on the nature of the deficit observed. Corollary studies have not been performed in European languages and it is not known whether ALS patients exhibit similar changes in performance between spelling regular and irregular words in English. In addition to detailed assessments of spelling errors, reading abilities also need to be explored in ALS. Both reading and writing paradigms should consider regularity of

letter-to-sound correspondences of the words. Phonological and orthographic lexical processing also require evaluation in ALS. Finally, it is also important to note that longitudinal studies have failed to adequately assess the progression of language changes in ALS. To date, findings are inconsistent due to high attrition rates and small sample sizes at follow-up assessments, and the lack of comparative healthy control samples which has compromised a proper evaluation of the effects of repeated testing.

Neuropsychological studies are now core in the search for biomarkers in ALS. We now know that ALS patients can present with isolated cognitive dysfunction (ALSci), isolated behavioural changes (ALSbi) or both (ALScbi) (Strong et al., 2017), and that distinct sub-phenotypes of behavioural change exist (Burke et al., 2017). However, important questions remain relating to specific cognitive sub-phenotypes in ALS. The current findings indicate that language impairment is likely to be an important feature of ALS, although with only a few samples representing incident cases, little is known about the precise incidence, nature or progression of language deficits. Moreover, as few studies have explored language changes in the context of executive dysfunction, it is currently unknown whether a specific language sub-phenotype exists in ALS, or whether language impairment always occur in conjunction with impairment in executive function.

Methodological Implications

We have identified a series of important methodological shortfalls in the study of language in ALS. Most studies are characterised by small, prevalent samples. The use of prevalent cases, although increasing the number of potential participants, does not offer an accurate picture of the incidence of deficits. Prevalent cohorts tend to over-represent patients with better prognoses (i.e. survival bias), which may underestimate the phenotype of those with rapidly progressive disease and poorer prognoses, and over-estimate the types of cognitive change that occur later in the course of the disease. As most cohorts studied are clinic-based, referral bias can increase the risk of selective case ascertainment (e.g. if clinics specialise in cognition). In population-based studies, where nearly complete ascertainment is achieved, phenotypic characterisations are more likely to provide the full range of deficits. Only two cross-sectional population-based studies have addressed cognitive changes in ALS, and neither incorporated a comprehensive language battery (Table 3.2). Language assessment is also influenced by motor deficits. Corrections for motor impairment have not always been applied and some studies excluded severely motor compromised participants who had difficulty performing on language testing, thus probably biasing the actual prevalence of language deficits.

The study of language in ALS presents with additional challenges. Behavioural changes such as apathy or social withdrawal can interfere with language output. Other factors can adversely influence cognitive performance, such as depression, hypoventilation with carbon dioxide

retention or use of medication. All these aspects need to be controlled for in order to minimise their confounding effects.

Future Perspectives

There is a need to define more clearly the incidence, nature and progression of language changes in the ALS-FTSD and to establish the role that executive dysfunction has on language processing. Cognitive phenotyping in ALS requires large population-based incident cohorts and the use of broad neuropsychological batteries. These should include comprehensive evaluations of language functions with adequate adaptations for motor disability. Longitudinal tracking of cognitive phenotypes in ALS should also be completed using large population-based samples. Learning effects derived from repeated testing also should be controlled for by using appropriate matched control data. Apart from demographically matched healthy control groups, comparisons to other disease control groups with and without language dysfunction are also necessary. At-home assessments help reducing attrition rates allowing the involvement of participants who are more severely disabled and are unable to attend the clinic.

Even though this review has focused on language change in non-demented ALS patients, the profile and nature of language changes in ALS-FTD also needs consideration to discern whether these overlap with those characteristic of PPA, or whether they represent a specific phenotype associated with ALS-FTD, as has been recently suggested (Saxon, Thompson, et al., 2017). Further studies are needed to compare the profile of language decline in ALS-FTD to that of ALS and pure FTD. To this end, the use of adequate updated consensus criteria for the diagnosis of bvFTD (Rascovsky et al., 2011) and PPA (Gorno-Tempini et al., 2011) is crucial. In addition, the premise of ALS and FTD as two extremes of a continuum raises the question as to whether the short duration of the disease actually prevents the development of cognitive impairment in all patients with ALS. Further longitudinal studies are necessary to explore this issue. And finally, there is a need to integrate findings from neuropsychology, neuroimaging, neuropathology and genetics to fully elucidate the neurobiological process underpinning cognitive, behavioural and motor decline in ALS.

See reference below for publication of this systematic review:

Pinto-Grau, M., Hardiman, O., & Pender, N. (2018). The Study of Language in the Amyotrophic Lateral Sclerosis - Frontotemporal Spectrum Disorder: a Systematic Review of Findings and New Perspectives. *Neuropsychol Rev, 28*(2), 251-268. doi:10.1007/s11065-018-9375-7

3.3. Cognition and Neuroimaging Findings in ALS

Advanced structural and functional neuroimaging techniques have been applied with the aim to discover biomarkers that inform disease phenotyping in ALS. The use of neuroimaging to examine the brain non-invasively has brought important insights not only on the motor networks but also on the extra-motor pathology involved in ALS (Turner et al., 2012). Neurocognitive correlates have also been explored, with the aim to link specific profiles of cognitive impairment to specific areas of extra-motor involvement (Christidi, Karavasilis, Rentzos, et al., 2018). Anatomical areas of vulnerability in ALS consistent with the pattern of clinical and pathological manifestations have been described (Figure 3.4: Bede et al., 2016).

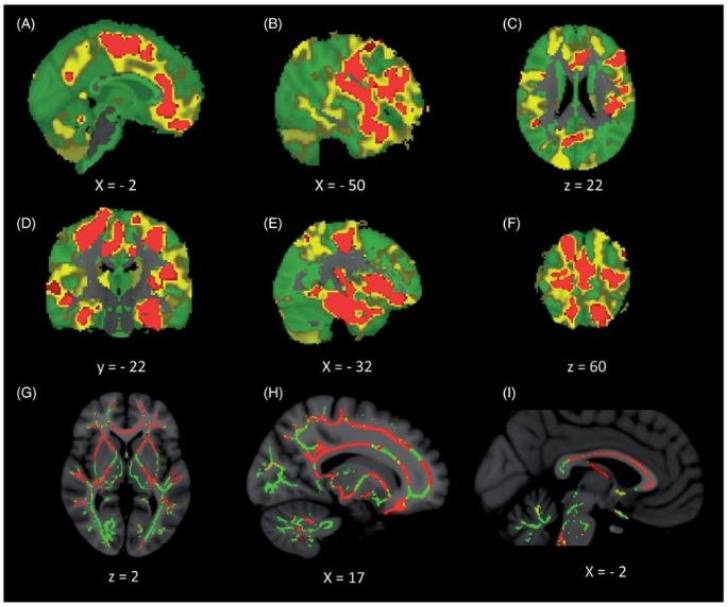

Figure 3.4. Anatomical areas of selective vulnerability in ALS. From Bede et al. (2016). Grey and white matter alterations are represented in red, unaffected brain regions are in green, and yellow represents unthresholded contrast results between ALS patients and healthy controls.

Voxel-based morphometry (VBM) and surface-based morphometry (SBM), both whole-brain structural MRI techniques which allow for the quantification of grey and white matter volumes, have been employed in the study of structural cerebral changes in ALS. A meta-analysis of VBM studies (Chen & Ma, 2010), including 84 ALS patients and 81 healthy controls, showed significant grey matter loss in the right precentral gyrus in ALS compared to controls. No consistent extra-motor changes were observed, although descriptive analyses showed grey matter atrophy in the cingulate gyrus bilaterally and the left inferior parietal lobe in 75% of the studies, and in the right lentiform nucleus and the left middle frontal gyrus in 50% of the studies. Significantly decreased grey matter volume has been reported in ALS-FTD patients in comparison to ALS patients as well as other disease controls (Rajagopalan & Pioro, 2014). The areas of significant reduced atrophy in this study included prefrontal areas, the paracingulate gyrus, inferior and middle temporal (or fusiform) gyrus, the hippocampus, amygdala, and

cerebellum. Although no significant atrophy compared to controls was observed in patients without comorbid dementia, the degree of cortical loss in ALS in this study may have been underestimated due to the use of neurologic disease controls. In fact, patterns of extra-motor cortex involvement, specifically on frontal, temporal and occipital regions, have been observed in cognitively intact patients (Bede, Bokde, Elamin, et al., 2013). A recent study showed reduced grey matter volumes on the anterior cingulate cortex, the inferior frontal gyrus, the orbitofrontal gyrus, the fusiform gyrus and the left cerebellum in ALS, with more widespread involvement of orbitofrontal, inferior frontal and anterior cingulate areas as well as insular, amygdala/hippocampus and superior temporal involvement in patients with impaired cognition (Christidi, Karavasilis, Riederer, et al., 2018). Longitudinally, a VBM study reported progressive atrophy of extra motor areas in ALS, including the frontal, temporal and parietal lobe bilaterally (Senda et al., 2011). Longitudinal changes in the basal ganglia have also been reported (Menke et al., 2014).

Some VBM studies have looked at structural changes in ALS and its relation to specific cognitive and behavioural deficits. Mioshi et al. (2013) showed a gradient of frontal and temporal atrophy across the ALS-FTD continuum, which was associated with executive dysfunction and behavioural change. White matter density changes have been described in the occipitofrontal fasciculus, the cingulum, the superior longitudinal fasciculus and the anterior commissure, related to verbal fluency deficits in ALS (Abrahams, Goldstein, et al., 2005). Correlations between phonemic verbal fluency performance and grey matter volume in the inferior frontal and dorsolateral prefrontal cortex have also been described (Menke et al., 2014). Performance on tasks of action and object knowledge have also been correlated with atrophy on the dorsolateral prefronal and the inferior frontal cortex (M. Grossman et al., 2008). Increased apathy scores have been correlated to reduced grey matter volume in the right dorsolateral prefrontal cortex, and the orbitofrontal cortex and frontal pole bilaterally (Tsujimoto et al., 2011).

SBM studies in ALS, which measure cortical thickness, have shown precentral gyrus thinning (Chiò et al., 2014; Turner et al., 2012). Cortical thinning has also been observed in frontotemporal and parietal regions, particularly on the left precuneus and the right fusiform gyrus (Schuster et al., 2014). Atrophy in subcortical structures, including the hippocampus, caudate nucleus and nucleus accumbeus, has been described too (Turner & Verstraete, 2015). A recent study demonstrated reduced cortical thickness in cognitively impaired ALS patients in the left inferior frontal gyrus, right anterior cingulate cortex, bilateral insula, right temporal pole and right inferior temporal gyrus (Consonni et al., 2018). In this study, strong correlations between naming abilities and cortical thickness in the inferior frontal gyrus, the insula and the temporal pole were also reported. The same authors also showed significant correlations

between different behavioural profiles and cortical thickness in distinct neuroanatomical regions, specifically between bilateral orbitofrontal thinning and apathy, right cingulate and frontotemporal thinning and disinhibition, and left precuneus and dysexecutive behaviours (Consonni, Cappa, Dalla Bella, Contarino, & Lauria, 2019).

White matter tracts have been studied in ALS using diffusion tensor imaging (DTI). Decreased fractional anisotropy in the corticospinal tract and middle-posterior corpus callosum, which connects motor and premotor cortices, has been reported (Chiò et al., 2014; Turner et al., 2012). Involvement of the left superior longitudinal fasciculus has been related to behavioural changes in ALS (Trojsi et al., 2013). Correlations between executive dysfunction and DTI changes in the corpus callosum, corticospinal tract and the long association tract (cingulum, inferior longitudinal, inferior fronto-occipital and uncinate fasciculi) have been described (Sarro et al., 2011). The same authors also reported correlations between verbal fluency deficits and reduced white matter in the left cingulum (Sarro et al., 2011). White matter changes in the left inferior frontal gyrus and the anterior prefrontal cortex have also been correlated to verbal fluency deficits in ALS (Pettit et al., 2013). Apathy has been related to white matter changes in the right anterior cingulum (Woolley et al., 2011). A longitudinal DTI study has shown reduced white matter in the brainstem, limbic pole and temporal lobe in ALS after a six-month follow-up (Senda et al., 2011).

Functional neuroimaging techniques have been used to explore the pattern of brain activation in ALS. Resting-state fMRI (rs-fMRI) has shown reduced functional connectivity in sensorimotor areas and in extra-motor areas such as medial frontal and parietal regions, including the precuneus, as well as the cingulate cortex and the inferior temporal gyrus (Turner & Verstraete, 2015). Compared to healthy controls, an ALS rs-fMRI study showed decreased connectivity in the right inferior orbitofrontal gyrus and the left inferior frontal cortex, and increased connectivity in the left precuneus, the right angular gyrus, and the left inferior parietal lobe and left middle cingulum (Agosta et al., 2013). Executive function was correlated to angular gyrus, precuneus and cingulate cortex connectivity by the same authors.

fMRI studies during the performance of motor and cognitive tasks have been undertaken in ALS. These studies have shown premotor and higher order cortical regions involved in motor learning, such as the basal ganglia and the cerebellum, are activated during motor-based tasks (Turner et al., 2012). Abnormal cerebral activation of fontal, temporal and parietal areas, as well as areas in the cingulate cortex have been shown in ALS during performance of word retrieval tasks (Abrahams et al., 2004). Furthermore, abnormal activation of middle frontal, middle temporal and anterior cingulate areas have been described during performance of inhibitory tasks (Goldstein et al., 2011; Witiuk et al., 2014).

Radiotracer imaging, specifically PET and SPECT, have been employed in ALS to investigate metabolic brain changes that are related to specific cognitive changes. PET and SPECT studies have shown reduced uptake in frontotemporal and fronto-subcortical areas in ALS, which correlate with deficits on word retrieval, including verbal fluency and confrontation naming (Abrahams et al., 1996; Kew et al., 1993; Ludolph et al., 1992; Wicks et al., 2008), as well as spelling (Ichikawa et al., 2008; Yabe et al., 2012). These perfusion changes become increasingly prominent as we move along the ALS-FTD continuum (Canosa et al., 2016; Talbot et al., 1995).

Finally, nuclear magnetic resonance (NMR) spectroscopy, a non-invasive technique used to study metabolic changes in the brain, has shown decreased metabolic ratios in extra-motor areas in the frontal, mid-cingulate and parietal cortex, as well as in the thalamus and basal ganglia (Chiò et al., 2014; Turner et al., 2012).

In conclusion, neuroimaging studies have extensively confirmed the involvement of extra-motor cerebral areas in ALS, these mainly encompassing frontal, temporal and parietal regions, as well as the cingulate cortex and subcortical structures. However, inconsistent results exist due to common methodological limitations in imaging studies (i.e. small sample sizes, suboptimal patient characterisation, lack of disease controls, deficient consideration of laterality and asymmetry of findings, and use of single-modality imaging techniques rather than a multi-modal approach), which add on to the challenging heterogeneity of ALS (Bede & Hardiman, 2014). Moreover, correlations between neuroimaging parameters and neuropsychological and clinical metrics, including neuropsychological measures, have not been extremely successful most likely due to complex and heterogeneous biological basis of clinical manifestations and the fact that individual outcome measures only capture part of this clinical variety (Verstraete et al., 2015).

3.4. Genetics and Cognition in ALS

Patterns of extra-motor change in ALS are likely to be defined by complex genetic factors (Bede, Bokde, Byrne, et al., 2013). The hexanucleotide repeat expansion in the C9orf72 gene is an important contributor to extra-motor involvement in ALS (Floeter & Gendron, 2018). Extensive frontotemporal cortical and subcortical pathology in association with the C9orf72 positive genotype have been described in comparison to relatively limited extra-motor pathology in C9orf72 negative ALS patients (Bede, Bokde, Byrne, et al., 2013). PET studies have shown hypometabolism in the left frontal and superior temporal cortex as well as cingulate areas, the insula, caudate nucleus and thalamus in C9orf72 positive patients compared to patients without the expansion (Cistaro et al., 2014). Moreover, a significantly higher frequency of co-morbid FTD in ALS patients with the C9orf72 repeat expansion has been described (Byrne et al., 2012). An increased incidence of psychotic symptoms has also been

described in patients with ALS-FTD (Lillo, Garcin, Hornberger, Bak, & Hodges, 2010), and this has been linked to the presence of the C9orf72 repeat expansion (Snowden et al., 2013). Most ALS-FTD with the C9orf72 mutation meet criteria for the diagnosis of bv-FTD, and no language-variant FTD has been reported in the context of this mutation (Boeve et al., 2012; Boeve & Graff-Radford, 2012). One case of ALS-FTD with combined behavioural and semantic deficits has been described (Snowden et al., 2013).

Neuropsychological assessments in C9orf72 positive patients have been limited due to small samples and retrospective studies (see Patel & Sampson, 2015 for a review), and most have focused on performance on executive function tasks in ALS-FTD cases. Increased apathy and poorer executive function in C9orf72 positive patients have been reported, corresponding to frontal cortical atrophy (Byrne et al., 2013). Irwin et al. (2012) reported significant greater decline in phonemic verbal fluency measures on longitudinal testing in C9orf72 positive patients with FTLD, with and without ALS, which was related to frontal and parietal atrophy and with more severe mid-frontal ubiquitin-positive inclusions and neuronal loss. In this study, no significant differences were observed on verbal fluency measures between C9orf72 positive and C9orf72 negative ALS patients with no comorbid dementia. Deficits in confrontation naming tests have also been evaluated in C9orf72 positive patients, and higher scores on the Boston Naming Test in C9orf72 repeat expansion carriers compared to non-carriers have been reported (Byrne et al., 2012). Snowden et al. (2013) reported equal prevalence of naming and semantic deficits on a C9orf72 positive and a C9orf72 negative ALS-FTD sample.

3.5. Conclusion

The three introductory chapters presented here have reviewed relevant literature relating to ALS and the neuropsychological presentations characteristic of this complex multisystem disease, with a particular emphasis on language. ALS is now understood as a frontotemporal spectrum disorder, and there is evidence of the presence of distinct phenotypes within this disease spectrum. The systematic review carried out in this chapter revealed that language change is a significant finding in ALS, particularly in the domains of word retrieval, spelling and grammatical processing, and highlighted the importance of investigating this further in a population-based incident sample. In chapter 2, a detailed review of the language system was presented, broken down into different processes. This research aims to address the assessment of language from a psycholinguistic approach, and the understanding of the different processes that underlie language function will be core to interpret the results.

In this chapter, we have also highlighted the extensive evidence of extra-motor involvement in ALS revealed by neuroimaging studies, mainly comprising frontostriatal and frontotemporal areas, and how these relate to specific neuropsychological correlates, primarily executive

dysfunction but also language change in some instances. The literature also shows that the hexanucleotide repeat expansion in the C9orf72 gene is a significant contributor to frontotemporal pathology in ALS, and therefore to neuropsychological deficits. All the information presented in the introductory chapters, particularly chapter 3, have informed the hypothesis defined in this research, which are presented in detail in the following chapter.

CHAPTER 4 Outline.

Thesis Objective, Aims and Hypotheses

4.1. Why Study Language in ALS? Significance of this Research Project

4.2. The Primary Objective

4.3. Aims and Hypotheses

4.3.1. Aim 1

4.3.2. Aim 2

4.3.3. Aim 3

4.3.4. Aim 4

4.3.5. Aim 5

4.3.6. Aim 6

CHAPTER 4.

Thesis Objective, Aims and Hypotheses

4.1. Why Study Language in ALS? Significance of this Research Project

As described in the previous chapter, ALS is a complex multisystem disease and investigation into the existence of different phenotypes within this disease spectrum has been the purpose of much recent research in this area. Specifically, in the area of neuropsychology, research has focused on the identification of cognitive and behavioural changes that may represent phenotypic markers for distinct disease sub-phenotypes. However, up to date, all population-based neuropsychological studies have focused on executive dysfunction and behavioural change, and language has been neglected. Considering the above, this work is a natural continuation of the ongoing deep phenotyping of ALS in an incident population-based setting that considers the whole cognitive and behavioural spectrum of symptoms characteristic of this disease.

There are many potential impacts of this research, which have been subcategorised as follows:

a. *Disease phenotyping*

ALS is a heterogeneous disease characterised by categorical differences in cognitive and behavioural change, in addition to clinical presentation, rate of progression and genotype. This study provides further data relative to disease phenotyping considering all factors outlined.

b. *Biomarker development*

The investigation of cognitive and behaviour sub-phenotypes in relation to clinical presentation and genetic contributors informs the development of disease biomarkers. Longitudinal evaluations are also a marker of disease progression (i.e. spread of the disease), which are also investigated here in relation to other clinical factors.

c. *Diagnostics*

Accurate diagnostic tools are required to identify the presence of cognitive decline and behavioural change in ALS. In light of the recent publication of revised diagnostic criteria for frontotemporal syndromes in the ALS-FTSD (Strong et al., 2017), the establishment of the profile of language dysfunction characteristic of ALS is crucial to guarantee an accurate diagnosis of the whole spectrum of cognitive and behavioural change characteristic of this disease.

d. Treatment, care and disease management

Accurate diagnosis of cognitive and behavioural status allows for informed decisions regarding treatment options and future care plans to be made. Moreover, cognitive and behavioural changes contribute to caregiver burden and early detection permits prompt intervention.

e. Prognosis

The identification of factors that influence disease progression, including cognitive and behavioural status, is also relevant for prognostication purposes.

f. Clinical trials

Previous clinical trials in ALS may have been unsuccessful due to disease heterogeneity, as recruitment criteria were not based on parameters that selected homogeneous patient groups likely to respond equally to treatment. Disease markers are required to stratify patients in such homogeneous groups of potential responders. Thus, accurate cognitive phenotyping in ALS is required as a stratification parameter in clinical trials, as it is the development of prognostic markers to assess drug efficacy.

4.2. The Primary Objective

The primary working hypothesis of this study is that a subgroup of ALS patients exhibit changes in language, which represent a distinct cognitive sub-phenotype. This work builds on previous work from the Irish National ALS Research team that has focused on the presence of executive dysfunction (Elamin et al., 2013; Elamin et al., 2011; Phukan et al., 2012) and behavioural change (Burke et al., 2017). This work further explores the likelihood of heterogeneity within the cognitive phenotypes associated with ALS which, in turn, may enable the generation of disease clustering based on different clinical trajectories and pathogenic mechanisms. In order to test this multifaceted primary hypothesis, six different aims were established. For each aim, several hypotheses and their rationale are outlined.

4.3. Aims and Hypotheses

4.3.1. Aim 1

To investigate the incidence and nature of language change in a large population-based cohort of incident ALS patients, compared to a population-based age-, gender- and education-matched healthy control sample.

Hypothesis: Language change of a diverse nature at diagnosis is characteristic of ALS patients not meeting criteria for FTD.

On the basis of the systematic review undertaken in chapter 3, the following assumptions are formulated:

Assumption 1: Difficulties in confrontation naming in ALS are explained by word retrieval difficulties rather than by a pure semantic deficit. Consequently, improved performance after the presentation of phonemic cues is predicted.

Assumption 2: Semantic processing is spared, at least in early stages of the disease.

Assumption 3: Verbal fluency deficits are present in a high proportion of ALS patients, and in most cases, impairment on executive-mediated processes explain decreased performance. Accordingly, greater impairment on phonemic verbal fluency in comparison to semantic verbal fluency paradigms is expected, and poorer performance in restricted phonemic paradigms compared to standard phonemic conditions is predicted. However, spared access to the lexicons is also required in the execution of verbal fluency tasks. Therefore, it is predicted that word retrieval deficits contribute to verbal fluency deficits in ALS to some degree, independently of executive dysfunction.

Assumption 4: Considering the role of the premotor cortex in relation to action semantics, we anticipate ALS patients to exhibit more difficulties with the processing of action words in comparison to nouns or objects.

Assumption 5: Based on results from Japanese studies assessing spelling deficits in ALS, we anticipate that a decline in performance on spelling tasks is present in ALS. Specifically, a higher difficulty is predicted in the spelling of irregular words, compared to words that follow a regular phoneme-to-grapheme conversion. In accordance, regularisation errors are expected.

Assumption 6: Although there is no existing evidence on reading abilities and lexical processing in ALS, it is hypothesised that reading abilities are spared and that the difficulty with orthographic representations is at an output level, thus solely affecting spelling. Accordingly, unimpaired performance on visual lexical decision as well as on word reading is predicted. Phonological lexical processing is hypothesised to remain intact in ALS, given spared semantic processing, and therefore normal performance on an auditory lexical decision tasks is expected.

Assumption 7: Considering extant evidence in the ALS literature, we hypothesise that grammatical and syntactic comprehension deficits are present in ALS and are evident when processing both auditory and written information.

4.3.2. Aim 2

To assess the relationship between language change and changes in executive function in a large population-based incident cohort of ALS patients.

Hypothesis: Although pure language decline occurs in ALS, it is predicted that these changes are also associated with executive dysfunction to some extent. This is especially relevant for grammatical and syntactic processing of auditory input, given the role of working memory in temporarily holding the complex auditory information that is being processed.

4.3.3. Aim 3

To establish the incidence of the various frontotemporal syndromes of ALS on a representative population-based sample, considering revised diagnostic criteria (Strong et al., 2017).

Hypotheses: A pure language sub-phenotype exists in ALS, along with a pure executive sub-phenotype and a language-plus-executive dysfunction sub-phenotype. A high proportion of ALS patients are cognitively unimpaired at diagnosis, and as per previous ALS population-based incident studies, a small proportion of patients (around 15%) meet criteria for FTD, mostly bvFTD but also language-variants. Regarding behaviour, no incident studies exist, but based on previous reports on the prevalence of apathy in ALS, it is predicted that sole behavioural change (ALSbi) is more frequent than cognitive decline alone (ALSci) at early stages, and that the majority of impaired patients meet criteria for ALScbi.

4.3.4. Aim 4

To assess the evolution of frontotemporal decline in ALS. Specifically, to assess longitudinal changes in language, executive function and behaviour, and to establish the prevalence of frontotemporal syndromes as disease progresses, considering revised consensus criteria (Strong et al., 2017).

Hypotheses: Comparing the current incidence of cognitive impairment in ALS (around 35%) and its prevalence (around 50%), some ALS patients who were cognitively intact at diagnosis are expected to develop cognitive impairment with disease progression, including language dysfunction. It is predicted that not all ALS patients present with cognitive impairment after a year follow up, although a decline of varying degrees from baseline is expected, representing disease spread that occurs at different rates. Relating to language, according to extant literature suggesting a higher vulnerability of language processes to disease progression (Abrahams, Leigh, et al., 2005; Elamin et al., 2013; Gordon et al., 2010), further decline will occur on language functions, as well as on executive dysfunction and behaviour. Based on evidence from the systematic review in chapter 3, it is also hypothesised that a proportion of ALS patients develop semantic processing deficits as the disease progresses.

4.3.5. Aim 5

To investigate the relationship between cognitive/behavioural phenotypes and demographic and clinical features, including the influence that the diagnosis of a frontotemporal syndrome has on motor progression and survival in ALS.

Hypotheses: It is predicted that there is no relationship between age and the presence of a frontotemporal syndrome, however, bulbar-onset ALS and female gender are hypothesised to be related to a higher risk of frontotemporal dysfunction, consistent with existing evidence (Abrahams et al., 1997; Lomen-Hoerth et al., 2003; Montuschi et al., 2015; Palmieri et al., 2015; Schreiber et al., 2005). At initial stages, motor disease severity is expected to be independent of cognitive decline, which indicates different patterns of disease depositions in the brain at onset. However, considering that executive dysfunction has already been shown to be a predictor of reduced survival as it has the diagnosis of comorbid FTD (Elamin et al., 2011; Tsermentseli et al., 2012), the presence of any form of frontotemporal syndrome in ALS is considered a sign of more aggressive disease, spreading more rapidly across the brain. This also affects the rate of motor progression and, in turn, has an impact on survival. Therefore, as disease progresses, the presence of cognitive and behavioural dysfunction is expected to be associated with increased motor disability and reduced survival.

4.3.6. Aim 6

To assess if the presence of the C9orf72 hexanucleotide repeat expansion is associated with a higher incidence of frontotemporal syndromes in ALS. The influence that a positive family history (i.e. presence of at least one biological relative within three generations diagnosed with ALS and/or FTD) in the absence of an identified genetic mutation has on the presence of frontotemporal dysfunction is also explored.

Hypotheses: Given that the presence of the hexanucleotide repeat expansion in the C9orf72 gene is an important contributor to frontotemporal pathology in ALS, a higher degree of frontotemporal involvement is expected in C9orf72 repeat expansion carriers, including cognitive and behavioural change. Regarding the presence of a family history of ALS and/or FTD in the absence of an identified genetic mutation, this is also expected to be related to a higher incidence of frontotemporal syndromes, as the presence of a genetic contributor is anticipated to involve a higher degree of extra-motor pathology.

CHAPTER 5 Outline.

Methodology

5.1. Study Design

5.2. Participant Recruitment

- 5.2.1. Patient Recruitment
- 5.2.2. Healthy Control Recruitment
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  - 5.4.2.1. Language
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CHAPTER 5.

Methodology

5.1. Study Design

This research project employed an observational, prospective, longitudinal, case-control, population-based design, that recruited incident cases. The particulars of the study methods are specified in subsequent sections.

5.2. Participant Recruitment

5.2.1. Patient Recruitment

Newly diagnosed ALS patients in the Republic of Ireland attending the National Specialist MND Clinic at Beaumont Hospital Dublin during the recruitment period (i.e. December 2014 to August 2017) were identified through the Irish ALS Register (Rooney et al., 2013; Traynor et al., 1999) and invited to participate in the study. The identification of potential participants through a population-based ALS register allowed for the study to have a population-based design and therefore to represent the entire phenotypic spectrum. All patients underwent initial assessment within the first year of diagnosis, thus representing an incident cohort. The population-based design reduces referral and selection bias; the incident design, survival bias.

All potential participants were approached by the PhD Candidate (MPG) during their attendance at the National Specialist MND Clinic, with the exception of those who expressed no interest in participation in research endeavours in advance. A patient information leaflet with comprehensive details on what the participant's involvement in the project would entitle was handed out. Potential participants were asked to take the information with them and read it at their own time, and were explained that a phone call would follow-up to discuss their potential engagement in the project. A period of approximately ten days was given to read the information leaflet and allow for an informed decision to be made.

Following this time, potential participants were contacted by phone to explore their interest in participating in the project, and the opportunity was given to ask for any further enquires they may have had. For those who confirmed their interest in participation, a suitable date and time for an initial assessment was arranged. Participants were offered the option of attending the Psychology Department in Beaumont Hospital to undergo neuropsychological assessment, or if preferred, home-based assessments were also a possibility, to allow for the involvement of

participants with more advanced motor disability that were unable to travel. In cases where individuals declined participation in the project, the reason for the same was documented.

5.2.2. Healthy Control Recruitment

An age-, gender- and education-matched population-based healthy control sample was also recruited through a volunteer network held by the Academic Unit of Neurology, in the Trinity Biomedical Sciences Institute, and through board postings. All potential healthy control participants received a phone call to enquire about their interest in participating and to screen for possible exclusion factors. If the candidate was interested and suitable for participation, a home-based or hospital-based appointment was arranged. Prior to engaging in the assessment, a healthy control information leaflet was handed out to the participant and time to answer any queries regarding the project was offered. Patients' spouses or acquaintances represented 12% of control participants. This proportion was kept low to avoid overmatching.

5.2.3. Case Ascertainment: Inclusion and Exclusion Criteria

Case ascertainment was supervised by Senior Consultant Neurologist and ALS Specialist (OH) and Principal Clinical Neuropsychologist (NP), who also fulfil the role of PhD supervisors. Inclusion and exclusion criteria are detailed in Table 5.1. Inclusion criteria were different for patients and healthy controls, but same exclusion criteria applied for both groups.

Table 5.1. Inclusion and exclusion criteria for study participation.

INCLUSION CRITERIA	
Patients	✓ Having received a diagnosis of ALS in Ireland form December 2014 to August 2017. ✓ Meeting criteria for Possible, Probable or Definite ALS according to El Escorial Criteria. ✓ Residence in the Republic of Ireland for at least three years prior to diagnosis. ✓ Being 18 years of age or older.
Healthy Controls	✓ Irish-descendent. ✓ Being 18 years of age or older.
EXCLUSION CRITERIA	
Patients & Healthy Controls	× History of (other) neurological, psychiatric or medical conditions affecting cognition or the ability to perform on cognitive testing.[a] × History of premorbid learning disability or diagnosed specific learning difficulty. × Current use of high-dose psychoactive medication that adversely affect level of arousal or responsiveness and the ability to engage in cognitive testing.[b] × English not as primary language. × Family History of MND and/or FTD.[c]

[a] Among medical conditions affecting cognition, uncontrolled Diabetes Mellitus, Hepatitis C, HIV, or current or two-months previously recipient of chemotherapy treatment were encountered. Conditions affecting the ability to perform on cognitive testing included uncorrected visual impairment or hearing loss. Upper extremity disability affecting motor performance and speech disturbance were only considered in the case of healthy controls. The use of a gender and age-matched healthy control group enabled to control for the occurrence of common chronic medical conditions among populations.

[b] Based on a previous ALS population-based study published in Ireland (Phukan et al., 2012), these instances represent less than 5% of incident cases but are particularly relevant for those patients with FTD and evidence of psychotic symptoms.

[c] This exclusion criterion only applies for healthy controls.

In cases where a reason for exclusion became apparent in the course of the assessment, data collection was completed but excluded from analysis, and the participant was informed that no follow-up would be made for further participation.

5.2.4. Longitudinal Study Design

Longitudinal assessments were carried out with both patients and healthy controls. The assessments were administered at four time points, every four months, which represents a year follow-up. This close interval between repeat assessments was selected to allow for meaningful longitudinal data to be collected, given the high attrition rate that accompanies disease progression in ALS. Although it can be argued that this short retest interval can intensify practice effects, these have been shown to be present as far out as 2.5 years post-baseline testing and therefore extending this interval would not control for them (Duff, 2012). Instead, these will be addressed by applying specific statistical techniques, detailed below.

Participants were informed during their first interaction with the researcher that three follow-up assessments were planned after the initial one. Additionally, at the end of the first, second and third visit, participants were asked for consent to be contacted again by phone in four months to enquire about their continued interest in participating. Engagement in research was discontinued in the following instances: (1) decline of further involvement, (2) development of disability that precluded further participation or of a medical condition that denoted an exclusion criterion, or (3) death. No follow-up assessments were performed on ALS patients who also fulfilled criteria for the diagnosis of FTD.

5.3. Ethical Considerations and Data Protection

The present research study is a subproject of a larger project investigating neuropsychological and functional correlates in neurodegenerative diseases, with granted full ethics approval from the Beaumont Hospital Ethics Medical Research Committee (REC reference 13/102). Neuropsychological data was collected under this ethics approval. Blood samples for genetic testing were obtained as part of a large scale research project investigating genetic contributors to ALS, also granted full ethics approval by the Beaumont Hospital Ethics Medical Research Committee (REC reference 05/49). Finally, data on caregiver burden was obtained from two separate studies investigating the patient and caregiver journey through ALS which were also granted full ethical approval from the Beaumont Hospital Ethics Medical Research Committee (REC references 12/84 & 16/44).

At the recruitment stage, all potential participants were provided with comprehensive information about what their engagement with the study would imply, and enough time was given to discuss this with family members or other relevant supports. An opportunity to

answer queries was also offered. Before obtaining their consent, it was assured that participants understood the risks and benefits of engaging in the study and that an informed decision was made. Participants were also informed of their right to refuse or withdraw from the study at any stage if desired and, in the case of patients, that this would not have an impact on their clinical care. Written informed consent was obtained from all participants at each assessment time. In the case of ALS patients not fulfilling criteria for FTD, mental capacity to give informed consent was assumed. In cases where the patient was not able to physically sign the consent form due to motor disability, verbal consent was obtained and a next of kin was asked to sign the consent form on their behalf, if one was present. For ALS patients also meeting criteria for dementia, it was assured that a next of kin was always present at the time of recruitment, discussion of potential participation and consenting.

Although no potential risks are likely to result from participation in neuropsychological data collection, this can sometimes cause fatigue, stress or can increase anxiety levels. Patients were informed that they could take breaks at their convenience or discontinue the assessment at any point, if desired. Participants were always informed of the identity and role of the person who would visit them in their homes, who would always bring an ID card. In the case of patients, all of them would have previously met the examiner in person at their attendance to the specialist MND clinic. In cases where the assessment took place in the Psychology Department at Beaumont Hospital, the participant was directed to the same or collected at the main entrance of the hospital, if preferred. None of the assessments proceeded if it was not within the best interest of the participant.

All information and data obtained from participating individuals was treated in a strictly confidential manner according to the stipulations of the Data Protection Acts 1988-2018. Data was initially collected in paper format and such hard copies were stored in a secured filing cabinet at the Trinity Biomedical Sciences Institute, which could only be accessed by investigators involved in the project. After going through a careful scoring process, data was transferred to a computerised master sheet using Microsoft Excel (spreadsheet software) 2013. Soft copies of the data were stored on a password-protected computer to which only researchers directly involved in the project had access. A unique code was assigned to each participant and this identifier was entered into the database, which did not contain identifying information in order to ensure anonymity. Names and other personal identifiers, linked to this anonymous code, were kept on a separate code-breaker password-protected sheet, stored in encrypted format with access limited to the same researchers. No health-related data was saved with the identification data.

All data obtained was used solely for research purposes, and no identifying information has been shared, presented or published. As per ethics approval, data will be stored for five years

after the end of the project to be able to clarify any queries that may arise following the publication of results. Hard copies of the data will subsequently be disposed in confidential waste bins.

5.4. Measures

5.4.1. Demographic and Clinical Data

Semi-structured interviews were employed to collect demographic and clinical data. Demographic data, collected for both patients and healthy controls, included: (1) date of birth, (2) gender, (3) handedness, (4) education, including age at time of cessation of formal education, number of total years and highest qualification obtained, (5) marital status, and (6) occupation and employment status.

Clinical data, collected for all ALS patients, included: (1) date and age at onset of symptoms, (2) site of onset (i.e. bulbar, spinal or thoracic/respiratory), (3) date of diagnosis, (4) family history of MND or other neurological or psychiatric conditions, (5) relationship to the main caregiver, (6) use of external care (i.e. homecare), and if so, number of hours per week, (7) use of NIV, and if so, duration per day (i.e. hours of use per 24h) and frequency of use per week (i.e. number of days) and, (8) whether enteral feeding tube (i.e. RIG/PEG) is in place. Both patients and healthy controls were also further screened for the presence of any exclusion criteria that may had not been identified during the recruitment process, and they were also enquired about their medication regime and weekly alcohol intake.

For patients, gathered clinical information was contrasted to that contained in the ALS Register to ensure consistency and accuracy of the same. In the case of an inconsistency, information from the ALS Register prevailed, given the high standards followed during the process of data collection for the register, which involves a meticulous medical chart review and data is always contrasted with Senior Consultant Neurologist and ALS Specialist (OH) in case of uncertainty. El Escorial Criteria category for each patient was extracted from the ALS Register.

Demographic and clinical characteristics of ALS non-participants (i.e. potential patient participants that were not captured or not suitable for participation) were also extracted from the ALS Register for these to be compared to the demographics of the patient sample. The aim of this was to provide with an estimate of the degree to which the patient sample embodies a true representation of the incident ALS population in Ireland.

Considering the respiratory status of most ALS patients over the course of the disease, arterialised tissue capillary blood gas tensions were measured to control for any effect that lower oxygen and higher carbon dioxide levels in the blood may have on cognitive

performance. To this aim, the TOSCA 500 non-invasive transcutaneous sensor was used (Rafiq et al., 2012). Peripheral capillary oxygen saturation ($Sp0_2$), an estimate of arterial oxygen saturation or amount of oxygenated haemoglobin in blood (SaO_2), and carbon dioxide partial pressure ($PaC0_2$) levels were recorded. Finally, the ALSFRS-R was also administered at each assessment time point in order to assess disease severity and motor progression. The ALSFRS-R total score was considered, as well as limb, bulbar and respiratory sub-scores.

5.4.2. Neuropsychological Assessment

Cognitive functioning was assessed using a comprehensive battery of neuropsychological tests. For this work, a key focus was given to language abilities and other cognitive domains including executive function, social cognition, behaviour and intellectual function. Table 5.2 summarises neuropsychological tests used to assess such cognitive functions, and these are described in more detail in subsequent sections. Moreover, as part of the same battery of tests, participants also underwent assessment of memory and visuospatial ability, which permitted an accurate diagnosis of comorbid dementia within our ALS sample. The specifics on the additional tests administered are detailed in Appendix F (page 356).

Table 5.2. Neuropsychological assessment.

<table>
<tr><th colspan="2">Assessment Tool</th><th colspan="3">Cognitive Function</th></tr>
<tr><td colspan="5">Intellectual Function</td></tr>
<tr><td colspan="2">Test of Premorbid Function UK</td><td colspan="3">Premorbid intellectual ability</td></tr>
<tr><td colspan="2">Raven's Coloured Progressive Matrices</td><td colspan="3">Current intellectual functioning</td></tr>
<tr><td colspan="5">Language</td></tr>
<tr><td rowspan="7">Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)</td><td>Auditory & Visual Lexical Decision</td><td rowspan="7">Measures a wide range of aspects of language functioning from a psycholinguistic perspective</td><td colspan="2">Phonological and orthographic lexical processing</td></tr>
<tr><td>Spelling of Words (by regularity) & Pseudowords</td><td>Spelling</td><td rowspan="2">(Dual-Route Model)</td></tr>
<tr><td>Reading of Words (by regularity) & Pseudowords</td><td>Reading</td></tr>
<tr><td>Homophone Definition & Regularity</td><td colspan="2">Lexical reading and semantic knowledge</td></tr>
<tr><td>Spoken & Written Word – Picture Matching</td><td colspan="2">Semantic knowledge</td></tr>
<tr><td>Auditory & Written Sentence – Picture Matching</td><td colspan="2">Grammatical and syntactic comprehension</td></tr>
<tr><td>Auditory Comprehension of Verbs & Adjectives</td><td colspan="2">Word processing</td></tr>
<tr><td colspan="2">Boston Naming Test (abbreviated version)</td><td colspan="3">Confrontation naming task; measures word retrieval and semantics for nouns</td></tr>
<tr><td colspan="2">Action Naming Test (abbreviated version)</td><td colspan="3">Confrontation naming task; measures word retrieval and action semantics</td></tr>
<tr><td colspan="2">Pyramids and Palm Tree Test (14-item version)</td><td colspan="3">Measures semantic knowledge</td></tr>
</table>

Table 5.2 (continued). Neuropsychological assessment.

Assessment Tool		Cognitive Function
Executive Function		
Verbal Fluency	FAS test	Phonemic and semantic fluency paradigms
	Restricted Verbal Fluency (letter C)	
	Semantic Fluency (Animals)	
	Action Fluency test	
Digit Span	Forward	Measures attention and working memory
	Backward	
Colour-Word Interference Test	Colour Naming	Measures various dimensions of executive control including selective attention, inhibitory control, cognitive flexibility and error monitoring. It is also a measure of speed processing.
	Word Reading	
	Inhibition	
	Inhibition/Switching	
Sorting Test		Measures abstract reasoning, concept formation, cognitive flexibility, modality-specific problem-solving (verbal/perceptual) and goal-directed behaviour
Social Cognition		
Conflicting Emotional Prosody		Measures the ability to recognise and name prosodic affect which is not always congruent with the semantic content of the message
Reading the Mind in the Eyes test		Evaluates affective theory of mind and the ability to infer mental states
Behaviour		
Beaumont Behavioural Inventory		Assesses behavioural change, rated by the carer
Mood		
Hospital Anxiety and Depression Scale		Screens for mood disturbances, specifically anxiety and depression

The neuropsychological assessment was carried out in a fixed order and participants were encouraged to take short breaks in between tests if needed, to minimise the effects of fatigue. The whole battery took approximately 2.5 hours to complete.

Tests which minimised the effects of motor and bulbar disability were selected. The majority of chosen tasks were untimed, but adjustments for reduced motor or speech speed were applied for tasks that required timing (i.e. verbal fluency and the colour-word interference test). Specific adjustments implemented to the scoring of these tasks are detailed below, when such neuropsychological tests are described thoroughly.

Moreover, in cases of loss of hand dexterity or anarthria, adaptations were also applied to the administration of the task so it could still be performed by the patient. Such task adjustments are also described for each test in subsequent sections. Adjustments were not possible for all tasks nonetheless, and consequently some tests could not be administered in patients with loss of hand dexterity or anarthria.

Neuropsychological battery selection, administration and scoring was supervised by Principal Clinical Neuropsychologist and PhD Supervisor (NP). Patient neuropsychological assessments were always performed by the PhD Candidate (MPG), and accurately trained research assistants supported healthy control data collection. Inter-rater reliability evaluations were performed for each research assistant to ensure that data was collected and scored consistently between raters.

Succeeding sections describe in detail the various neuropsychological tests utilised, organised by cognitive domain.

5.4.2.1. Language

Careful selection of a comprehensive battery of language tests that allowed for the assessment of the various aspects of language processing was a priority of this study. Most tests selected are from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA: Kay et al., 1992), complemented by other tasks. The PALPA was chosen over other available language batteries because of its functional approach, which enables the assessment of the nature of the difficulties at the different stages of language processing, and it therefore allows for a systematic evaluation of the different hypothesis formulated in chapter 4. The psychometric properties of the PALPA were evaluated as part of this work, and results are presented in Chapter 6 (Refer to Section 6.3.1, page 164). Described below are details of each language test applied.

- PALPA Auditory Lexical Decision (Imageabiliy & Frequency)

This task assesses auditory lexical processing by asking the subject to decide whether a spoken utterance is a real word or not. Accordingly, access to the phonological input lexicon is evaluated. Deciding if an utterance heard is a word or not can be made without knowing its meaning and therefore access to the semantic system is not necessary to carry out this task. The effect that word frequency and imageability have on word recognition is considered.

Scoring: the number of total correct responses (i.e. true positives) is recorded, as well as the number of High/Low Frequency (HF/LF) and High/Low Imageability (HI/LI) correctly identified items, and the combinations between them (i.e. total correct HFxHI, HFxLI, LFxHI, and LFxLI items).

Task adjustments: this task can be performed by giving a verbal response or by nodding when recognizing a real word. Therefore, no adjustments were required.

- PALPA Visual Lexical Decision (Imageability & Frequency)

This task assesses lexical decision for written stimuli by asking the subject to decide if a written string of letters is a real word or not. Thus, access to the orthographic input lexicon is evaluated,

and similar to the previous task, the effects of frequency and imageability on word recognition are investigated. To be able to perform on this task, access to the semantic system is not necessary given that the subject can recognise a written word not knowing what it means.

Scoring: same scoring as for Auditory Lexical Decision applies.

Task adjustments: this task is performed by marking the words that are recognised from a sheet that includes both real and pseudowords. For patients with loss of hand dexterity, the answer was called out to the examiner, who marked the answer sheet for them.

- PALPA Word Spelling (Regularity)

This task assesses the ability of the subject to spell through dictation a series of words, considering their regularity. Testing the regularity effect allows for the assessment of the dual-route model of spelling, together with the assessment of pseudoword spelling through dictation (see next task). Regular and irregular words are matched by word frequency, imageability, grammatical class and length (i.e. number of letters, syllables and morphemes).

Scoring: the number of total correct responses as well as the number of total correct regular and total correct irregular words spelled are considered. A qualitative analysis of the type of errors made was also performed.

Task adjustments: this task could only be completed if the ability to grip the pen and perform legible writing was maintained.

- PALPA Non-word Spelling

This task requires to spell through dictation auditory strings of letters that do not constitute real words. It is important for the administration of this task that the subject understands that the auditory utterances to be spelled are not real ones.

Scoring: the total number of correct responses is considered. As per administration guidelines, any spelling form that follows a sound-spelling correspondence is accepted as correct.

Task adjustments: as in the previous task, only participants able to perform legible writing could carry this task out.

- PALPA Word Reading (Regularity)

This task assesses reading ability, also considering regularity of the words. Together with the next task, it allows for the assessment of the dual-route model of reading. In this case, regular and irregular words are also matched by word frequency, imageability, grammatical class and length (i.e. number of letters, syllables and morphemes).

Scoring: the number of correct regular, irregular and total correct read words is considered.

Task adjustments: this task could only be performed if some degree of intelligible speech was maintained.

- PALPA Non-word Reading

This task involves the reading of written letter strings which are not real words. When administering this task, it is important to ensure that the subject understands that the written letter strings to be read are not real words, but that they are pronounceable.

Scoring: the number of total correct responses is considered.

Task adjustments: as in the previous task, only participants with some level of intelligible speech could perform.

- PALPA Homophone Definition & Regularity

This task assesses the ability to define a homophone (i.e. a word that has another word with the same pronunciation but different spelling and meaning; e.g. tail and tale), and then pronounce it. This task also allows to assess the dual-route model of reading. To be able to define a homophone, the subject must recognise the spelling form of the word to retrieve its meaning, rather than accessing it from its pronunciation (i.e. access the semantic system from the orthographic input lexicon). An intact lexical reading route is therefore required to perform this task. Additionally, this task also considers the effect that word regularity has on homophone definition. If a subject has difficulty reading through the lexical route and uses a grapheme-to-phoneme conversion strategy, not considering the spelling form of the word, the wrong homophone may be defined in the case of regular words. Due to this, an inability to correctly read irregular words will be observed.

Scoring: the number of total correctly regular and irregular words defined is considered, as well as the total number of regular and irregular words correctly read. Totals for correctly defined and correctly read words are also obtained.

Task adjustments: this task requires speech abilities to be relatively preserved to be able to perform. Patients with no speech were asked to write down the definition of each word. In these cases, reading could not be assessed.

- PALPA Spoken Word – Picture Matching

On this task the subject is given a spoken word and is asked to select the picture that corresponds to it from five different options. The other four pictures represent different types of distractors (i.e. close semantic, distant semantic, visually similar or unrelated). Half of the close semantic distractors are also visually similar to the target item (i.e. *sv*). Also, the visually similar and unrelated distractors are semantically related to each other but not to the target

item, as having more than one pair of items related semantically avoids a response based on a perceived semantic relation. This task assesses semantic knowledge, matching verbal representations to pictures (i.e. access to semantics through the phonological input lexicon).

Scoring: the number of total correct responses is considered, as well as the types of distractors selected in case of error.

Task adjustments: this task requires the subject to point at the correct picture and therefore it can be performed in cases of anarthria or inability to write. If no purposeful movement of the arm and hand was present, the subject was asked to indicate the location of the picture (i.e. top, middle left/right, or bottom left/right).

- PALPA Written Word – Picture Matching

This task is of the same nature of the previous one, but on this occasion the subject is required to read a written word. The subject is discouraged from reading the word aloud. The same type of distractors are included here. This task assesses semantic knowledge by matching written representations to pictures (i.e. access to semantics through the orthographic input lexicon).

Scoring: same scoring applies as on previous task.

Task adjustments: same adjustments applied as on pervious task.

In both previous tasks, the type of errors observed indicate a different kind of impairment. According to the test developers, selection of a close semantic distractor suggests a high-level semantic impairment, selection of a distant semantic distractor indicates a widespread semantic deficit, selection of a visually similar distractor can indicate a perceptual deficit, and selection of an unrelated semantic distractor indicates a severe semantic processing deficit (Kay et al., 1992). When selecting a semantically and visually related distractor, both a semantic or a visual deficit can explain the error (Cole-Virtue & Nickels, 2004).

- PALPA Auditory Sentence – Picture Matching

This task consists of giving the subject a spoken sentence and three picture choices, and the picture that matches the sentence must be chosen. One repetition of the sentence is allowed upon request. The non-target pictures or distractors include: lexical distractors for the subject (ls), object (lo), verb (lv) or adjective (la); pictures where the subject and object have been reversed (r); or where the amount "more/less" needs to be compared between pictures (ca). This task assesses grammatical and syntactic comprehension of heard sentences, and different types of sentences are considered including reversible vs non-reversible, active vs passive, gapped sentences (i.e. where an element of the sentence is not made specific and therefore it needs to be inferred), and sentences that involve converse relations.

Scoring: total correct responses and correct responses for each sentence type are considered.

Task adjustments: this task can be performed in case of anarthria or in case of inability to write as it only requires pointing. If the subject had restricted arm and hand movement due to motor disability, they were asked to indicate the location of the picture (i.e. top, middle or bottom).

- PALPA Written Sentence – Picture Matching

On this task a sentence and three pictures are also given to the subject, but on this occasion the sentence is shown in a written format and the subject is required to read it and to make the correct picture choice. The subject is encouraged to read the sentence silently. This task assesses grammatical and syntactic comprehension of written sentences, and the same types of sentences and distractors as on the previous task apply.

Scoring: same scoring applies as on previous task.

Task adjustments: same adjustments applied as on previous task.

- PALPA Auditory Comprehension of Verbs and Adjectives

This task assesses the comprehension of verbs and adjectives used on the two previous tasks. The subject is given a word (verb or adjective) and a definition of the same, and is required to say if the definition is correct or incorrect.

Scoring: the total number of verbs and adjectives correctly identified are considered.

Task adjustments: no task adjustments were needed in this case. The subject could either answer verbally or nod their head when the answer was correct.

- Boston Naming Test

The Boston Naming Test (BNT: E. Kaplan et al., 1983) is the most commonly employed confrontation naming task and it is used to assess word retrieval and semantic knowledge for nouns. For this project, a short 30-item version of the test was used (Graves, Bezeau, Fogarty, & Blair, 2004). This short form of the BNT has proven to have excellent internal consistency (Cronbach's Alpha = .90), adequate construct validity (correlation with full BNT form: r = .98), and almost perfect classification agreement (Cohen's kappa coefficient = .91).

On this task, a picture is presented to the subject and is asked to name it. According to standard administration protocol, if a subject misinterprets an image or has difficulty naming the same, a semantic cue is given. If the subject still fails to name the object, a standard phonemic cue is provided, which consists of the underlined initial phonemes of the word. The stimuli are presented in order of word frequency.

Scoring: items correctly named spontaneously as well as items named after provision of semantic or phonemic cue are considered. A total correct score is also obtained through the addition of spontaneous correct responses plus correct responses after stimulus-cued conditions.

Task adjustments: this task usually requires a verbal response. In the case of anarthric patients, a written response was requested. Spelling mistakes were not considered in this case, as long as it was clear that the subject referred to the target word.

- Action Naming Test

The Action Naming Test (ANT: Obler & Albert, 1979) is a confrontation naming task used to assess the retrieval and semantics of action-words or verbs. The Action Naming Test is as the Boston Naming Test in terms of configuration and administration, and therefore it also considers the provision of semantic and phonemic cues when appropriate. In this case, any form of the verb (i.e. infinitive, gerund or participle) is considered as a correct answer. A short version of the test created as a sub-study of this project was used and its psychometric properties were evaluated (refer to chapter 6, section 6.3.2, for more details).

Scoring: same scoring applies as on pervious task.

Task adjustments: same adjustments applied as on previous task.

- Pyramids and Palm Trees Test

The Pyramids and Palm Trees Test (PPT: Howard & Patterson, 1992) is a test of semantic knowledge in which the subject is presented with a picture triad and asked to match a target picture to the most related one of two objects illustrated below. Although this test allows for different versions to be performed mixing verbal, visual and written stimuli, visual stimuli was used in this case. Therefore, this task complements the other two previous word-picture matching tasks by assessing access to semantics through the visual recognition system.

An abbreviated 14-item version was used (Breining et al., 2015). This abbreviated form has proven to be adequate to identify individuals with clinically significant semantic memory impairment (for a score <13, specificity = 96%, sensitivity = 71%, area under the curve = 0.88, $p < .001$).

Scoring: total correct responses are considered.

Task adjustments: in this case, the subject can either name or point at the appropriate picture, and therefore no adjustments were required.

5.4.2.2. Executive Function and Social Cognition

Given the heterogeneous nature of executive control, selection of executive tasks aimed to evaluate as many executive processes as possible while minimizing the number and duration of tests chosen, to minimise patient fatigue. Selected executive tasks are described next.

- Verbal Fluency

Verbal fluency tests require the subject to produce as many different words as possible beginning with a certain letter or belonging to a designated semantic category within 60 seconds. Four verbal fluency paradigms were used here, two phonemic and two semantic. For the phonemic paradigms, no names of people, places or numbers are allowed, and neither is giving the same word with different endings. Verbal fluency tasks place important demands on executive processes, as described in chapter 2, and because of this, they are included in this section. However, its language component is acknowledged.

The two phonemic paradigms considered are the FAS test (Benton, 1967) and a four-letter long restricted paradigm (Abrahams et al., 2000). The FAS test consists of three one-minute trials to generate as many words a possible beginning with the letter F, A and S. This phonemic verbal fluency paradigm has shown high internal consistency (Cronbach's alpha = .83) and adequate construct validity, with correlations with other sensitive phonemic fluency tasks ranging from .85 to .94 (Strauss et al., 2006). For the phonemic restricted paradigm, the subject is given a minute to generate four-letter long words beginning with the letter C. This restricted paradigm has shown a differential degree of difficulty compared to the unrestricted paradigm, placing heavier demands on the executive control system, and therefore being more sensitive to frontal lobe damage (Abrahams et al., 2000).

Regarding semantic paradigms, a 60-second animal fluency task and a 60-second action fluency task are considered. The 60-second animal fluency task was demonstrated to moderately correlate with other semantic categories such as clothing or food, with coefficients ranging from .66 to .71, and with the FAS (r = .34-.64; Strauss et al., 2006). Regarding the 60-second action fluency task, this has also proven adequate construct validity by using an hypothesis-driven approach which demonstrated significant associations with other equivalent measures (convergent validity), and nil associations with non-related measures (divergent validity; Woods et al., 2005). For all paradigms, the examiner must record all given words legibly on a blank page.

Scoring: the total number correct responses is taken, which is the sum of all accepted words given by the subject in each condition. For the FAS, this is the sum of all correct words given in the three one-minute trials. Rule violations including set-loss errors and repetitions are also counted.

Task adjustments: for severely dysarthric or anarthric patients, a written response was requested. In these cases, two-minute intervals were allowed per trial as written responses take longer than spoken ones. Spelling mistakes were not penalised as long as it was clear which the intended word was.

The VFI was then obtained to correct for the effect of motor or bulbar disability. To this aim, the subject was required to read (for spoken responses) or copy (for written responses) back all correct given words as quickly as possible, and the time taken to do this was recorded in seconds. Prior to this, the examiner crossed out incorrect responses, so the subject would not read/copy them.

The VFI was calculated using the following formula:

$$VFI = \frac{(time\ given - time\ taken\ to\ \text{copy/read}\ correct\ words\ generated)}{number\ of\ correct\ words\ generated}$$

The VFI represents the time taken to generate a new word in seconds, which can be understood as the average thinking time per word.

Spoken and written VFIs are not directly comparable, given that double time is allowed for written paradigms. Therefore, this data required further transformation. Conversion tables to transform spoken and written VFI scores into equivalent converted scores from 0 to 12 were created based on performance of healthy controls, as per procedure outlined by VFI developers (Table 5.3; Abrahams & Bak, 2013). Further information on the specific procedure followed for the creation of such conversion tables is detailed in chapter 6 (section 6.5).

Table 5.3. Guidelines to create FVI conversion tables.

Performance Bracket[a]	Converted Score
≥ M + 6.75SD	0
M + 5.25SD to M + 6.74SD	2
M + 3.75SD to M + 5.24SD	4
M + 2.25SD to M + 3.74SD	6
M + 0.75SD to M + 2.24SD	8
M – 0.75SD to M + 0.74SD	10
< M – 0.76SD	12

[a] M = healthy control mean; SD = healthy control standard deviation

- Digit Span

The Digit Span subtest from the Wechsler Adult Intelligence Scale Version IV (WAIS-IV: Wechsler, 2014) is a widely used task to assess attention and concentration as well as auditory sequential processing and working memory. Encoding, self-monitoring and rehearsal strategies are also involved. Two different tasks are involved: a forward and a backward condition. For the forward condition, the examiner calls out a sequence of digits to the subject, who is required to repeat the digits back in the same order. For the backward condition, the

examiner also calls out a sequence of digits, but this time the subject must recall them in reverse order. For both tasks, the length of the digit-string progressively increases, after completing two trials of the same length. The task is discontinued when the subject gets the two same length trials wrong. The WAIS-IV Digit Span subtest has adequate internal consistency (r_{xy} = .93) and construct validity, with high correlations observed with other working memory subtests (Wechsler, 2014).

Scoring: a point is given for each correct sequence correctly recalled, and the total number of correct forward and backward responses are considered. Moreover, the longest digit-string achieved for each condition is also taken into account (i.e. longest span).

Task adjustments: this task could not be completed verbally by all patients. Response cards with digits from 1 to 9 displayed in a 3x3 matrix in ascending order were used for anarthric patients, who responded by pointing at the digits in a forward or backward manner, depending on the condition. Selection of this adjustment method was based on evidence from Baddeley and Wilson (1985), who demonstrated that subvocal phonological coding can be used by anarthric patients to retain sequences, and therefore overt articulation is not essential for working memory.

- Colour-Word Interference Test

The Colour-Word Interference Test (CWIT) is a test based on the Stroop procedure, which assesses a range of executive processes, including selective attention, inhibitory control, cognitive flexibility and error monitoring. The version of the Stroop task chosen for this project is from the Delis-Kaplan Executive Function System (D-KEFS: Delis, Kaplan, & Kramer, 2001). This version of the Stroop task includes four different conditions. The Inhibition condition, which is the core Stroop paradigm, essentially assesses the ability to inhibit a salient response (i.e. reading the printed word, which is the name of a colour) to generate a conflicting response (i.e. naming the dissonant ink colour in which the word is printed). Two baseline conditions are also included, a Word Reading condition and a Colour Naming condition, which assess key skills needed to be able to complete the Inhibition paradigm. Finally, an addition of this version of the Stroop test in comparison to other Stroop paradigms is the inclusion of a fourth condition, the Inhibition/Switching condition, in which the subject must alternate between reading the word and naming the dissonant ink colour. This D-KEFS subtest has shown adequate internal consistency, with split-half reliability coefficients on a composite score derived by combining the two baseline conditions ranging from .62 to .86 across age bands. Moreover, positive intercorrelations were demonstrated between time-completion measures for the four conditions, which indicated adequate construct validity (Delis et al., 2001).

Scoring: the time taken to complete each condition as well as the number of corrected and uncorrected errors are considered.

Task adjustments: anarthric patients were not able to complete this task. Dysarthric patients were also in disadvantage given that they take longer to complete the task because of their articulation deficits. To control for the effect of bulbar disability, the Time Increase Proportion (TIP) index was created. The TIP calculates the increase in time proportion that takes to complete the Inhibition (condition 3) and Inhibition/Switching (condition 4) in comparison to the two baseline conditions (Word Reading or condition 1 and Colour Naming or condition 2). Prior to calculating the TIP, the mean time to complete condition 1 and 2 must be calculated: [(Time Colour Naming + Time Word Reading) / 2]. The following formula is applied:

$$TIP = \frac{(time\ to\ complete\ Condition\ 3\ or\ 4 - mean\ time\ to\ complete\ Condtions\ 1\ and\ 2)}{mean\ time\ to\ complete\ Condtions\ 1\ and\ 2}$$

Two TIPs were obtained per participant, one for Inhibition and one for Inhibition/Switching.

- Sorting Test

The Sorting Test from the D-KEFS (Delis et al., 2001) is a card sorting task in which the subject is presented with a set of six cards that contain a different word each and certain perceptual features. The cards can be sorted into various groups (i.e. two groups of three cards in each) considering the concepts and visual features. Two different testing conditions are included, a Free Sorting condition, where the subject is asked to find as many different ways of sorting the cards as possible and to describe the criteria used, and a Sort Recognition condition, where the examiner sorts the cards into two groups and the subject is asked to identify them. Two different sets of cards are used and each one can be grouped into eight different target sorts, three of them based on verbal/semantic information of the words (i.e., verbal descriptions) and five of them based on visual features of the cards (i.e., perceptual descriptions based on size, colour, shape, etc.). Both the accuracy of the target sorts and the accuracy of the description of the sorting criteria are considered for the Free Sorting condition, and only the latter applies for the Sort Recognition condition. Accuracy of descriptions is decided following guidelines for scoring from the test manual.

The Sorting Test measures a wide range of executive processes, the main one being abstract reasoning/concept formation and problem-solving, but also cognitive flexibility in switching between different concepts and the transfer of conceptual knowledge into goal-directed behaviour. The ability to inhibit previously given responses is also assessed. The subject must have sufficient basic information-processing abilities to read and understand the words and to

perceive the visual features of the cards for performance to tap on the higher executive processes required to complete this task.

Construct validity was established through correlational analyses showing robust correlations between the two card sets and total scores, between verbal and perceptual description scores, and between Free Sorting and Sort Recognition conditions. Moreover, adequate internal consistency was demonstrated, with split-half reliability coefficients ranging from .55 to .86 on Free Sorting and from .62 to .81 on Sort Recognition across age bands (Delis et al., 2001).

Scoring: a few measures are considered from this task, each one assessing different aspects of executive control:

1. *Total confirmed correct sorts*, a measure of abstract reasoning and the ability to form conceptual relationships. It also assesses the ability to initiate problem-solving behaviour.
2. *Confirmed correct verbal sorts* and *confirmed correct perceptual sorts*, a modality-specific concept reasoning and problem-solving measure.
3. *Non-target sorting responses*, which include:
    a. *Unconfirmed sorts*: correct sort but not confirmed by an accurate description.
    b. *Set-loss target sorts*: do not meet the basic rule of two groups of three cards. Reflect an inability to understand the task demands or to maintain cognitive set.
    c. *Repeated sorts*: measure the ability to inhibit previous responses. Reflect perseverative tendencies and cognitive rigidity or concrete thinking.
    d. *Non-target even sorts*: each one of the two card sets can be sorted in ten different ways, but only eight are target sorts, therefore the other two are non-target even sorts. These are not concerning if accompanied by the correct sort description, but may otherwise represent defective concept formation.
4. *Percent Sorting Accuracy,* measured as:
   [(Number Confirmed Correct Sorts / Number Attempted Sorts) x 100]
   This measure represents the percentage of sorts from the total that are accurate.
5. *Free Sorting Description Score*, a measure of reasoning and concept formation skills.
6. *Non-target free sorting description responses*, which include:
    a. *"Not" statements*: where the second group is described as not having the label or attribute of the first one. Reflect accurate abstract but segmented thinking.
    b. *"Close Calls"*: responses that are correct but generic. Reflect accurate but concrete thinking.
    c. *Incorrect descriptions*: inaccurate or erroneous descriptions. Reflect inaccurate and deficient concept-formation skills. If novel incorrect responses are given

for each sort, this can be explained by distractibility, impulsivity or disinhibition, whereas if the same incorrect responses are repeated, impaired concept-formation and perseveration are likely the cause.

d. *Repeated descriptions*: when a description is repeated within the same card set. Reflect an inability to inhibit previous conceptual formations and to engage with flexible thinking.
e. *Non-response descriptions*: a "don't know" response.
f. *Non-credit descriptions*: ubiquitous responses that can be considered an accurate description of the target sort but that could apply to all or most sets.
g. *Overly abstract descriptions*: accurate descriptions that lack specificity or detail. Reflect overly abstract thinking.

7. *Percent description accuracy*, measured as:
   [[Free Sorting Description Raw Score / (Number of Attempted Sorts x 4)] x 100]
   This measure indicates the percentage of points achieved relative to the maximum number of points that could have been achieved in the description score considering the number of attempted sorts. A low score indicates that the subject does not necessarily have a difficulty in perceiving and forming conceptual relationships, but rather, in expressing this conceptual relationship in an abstract manner.
8. *Sort recognition description score*, which assesses concept formation in a more structured condition where the subject is not required to sort the cards but only to find their conceptual relationship.
9. *Non-target sort recognition description responses*, which include the same ones detailed in bullet point 6. A common incorrect response pattern in this condition is to give 2-1 repeated descriptions, where the subject perceives any of the 7 non-target sorts for that trial, where 2 cards are in one group and the third one is in the other, and vice versa (e.g. "two big cards and one small card in one group, and two small and one big ones in the other group").
10. *Free sorting versus sort recognition contrast measure*, obtained as follows:
    [Sort Recognition Description Score - Free Sorting Description Score]
    This score provides information on the ability of the subject to form adequate conceptual relationships when the sorts are generated by the examiner, in comparison to the ability of forming such conceptual relationships with no prompting. If the subject is better in the former case, the more structured testing condition is probably enhancing performance. By contrast, if a higher score is obtained in the latter, distractibility or response perseveration of a previous salient rule can explain performance.

Task adjustments: Anarthric patients, not able to verbally describe the sorts, were required to give a written answer. If no movement of the arms and hands which permitted arranging the cards was present, the subject was asked to call out the cards belonging to a group. If speech and functional movement of the arms was lost, this task could not be performed.

- Reading the Mind in the Eyes Test

The Reading the Mind in the Eyes test (RMET: Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) is a social cognition task which assesses theory of mind (i.e. the ability to infer the others' mental states). To this aim, the subject is presented with a series of 35 black and white photographs of the eye-region of human faces and is asked to choose which of four words best describes the way in which the person is thinking or feeling. To be able to perform on this task, a lexicon of mental states and their meanings must be preserved. If the subject is unsure of the meaning of one of the presented words, the examiner is allowed to provide a definition and an example of use of such word, following administration guidelines protocol. The RMET has shown adequate internal consistency (Cronbach's alpha = .73) and it has proven to be a sensitive measure to assess social cognition in ALS (Burke et al., 2016).

Scoring: total correct responses are considered.

Task adjustments: the subject can either name or point at the correct answer, therefore no adjustments were needed to complete this task.

- Conflicting Emotional Prosody

Conflicting Emotional Prosody, from the Florida Affect Battery (FAB: Bowers, Blonder, & Heilman, 1998), is a prosody recognition task in which the subject is asked to listen to affectively intonated sentences and decide if the speaker sounds happy, sad, angry or neutral. Thirty six sentences are given, but in twenty-four of these, the emotional semantic content of the sentence is not congruent with the emotional intonation of the speaker. From these twenty-four incongruent trials, twelve are conflicting (i.e. the prosody and message are completely incompatible) and the other twelve are inconsistent (i.e. the prosody and message differ but are not completely incompatible). The subject must therefore disregard the content of the message and focus on the emotional prosody of the speaker. In the remaining twelve sentences, the intonation and content is emotionally congruent, thus conveying the same emotional meaning. Regarding psychometric properties, internal consistency has not been investigated in the Florida Affect Battery, but adequate test-retest reliability has been proven, with coefficients ranging from .89 to .97 (Bowers et al., 1998).

Scoring: the total number of correct conflicting, inconsistent and congruent responses are taken, and the sum of total conflicting and total inconsistent correct responses also provides a total incongruent score. A total correct score is also obtained.

Task adjustments: in this case, the subject can also name or point at the correct answer given that there is a card with the four possible answers displayed, and therefore no adjustments were needed.

5.4.2.3. Behaviour

- Beaumont Behavioural Inventory

The Beaumont Behavioural Inventory (BBI: Elamin et al., 2017; Pinto-Grau, Costello, et al., 2017) is a proxy-report behavioural assessment developed specifically for the evaluation of behavioural change in ALS. As an ALS-specific measure, the BBI covers the wide range of behaviours that can occur in ALS while correcting for the effect that motor disability can have on behaviour. The BBI is filled in by a carer or next of kin. The BBI has demonstrated good internal consistency (Cronbach's aplha = .89; Elamin et al., 2017), and adequate convergent and discriminant validity as well as 72% of diagnostic accuracy compared to another ALS-specific behavioural assessment (Pinto-Grau, Costello, et al., 2017).

Scoring: the BBI assesses behaviour considering two different timelines: 1) changes that occurred ten years prior to the onset of the motor neuron disease, and 2) changes that have occurred since the onset of the disease. Although the former is a valuable indication a cognitive/behavioural onset, for the purposes of this work only the latter score is considered as it assesses current behavioural status. In terms of cut-off for impairment, a score of ≥7 indicates a significant behavioural change and a score of ≥23 is highly sensitive and specific to ALS-FTD (Elamin et al., 2017; Pinto-Grau, Costello, et al., 2017).

Task adjustments: adjustments do not applied in this case as the BBI is filled in by a third person other than the patient.

5.4.2.4. Other Measures

- Test of Premorbid Function UK

The Test of Premorbid Function (TOPF: Wechsler, 2011) is used to estimate premorbid intellectual quotient (IQ). In this task, the subject is asked to read a series of words with an atypical spelling. Performance is discontinued after five consecutive errors. The TOPF is a measure of single-word pronunciation which rely on previous knowledge of the word. The rationale behind using a word reading task as a measure of premorbid ability is that this skill is less susceptible to brain damage compared to other cognitive skills (Wechsler, 2011).

The TOPF premorbid IQ estimate is based on an equation that combines performance on the word reading task and demographic variables. This prediction model has proven effective to identify significant decline in cognitive function in individuals with brain injury and progressive neurological disorders (Pearson Assessment, 2009). Moreover, the TOPF has been found to highly correlate with the WAIS-IV (Wechsler, 2014).

The fact that language impairment may render this measure less effective in obtaining an accurate estimate of premorbid IQ in ALS is acknowledged. However, reading scores have shown to provide a useful premorbid estimate in other diseases that present with affected reading abilities, such as AD (Paolo, Tröster, Ryan, & Koller, 1997). Moreover, demographic information including age, gender and years of education are also considered when obtaining an estimated IQ as per the procedure outlined in the TOPF, as regression equations that combine current reading ability and demographic data lead to more powerful IQ predictions and can diminish the issue outlined above (Wechsler, 2011).

Scoring: the number of total correct responses is considered, and age-, gender- and education-adjusted predicted IQ scores are obtained using the Scorer for PC provided in the test. Specifically, the following premorbid estimated measures are calculated: full scale IQ (FSIQ), verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI) and processing speed index (PSI).

Task adjustments: anarthric and severely dysarthric patients could not perform on this task.

- Raven's Coloured Progressive Matrices

The Raven's Coloured Progressive Matrices (Raven, Raven, & Court, 1998) is a non-verbal test of fluid reasoning (i.e. the capacity of solving novel problems using deductive reasoning), which is independent from acquired knowledge and is used as a measure of current intellectual function. The subject is presented with a page containing a pattern at the top with a missing piece and six small figures below, one of them which completes the above figure, and is asked to select the correct one. To be able to complete the task, the subject is required to determine the underlying rules or relationship between the parts displayed. There are 36 stimuli in total, divided into three sets of 12, each one including items of progressive increased difficulty. This test has shown good internal consistency (split-half reliability coefficient above .80) and adequate concurrent validity, with moderately strong correlations found with other conventional intelligent tests such as the Wechsler (Strauss et al., 2006).

Scoring: the total number of correct answers per set and across all sets are considered.

Task adjustments: the subject can name the number corresponding to the correct answer, or alternatively point at it. No adjustments were therefore needed.

- Hospital Anxiety and Depression Scale

A modified version of the Hospital Anxiety and Depression Scale (HADS) proven to have appropriate construct validity for use in MND (C. J. Gibbons et al., 2011) is used as a mood screen to control and adjust for the effect of mood disturbances on neuropsychological assessment performance. This modified version of the HADS, created using Rasch analysis, demonstrated good internal construct validity, adequate reliability and usefulness to measure psychological distress in patients with MND (C. J. Gibbons et al., 2011).

Scoring: the modified HADS total score or HADS-T presented by C. J. Gibbons et al. (2011) is used as a measure of negative affectivity or psychological distress. Revised cut-offs to classify patients are given by these authors. Accordingly, a score from 17 to 20 indicates a 'possible mood disorder' and a score ≥ 21 designates a 'probable mood disorder'.

Task adjustments: This version of the HADS is adapted for the use in MND by omitting items that are highly influenced by physical impairment (i.e. item 8 "I feel as if I am slowed down", item 10 "I have lost interest in my appearance", and item 11 "I feel restless as if I have to be on the move").

- Zarit Burden Interview

The Zarit Burden Interview (Zarit, Reever, & Bach-Peterson, 1980) is used to measure caregiver burden. This scale assesses the level of strain experienced by caregivers by asking 22 questions relating to the burden associated with functional and behavioural impairments of their loved one, for which carers have to indicate how often they feel that way on a 5-point scale (i.e. never, rarely, sometimes, quite frequently or nearly always). Adequate construct validity and high internal consistency (Cronbach's alpha = .92) has been reported for the Zarit Burden Interview (Hébert, Bravo, & Préville, 2000).

Scoring: scores on the Zarit Burden Interview range from 0 to 88, with higher scores indicating higher levels of burden. A score of ≥24 was derived as the cut-off to indicate burden in the caregiver (Schreiner, Morimoto, Arai, & Zarit, 2006).

Task adjustments: adjustments did not apply in this case as the Zarit Burden Interview is filled in by the patient's carer.

5.5. Genetic Screening

Genetic testing was carried out with the patient sample to detect repeat expansions in the C9orf72 gene. As this data belongs to a separate project, it was provided by a research manager in a database with an anonymous code assigned to each patient that was linked to the code that patients were assigned as part of this project. Therefore, genetic status of patients was blind to researchers involved in this project.

5.6. Cognitive and Behaviour Categorisation: Revised Diagnostic Criteria

Cognitive and behavioural categorisation of the ALS sample was based on revised consensus criteria for the diagnosis of frontotemporal syndromes in ALS described in chapter 3 (Strong et al., 2017). Revised criteria for the diagnosis of bvFTD (Rascovsky et al., 2011) and PPA (Gorno-Tempini et al., 2011) were used to diagnose ALS-FTD cases. As per guidelines, a carefully matched healthy control group was used to delineate the limits for abnormal performance, and these also underwent longitudinal assessments to control for the effect of repeated testing on performance. Although revised diagnostic criteria was published in the midst of data collection, patient categorisation was not performed until data collection was completed in November 2017.

5.7. Statistical Analyses

5.7.1. Power Analysis and Sample Size Calculations

A priori sample size calculations were undertaken to estimate minimum sample size required to have sufficient statistical power for detecting meaningful effects between groups. Data from a previous study performed in comparable populations (i.e. case-control population-based study of cognition in incident ALS cases; Phukan et al., 2012) was used to obtain necessary figure estimates to calculate sample sizes. Minimum sample sizes required were calculated for detecting meaningful differences (1) between patients and healthy controls, and (2) between cognitively impaired and cognitively unimpaired patients. Moreover, for the former, sample sizes required for comparing means as well as for detecting a meaningful difference in proportions were obtained, as per Whitley and Ball (2002). In all cases, p-value for significance was set at .05, and desired power was .8.

1) *Sample size calculations for comparing ALS patients versus healthy controls*:

As mentioned, two required sample sizes were calculated in this case: (a) minimum sample size to compare proportions given that the incidence of cognitive impairment in the patient group is to be obtained, and (b) minimum sample size for comparing means. These are described below.

a) *Sample size for a difference in proportions*:

Prior to calculating minimum sample size required, the standardised target difference expected between patients and healthy controls in the proportion of cognitive impaired is obtained. As per selected baseline study (Phukan et al., 2012), the proportion of cognitive

impairment in ALS is 34.1%, compared to 6.4% in healthy controls. The following formula is applied to obtain the standardised difference (d):

$$d = \frac{(p_1 - p_2)}{\sqrt{[\bar{p}(1-\bar{p})]}}$$

, where p1 and p2 are the proportions of cognitive impairment for each group, and $\bar{p}$ is the mean of the two (i.e. $[(p_1 + p_2)/2]$).

Thus, the standardised difference is:

$$d = \frac{0.341 - 0.064}{\sqrt{0.2025 * 0.7975}} = \frac{0.277}{0.402} = 0.69$$

Then, to obtain sample size requirements for comparing proportions, the following formula is applied:

$$n = \frac{[p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2} \text{ x } c_{p,power}$$

, where n is number of subjects required in each group, and $c_{p,power}$ is a constant defined by the selected power and cut-off for statistical significance (Whitley & Ball, 2002).

In this case:

$$n = \frac{[0.341(1-0.341) + 0.064(1-0.064)]}{(0.341 - 0.064)^2} \text{ x } 7.9 = \frac{0.28}{0.077} \text{ x } 7.9 = 28.7$$

Thus, in order to compare proportions, a minimum of 29 subjects per group is needed.

b) *Sample size for comparing means*:

Minimum sample size required per group to guarantee enough power to detect differences in mean scores between patients and controls were also calculated based on results from baseline study previously referred to (Phukan et al., 2012). Scores obtained on phonemic verbal fluency were considered, because impairment on this test is a widely recognised marker of cognitive dysfunction in ALS (Strong et al., 2017). Thus, performance on the two groups was as follows: patients (M = 19, SD = 27.3) and healthy controls (M = 8.3, SD = 4.8), with higher scores indicating poorer performance, as these represent the VFI.

Prior to calculating minimum sample size required per group, the standardised difference must be obtained using the following formula:

$$d = \frac{\text{Target Difference}}{\text{Pooled Standard Deviation}}$$

In this case:

$$d = \frac{19 - 8.3}{\sqrt{\frac{27.3^2 + 4.8^2}{2}}} = \frac{10.7}{19.6} = 0.55$$

Then, minimum sample size required per group can be obtained with the formula:

$$n = \frac{2}{d^2} \text{ x } c_{p,power}$$

In this case:

$$n = \frac{2}{0.55^2} \text{ x } 7.9 = 52.23$$

Therefore, a minimum sample size of 53 subjects per group is required to have enough power to detect differences between patients and controls.

2) *Sample size calculations for comparing cognitively impaired versus intact patients*:

In this case, sample size requirements were only estimated for comparing means, using the same formulas described above, and also considering performance on phonemic verbal fluency in the same study cited above (Phukan et al., 2012). VFI performance in this case was as follows: cognitively impaired patients (M = 42.8, SD = 50.2) and cognitively intact patients (M = 10.1, SD = 6.2). Considering these figures, minimum sample size required per group was calculated:

$$d = \frac{42.8 - 10.1}{\sqrt{\frac{50.2^2 + 6.2^2}{2}}} = \frac{32.7}{35.7} = 0.91$$

$$n = \frac{2}{0.91^2} \text{ x } 7.9 = 19.08$$

A minimum sample size of 20 subjects per group is required to detect meaningful differences between cognitively intact and cognitively impaired ALS patients.

Sample size requirements for longitudinal analyses were also estimated. When planning on comparing repeated measures, variance and correlation patterns between measurements need to be taken into account (Guo, Logan, Glueck, & Muller, 2013). Accordingly, the web-based sample size calculator GLIMMPSE (Kreidler et al., 2013) was employed to estimate sample size requirements for the longitudinal study design as this is one of the few available that consider correlation and variance patterns in sample size computations for multivariate designs (Guo

et al., 2013). Stating the primary hypothesis as a test of whether there is a *group x time interaction*, the difference in the pattern of means as well as variance and correlation patterns among repeated measures were estimated based on data from a previous case-control longitudinal population-based study of cognition in ALS carried out in Ireland (Elamin et al., 2013). The response variable of interest in this case was also phonemic verbal fluency, for the same reason stated above. A flexible structure correlation pattern was selected to estimate variability across time, with a base correlation of .8 and a smooth decay of .05, and a previously reported standard deviation for phonemic verbal fluency was used to estimate variability across responses. Desired power value was .8 and type one error rate was also set a .05, as previously. Considering results from the Hotelling-Lawley Trace statistic, required sample size is 54 subjects per group.

In longitudinal research, however, attrition or loss of cases over time needs to be taken into account. On previous longitudinal population-based studies carried out by the Irish National ALS Research team (Crockford et al., 2017; Crockford et al., 2018; Elamin et al., 2013), the lowest attrition rates recorded were of 50% for ALS patients and 40% for healthy controls in a year-long period. Accordingly, sample size requirements were adapted according to this by using the following formula from Whitley and Ball (2002):

$$N'' = \frac{N}{(1-q)}$$

, where N is the required sample size and q represents the attrition rate.

In this case:

$$N''(\text{patients}) = \frac{54}{(1-0.5)} = 108$$

$$N''\ (\text{healthy controls}) = \frac{54}{(1-0.4)} = 90$$

Therefore, to meet sample size expectations for longitudinal testing, a minimum sample of 108 patients is intended to be recruited over a recruitment period of 33 months, and a minimum sample of 90 healthy controls is optimum.

Given that several analyses are undertaken in this thesis that consider different sub-groups of varying size, the effect size is also computed for the various investigations undertaken and reported where appropriate in subsequent results chapters.

5.7.2. Statistical Methods

Several statistical methods have been used. Data was analysed on an individual case-by-case basis as well as by group comparisons.

At an individual level, z scores were computed based on performance of the healthy control sample for each measure, using the following formula:

$$z = \frac{(x_i - \bar{x})}{sd}$$

, where x_i is the raw score for each participant, and $\bar{x}$ and *sd* are the mean performance and standard deviation of the healthy control group. Z scores were adjusted for some tests to ensure that in all cases higher scores indicated better performance.

The cut-off index (COI) for abnormality was set at 1.65 standard deviations (or 5th percentile) below the control mean, as per revised diagnostic criteria (Strong et al., 2017). From a statistical point of view, this cut-off indicates a significant change in scores at an alpha level of $p < .05$, given that the region for impairment is fixed entirely in the left tail of the Z distribution (one-tailed 95% confidence interval; Figure 5.1).

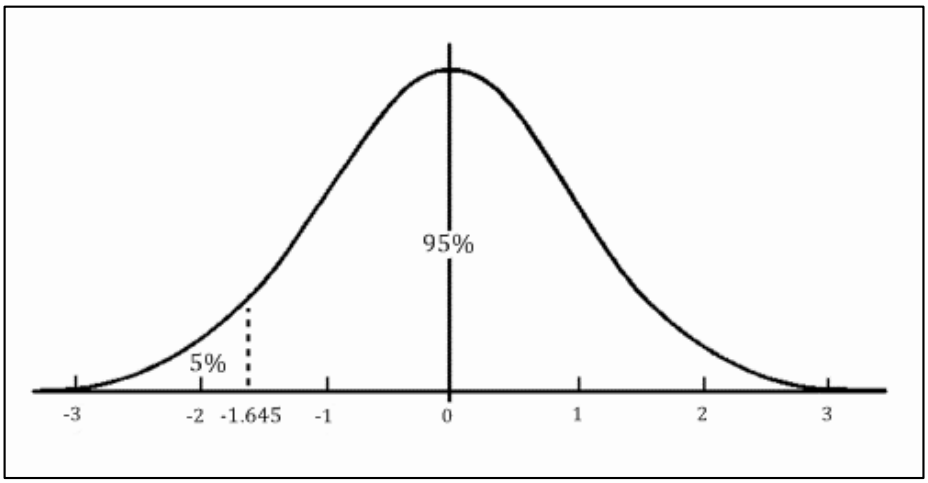

Figure 5.1. One-tailed standard normal distribution (α = .05)

Also at an individual level, statistical techniques to assess individual longitudinal performance and detect significant change over time were also used (Duff, 2012). These are explained in more detail in section 5.7.2.6.

At a group level, several statistical techniques were employed, including t-tests, tests to analyse categorical data, methods of analysis of variance, correlation and regression analyses, multilevel linear level modelling, survival analyses, and other techniques to examine psychometric characteristics. The specifics of each statistical method employed are detailed below.

All tests were two-sided and alpha level was set at .05, thus considering statistical significance at $p < .05$. Corrections for multiple comparisons and p-value adjustments were applied when necessary. Regarding descriptive statistics, data are presented as frequencies and percentages

for categorical variables and in the case of continuous variables, as mean and standard deviation or as median and range (i.e. minimum to maximum) or median and interquartile range (IQR). All statistical analyses were performed using RStudio 1.2.1335 for Windows (R-Studio Team, 2015).

5.7.2.1. T-tests and Non-Parametric Alternatives

Independent-samples t-test was used to compare mean scores between two groups and paired-samples t-test, to compare mean scores of repeated measures within the same participant. In both cases, the effect size was calculated by obtaining eta squared (η^2) using the formulas below, respectively.

Independent-samples t-test:

$$\eta^2 = \frac{t^2}{t^2 + (N1 + N2 - 2)}$$

Paired-samples t-test:

$$\eta^2 = \frac{t^2}{t^2 + (N - 1)}$$

Eta squared is interpreted as follows: small effect = 0.01, moderate effect = 0.06, and large effect = 0.14 (J. Cohen, 1988), and it represents the proportion of variance of the dependent variable explained by the independent variable.

Assumptions of normal distribution and homoscedasticity (i.e. homogeneity of variances) were checked a priori. If the assumption of homoscedasticity (assessed by means of Levene's test for equality of variances) was met, Student t-test was performed; otherwise, the Welch's t-test or unequal variances t-test was obtained. If the normality assumption, assessed using Shapiro-Wilk test (W), was not met and sample sizes were not considered robust (i.e. $n < 100$; Lumley, Diehr, Emerson, & Chen, 2002), non-parametric counterparts were used: Mann-Whitney-Wilcoxon rank-sum test for independent samples and Wilcoxon signed-rank test for matched pairs. The effect size estimate obtained in these cases was r, ($r = z/\sqrt{N}$), where N is the number of participants for the independent-samples test and the number of pairs for the paired-samples equivalent. The thresholds of r are 0.3 for a medium effect and 0.5 for a large effect (J. Cohen, 1988). Mood's median test or independent-samples median test was considered when equal variances could not be assumed, as this is a more robust test against extreme values or outliers.

Normal distribution of the difference between scores was also checked in the case of paired-samples t-test, although violation of this assumption was not considered concerning in sample

sizes above 30 participants (Boneau, 1960). Finally, the Kolmogorov-Smirnov test was used to assess equivalency in terms of the distribution of scores.

5.7.2.2. Tests for Categorical Data

Pearson's Chi-square test for independence (X^2) was used to compare distributions between categorical variables. In 2x2 contingency tables, Yate's continuity correction was applied to compensate for the overestimation of the chi-square statistic that occurs in such cases. In 2x2 comparisons where the assumption of minimum expected cell frequency of 5 was not met, the Fisher's Exact Probability Test was used instead. For larger contingency tables, post hoc tests were applied by examining the standardised residuals (i.e. a significant difference is considered when the standardised residual value lies outside of ±1.96). Regarding effect size, phi coefficient (φ) was obtained for 2x2 contingency tables, and Cramer's V was used for larger contingency tables:

$$\varphi \text{ or } V = \sqrt{\frac{X^2}{N(k-1)}}$$

, where N is the total number of observations and k refers to the number of columns or rows, whichever is smaller (i.e. 2 in case of φ). The strength of the effect size obtained by means of Phi or Cramer's V is interpreted as displayed in Table 5.4, depending on the degrees of freedom (i.e. k – 1).

Table 5.4. Interpretation of φ or V coefficients.

Degrees of freedom	Small	Medium	Large
1	0.10	0.30	0.50
2	0.07	0.21	0.35
3	0.06	0.17	0.29
4	0.05	0.15	0.25
5	0.04	0.13	0.22

From J. Cohen (1988)

McNemar's test was used to compare the distribution between categorical variables for two repeated or matched measures obtained from the same participant. Effect size was also obtained by means of Phi or Cramer's V. When more than two repeated measures had to be compared, Cochran's Q test was used instead, with post hoc tests run by means of McNemar's test and reported p-values adjusted using Bonferroni's correction. The maximum-corrected measure of effect size (η_Q^2) was obtained:

$$\eta_Q{}^2 = \frac{Q}{b(k-1)}$$

, where b is the number of respondents and k is the number of measures or conditions (Serlin, Carr, & Marascuillo, 1982).

5.7.2.3. Methods of Analysis of Variance

More complex group comparisons than those comparing two groups on a single continuous dependent variable were performed using analysis of variance (ANOVA).

One-way ANOVA was used when comparisons were performed between more than two groups or as univariate contrasts following multivariate ANOVA. Assumptions of normal distribution of the dependent variable within each group and of homoscedasticity were checked. In case of non-normality, when this was due to skewness rather than to the presence of extreme outliers, results were interpreted given that the F-test has proven to be a robust test for non-normal data, even with unequal sample sizes (Blanca, Alarcón, Arnau, Bono, & Bendayan, 2017). However, if equal variances could not be assumed, Welch's F test was reported instead. Homogeneity of variances was explored using the Bartlett Test of Homogeneity of Variances for normally distributed variables, and the Figner-Killeen Test of Homogeneity of Variances when normality could not be assumed. Given that large samples can produce significant effects on such tests even with small differences in variance, in sample sizes larger than 60 participants the Hartley's F_{max} or variance ratio was obtained by dividing the largest variance by the smallest. As per critical values table for Hartley's test, with *k* number of groups/conditions and *n – 1* degrees of freedom, a ratio below 1 is expected to consider the variances not significantly different in sample sizes larger than 60.

Group contrasts in the one-way ANOVA were performed using planned or post hoc comparisons, depending on our previously stated hypothesis. In the latter case, Bonferroni adjustment for multiple comparisons was applied to control for the increased chance of type I errors.

Effect size for one-way ANOVA analyses are reported by means of eta squared, obtained as follows:

$$\eta^2 = \frac{SS_{effect}}{SS_{total}}$$

, where SS_{effect} is the between groups sums of squares.

The Kruskal-Wallis Test was employed as a non-parametric alternative to the one-way ANOVA when the normality assumption was violated and sample sizes were not considered robust (i.e. $n < 30$). In this case, post-hoc tests were calculated by means of Mann-Whitney-Wilcoxon rank-sum test between pairs of groups, and Bonferroni adjustments were applied to correct for multiple comparisons.

One-way analysis of covariance (ANCOVA) was used when it was necessary to control for the influence that a third variable may have on the significant difference observed between groups.

Additional ANCOVA assumptions were tested in this case. First, to test the assumption of homogeneity of regression slopes, which presumes that the relationship between the dependent variable and the covariate is the same for each group, a regression line was fitted between the dependent variable and the covariate for each group, and similar slopes were expected. Accordingly, a non-significant interaction term was expected in order to assume homogeneous regression slopes. If the interaction term was however significant, this was kept in the model. Correlations among covariates were also explored, and if strong correlations (>.8) were observed between any of them, one was dropped so no highly correlated covariates were included. Finally, regarding the assumption of independence of the covariate and the independent variable, which implies that the groups must not differ on the covariate, it has been argued that in observational designs this assumption is irrelevant given that in such studies the independent variable is observed rather than manipulated (i.e. also called categorical predictor variable), and therefore participants cannot be randomised to experimental groups or matched on the covariate (Grace-Martin, 2008). Accordingly, results are interpreted as a more accurate estimate of the relationship between the independent and dependent variable at a given value of the covariate.

Effect size in ANCOVA is reported by means of partial eta squared (η_p^2), obtained as follows:

$$\eta_p^2 = \frac{SS_{effect}}{SS_{effect} + SS_{residual}}$$

Partial eta squared reports the proportion of the variance explained by the predictor variable accounting for the proportion of the variance explained by the covariate/s, and it is interpreted using the same guidelines as eta squared. Post hoc tests in ANCOVA were performed by means of Tukey's Honest Significance Test (HDS), given that adjusted means were compared.

Repeated measures ANOVA was used to compare more than two repeated measures on the same participant. The assumption of sphericity, which assumes that the variance of the difference between all pairs of within-subject comparisons are equal, was checked by means of Mauchly's Test. If sphericity was violated, the Greenhouse-Geisser correction (ε) was applied to the degrees of freedom to adjust the significance value to overcome the inaccuracy of the F-test caused by non-spherical data. Pairwise comparisons where undertaken, and the Bonferroni adjustment was applied to control for the familywise error rate.

Effect size in repeated measures ANOVA is reported by means of generalised eta squared (η_G^2):

$$\eta_G^2 = \frac{SS_{effect}}{\delta \text{ x } SS_{effect} + \sum SS_{measured}}$$

, where the denominator includes the summation of sums of squares for all subjects x repeated measures factor interactions measured, or $SS_{measured}$, and $\delta = 0$ when the number of measured

factors is one or more. Generalised eta squared is interpreted as follows: small effect = 0.02, moderate effect = 0.13, and large effect = 0.26 (Bakeman, 2005).

Multivariate analysis of covariance (MANCOVA) was used to compare performance between groups on a specific cognitive domain (i.e. language or executive function), considering the combination of tests included to assess this cognitive domain. The rationale behind using MANCOVA in these cases was to investigate if groups differed in terms of the overall cognitive domain, rather than focusing on single measures.

MANCOVA assumptions were tested in all cases. Multivariate normal distribution (i.e. multivariate normality within groups in all combined dependent variables) was assessed using Shapiro-Wilk test for multivariate normality as well as by obtaining Mahalanobis distances, which aim to detect outliers or cases that show an unusual pattern of scores across all dependent variables. Univariate normality for each dependent variable was also explored. If violation of normality assumption was not due to outliers but to skewness and sample size was > 20 in each cell, MANCOVA results were considered robust enough to be interpreted (Tabachnick & Fidell, 2007). In any other case (i.e. smaller sample sizes or a high number of outliers with very extreme scores), each situation was assessed individually.

Homogeneity of variance for each dependent variable, as well as homogeneity of variance – covariance matrices were also checked. Univariate equality of variances was checked for each dependent variable using Bartlett Test of Homogeneity of Variances for normally distributed variables, and Figner-Killeen Test of Homogeneity of Variances for non-normal variables. If the homoscedasticity assumption was violated for any dependent variable, a more stringent alpha p-value (i.e. 0.01) was considered to determine significance for that specific dependent variable. Homogeneity of variance – covariance matrices between groups was assessed using Box's M Test of Equality of Covariance Matrices. Given that in all cases sample sizes were unequal, if this assumption was violated, it was confirmed that groups with larger sample sizes had greater variances to consider the test robust. Otherwise, non-significant effects were trusted but results rejecting the null hypothesis were interpreted cautiously (Tabachnick & Fidell, 2007).

Correlations were also run between dependent variables to confirm the absence of multicollinearity. Ideally, moderate correlations between dependent variables were expected. If strong correlations (above 0.8) were observed between two variables thus indicating multicollinearity or singularity, one of the two was removed. The aforementioned assumptions relating to analysis of covariance detailed above were also checked for MANCOVA.

Pillai's trace (V) was the statistic of choice in MANCOVA analyses to designate if a significant difference existed among groups on the combination of dependent variables, as this is a more

robust statistic in cases of violations of assumptions or unequal sample sizes (Tabachnick & Fidell, 2007). Bonferroni corrections were applied to significance values on univariate contrasts to adjust for the higher risk of type I error caused by multiple testing. Effect size was also calculated by means of partial eta squared.

5.7.2.4. Correlation and Regression Techniques

Statistical techniques to explore relationships between variables have also been used, including correlational methods and regression analysis. Bivariate correlations were carried out by obtaining the Pearson product-moment correlation coefficient (r). The direction and strength of the relationship as well as the significance level of the same are reported. When informative, the amount of shared variance was obtained by squaring Pearson's coefficient (i.e. R^2). Holm correction for multiple comparisons was used to adjust p-values and reduce the risk of type I error when multiple correlations among variables were performed. In cases where sample sizes were small (i.e. < 30) and data was not normally distributed, Spearman's correlation coefficient (r_s) was used instead. Partial correlations were used to evaluate the relationship between two variables while controlling for the effect of a third one.

Regression methods were employed to further explore the relationship between variables by determining statistically significant predictors, as well as for prediction purposes. Simple linear regression was used when there was only one predictor of interest, and multiple linear regression was employed when the influence of several predictors was investigated.

In both cases, assumptions were assessed. The assumption of normality of the residuals was visually checked by inspecting the histogram of standardised residuals as well as with the Q-Q plot of standardised residuals plotted against their theoretical quantiles based on the regression model. The Shapiro-Wilk test was also used to assess normality of the standardised residuals. The presence of outliers (i.e. cases with a standardised residual outside ±3) and high leverage values (i.e. cases with hat values[1]) was inspected, as well as the presence of high influence observations (i.e. outliers with high leverage), which tend to have an important effect on the regression line. Cook's distances (D_i) were obtained for each observation to identify high influential cases. D_i values above 0.5 were scrutinised, and values above 1 were excluded.

The linearity of the relationship between the outcome and the predictors (i.e. the means of the outcome variable at each increase of the predictor variable/s can be placed along a straight line) was assessed by plotting the relationship between the fitted and the observed values of the outcome variable, as well as by plotting the relationship between the fitted values and the

[1] A measure of the extent to which an observation influences the direction of the regression line, which is 2 -3 times greater than the average leverage value, defined as $(k + 1)/n$, where k is the number of predictors and n is the number of participants.

residuals for each individual predictor. Curvature tests were also obtained (i.e. Tukey's test for non-additivity when plotting against fitted values).

The assumption of homoscedasticity of the residuals was checked using the non-constant variance test (NCV), which looks at the relationship between the fitted values and the variance of the residuals. If a significant result was obtained, thus indicating non-homogeneous variance of the residuals, the parameters of the model were estimated using sandwich heteroscedasticity corrected matrix estimators.

Finally, multicollinearity (i.e. high correlations between two or more predictors thus indicating a strong linear relationship between them) was assessed by calculating the variance inflator factor (VIF) for each predictor variable, which estimates the amount of variance in the regression coefficient that is caused by multicollinearity. VIF values close to 1 and under 5 were expected. Any predictor variable with a VIF of 10 or more was removed from the model.

Logistic regression was employed when the outcome variable was categorical (i.e. binary logistic regression for a binary categorical outcome variable and multinomial when the outcome variable was defined by more than two categories). The goodness of fit requisite of expected frequency per cell greater than 1 and no more than 20% of cells with frequency less than 5 was met in all cases. Moreover, analysis was discontinued in cases with complete separation (i.e. the outcome variable being perfectly predicted by one or a combination of predictors). The assumptions of independence of errors, multicollinearity between predictors, and linearity between continuous predictors and the logit of the outcome variable were checked in all cases. Nagelkerke's R^2 (R_N^2) is reported as a measure of goodness of fit.

5.7.2.5. Multilevel Linear Models

A mixed design (i.e. combining between-groups and repeated-measures analyses) was implemented to assess longitudinal data. Specifically, a generalised linear mixed model implemented as a multilevel model was employed. This was chosen over mixed ANOVA given its advantages in comparison to the latter (Finch, Bolin, & Kelley, 2016). First, multilevel models permit modelling of the relationship between observations where the assumption of independence of observations is not met (i.e. these are correlated). This is common in longitudinal designs where the same participant is assessed in more than one occasion. Likewise, multilevel models also allow for the variability in regression slopes to be modelled to overcome situations where the assumption of homogeneity of regression slopes is not met. This is achieved by specifying the type of covariance structure (i.e. the form of the variance-covariance matrix) adequate to that specific model. Also, multilevel modelling does not require the assumption of sphericity. Moreover, multilevel models handle non-complete data cases better than ANOVA analyses. Thus, if random missing data is present for a case at a specific

time point, parameters are estimated based on data that is available and therefore that case does not need to be excluded from the whole analysis.

Regardless of the above, multilevel linear models are based on the same principles as linear regression and therefore the assumptions that hold for the latter need to be checked here too. Accordingly, multicollinearity, normality and constant variances of residuals, and the linearity of the relationship between outcome and predictors were checked. The VIF was calculated to assess multicollinearity between predictors, and any predictor with a value higher than 10 was removed from the model. In cases where the assumption of normality of the residuals was not met, the presence of influential cases was investigated and observations with D_i values above 1 were excluded. The plot of fitted values against residuals was explored to assess the assumptions of homoscedasticity of the residuals and linearity. A random array of dots dispersed evenly around zero was expected, with any kind of curvature indicating a violation of the assumption of linearity, and funnel-shape patterns indicating heteroscedasticity of the data.

An additional assumption of multilevel models is the normal distribution of random coefficients. Although this was checked in all cases, violations of this assumption were not considered alarming considering existing evidence from simulations which indicate that this assumption is often unrealistic and that substantial violations of the same do not have much impact on the estimates in the fixed component of the model (Bell, Fairbrother, & Jones, 2018).

Multilevel models were compared using chi-square likelihood ratio tests. Goodness of fit for each model was assessed by means of Akaike's information criterion (AIC), which corrects for the number of parameters estimated, with smaller values representing better-fitting models. Moreover, significance tests for fixed effects on the full model were also considered and effect sizes for each significant effect were calculated using the following formula:

$$r = \sqrt{\frac{t^2}{t^2 + df}}$$

According to J. Cohen (1988), the correlation coefficient used as an effect size measure is interpreted as follows: small effect = 0.10, medium effect = 0.30, moderate effect = 0.50, and large effect = 0.70.

5.7.2.6. Methods to Explore Individual Reliable Change

In addition to statistical methods to compare longitudinal neuropsychological performance between groups, statistical techniques to detect significant change in individual cases were also employed. Specifically, four methods previously used to detect significant change in individual neuropsychological test performance were employed, two of them based on the Reliable

Change Index (RCI) and the other two, on standardised regression-based methods (Temkin, Heaton, Grant, & Dikmen, 1999). Each one of these is described below.

1) Method 1 – *The Jacobson and Truax RCI*

The RCI is a measure of statistical reliable change between two scores, which assesses if the difference observed between them is due to real change rather than due to measurement error or chance. The RCI is a ratio with a numerator that represents the observed change in scores for a given individual and a denominator that accounts for the presence of measurement error. The first RCI method employed is the one proposed by Jacobson and Truax (1991), derived using the following formula:

$$RCI = \frac{x_2 - x_1}{SE_{diff}}$$

, where x_1 is the baseline score, x_2 is the follow-up score, and S_{diff} is the standard error of the difference between the two scores. The S_{diff} represents the range of chance variation due to error or, in other words, the spread of the distribution of change scores in the hypothetical case that no real change had occurred. This is obtained from the standard error of measurement (SEM) of the test by applying the following formula:

$$SE_{diff} = \sqrt{2(SEM)^2}$$

The SEM is calculated as:

$$SEM = s_1\sqrt{1 - r_{xx}}$$

, where s_1 is the standard deviation at time 1 and r_{xx} is the reliability coefficient of the relevant comparison group, in our case this being the healthy control sample.

The error measured by a test is assumed to follow a normal distribution, with mean 0 and standard deviation representing the SEM. Accordingly, 95% of errors will lie within ±1.96 standard errors (two-tailed 95% confidence interval). Thus, in the RCI ratio, when the numerator exceeds the denominator by ±1.96, the change occurred is considered to be statistically reliable ($p<.05$) or in other words, change that occurred beyond that of chance variation and therefore not solely reflecting the effect of measurement error.

However, in the context of neuropsychological measures, a two-tailed 90% confidence interval (±1.645, $p<.10$) is usually applied (Duff, 2012). In this case, 90% of cases are expected to fall within the 'non-changed' range, and 10% are expected to exceed the ±1.645 cut-off point, 5% in a positive direction and the other 5% in a negative direction (Figure 5.2).

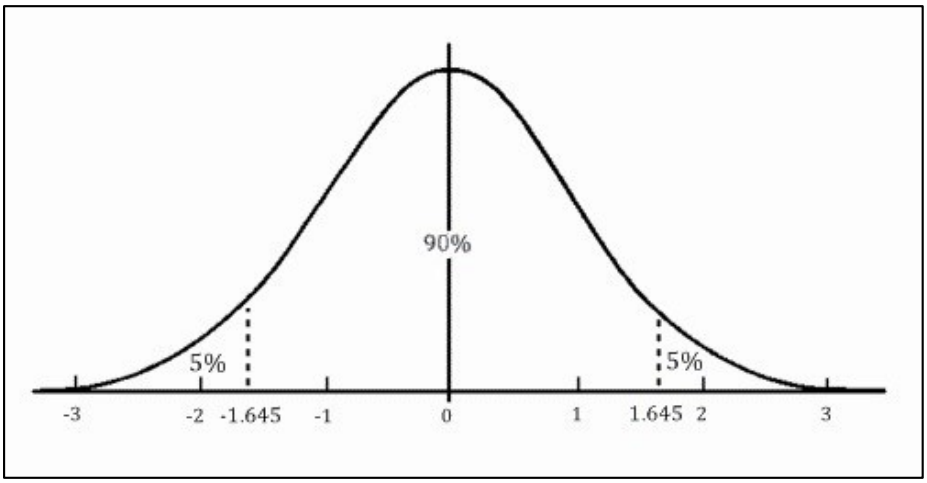

Figure 5.2. Two-tailed standard normal distribution (α = .10)

In our case, the latter cut-off for reliable change was employed. Moreover, prediction intervals or thresholds for reliable change (i.e. the number of points a score needs to increase/decrease for the change to be considered significantly reliable) were obtained as follows:

$$\pm\Delta X = 1.645\left(SE_{diff}\right)$$

The Jacobson and Truax RCI method was originally developed for the use in measures of psychological constructs such as depression or anxiety. Its use in neuropsychological measures therefore presents one important caveat: it does not account for practice effects on repeated testing (Duff, 2012). The next RCI method employed addresses this issue.

2) Method 2 – *The Chelune's RCI*

Chelune, Naugle, Lüders, Sedlak, and Awad (1993) adjusted the RCI to account for practice effects. Accordingly, they proposed to subtract the mean practice effects of the normative group from the individual's discrepancy score, as follows:

$$RCI = \frac{(x_2 - x_1) - (M_2 - M_1)}{SE_{diff}}$$

, where M_1 is the control group's mean at time 1, and M_2 is the control group's mean at time 2.

Later, Iverson (2001) pointed out that the previous formula does not control for variability in Time 2 scores and adapted the denominator (i.e. SE_{diff}) to account for it by considering the standard deviation of the normative sample at time 1 (s_1) and at time 2 (s_2):

$$SE_{diff} = \sqrt{(s_1\sqrt{1 - r_{xx}})^2 + (s_2\sqrt{1 - r_{xx}})^2}$$

In this case, prediction intervals were calculated as follows:

$$\pm\Delta X = (M_2 - M_1) \pm 1.645\left(SE_{diff}\right)$$

This RCI method is a more accurate estimate of reliable change given that it considers mean practice effects, variability at time 1 and time 2, and test-retest reliability. However, another important variable that can affect repeated testing is regression to the mean, that is, in repeat assessments, a given follow-up score tends to drift towards the population mean. This phenomenon not only affects those scores that drift up or down toward the population mean, but also those scores that remain stable or deviate more from the mean, as these probably convey more change than that reflected on a given raw score (Duff, 2012). Therefore, it is important to correct for regression to the mean when comparing pre- and post- individual measures. Regression-based methods, described next, introduce this correction.

3) Method 3 – *Simple Standardised Regression-based Approach*

Standardised regression-based methods use regression equations to predict retest scores based on baseline scores and other potential predictors, and examine the discrepancy between predicted and obtained retest scores (Crawford & Garthwaite, 2006). The simple standardised regression-based approach is based on simple linear regression analyses and therefore predicts retest scores based solely on baseline scores. Compared to the previous RCI methods explained, this approach accounts for regression to the mean effects, along with measurement error and practice effects (Temkin et al., 1999).

The simple standardised regression-based approach predicts the retest score by applying the simple linear regression equation with the baseline score as the predictor variable, as follows:

$$\hat{Y} = \beta_0 + \beta_1 X$$

, where $\hat{Y}$ is the predicted retest score, X is the baseline score, β_1 is the regression slope, and β_0 is the regression intercept.

Once a predicted retest score is obtained, this is compared to the actual observed retest score of the individual, and the frequency of the discrepancy between them is then tested using the same method outlined above for the RCI:

$$RCI = \frac{(Y - \hat{Y})}{SEE}$$

, where Y is the observed retest score, $\hat{Y}$ is the predicted retest score, and SEE is the residual standard error of the regression equation.

Similarly to the RCI, discrepancies that fall outside the ±1.645 cut-off are considered statistically significant and therefore are thought to indicate reliable change.

Prediction intervals for simple standardised regression-based models were calculated as:

$$\pm(Y - \hat{Y}) = 1.645(SEE)$$

4) Method 4 – *Complex Standardised Regression-based Approach*

Complex standardised regression-based models are based on multiple linear regression analyses and, in addition to baseline scores, these include other moderating effects of repeated-measures performance as predictor variables in the model. These models account for the effect of measurement error, practice effects, regression to the mean and any other moderating factors that have been included in the multiple linear regression equation:

$$\hat{Y} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_j X_j$$

, where X_1 is the baseline score and X_2 to X_j represent any other predictor variable included in the model, multiplied by their own regression slopes.

Prediction intervals in this case were obtained using the same formula as per simple standardised regression-based models.

5.7.2.7. Survival Analysis

Survival analysis was performed using the Kaplan-Meier method. Accordingly, Kaplan-Meier plots of survival probabilities were obtained to characterise survival curves and the log-rank test was used to compare these between groups. Moreover, Cox proportional-hazard regression analysis was employed to adjust for the effect of covariates on survival.

5.7.2.8. Measures of Psychometric Properties

Finally, psychometric properties of some neuropsychological measures were assessed by means of reliability and validity.

Regarding reliability, intra-class correlations (ICC) were employed to assess inter-rater and test-retest reliability. A single-rater, absolute-agreement, two-way random-effects ICC model was used for inter-rater reliability analyses, and a mean-rating, consistency, two-way fixed-effects model was selected for test-retest reliability assessments. For test-retest reliability, a random-effects model would not be appropriate as repeated measures cannot be understood as random samples (Koo & Li, 2016). Internal consistency was measured using Cronbach's alpha reliability coefficient, and other reliability measures such as split-half reliability and parallel forms reliability were also employed.

Concerning validity, construct and criterion-related validity were assessed through correlational analyses. Moreover, agreement between two classification methods was examined by obtaining diagnostic accuracy and efficiency measures, including the true-positive rate, the true-negative rate, and the relative observed agreement or correct classifications:

$$Sensitivity = true\ positives\ /\ (true\ positives + false\ negatives)$$

$$Specificity = true\ negatives\ /\ (true\ negatives + false\ positives)$$

$$Accuracy = (true\ positives + true\ negatives)\ /\ total\ observations$$

Predictive powers were also calculated:

$$Positive\ Predictive\ Value\ (PPV) = true\ positives\ /\ (true\ positives + false\ positives)$$

$$Negative\ predictive\ Value\ (NPV) = true\ negatives\ /\ (true\ negatives + false\ negatives)$$

The Kappa measure of agreement or Cohen's Kappa Coefficient (κ), which accounts for the probability of agreement based on chance, was also obtained:

$$k = \frac{(Relative\ observed\ agreement - Probability\ of\ agreement\ based\ on\ chance}{(1 - Probability\ of\ agreement\ based\ on\ chance)}$$

Cohen's Kappa Coefficient's interpretation is shown in Table 5.5.

Table 5.5. Interpretation of *K* coefficient.

K	Level of agreement
0 - .20	None
.21 - .39	Minimal
.40 - .59	Weak
.60 - .79	Moderate
.80 - .90	Strong
>.90	Almost perfect

From McHugh (2012)

CHAPTER 6 Outline.

Results Part I:

An Initial Analysis of Healthy Control Data

CHAPTER 6.

Results Part I:

An Initial Analysis of Healthy Control Data

6.1. Introduction

This first results chapter does not yet address any of the aims described in chapter 4, but instead it focuses on data extracted from healthy controls. Results described in this chapter are a first step which is needed to then examine patient data and, consequently, address the aims of this work. Concerning the content, this chapter initially presents demographic characteristics of the healthy control sample. Two psychometric studies are then undertaken on two language measures which have been adapted for their administration to the patient cohort. Lastly, the profile of neuropsychological performance of our population-based healthy control sample is described.

6.2. Demographic Characteristics of the Healthy Control Sample

A hundred healthy control participants were recruited as part of this study. Demographics of this sample are presented in Table 6.1.

Table 6.1. Demographic characteristics of the healthy control sample (n = 100).

Age *M±SD* years *Range*		64.0 ± 10.4 (34 – 89)
Gender %	Females Males	31 69
Handedness %	Right Left	91 9
Years of formal education *M±SD* years		15.2 ± 3.81
Highest level of education achieved %	Primary Education Lower Secondary Upper Secondary Advanced / Higher Certificate Ordinary Bachelor Degree / National Diploma Honours Bachelor Degree / Professional Qualification Postgraduate Diploma / Master's Degree Doctorate Technical / Vocational	13 9 29 10 8 11 11 1 8
Employment Status %	Employed Unemployed Retired	45 7 48

Table 6.1 (continued). Demographic characteristics of the healthy control sample (n = 100).

Marital Status %	Single	10
	Married	86
	Widowed	4
	Separated	0
Peripheral capillary oxygen saturation levels – $Sp0_2$ *M±SD* %		98.1 ± 0.85
Carbon dioxide partial pressure – $PaC0_2$ *M±SD* kPa		4.94 ± 0.71

More specifically, on arterialised tissue capillary blood gas tensions, all healthy controls had normal pulse oximeter readings (i.e. from 95% to 100%), and 3 had $PaCO_2$ levels > 6.0 kPa.

6.3. Adaptation of Language Measures: Psychometric Properties

Two preliminary studies on healthy control data were undertaken to assess the psychometric properties (i.e. validity and reliability) of two of the language measures included in our assessment protocol for which reliability and validity had not been adequately assessed before: the PALPA battery and the Action Naming Test (ANT). In the case of the ANT, two short parallel forms of the test were created and their equivalency and comparability were evaluated. Sections 6.3.1 and 6.3.2 present these two studies, the results of which are analysed and discussed separately.

6.3.1. Validation and Standardisation of the PALPA

6.3.1.1. Background

One important criticism of the PALPA assessment is the lack of proper standardisation and evaluation of its validity and reliability (Wertz, 1996). Although descriptive statistics on the performance of 32 healthy subjects are reported for some subtests (Kay et al., 1992) and further normative data was published for some reading tasks (Nickels & Cole-Virtue, 2004), the PALPA has not been fully standardised and its psychometric properties have not been adequately assessed.

The PALPA was developed as a battery that allows for flexibility in the type of tests to administer and in what order, depending on the clinician's hypothesis. This presents challenges at a psychometric level when considering the effect that order of subtest administration can have on reliability (Wertz, 1996), and at a clinical level, where the practicing clinician is expected to have a broad knowledge of the underlying model to be able to adopt a hypothesis-driven approach (Marshall, 1996). Considering this, for the purpose of this study, a standardised protocol with specific PALPA subtests that allow for a comprehensive assessment of the main language processing abilities was selected.

The aim of this study was to standardise and evaluate reliability and validity of the above-mentioned PALPA protocol. In terms of reliability, internal consistency and test-retest reliability were assessed. Construct validity was assessed by means of inter-correlational analyses with the hypotheses that (1) significant correlations would be observed between PALPA subtests given that all measure elements of language processing, with stronger correlations expected between those tests that measure similar language domains, and that (2) PALPA subtests would be consistently correlated with external variables such as age, education and IQ. A complementary analysis comparing the Auditory Sentence – Picture Matching PALPA subtest to another test of grammatical comprehension, the Test for Reception of Grammar Version 2 (TROG-2: Bishop, 2003), was undertaken.

6.3.1.2. Methods

Participants

The normative sample was composed of the one hundred healthy controls recruited as part of this work, whose demographic characteristics have been described in section 6.3. Additionally, the PALPA Auditory Sentence – Picture Matching task and the TROG-2 were administered to a sample of 35 healthy participants (Age in years: M = 64.2, SD = 7.88; Gender: 19 males, 16 females; Education in years: M = 14.27, SD = 3.98), recruited as part of a previously mentioned project investigating neuropsychological and functional correlates in neurodegenerative diseases (refer to section 5.3 for details). The same exclusion criteria as in section 5.2.3 applied.

Measures

Twelve PALPA subtests were included for this study's protocol. Among these were lexical decision tasks (auditory and visual) to evaluate the phonological and orthographic input lexicons, and reading and writing paradigms that consider word regularity and pseudoword processing to assess the dual-route theory. Also included were word-picture matching tasks (spoken and written) to measure semantic processing, and auditory and written sentence comprehension tasks. Two additional tasks assessing the processing of homophones and verb/adjective comprehension were also considered. The specifics of the PALPA subtests selected have been described in chapter 5 (section 5.4.2.1). Given that most PALPA subtests comprise the same items for spoken and written tasks and to avoid duplicates, items from such tasks were divided into two sets that constitute a spoken and a written paradigm with no repeat items. Specific items contained in each task are detailed in Appendix G (see Tables 1 to 4, pages 357-362).

Other measures considered include the TOPF and the TROG-2, the former to obtain an estimate of premorbid IQ and the latter, to further assess grammatical comprehension. The TROG-2 is similar to the PALPA Auditory Sentence – Picture Matching as the subject is also given a spoken

sentence and must select the correct picture from four choices. The TROG-2 also tests different grammatical constructions of varied difficulty.

Procedure

The PALPA protocol was administered following a standard procedure: all tests were administered in the same session, following a pre-established order and consistently with the instructions specified in the manual. As part of our longitudinal design, participants were re-approached four months after first testing to undergo repeat assessment for test-retest reliability estimation and evaluation of practice effects.

Statistical Methods

In terms of reliability analysis, internal consistency and test-retest reliability were evaluated. Cronbach's alpha coefficient was used as a measure of internal consistency of the selected PALPA protocol, or between PALPA subtests, with the hypothesis that they all measure the same construct, language. Cronbach's alpha reliability coefficient could not be obtained within individual subtests because of the high proportion of items with zero variance, due to ceiling effects. Test-retest reliability of repeat PALPA measures was also evaluated using ICC, specifically a mean-rating, consistency, two-way fixed-effects model (Koo & Li, 2016). Practice effects were explored using paired-samples t-tests.

In terms of validity, construct validity was assessed by means of inter-correlational analyses between PALPA subtests using Pearson's product-moment correlations. Furthermore, criterion-related validity was explored by analysing the relationship between PALPA subtests and other external variables: age, education and IQ.

Lastly, for standardisation purposes, raw scores for each PALPA subtest were converted into scaled scores (M = 10, SD = 3) based on mean performance from the normative sample using the formula: [Scaled Score = (((Observed Score – Sample M) / Sample SD) x 3) + 10]. Inferential norming, based on polynomial regression, has been proven adequate for the development of adjusted normative data when sample sizes per group are small (Zhu & Chen, 2011). However, this method could not be applied here as PALPA data is not normally distributed (Shapiro-Wilk normality tests for all PALPA subtests: $p < .05$). This is due to the presence of a low ceiling (i.e. a high proportion of examinees' scores being near or at the highest possible total), causing the distribution of scores to be truncated. Instead, predicted PALPA scores from premorbid intellectual ability were obtained based on linear regression (Crawford & Garthwaite, 2006).

6.3.1.3. Results

Demographic characteristics of the normative sample were described in Table 6.1. Premorbid IQ was estimated as follows: M = 104, SD = 12.8, range = 77–135.

Reliability

Consistency of the PALPA protocol selected for this study was as follows: Cronbach's alpha coefficient = .79, 95% CI [.74, .83]. Concerning test-retest reliability, 79 participants completed follow-up assessment at 4 months and therefore attrition rate was 21%. Test-retest reliability and practice effects analyses are presented in Table 6.2. Test-retest reliability was moderate to excellent for most PALPA subtests, with ICCs ranging from .62 to .93 and significant agreements between test occasions. Lower ICCs were observed for four subtests: Auditory Comprehension of Verbs and Adjectives, and for both Word – Picture Matching tasks. These results were caused by low ceilings on these tasks and a high amount of items with variance 0, and by an inconsistency of the errors between time points within individuals that did not obtain a maximum score.

Regarding practice effects (Table 6.2), significant results were only observed for two PALPA tasks (Auditory Lexical Decision and Homophone Definition x Regularity), with the remaining subtests showing no effects of prior exposure. For Auditory Lexical Decision, no significant differences were found on real word recognition (True positives Time 1: M = 39.9, SD = 0.30; Time 2: M = 39.9, SD = 0.42), $t(78) = 0.90$, p = .37, but a significant lower rate of false positives was observed at second assessment (True negatives Time 1: M = 32.8, SD = 5.78; Time 2: M = 35.4, SD = 4.44), $t(78) = -4.46$, p < .0001. For Homophone Definition x Regularity, significantly better performance was seen for regular words on word reading (Regular: Time 1 M = 9.94, SD = 0.25; Time 2 M = 10, SD = 0, $t(78) = -2.30$, p = .02. Irregular: Time 1 M = 9.57, SD = 0.71; Time 2 M = 9.70, SD = 0.69, $t(78) = -1.69$, p = .10), and for irregular words on word definition at follow-up (Regular Time 1 M = 9.63, SD = 0.68; Time 2 M = 9.63, SD = 0.64, $t(78) = 0.01$, p = .99. Irregular: Time 1 M = 9.44, SD = 0.84; Time 2 M = 9.62, SD = 0.77, $t(78) = -2.11$, p = .04).

Validity

Inter-correlational analyses between PALPA subtests (Table 6.3) showed significant positive correlations between most subtests, thus indicating good construct validity. Three subtests (Auditory Comprehension of Verbs, Adjectives, and Written Word – Picture Matching) showed inconsistent correlations with other PALPA subtests, driven by low ceilings. The only PALPA task that did not correlate with most other language tasks was Non-Word Spelling. Significant correlations were observed between most pairs of tasks assessing the same language construct: lexical decision (auditory, visual), homophone definition (reading, definition), auditory comprehension of words (verbs, adjectives), spelling and reading (words, pseudowords), and sentence comprehension (spoken, written). No correlation was found between Word – Picture Matching tasks, given that inconsistent errors were made on them.

Table 6.2. Test-retest reliability and practice effects analysis (n = 79).

Measure	Time 1 *M* ± *SD*	Time 2 *M* ± *SD*	Test-retest Reliability[a]						Practice Effects[b]		
			ICC	95% CI	F Test with True Value 0				t(df)	*p*	η^2
					F-test	*df1*	*df2*	*p*			
Auditory Lexical Decision	72.7 ± 5.81	75.3 ± 4.45	.65	[.45, .78]	2.9	78	78	<.0001	-4.34(78)	<.0001	.19
Visual Lexical Decision	58.5 ± 2.29	58.7 ± 1.91	.62	[.40, .75]	2.6	78	78	<.0001	-0.71(78)	.48	.006
Homophone Definition - Definition	19.1 ± 1.29	19.3 ± 1.18	.86	[.79, .91]	7.3	78	78	<.0001	-1.83(78)	.07	.04
Homophone Definition - Reading	19.5 ± 0.78	19.7 ± 0.69	.76	[.63, .85]	4.3	78	78	<.0001	-2.63(78)	.01	.08
Auditory Comprehension of Verbs	26.7 ± 0.59	26.8 ± 0.44	.37	[.01, .60]	1.6	78	78	.02	-1.22(78)	.23	.02
Auditory Comprehension of Adjectives	13.9 ± 0.27	13.9 ± 0.25	.23	[-.21, .50]	1.3	78	78	.13	-0.33(78)	.74	.001
Word Spelling	37.8 ± 2.64	37.8 ± 2.61	.94	[.91, .96]	17	78	78	<.0001	0.46(78)	.65	.003
Non-Word Spelling	10.4 ± 1.30	10.5 ± 1.38	.65	[.45, .78]	2.9	78	78	<.0001	-0.46(78)	.64	.003
Word Reading	59.2 ± 1.36	59.3 ± 1.29	.84	[.74, .90]	6.1	78	78	<.0001	-1.13(78)	.26	.02
Non-word Reading	10.8 ± 1.40	11.0 ± 1.07	.74	[.59, .83]	3.8	78	78	<.0001	-1.09(78)	.28	.02
Spoken Word – Picture Matching	19.9 ± 0.36	19.9 ± 0.25	.50	[.22, .68]	2.0	78	78	.001	-1.27(78)	.21	.02
Written Word – Picture Matching	19.9 ± 0.37	19.9 ± 0.25	.30	[-.09, .55]	1.4	78	78	.06	-1.40(78)	.17	.02
Auditory Sentence – Picture Matching	28.7 ± 1.86	28.9 ± 1.42	.68	[.50, .80]	3.1	78	78	<.0001	-1.17(78)	.24	.02
Written Sentence – Picture Matching	29.1 ± 1.35	29.2 ± 1.13	.75	[.61, .84]	4.0	78	78	<.0001	-0.71(78)	.48	.007

[a] Intra-class correlations

[b] Paired-samples t-test

Table 6.3. Intercorrelations between PALPA subtests.

Subtests	Auditory Lexical Decision	Visual Lexical Decision	Homophone Definition – Definition	Homophone Definition – Reading	Auditory Comprehension of Verbs	Auditory Comprehension of Adjectives	Word Spelling	Non-Word Spelling	Word Reading	Non-word Reading	Spoken Word - Picture Matching	Written Word - Picture Matching	Auditory Sentence – Picture Matching	Written Sentence – Picture Matching
Auditory Lexical Decision	1													
Visual Lexical Decision	r=.58***	1												
Homophone Definition – Definition	r=.30***	r=.43***	1											
Homophone Definition – Reading	r=.37***	r=.55***	r=.74***	1										
Auditory Comprehension of Verbs	r=.30***	r=.20*	r=.18	r=.15	1									
Auditory Comprehension of Adjectives	r=.18	r=.05	r=.12	r=.10	r=.66***	1								
Word Spelling	r=.32***	r=.54***	r=.72***	r=.68***	r=.34***	r=.16	1							
Non-Word Spelling	r=.31***	r=.36***	r=.32*	r=.32***	r=.25**	r=-.09	r=.41***	1						
Word Reading	r=.28**	r=.43***	r=.65***	r=.58***	r=.24**	r=.28***	r=.65***	r=.33	1					
Non-word Reading	r=.27**	r=.47***	r=.50***	r=.47***	r=.19	r=.15	r=.64***	r=.27*	r=.61***	1				
Spoken Word – Picture Matching	r=.47***	r=.57***	r=.23**	r=.27**	r=.13	r=.05	r=.32***	r=.18	r=.28***	r=.32***	1			
Written Word – Picture Matching	r=.00	r=.19	r=.30***	r=.25**	r=.22*	r=.24**	r=.28***	r=-.06	r=.47***	r=.30***	r=.07	1		
Auditory Sentence – Picture Matching	r=.48***	r=.40***	r=.42***	r=.42***	r=.47***	r=.40***	r=.43***	r=.18	r=.50***	r=.29***	r=.35***	r=.18	1	
Written Sentence – Picture Matching	r=.33***	r=.34***	r=.44***	r=.33***	r=.34***	r=.29***	r=.34***	r=-.07	r=.39***	r=.34***	r=.29***	r=.30***	r=.55***	1

Note. p-values adjusted using Holm correction for multiple comparisons.
*p<.05, **p<.01, ***p<.001

Regarding correlational analyses between the PALPA subtests and other external variables (Table 6.4), nil correlations were observed between most subtests and age. Weak negative significant correlations were observed between age and Auditory Comprehension of Verbs, Spoken Word – Picture Matching, and Auditory Sentence – Picture Matching, all these tasks being auditory. A moderate negative correlation was found between age and Auditory Lexical Decision. This correlation was not with true positives or real words recognised ($r = -.15$, $p = .14$), but with the number of true negatives ($r = -.39$, $p < .0001$), indicating that increasing age is related to a higher number of false positives or non-words identified as words. Significant positive correlations were found between PALPA subtests and education and IQ. The only PALPA subtest that did not correlate with education was Non-Word Spelling, but this weakly correlated with IQ. A nil correlation between Spoken Word – Picture Matching and education was also found, again likely due to the nature of the data. Consistent correlations between PALPA subtests and demographic variables further support construct validity.

Table 6.4. Correlations between PALPA subtests and demographic variables.

Subtests	Age	Years of Education	FSIQ
Auditory Lexical Decision	r=-.40***	r=.30***	r=.40***
Visual Lexical Decision	r=-.16	r=.20*	r=.44***
Homophone Definition – Definition	r= .02	r=.35***	r=.58***
Homophone Definition – Reading	r= .00	r=.27**	r=.50***
Auditory Comprehension of Verbs	r=-.20*	r=.25**	r=.34***
Auditory Comprehension of Adjectives	r=-.19	r=.23*	r=.26**
Word Spelling	r=-.04	r=.36***	r=.60***
Non-Word Spelling	r=-.18	r=-.02	r=.21*
Word Reading	r=-.03	r=.24*	r=.52***
Non-word Reading	r=-.06	r=.30***	r=.54***
Spoken Word – Picture Matching	r=-.25**	r=.19	r=.28**
Written Word – Picture Matching	r= .07	r=.28***	r=.33***
Auditory Sentence – Picture Matching	r=-.24*	r=.31***	r=.44***
Written Sentence – Picture Matching	r=-.19	r=.31***	r=.44***

Note. p-values adjusted using Holm correction for multiple comparisons.
*p<.05, **p<.01, ***p<.001

Pearson's product-moment correlations were also run between scores on the Auditory Sentence – Picture Matching PALPA subtest and the TROG-2, and a significant strong positive correlation was observed between them ($r = .80$, $p < .0001$). These two tasks also correlated consistently with external variables such as age (PALPA: $r = -.38$, $p = .02$; TROG-2: $r = -.43$, $p = .01$) and education (PALPA: $r = .40$, $p = .02$; TROG-2: $r = .49$, $p = .003$).

Standardisation

Normative data for the PALPA is displayed in Appendix G. Scaled scores for each subtest total score and for some sub-scores are included (Table 5, Appendix G, pages 363-365). No age adjustments were made on normative data based on results from prior correlational analysis. IQ-adjusted normative data for each PALPA subtest was generated using simple linear

regression. Given the high positive correlation that exists between education and IQ in our cohort ($r = .82$, $p < .0001$), only IQ-adjusted norms were created on the basis that IQ is a more reliable estimate of functioning than education, which is context-mediated. For each simple linear regression model, estimated FSIQ was included as the predictor variable (X), and the regression coefficient or slope (β) was used to calculate the change in PALPA raw scores (outcome variable Y) for a one-point change in IQ [$Y = \text{intercept} + \beta X$]. 95% prediction interval bounds [$Y \pm 1.96s$, where *s* is the residual standard error] were calculated around each value of the outcome variable (PALPA scores) and are reported for each value of the predictor variable IQ. Simple linear regression results are detailed in Table 6.5. F-tests are not reported as these are considered redundant for simple linear regression models, given that they also test the relationship between a single predictor and the outcome variable, as with the t-test. Coefficients of determination (R^2) are not reported here either as correlation coefficients (r) have been described above. The assumption of normality of residuals was not met in all cases due to the presence of outliers (standardised residuals outside ±3; a maximum of two were observed for one same model). Cook's distance (D_i) indicated the presence of one high influence observation ($D_i > 0.5$) for Auditory Comprehension of Adjectives, one for Auditory Comprehension of Verbs, and one for Non-Word Reading. As none of these had a D_i greater than 1, they were not excluded from the analysis. Assumption of homoscedasticity was only met for Non-Word Spelling, and coefficients were corrected using sandwich heteroscedasticity corrected matrix estimators for all other cases. Predicted PALPA scores from estimated premorbid FSIQ are presented in Appendix G (Table 6, pages 366-367).

Table 6.5. Regression models to predict the effect of IQ on PALPA performance.

	β	SEE	t-test	*p*
Auditory Lexical Decision	0.18	0.039	4.75	<.0001
Visual Lexical Decision	0.09	0.018	4.81	<.0001
Homophone Definition – Definition	0.06	0.009	6.41	<.0001
Homophone Definition – Reading	0.03	0.006	5.15	<.0001
Auditory Comprehension of Verbs	0.02	0.007	3.14	.002
Auditory Comprehension of Adjectives	0.008	0.004	2.12	.04
Word Spelling	0.14	0.022	6.44	<.0001
Non-Word Spelling	0.03	0.013	2.15	0.03
Word Reading	0.05	0.009	5.63	<.0001
Non-Word Reading	0.06	0.012	4.76	<.0001
Spoken Word – Picture Matching	0.008	0.003	2.45	.016
Written Word – Picture Matching	0.01	0.003	3.39	.001
Auditory Sentence – Picture Matching	0.07	0.010	7.22	<.0001
Written Sentence – Picture Matching	0.05	0.009	5.22	<.0001

6.3.1.4. Discussion

The reliability and validity of a selected protocol of subtests from the PALPA were evaluated in this study. Normative data and PALPA predicted scores based on IQ are also presented.

In terms of reliability, high internal consistency indicated that the different subtests of the PALPA selected for this study correlated well with each other. On test-retest reliability analyses, excellent ICCs were obtained for most PALPA subtests. For four exceptions observed (Auditory Comprehension of Verbs, Auditory Comprehension of Adjectives, Spoken Word – Picture Matching, and Written Word – Picture Matching), lower ICCs indicate that the errors made by participants who did not obtain the maximum score were not consistent within time points. This means that participants who made errors at assessment time 1 performed accurately at assessment time 2, and vice versa. This could indicate that these errors do not represent genuine language deficits as performance within individuals would be expected to be consistent, given that no learning effects are observed for these tasks. Instead, these could be the result of random error such as low attention, impulsivity, etc. Practice effects are not observed for most PALPA tasks, with only two exceptions. In the case of Homophone Definition x Regularity, an effect of prior exposure was observed when reading regular words and defining irregular words. For Auditory Lexical Decision, an improvement with repeat exposure was seen with a reduction of false positives. Familiarity with the test and items most likely played a role on such improvements in performance.

Regarding validity, significant positive correlations between PALPA subtests indicate good construct validity. Further evidence supporting this was provided by correlations between PALPA subtests and demographic variables that followed the same pattern. Thus, no correlations between PALPA subtests and age, and positive significant correlations between PALPA subtests and education and IQ were observed. Non-Word Spelling was the only task that did not correlate with most PALPA subtests or with education. Regarding the effect of age, there was an increasing number of false positives with age on the Auditory Lexical Decision task. Nevertheless, false positive errors reduced with repeat assessment. Furthermore, most PALPA subtests assessing the same language construct correlated with each other. The only exception was found for the Word – Picture Matching tasks, where spoken and written paradigms did not correlate. These results indicate an inconsistency in performance on these tasks (individuals who made mistakes on the spoken paradigm performed well on the written one, and vice-versa) and support the idea that the errors committed on these tasks are most likely attentional rather than language driven. In examining the data qualitatively, SV errors (close semantic plus visual distractors) were the most frequently observed. According to Cole-Virtue and Nickels (2004), SV distractors are semantically closer to the target item than the sole semantically related distractors, making these kind of errors more prone.

Normative data in the form of scaled scores are presented for each subtest of the PALPA as well as for some sub-scores within tests. Based on an observed relationship between IQ and PALPA

performance, predicted PALPA scores on the basis of estimated premorbid FSIQ were also derived.

The selection of a specific protocol which does not include the whole range of PALPA subtests can be seen as a limitation, as it can be argued that this approach limits one of the strengths of the PALPA, the flexibility of its hypothesis-driven approach to test aphasic patients. The rationale for selecting a specific protocol to be psychometrically assessed and standardised is twofold: on one hand, it would not have been feasible to undertake this study with the whole PALPA battery, which includes 60 subtests in its totality, and on the other hand, a specific protocol which assesses the main language constructs included in the PALPA allows for the application of this psycholinguistic approach to disease populations other than aphasia. As stated by Basso (1996, p. 193), "a shorter 'core' battery to be used for all patients would have been more practical. Whenever this is the case, this 'core' battery should be supplemented with more detailed examinations for specific disorders".

In conclusion, this study has proven the adequate psychometric properties of a protocol of language subtests from the PALPA. This protocol is administered to the patient cohort to evaluate language change in ALS from a psycholinguistic perspective focusing on the main language functions of interest.

6.3.2. Development of Two Parallel Short Forms of the ANT

6.3.2.1. Background

A second study based on healthy control data aimed to develop two shortened forms of the ANT and assess their psychometric properties. Confrontation naming tasks such as the Boston Naming Test or the ANT in their full forms are long tests which can be challenging for patients with neurological conditions, who can experience difficulties with sustaining attention, fatigue, lack of motivation and frustration, or because of time constraints during assessments. Shortened forms of the Boston Naming Test exist (Fastenau, Denburg, & Mauer, 1998; Franzen, Haut, Rankin, & Keefover, 1995; Graves et al., 2004; Lansing, Ivnik, Cullum, & Randolph, 1999; Saxton et al., 2000; Williams, Mack, & Henderson, 1989). These are useful in the context of extensive neuropsychological assessments to overcome the aforementioned limitations, and can also serve as alternate forms in test-retest evaluations such as longitudinal and pre-post intervention assessments. Considering the above, two shortened forms of the ANT were created following a split-half procedure and their equivalency, reliability and comparability to the full form were assessed. Internal consistency was also explored. Moreover, as an additional measure of equivalency and comparability between ANT forms, their relationship with demographic variables was explored, with the hypothesis that if the three forms are equivalent, demographic characteristics should influence performance on them to the same degree.

6.3.2.2. Methods

Participants

This study was performed on the same normative sample composed by the hundred healthy control participants recruited as part of this work.

ANT split-forms development and administration

The ANT is a 57-item confrontation naming task where individuals are presented with images of actions and asked to name them. Items on the ANT range from more frequent and easy to name to rarer and more complex. A split-half procedure was used to create the two short forms of the ANT, with the aim to preserve the whole content range of the full test and maintain word frequency and item difficulty rate, which ensures generalizability across different populations. Accordingly, item selection for the short forms was based on the order of items on the original form, assigning odd-numbered items into form A and even-numbered items into from B to achieve item matching for word frequency and complexity.

The test was administered according to the standard administration protocol (Obler & Albert, 1979). All items were presented in the pre-established order, as no discontinuation rules exist. If a subject misinterpreted one of the images or had difficulty naming the same, a semantic cue was given. If the subject still failed to name the action, the examiner provided a phonemic cue. Items were scored according to the number of items correctly named spontaneously, number of items named after provision of semantic cue, and number of items correctly named after phonemic cue. A total correct score was also calculated through the addition of spontaneous correct responses plus correct responses after stimulus-cued conditions. Any form of the verb given (infinitive, gerund or participle) was considered correct.

During the process of item assignment for the development of the short ANT forms, 29 items were allocated to Form A and 28 items to Form B. After completion of data collection, item 43 from the original form (*Exercising*) was excluded from analysis due to the ambiguity of this concept. The term 'exercising' represents a superordinate concept, whereas the designated picture characterises a subordinate concept belonging to this general category. As a consequence, this image elicited more specific responses such as 'yoga', 'gymnastics' or 'balancing' and a large proportion of participants required further prompting for the target word 'exercising' to be recalled. Thus, each final alternate form of the ANT consists of 28 items. Items composing each short form of the ANT are detailed in Appendix H (Table 1, page 368).

Statistical Analysis

Equivalency of the two ANT alternate forms was assessed by checking whether their mean and distribution of scores differed significantly. Paired-samples t-test was used to compare mean

performance scores on both short forms, and the Kolmogorov-Smirnov test was used to assess equivalency of the distribution of scores.

Cronbach's alpha reliability coefficient could not be used as a measure of internal consistency in this case given the nature of the data. As the most frequent and easy items of the ANT were answered correctly by all participants, variance for these items was zero and therefore they were removed from the analysis, thus impeding proper calculation of this internal consistency index. Alternatively, split-half reliability was obtained as a measure of internal consistency of the full form based on split-half forms reliability. Correlation between forms (r_{xy}) was obtained, to subsequently calculate the Spearman-Brown split-half reliability coefficient [$r_{sb} = 2r_{xy} / (1 + r_{xy})$]. The standard error of measurement [$SEM = SD\sqrt{1 - r_{sb}}$] was also obtained for each form of the ANT and for the full form. This can be then used to calculate 95% confidence intervals for each observed score [95% CI = Observed Score ± 1.96(SEM)]. Parallel forms reliability was also assessed by performing Pearson's product-moment correlations between forms A and B. Comparability of the two alternate forms to the full form was also assessed through Pearson's product-moment correlations.

The relationship between the three forms of the ANT and continuous demographic variables such as age, years of education and IQ was explored using Pearson's product-moment correlations. The influence of gender was investigated using the non-parametric test for two independent samples, the Mann-Whitney-Wilcoxon rank-sum test. This was based on the rationale that the ANT has a low ceiling and is characterised therefore by a truncated distribution of scores, and also because of the small sample size for the female group. Multiple linear regression analyses were further performed to assess the effect of demographic characteristics on ANT performance.

6.3.2.3. Results

Mean performance for Form A, Form B and full form of the ANT is presented in Table 6.6. Results are detailed considering total spontaneous correct responses, correct semantic-cued and phonemic-cued responses, and total correct responses after cueing. Results on paired-samples t-tests indicate that the two short forms of the ANT are equivalent in terms of mean performance when considering total correct spontaneous responses and total correct responses after cueing. Whilst performance on both short forms was equivalent considering the number of responses evoked after the presentation of semantic cues, Form A elicited a higher number of correct responses after presentation of phonemic cues compared to Form B. Regarding equivalency of the distribution of scores, Kolmogorov-Smirnov tests demonstrated no significant differences between the two alternate forms of the ANT for any of the scores considered.

Table 6.6. Mean and standard deviations for Form A, Form B and full ANT, and comparisons between the two alternate forms.

	ANT Form A		ANT Form B		Equivalency of Alternate Forms				ANT Full Form	
					Mean Scores[a]		Distribution[b]			
	M ± *SD*	SEM	*M* ± *SD*	SEM	t(df)	*p*	D	*p*	*M* ± *SD*	SEM
Total Correct Spontaneous Responses	26.3 ± 1.68	0.58	26.4 ± 1.82	0.63	-0.99(99)	.33	0.08	.91	52.8 ± 3.28	1.14
Total Correct Semantic-cued Responses	0.45 ± 0.66	0.23	0.37 ± 0.66	0.23	1.09(99)	.28	0.08	.91	0.82 ± 1.10	0.38
Total Correct Phonemic-cued Responses	0.51 ± 0.99	0.34	0.35 ± 0.76	0.26	2.47(99)	.02	0.06	.99	0.86 ± 1.64	0.57
Total Correct Responses After Cueing	27.3 ± 1.25	0.43	27.2 ± 1.45	0.50	1.30(99)	.20	0.07	.97	54.4 ± 2.54	0.88

[a] Paired-samples t-test

[b] Kolmogorov-Smirnov test

Prior to conducting reliability analyses, data coding was transformed to include all four possible answers per item in each case. Thus, coding was as follows: 4 = correct as spontaneous response; 3 = correct after semantic cue; 2 = correct after phonemic cue; 1 = incorrect answer.

Considering internal consistency, correlation between forms (r_{xy}) equalled .79, therefore Spearman-Brown Split-Half Coefficient (r_{sb}) was: [2 x .79 / (1 + .79)] = .88. This indicates good reliability of the full original test based on split-forms equivalence. Standard errors of measurement for each form of the ANT are incorporated in Table 6.6.

Parallel forms reliability coefficients are presented in Table 6.7. Strong to very strong positive correlations were observed between forms A and B of the ANT when considering spontaneous responses, responses after phonemic cue and total correct responses after cueing. However, a significant positive weak correlation was observed between alternate forms when considering correct responses after semantic cueing. Regarding comparability of the full form of the ANT to the two alternate forms, strong positive correlations were observed in all cases, all reaching statistical significance.

Table 6.7. Correlational analyses between ANT forms.

	Total Correct Spontaneous Responses		
	ANT Form A	ANT Form B	ANT Full Form
ANT Form A	1		
ANT Form B	r=.76***	1	
ANT Full Form	r=.93***	r=.94***	1

*p<.05, **p<.01, ***p<.001

Table 6.7 (continued). Correlational Analyses between ANT forms.

	Correct Responses after Semantic Cue		
	ANT Form A	ANT Form B	ANT Full Form
ANT Form A	1		
ANT Form B	r=.38***	1	
ANT Full Form	r=.83***	r=.83***	1
	Correct Responses after Phonemic Cue		
	ANT Form A	ANT Form B	ANT Full Form
ANT Form A	1		
ANT Form B	r=.76***	1	
ANT Full Form	r=.95***	r=.92***	1
	Total Correct Responses		
	ANT Form A	ANT Form B	ANT Full Form
ANT Form A	1		
ANT Form B	r=.77***	1	
ANT Full Form	r=.93***	r=.95***	1

*p<.05, **p<.01, ***p<.001

Regarding the influence of demographic characteristics on ANT performance, it was found that all forms of the ANT correlated equivalently to age, education and IQ. Thus, both alternate forms of the ANT correlated negatively with age when considering total spontaneous correct responses (Form A: r = -.35, p = .0003; Form B: r = -.28, p = .005), but no correlations were observed for any of the two forms when considering total correct responses after cueing (Form A: r = -.10, p = .30; Form B: r = -.19, p = .06). Years of education significantly correlated with both short forms of the ANT when considering total correct responses after cueing (Form A: r = .28, p = .005; Form B: r = .27, p = .006), and weaker correlations were found when spontaneous correct responses were considered, the correlation with Form B being significant (Form A: r = .15, p = .14; Form B: r = .21, p = .04). IQ showed a similar pattern to years of education but with stronger correlations when total correct responses were considered (Form A: r = .44, p < .0001; Form B: r = .40, p < .0001), and significant correlations were also observed in this case when spontaneous correct responses were taken into account (Form A: r = .30, p = .003; Form B: r = .36, p = .0003). In fact, a significant strong positive correlation was observed between years of education and IQ (r = .82, p < .0001). Finally, when considering the original long form of the ANT, a similar pattern of correlations was observed: age and spontaneous correct responses (r = -.33, p = .0007), age and total correct responses (r = -.16, p = .12); years of education and spontaneous correct responses (r = .19, p = .06), years of education and total correct responses (r = .29, p = .003); IQ and spontaneous correct responses (r = .35, p = .0003), IQ and total correct responses (r = .45, p < .0001).

Gender comparisons on ANT performance are shown in Table 6.8. No significant relationships were found between gender and total correct spontaneous responses for any of the two alternate forms of the ANT nor for the full original form. However, in all three cases, females performed significantly better than males on the number of post-cueing correct responses.

Table 6.8. Gender comparisons on performance on the ANT.

		Males n = 69 *Mdn* (range)	Females n = 31 *Mdn* (range)	W[a]	*p*
Total Correct Spontaneous Responses	**ANT Form A**	27 (20-28)	27 (22-28)	881	.15
	ANT Form B	27 (19-28)	27 (23-28)	941	.32
	ANT Full Form	53 (41-56)	54 (45-56)	888	.17
Total Correct Responses After Cueing	**ANT Form A**	28 (23-28)	28 (27-28)	664	.0003
	ANT Form B	28 (20-28)	28 (25-28)	733	.003
	ANT Full Form	55 (43-56)	56 (53-56)	657	.0005

[a] Mann-Whitney-Wilcoxon rank-sum test

Multiple linear regression was used to assess the interactions demographic variables have on total correct spontaneous responses and total correct responses after cueing on the ANT. Three different models were built (i.e. Form A, Form B and Full Form) for each of the two scores. Age and IQ were included in the regression models as predictors. Years of education was not included due to its strong significant positive correlation to IQ, to avoid collinearity effects. The variance inflator factor for the predictor variables in all models was very close to 1 in all cases, indicating no collinearity effects. Although normality of residuals assumption was not met due to the presence of outliers or observations with standardised residual values outside ±3 (a maximum of two were identified in one same model), Cook's distance (D_i) values were smaller than .5 in all cases, ruling out the presence of significantly influential outliers. Curvature tests indicated that the assumption of linearity between the residuals and the outcome was met for each individual predictor in all models. The assumption of homoscedasticity was not met for any of the models, and therefore parameters were estimated using sandwich heteroscedasticity corrected matrix estimators.

Multiple linear regression results are detailed in Table 6.9. Both predictors, age and IQ, had a significant effect on the number of spontaneous responses given for all three models. When considering total correct responses after cueing, although only IQ was a significant predictor for ANT Form A and for the ANT full original form, both age and IQ significantly predicted performance on the ANT Form B.

Table 6.9. Regression models to predict the effect of age and IQ on ANT performance.

			β[a]	SEE [a]	t-test [a]	*p* [a]	R^2 [b]	F(2,97)	*p*[c]
Total Correct Spontaneous Responses	**ANT Form A**	Age	-0.06	0.012	-4.74	<.0001	.215	13.3	<.0001
		IQ	0.04	0.011	3.64	.0004			
	ANT Form B	Age	-0.05	0.014	-3.44	.0008	.206	12.6	<.0001
		IQ	0.05	0.014	3.72	.0003			
	ANT Full Form	Age	-0.01	0.023	-4.67	<.0001	.236	15.0	<.0001
		IQ	0.09	0.023	4.03	.0001			

[a] Parameters obtained using sandwich heteroscedasticity corrected matrix estimators.

[b] R^2 is used to represent the proportion of the variance from the outcome variable explained by age and IQ in each model. R^2 is chosen here over Adjusted R^2 given that all models use the same predictors and therefore there is no need for adjustment.

[c] Bonferroni adjusted p-value for statistical significance: $p = .008$

Table 6.9 (continued). Regression models to predict the effect of age and IQ on ANT performance.

			β[a]	SEE [a]	t-test [a]	*p* [a]	R^2 [b]	F(2,97)	*p*[c]
Total Correct Responses After Cueing	**ANT Form A**	Age	-0.01	0.011	-1.24	.22	.208	12.8	<.0001
		IQ	0.04	0.009	5.11	<.0001			
	ANT Form B	Age	-0.03	0.011	-2.31	.02	.199	12.0	<.0001
		IQ	0.05	0.010	4.54	<.0001			
	ANT Full Form	Age	-0.04	0.021	-1.91	.06	.226	14.2	<.0001
		IQ	0.09	0.018	5.01	<.0001			

[a] Parameters obtained using sandwich heteroscedasticity corrected matrix estimators.

[b] R^2 is used to represent the proportion of the variance from the outcome variable explained by age and IQ in each model. R^2 is chosen here over Adjusted R^2 given that all models use the same predictors and therefore there is no need for adjustment.

[c] Bonferroni adjusted p-value for statistical significance: $p = .008$

6.3.2.4. Discussion

We have developed, standardised and evaluated the psychometric properties of two short parallel forms of the ANT, a confrontation naming action-word retrieval task. Results indicate that the two forms are equivalent in terms of mean performance and distribution of scores when considering correct spontaneous responses as well as total correct responses after cueing. Although ANT Form A and ANT Form B are also equivalent when considering correct responses after semantic cueing, phonemic cueing prompted a higher number of accurate responses in Form A compared to Form B.

Regarding reliability, internal consistency of the whole form based in split-form reliability was high (r_{sb} = .88). Parallel forms reliability also indicated that the two forms are strongly equivalent when considering the number of responses given spontaneously and the improvement on performance after presentation of a phonemic cue. However, a weak correlation was observed between alternate forms on performance after semantic cueing. Nevertheless, the two parallel forms were highly comparable to the full form of the ANT, indicated by the very strong significant positive correlations found between all scores on Form A and B and the full form of the test.

The effect of demographic variables on ANT performance was also assessed, and performance on all three forms was influenced by demographics equally when considering total spontaneous responses. Our findings provide strong evidence that age and IQ are significant predictors of action word retrieval. However, when considering total correct responses given after cueing, age had no effect for ANT Form A and ANT Full Form, but it was found to be a significant predictor of total correct responses given on ANT Form B. Regarding IQ, this was a significant predictor of the number of responses given after cueing in all three ANT forms.

Our result that age is an important contributor to action word finding difficulties is concordant with previous studies that have shown declining performance in spontaneous action naming as age increases (Barresi, Nicholas, Tabor Connor, Obler, & Albert, 2000; MacKay, Connor,

Albert, & Obler, 2002; Nicholas, Obler, Albert, & Goodglass, 1985; Ramsay, Nicholas, Au, Obler, & Albert, 1999). These studies showed that the nature of the naming difficulty arising with age is of retrieval nature rather than a semantic degradation of the underlying concept, given that age did not influence performance after the presentation of cues. This is further supported by our findings that age had no effect on post-cueing performance on the ANT Full Form as well as on ANT Form A.

The effect of education in action naming has not been systematically studied, although it has been shown to be an important predictor of performance on the Boston Naming Test (Hawkins & Bender, 2002). Our results suggest that education also influences performance on action naming, principally on the total amount of correct responses that are given post-cueing. Education was not significantly correlated with the number of spontaneous responses given in ANT Form A and on the ANT Full Form, but it was weakly correlated to Form B. Previous research showed that action word retrieval seems to decline with age independently of the education level (Ramsay et al., 1999), which would be concordant with our findings relating to Form A and Full Form of the ANT. In all three forms, education and also IQ had an influence on the total amount of responses healthy participants are able to generate, even after the provision of phonemic cues, thus correcting for the effect of word retrieval difficulties. This could mean that if a person is not able to recall the word after the presentation of a phonemic cue, it may be because that word is not part of the vocabulary of the person. Although this is only an assumption, vocabulary level has been, in fact, related to performance on the Boston Naming Test (Hawkins & Bender, 2002; Hawkins et al., 1993). To further clarify this matter, investigations into whether the person can match the picture of that action to a semantically related picture would show if the deficit is a loss of semantic knowledge of that action or if it is due to the word to name it not being in the person's lexicon to express it.

Finally, gender had no effect on action word retrieval or total spontaneous responses given, but females performed significantly better than males after the presentation of cues. This was equivalent for the three ANT forms.

Overall, our results indicate that the two parallel short forms of the ANT are equivalent when considering total spontaneous responses and total correct responses after cueing, but semantic and phonemic cues evoke different responses on the two forms. Moreover, ANT Form A and ANT Form B are affected differently by demographics. Specifically, education and the total spontaneous responses given on Form B weakly correlate, and age seem to be a significant predictor of the total correct responses given on this same ANT Form. These effects of demographic characteristics are not encountered for ANT Form A nor for the ANT Full Form, which is concordant with the literature. In that regard, Form A seems to be more equivalent to

the ANT Full Form in comparison to Form B. The former is administered to the patient sample to investigate action word naming.

This work is limited by the use of a split-half procedure for the development of the short forms, rather than a more appropriate procedure for the optimal selection of items that best measure the specific ability of a test, such as item response theory (IRT). This methodology was used to ensure preservation of the entire range of items in terms of frequency and complexity thus guaranteeing generalizability across populations.

6.4. Neuropsychological Performance of the Healthy Control Sample

This section presents descriptive data on neuropsychological performance of the healthy control sample. Table 6.10 depicts mean performance on all neuropsychological measures administered, which are considered in subsequent chapters to analyse cognitive performance in our population-based incident ALS sample. Neuropsychological measures described below include the domains of intellectual ability, language, executive function, behaviour and mood.

Table 6.10. Healthy controls' performance on neuropsychological measures.

Neuropsychological Measure		Mean Performance *M ± SD*	Maximum Score[b]
Test of Premorbid Function (TOPF) – FSIQ		104 ± 12.8	n/a
Raven's Coloured Progressive Matrices		29.8 ± 4.63	36
PALPA Lexical Decision	Auditory	72.5 ± 5.84	80
	Visual	58.3 ± 2.54	60
PALPA Spelling	Regular Words	19.7 ± 0.68	20
	Irregular Words	18.1 ± 2.56	20
	Pseudowords	10.1 ± 1.68	12
PALPA Reading	Regular Words	29.9 ± 0.39	30
	Irregular Words	29.3 ± 1.11	30
	Pseudowords	10.8 ± 1.38	12
PALPA Homophone Definition & Regularity	Definition – Regular	9.64 ± 0.69	10
	Definition – Irregular	9.44 ± 0.85	10
	Reading – Regular	9.92 ± 0.27	10
	Reading – Irregular	9.55 ± 0.75	10
PALPA Word – Picture Matching	Spoken	19.9 ± 0.37	20
	Written	19.8 ± 0.43	20
PALPA Sentence – Picture Matching	Auditory	28.5 ± 1.99	30
	Written	29.1 ± 1.32	30
PALPA Auditory Comprehension of:	Verbs	26.7 ± 0.89	27
	Adjectives	13.9 ± 0.40	14
Boston Naming Test	Spontaneous Responses	25.6 ± 3.54	30
	After Semantic Cue	0.31 ± 0.61	30
	After Phonemic Cue	1.71 ± 1.83	30
	Total Correct Post-cueing	27.7 ± 2.83	30

[a] Higher scores indicate poorer performance.

[b] Maximum possible score obtainable.

Table 6.10 (continued). Healthy controls' performance on neuropsychological measures.

Neuropsychological Measure		Mean Performance *M* ± *SD*	Maximum Score[b]
Action Naming Test – Version A	Spontaneous Responses	26.3 ± 1.68	28
	After Semantic Cue	0.45 ± 0.66	28
	After Phonemic Cue	0.51 ± 0.99	28
	Total Correct Post-cueing	27.3 ± 1.25	28
Pyramids and Palm Trees Test		13.9 ± 0.20	14
FAS test – VFI[a]		4.45 ± 2.65	n/a
Restricted Phonemic Fluency (letter C) – VFI[a]		11.4 ± 10.4	n/a
Semantic Fluency (Animals) – VFI[a]		2.93 ± 1.08	n/a
Action Fluency Test – VFI[a]		3.75 ±1.74	n/a
Digit Span	Forward span	7.03 ±1.22	9
	Backward span	4.92 ± 1.16	8
Colour Word Interference Test	Word Reading & Colour Naming – mean time[a]	28.6 ± 5.81	n/a
	Inhibition – TIP[a]	1.38 ± 0.52	n/a
	Inhibition/Switching – TIP[a]	1.47 ± 0.53	n/a
Sorting Test	Free Sorting – Correct Sorts	3.35 ± 2.22	16
	Free Sorting – % sorting accuracy	38.1 ± 11.9	100
	Free Sorting – Description	31.7 ± 8.85	64
	Sort Recognition – Description	33.4 ± 9.06	64
Reading the Mind in the Eyes Test		23.5 ± 4.44	36
Conflicting Emotional Prosody	Congruent	11.2 ± 1.15	12
	Incongruent – Conflicting	3.86 ± 2.96	12
	Incongruent – Inconsistent	9.02 ± 2.76	12
Beaumont Behavioural Inventory[a]		4.08 ± 6.51	123
HADS-T[a]		4.62 ± 3.59	33

[a] Higher scores indicate poorer performance.

[b] Maximum possible score obtainable.

Focusing on verbal fluency paradigms, healthy control data described in Table 6.10 refers to spoken VFIs. However, 16 ALS patients from our population-based sample were unable to perform this task verbally and therefore a written response was required (Age: $M = 63.6$, $SD = 6.38$; Education: $M = 13.3$, $SD = 3.52$). As explained in chapter 5, spoken and written VFIs are not directly comparable and therefore these data required further transformation into an equivalent scale. Accordingly, conversion tables were created following the procedure outlined in Table 5.3. Conversion tables for spoken VFI were generated considering VFI performance descriptives outlined in Table 6.10. For the creation of conversion tables for written paradigms, additional data was collected on a separate healthy control sample from the previously mentioned project investigating neuropsychological and functional correlates in neurodegenerative diseases, which was individually matched to the patient cohort that performed verbal fluency tasks giving a written response by age ($M = 63.8$, $SD = 9.11$), $t(30) = -0.07$, $p = .95$, and education ($M = 13.9$, $SD = 3.06$), $t(30) = -0.54$, $p = .60$. Generated VFI conversion tables are depicted in Table 6.11.

Table 6.11. VFI conversion tables.

FAS test

Spoken VFI	Written VFI	Converted Score
< 2.4	< 2.3	12
2.4 to 6.3	2.3 to 4.8	10
6.4 to 10.3	4.9 to 7.3	8
10.4 to 14.3	7.4 to 9.9	6
14.4 to 18.3	10.0 to 12.4	4
18.4 to 22.2	12.5 to 14.9	2
≥ 22.3	≥ 15.0	0

Restricted Phonemic Fluency (letter C)

Spoken VFI	Written VFI	Converted Score
< 3.5	< 2.5	12
3.5 to 19.0	2.5 to 21.8	10
19.1 to 34.6	21.9 to 41.2	8
34.7 to 50.1	41.3 to 60.6	6
50.2 to 65.7	60.7 to 79.9	4
65.8 to 81.2	80.0 to 99.3	2
≥ 81.3	≥ 99.4	0

Semantic Fluency (Animals)

Spoken VFI	Written VFI	Converted Score
< 2.0	< 1.4	12
2.0 to 3.6	1.4 to 4.2	10
3.7 to 5.3	4.3 to 7.0	8
5.4 to 6.9	7.1 to 9.9	6
7.0 to 8.5	10.0 to 12.7	4
8.6 to 10.1	12.8 to 15.5	2
≥ 10.2	≥ 15.6	0

Action Fluency Test

Spoken VFI	Written VFI	Converted Score
< 2.3	< 2.0	12
2.3 to 5.0	2.0 to 8.6	10
5.1 to 7.6	8.7 to 15.4	8
7.7 to 10.2	15.3 to 21.7	6
10.3 to 12.8	21.8 to 28.3	4
12.9 to 15.4	28.4 to 34.9	2
≥ 15.5	≥ 35.0	0

Note. VFI mean and standard deviation values used to obtain conversion tables:
FAS test (spoken $M = 4.45$, $SD = 2.65$; written $M = 3.64$, $SD = 1.69$)
Restricted phonemic fluency (spoken $M = 11.4$, $SD = 10.4$; written $M = 12.3$, $SD = 12.9$)
Animals (spoken $M = 2.93$, $SD = 1.08$; written $M = 2.89$, $SD = 1.89$)
Action fluency test (spoken $M = 3.75$, $SD = 1.74$; written $M = 5.38$, $SD = 4.39$)

6.5. Summary of Findings

This initial results chapter presents findings of two preliminary studies assessing the psychometric properties of two measures of language processing subsequently used to assess language performance within the patient sample. The accurate assessment of the validity and reliability of neuropsychological instruments is an essential first step to ensure that test results are appropriate, meaningful and trustworthy.

The first study, evaluating the psychometric properties of a selected protocol of subtests from the PALPA battery, demonstrated high internal-consistency between PALPA subtests as well as moderate to excellent test-retest reliability coefficients. Adequate construct validity was also confirmed, with significant positive correlations among PALPA subtests, especially between those pairs of subtests that assess the same language construct. Moreover, consistent correlations between PALPA subtests and demographic characteristics, specifically nil or weak negative correlations with age and significant positive correlations with education and IQ, further supported construct validity. The complementary investigation comparing the PALPA Auditory Sentence – Picture Matching subtest to the TROG-2 revealed a significant strong positive correlation between the two tasks and consistent correlations with age and education, which indicates adequate convergent validity. Overall, results from this study confirmed the adequate psychometric characteristics of the selected PALPA protocol for this study.

The second study aimed at developing two shortened forms of the ANT and assessing their equivalency, reliability and comparability to the full form. Results from this study indicated that the two alternate ANT forms are equivalent when considering the number of correct spontaneous responses and total correct post-cueing responses given, although the two forms elicit different responses following the presentation of semantic and phonemic cues. Moreover, age seems to differently affect performance on the number of total correct responses given on the two ANT alternate forms. Therefore, the two alternate forms, although equivalent to a degree, show some inconsistencies. Form A appears to be more comparable to the full ANT form than Form B. The former is therefore the one administered to the patient sample.

Demographic characteristics and neuropsychological performance of our population-based healthy control sample have also been described in this chapter. Moreover, VFI conversion tables to transform spoken and written VFIs into an equivalent scale have also been generated. Data presented in this chapter is an initial investigation into healthy control data, which sets the context for the examination of patient data.

CHAPTER 7 Outline.

Results Part II:

The Incidence & Profile of Neuropsychological Change in ALS

CHAPTER 7.

Results Part II:

The Incidence & Profile of Neuropsychological Change in ALS

7.1. Introduction

This chapter addresses aims 1 to 3 of the present work. Therefore, cross-sectional patient neuropsychological data is analysed. Firstly, the incidence and nature of language change in the ALS cohort is investigated, as well as its relationship to executive dysfunction, to then examine the incidence of frontotemporal syndromes in this population-based cohort. To begin with, capture rates and clinical and demographic characteristics of the patient sample are described.

7.2. Population-Based Sampling of an ALS Incident Cohort

7.2.1. Patient Cross-Sectional Capture Rates

Two hundred and seventy-five ALS cases were diagnosed in the Republic of Ireland and attended the National Specialist MND Clinic at Beaumont Hospital during the period from December 2014 to August 2017, as per the Irish ALS Register. A flow chart of capture rates is illustrated in Figure 7.1, where patient recruitment processes are summarised, including non-capture and non-suitability rates.

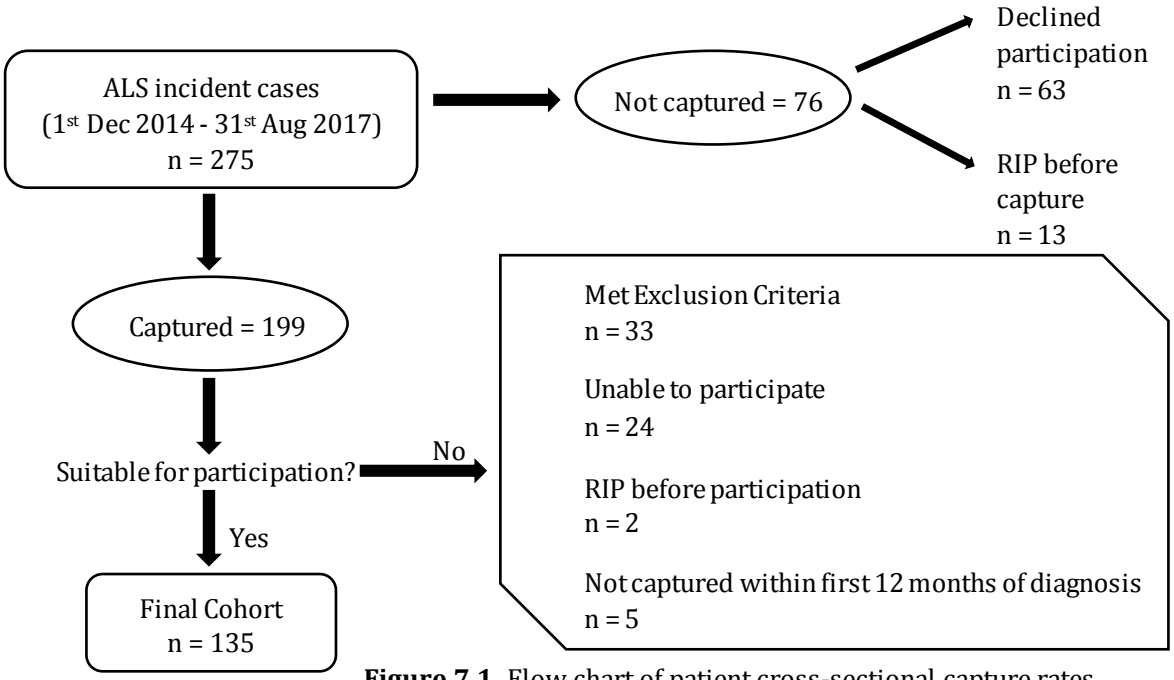

Figure 7.1. Flow chart of patient cross-sectional capture rates

From the 275 incident cases, 199 (72%) were captured, 63 (23%) declined participation and 13 (5%) were deceased prior to being approached. Out of the 199 captured cases, 64 (32%) were not suitable for participation. This resulted in a final ALS cohort of 135 cases.

Focusing on cases that were not suitable for participation, 33 (52%) did not meet inclusion criteria or met exclusion criteria, 24 (37%) were unable to participate for various reasons detailed below, 2 (3%) passed away before the assessment could be carried out, and 5 (8%) were captured more than a year post-diagnosis. Table 7.1 details reasons for exclusion and inability to participate.

Table 7.1. Reasons and rates of patient exclusion and inability for study participation.

EXCLUDED CASES
▪ History of other neurological (n = 7), psychiatric (n = 9) or medical (n = 1) conditions affecting cognition or the ability to perform on cognitive testing (n = 1).[a]
▪ History of premorbid learning disability (n = 1).
▪ Current use of high-dose psychoactive medication that adversely affects level of arousal or responsiveness, and the ability to engage in cognitive testing (n = 8).
▪ Diagnosed outside the Republic of Ireland (n = 1).
▪ English not the primary language (n = 3).
▪ Atypical disease course suggestive of variant (n = 2), including a very slow progressing pure lower motor neuron presentation and a very slow progressing pure upper motor neuron degeneration.
CASES UNABLE TO PARTICIPATE
▪ Severe motor disability that prevented from engaging with cognitive testing (n = 22).
▪ Illiteracy (n = 1).
▪ Inability to participate due to social circumstances (n = 1).

[a] Cerebrovascular accident (CVA; n = 2), brain tumour (n = 1), parkinsonism (n = 1), spinocerebellar ataxia (n = 1), epilepsy (n = 2), Asperger syndrome (n = 1), bipolar disorder (n = 2), schizophrenia (n = 2), schizoaffective disorder (n = 1), psychosis (n = 1), psychiatric comorbidity not specified (n = 1), alcohol dependence syndrome (n = 1), HIV (n = 1), and macular degeneration (n = 1).

7.2.2. Patient Clinical and Demographic Characteristics

Demographic and clinical characteristics of the final patient cohort are detailed in Table 7.2. Mean age at study participation was 63 years. There is a higher proportion of males, and most participants were right handed. Mean years of formal education was 14, and only 21% of patients were still working. Most participants were married and the spouse fulfilled the role of main caregiver. Mean age at symptom onset was 61 years and mean age at diagnosis was 62, median time from onset to diagnosis being 12 months. Regarding site of onset, 68% of the patients had spinal onset ALS, 28% bulbar onset, and 4% respiratory onset. Concerning family history, 24% of the sample was considered familial ALS, and 51% and 42% had a family history of other neurological and psychiatric conditions, respectively. Regarding disease management, 84% were taking Riluzole, 11% had external homecare, 20% were using NIV, and only 4% had an enteral feeding tube in place. In terms of disease severity, mean score on the ALSFRS-R total

was 36 out of 48, 10 out of 12 on the bulbar sub-score, 17 out of 24 on the limb sub-score, and 10 out of 12 on the respiratory sub-score. No patients showed evidence of hypoxaemia, defined as oxygen saturation < 90%, and only 3 (2%) had abnormal pulse oximeter readings (i.e. < 95%). Eleven patients (9%) had $PaCO_2$ levels > 6.0 kPa, which indicates CO_2 retention.

Table 7.2. Demographic and clinical characteristics of the final patient cohort (n = 135).

Age *M±SD* years		63.0 ± 10.7
Gender n(%)	Females	50 (37)
	Males	85 (63)
Handedness n(%)	Right	121 (90)
	Left	14 (10)
Years of formal education *M±SD* years		14.4 ± 3.60
Highest level of education achieved n(%)	Primary Education	27 (20)
	Lower Secondary	24 (18)
	Upper Secondary	23 (17)
	Advanced / Higher Certificate	10 (8)
	Ordinary Bachelor Degree / National Diploma	6 (4)
	Honours Bachelor Degree / Professional Qualification	12 (9)
	Postgraduate Diploma / Master's Degree	18 (13)
	Doctorate	0
	Technical / Vocational	15 (11)
Currently working n(%)		28 (21)
Marital Status n(%)	Single	10 (7)
	Married	100 (74)
	Widowed	11 (8)
	Separated	14 (11)
Age at onset *M±SD* years		61.3 ± 10.6
Site of onset n(%)	Spinal	91 (68)
	Bulbar	38 (28)
	Thoracic / Respiratory	6 (4)
Age at diagnosis *M±SD* years		62.7 ± 10.8
Diagnostic Delay *Mdn* (*IQR*) months		12 (17)
Familial ALS[a] n(%)		33 (24)
Family History of other Neurological Conditions n(%)		69 (51)
Family History of Psychiatric Conditions n(%)		57 (42)
Riluzole use n(%)		114 (84)
Caregiver Relationship n(%)	Spouse	95 (70)
	Child	21 (16)
	Other family member / friend	18 (13)
	Hospice	1 (1)
External homecare n(%)		15 (11)
Use of NIV n(%)		27 (20)
Enteral feeding tube in place n(%)		6 (4)
ALSFRS-R total score *M±SD* score		36.2 ± 7.02
ALSFRS-R bulbar sub-score *M±SD* score		9.63 ± 2.66
ALSFRS-R limb sub-score *M±SD* score		16.6 ± 5.01
ALSFRS-R respiratory sub-score *M±SD* score		10.0 ± 3.05
Peripheral capillary oxygen saturation levels - $Sp0_2$ *M±SD* %		97.1 ± 1.42
Carbon dioxide partial pressure - $PaC0_2$ *M±SD* kPa		5.38 ± 0.56

[a] Familial ALS is defined with the presence of at least one biological relative within three generations diagnosed with ALS and/or FTD.

Demographic and clinical characteristics for non-participants, including non-captured (n = 76) and unsuitable participants (n = 64), were also extracted from the Irish ALS Register. No significant differences were observed between participants and non-participants in terms of gender rates (non-participants: 32% females, 68% males), $X^2(1) = 0.53$, p = .47; age at onset (non-participants: $M = 63.7$, $SD = 11.1$), $t(273) = -1.77$, p = .08; site of onset (non-participants: 63% spinal, 31% bulbar, 6% thoracic/respiratory), $X^2(2) = 0.94$, p = .62; age at diagnosis (non-participants: $M = 65.1$, $SD = 11.3$), $t(273) = -1.82$, p = .07; and diagnostic delay (non-participants: $Mdn = 11$), $W = 8989$, p = .48.

Regarding survival, by the end of August 2018, a year post-finalisation of recruitment period, 75% of non-participants (n = 105) were deceased, in contrast to 52% of participants (n = 70), $X^2(1) = 14.93$, p = .0001, $\varphi = .24$. Median survival (in months) for non-participants was significantly shorter than for participants (non-participants: $Mdn = 24$, $IQR = 17.6$; participants: $Mdn = 33$, $IQR = 20.8$), $W = 2340$, p < .0001, r= .31. These results are driven by a percentage of non-participants (53%) who suffered from a more aggressive presentation, leading to death within the first year of diagnosis. Only 17% of participants were deceased within the first 12 months of diagnosis, $X^2(1) = 21.66$, p < .0001, $\varphi = .36$. When patients with an aggressive form of the disease were excluded, no significant difference was observed between participants and non-participants in median survival (non-participants: $Mdn = 31$, $IQR = 17.4$; participants: $Mdn = 36$, $IQR = 19.5$), $W = 1214$, p = .20.

Focusing again solely on the participating ALS cohort, this and the healthy control sample, whose demographic characteristics were described in chapter 6 (section 6.3), were accurately matched for age, gender, handedness, years of formal education and estimated premorbid intellectual ability. Results are detailed in Table 7.3.

Table 7.3. Demographic characteristics comparison between ALS patients and healthy controls.

		ALS Cohort n = 135	**HC Cohort** n = 100	**t(df) / X^2(df)**	***p***
Age *M±SD* years		63.0 ± 10.7	64.0 ± 10.4	0.69(233)[a]	.49
Gender n(%)	Females	50 (37)	31 (31)	0.68(1)[b]	.41
	Males	85 (63)	69 (69)		
Handedness n(%)	Right	121 (90)	91 (91)	0.02(1)[b]	.90
	Left	14 (10)	9 (9)		
Years of Formal Education *M±SD* years		14.4 ± 3.60	15.2 ± 3.81	1.54(233)[a]	.13
Premorbid Intellectual Ability *M±SD* IQ		*n = 123* 103 ± 13.5	104 ± 12.8	1.03(221)[a]	.31

[a] Student t-test (t). Equal variances were assumed in all cases, as per Levene's test.

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

7.3. The Incidence and Nature of Language Change in ALS

This section addresses the first aim of this work, which intends to investigate the incidence and nature of language changes in a population-based cohort of ALS patients in comparison to a demographically-matched healthy control sample. All ALS patients were evaluated within the first year of diagnosis. Mean time from diagnosis to assessment was 3.91 months (*SD* = 2.59), and mean time from onset to assessment was 20.8 months (*SD* = 15.3, *Mdn* = 16, *IQR* = 15).

7.3.1. Language Performance: Between-Group Comparisons

The first step in examining the existence and nature of language change in our ALS cohort was to compare performance on language measures between patients and controls. Eighteen ALS patients from our cohort met criteria for FTD (i.e. ALS-FTD). Further details regarding such diagnoses are provided in section 7.5.1. However, this is noted because these patients are excluded from further analyses in the present section, which aims to investigate the profile and incidence of language change in ALS patients not meeting criteria for dementia.

Non-demented ALS patients (i.e. ALS; n = 117) and healthy controls were also matched by demographics, including age, gender, handedness, years of formal education, premorbid intellectual ability, as well as current intellectual function (Table 7.4).

Table 7.4. Demographic characteristics comparison between non-demented ALS patients and healthy controls.

		ALS Patients n = 117	**Healthy Controls** n = 100	**t(df) / X^2(df)**	***p***
Age *M±SD* years		62.4 ± 10.9	64.0 ± 10.4	1.13(215)[a]	.26
Gender n(%)	Females Males	42 (36) 75 (64)	31 (31) 69 (69)	0.38(1)[b]	.54
Handedness n(%)	Right Left	105 (90) 12 (10)	91 (91) 9 (9)	0.007(1)[b]	.93
Years of Formal Education *M±SD* years		14.4 ± 3.52	15.2 ± 3.81	1.60(215)[a]	.11
Premorbid Intellectual Ability *M±SD* IQ		*n = 108* 103 ± 13.4	104 ± 12.8	0.51(206)[a]	.61
Current Intellectual Function[c] *M±SD* IQ		96.7 ± 15.5	100 ± 15.1	1.59(215)[a]	.11

[a] Student t-test (t). Equal variances were assumed in all cases, as per Levene's test.

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[c] Z scores on the Raven's Coloured Progressive Matrices were transformed to IQ Scores (*M* = 100, *SD* = 15) by applying the following formula: IQ score = [(Z score x 15) + 100].

ALS patients and healthy controls were also compared in terms of mood and arterialised tissue capillary blood gas tensions. Regarding mood, most patients (93%) had normal scores on the HADS-T, and only 3 were classified as 'possible mood disturbance' and 3 as 'probable mood disturbance'. All healthy controls were classified as normal. A significant difference was

observed between ALS patients and healthy controls' scores when the distributions of scores were compared (ALS [n = 84] *Mdn* = 5, *IQR* = 6; HC [n = 64] *Mdn* = 4, *IQR* = 4.25), *W* = 1923, p = .006, and this significant difference was also present when the medians were compared (Mood's Median Test, p = .04). This is likely due to the influence that the six ALS patients scoring within the clinically impaired range have on the distribution of scores. Regarding arterialised tissue capillary blood gas tensions, ALS patients had lower levels of $Sp0_2$ (ALS *M* = 97.1, *SD* = 1.45; HC *M* = 98.1, *SD* = 0.85), *t*(188.52) = 5.95, p < .0001, η^2 = .14, and higher $PaC0_2$ levels (ALS *M* = 5.37, *SD* = 0.56; HC *M* = 4.94, *SD* = 0.70), *t*(213) = -5.00, p < .0001, η^2 = .11.

Multivariate analysis of covariance (MANCOVA) was used to compare performance on language measures between ALS patients and healthy controls. Selection of language measures incorporated in this analysis aimed to include the main language domains assessed: lexical processing (i.e. PALPA Lexical Decision), word spelling (i.e. PALPA Word Spelling), word reading (i.e. PALPA Word Reading), semantic processing (i.e. PALPA Word – Picture Matching), word naming (i.e. Boston Naming Test) and syntactic/grammatical processing (i.e. PALPA Sentence – Picture Matching). The differentiation between auditory/spoken and visual/written stimuli for lexical decision, word-picture and sentence-picture matching tasks as well as the distinction between regular and irregular words for reading and spelling paradigms of the PALPA were not yet considered, but are explored in subsequent sections. Verbal fluency paradigms are not included here either but are rather examined in later sections, given their high executive component. Mood and arterialised tissue capillary blood gas tensions were considered as covariates.

MANCOVA assumptions were explored a priori. Although multivariate and univariate normality was not assumed, Mahalanobis distances indicated that no extreme outliers were present. Only four cases exceeded the critical value of 22.5 (obtained from the chi-square distribution table at an alpha value of .001 considering degrees of freedom as the number of dependent variables, n = 6) and values were not too extreme, therefore these participants were kept in the analysis. Univariate equality of variances was only proven for the PALPA Lexical Decision and Word – Picture Matching tasks. Therefore, a more stringent p-value was set for statistical significance for all other tasks. The assumption of homogeneity of variance–covariance matrices was violated. Although this can indicate unequal matrices, this test is also very sensitive to violations of multivariate normality. Given that larger samples were generally those with greater variances, and that deviations from normality were due to skewness rather than outliers, results from MANCOVA were considered robust. Moderate correlations (i.e. between .40 and .70) were observed between variables, thus ruling out multicollinearity. No strong correlations were observed between covariates, and the assumption of homogeneity of regression slopes was overall met in the three cases (i.e. HADS-T, $Sp0_2$ and $PaC0_2$ levels).

Results from multivariate tests indicated that there was a significant difference in language performance between ALS patients and healthy controls, $F(6,120) = 5.103$, $p < .0001$, $V = .20$. None of the covariates included was a significant predictor of language performance: mood, $F(6,120) = 1.27$, $p = .28$, $V = .06$; SpO_2 levels, $F(6,120) = 2.07$, $p = .06$, $V = .09$; and $PaCO_2$ levels, $F(6,120) = 0.74$, $p = .62$, $V = .04$.

Given that missing data, specifically on the HADS-T and on word reading and writing, reduced the number of participants included in the MANCOVA analysis, univariate contrasts were performed using a series of one-way ANOVAs. None of the covariates was kept in the analysis given their non-significant effect on previous MANCOVA analysis. Results from univariate tests are shown in Table 7.5. Univariate contrasts indicated that patient scores were lower overall in comparison to healthy controls, except for the PALPA Word – Picture Matching task. However, lower performance of the patient group was only significant for four of the language measures: PALPA Word Spelling, PALPA Word Reading, Boston Naming Test (i.e. spontaneous responses) and PALPA Sentence – Picture Matching, the first two not surviving correction for multiple comparisons. Effect sizes were small to medium.

Further analyses were undertaken to investigate the proportion of ALS patients in comparison to healthy controls that were impaired on each language task. Results are also presented in Table 7.5. The proportion of impaired individuals was higher for the patient group in comparison to controls for all language measures, except for the PALPA Word – Picture Matching task. However, results from Pearson's Chi-square test for independence demonstrated that this higher proportion of impaired patients compared to controls was significant only for the number of spontaneous responses given on Boston Naming Test as well as for the PALPA Sentence – Picture Matching Task, with small effect sizes. These results are concordant with previously reported ANOVA results.

Overall, results presented in this section indicate that when considering language as a construct, ALS patients perform significantly poorer compared to healthy controls, but deficits in this cognitive domain seem to be confined to word naming and syntactic/grammatical processing abilities. Although ALS patients also seem to present with reduced reading and spelling abilities compared to controls, these results do not survive multiple comparisons correction. Moreover, effect sizes were small to medium in all cases, given that only a proportion of ALS patients present with language deficits. These findings pose new questions, not only regarding the incidence, but also regarding the nature of language deficits in ALS. For instance, are spelling and reading difficulties in ALS confined to a specific type of word? Are naming deficits of semantic degradation nature or are these caused by word retrieval deficits? And, to what extent executive dysfunction contribute to syntactic/grammatical processing deficits in ALS? This unanswered questions are addressed in section 7.3.2.

Table 7.5. Performance of ALS patients in comparison to healthy controls on language measures.

Language Measure	ALS Patients n = 117		Healthy Controls n = 100		Intergroup differences					
					Mean performance[a]			% of impairment[b]		
	M ± *SD*	Nº of impaired (%)[c]	*M* ± *SD*	Nº of impaired[c]	F(df)	*p*[e]	η^2	X^2(df)	*p*	φ
PALPA Lexical Decision	129 ± 6.59	9 (8)	131 ± 7.63	5	3.90(1,214)	.05	.02	0.30(1)	.59	.06
PALPA Word Spelling	36.7 ± 3.95	14 (14)	37.7 ± 2.95	7	4.11(1,181.5)[d]	.04	.02	1.98(1)	.16	.12
PALPA Word Reading	58.8 ± 1.70	17 (16)	59.2 ± 1.29	11	4.36(1,193.5)[d]	.04	.02	0.77(1)	.38	.08
PALPA Word – Picture Matching	39.8 ± 0.62	3 (3)	39.7 ± 0.59	5	1.55(1,211)	.21	.007	0.29(1)[f]	.48	.06
Boston Naming Test	23.6 ± 4.37	21 (18)	25.6 ± 3.54	8	14.0(1,213.2)[d]	.0002	.06	3.89(1)	.05	.15
PALPA Sentence – Picture Matching	55.2 ± 4.04	23 (20)	57.6 ± 2.95	7	25.8(1,203.8)[d]	<.0001	.11	6.75(1)	.009	.19

n = 99

n = 105

[a] One-way ANOVA.

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[c] Abnormal performance considered as 1.65 SD below the control mean, as per Revised Diagnostic Criteria (Strong et al., 2017).

[d] Welch's F-ratio.

[e] Bonferroni adjusted p-value for statistical significance: $p = .008$.

[f] Fisher's Exact Probability Test.

7.3.2. Further Investigations on Language Performance in ALS

Based on the systematic review of language in ALS presented in chapter 3, a series of assumptions were formulated as part of Aim 1 (refer to section 4.3.1 in chapter 4 for details). The following subsections address outstanding questions regarding the profile of language change in ALS that are necessary to examine these assumptions.

7.3.2.1. Word Retrieval

Word retrieval has been assessed in our ALS cohort by means of confrontation naming. As shown in Table 7.5, ALS patients performed significantly poorer than healthy controls on the number of correct spontaneous responses given on the Boston Naming Test.

However, as explained in chapter 2, when interpreting results from the Boston Naming Test it is important to consider that low performance on spontaneous responses can result from two types of deficits: difficulties of access/retrieval or degradation of semantic knowledge. Our assumption regarding confrontation naming performance in ALS was that deficits on this task are due to word retrieval difficulties rather than a pure semantic deficit. To investigate if deficits observed in our ALS sample are of access or degradation nature, performance after the presentation of cues was analysed. In relation to our assumption that deficits are caused by difficulties of word access, improved performance following the presentation of phonemic cues was anticipated. Investigations on this matter are depicted in Table 7.6.

Table 7.6. Performance of the ALS sample on the Boston Naming Test, considering post-cueing responses (mean performance).

	Spontaneous responses	**Semantic cue**	**Phonemic cue**	**Mean performance**[a]			
				F(df)	**ε**	***p***	**η_G^2**
Mean performance *M ± SD*	23.6 ± 4.37	24.1 ± 3.98	28.2 ± 2.12	232.8 (1.1,124.5)	0.546	<.0001	.24
				Mean Difference		***p***[b]	
	23.6 ± 4.37	24.1 ± 3.98		-0.50		<.0001	
	23.6 ± 4.37		28.2 ± 2.12	-4.60		<.0001	
		24.1 ± 3.98	28.2 ± 2.12	-4.10		<.0001	

[a] One-way repeated measures ANOVA, with Greenhouse-Geisser correction.

[b] Pairwise comparisons, adjusted for multiple comparisons using Bonferroni correction.

Results from one-way repeated measures ANOVA indicate that there is a significant difference in performance between conditions. Pairwise comparisons show that performance significantly improved after the presentation of both semantic and phonemic cues. Looking at descriptive data, an increase by less than one point on average is observed on mean performance after the presentation of semantic cues, and an increase of almost five points on

average is observed after presenting with phonemic cues. These results suggest that phonemic cues may have a stronger influence on improvement than semantic ones. This is supported by the fact that ALS patients and healthy controls significantly differed on performance after presentation of semantic cues, with patients performing significantly poorer (ALS M = 24.1, SD = 3.98; HC M = 25.9, SD = 3.25), $t(213.4) = 3.79$, p = .0002, $\eta^2 = .06$, but no significant difference in performance was observed after presentation of phonemic cues (ALS M = 28.2, SD = 2.12; HC M = 27.7, SD = 2.83), $t(181.7) = -1.46$, p = .14.

Percentage of impairment on each condition was also analysed (Table 7.7). Cochran's Q test results also show a significant difference among conditions. Post hoc tests indicate a change after the presentation of phonemic cues, with a significant number of ALS patients who were impaired on the previous two conditions normalizing performance. No improvement was observed following semantic cueing, but instead a non-significant increase in the percentage of impaired patients was actually seen when compared to spontaneous responses. These findings are a result of the performance of five participants, who were unimpaired when considering spontaneous responses but did not improve following semantic cueing. Therefore, they were considered to be within the impaired range on semantic cueing performance given that the cut-off, based on healthy control performance, had increased.

Table 7.7. Performance of the ALS sample on the Boston Naming Test, considering post-cueing responses (percentage of impairment).

	Spontaneous responses	Semantic cue	Phonemic cue	% of impaired[a]		
				Q(df)	*p*	η_Q^2
Nº of impaired (%)	21 (18)	26 (22)	5 (4)	34.4(2)	<.0001	.15
				% Difference	*p*[b]	
	21 (18)	26 (22)		4	.07	
	21 (18)		5 (4)	14	.0002	
		26 (22)	5 (4)	18	<.0001	

[a] Cochran's Q test.

[b] Post hoc tests (McNemar's test), adjusted for multiple comparisons using Bonferroni correction.

Overall, these results support our assumption that deficits on performance on confrontation naming in ALS are due to word retrieval difficulties which significantly improve after the presentation of phonemic cues, and suggest that semantic knowledge is spared. This postulation bring us to our second assumption, addressed in the following section.

7.3.2.2. Semantic Processing

Our second assumption was that semantic processing is spared in ALS, at least in early stages of the disease. Results from the previous section, which showed that deficits on confrontation naming are not due to semantic processing deficits but to word retrieval difficulties, support

this hypothesis. Moreover, results in Table 7.5 show that no significant differences exist between ALS patients and healthy controls on word – picture matching tasks.

However, as explained in chapter 2, the semantic system can be accessed through three different input routes: the phonological input lexicon (when we are processing a spoken word); the orthographic input lexicon (when a written word is processed); and the visual recognition system (when we are processing an image or picture). Semantic processing in our ALS sample was evaluated using these three different modalities to assess for the presence of modality-specific deficits. Accordingly, three different semantic tasks were considered where the input was of different nature, and it had to be matched to a visual output (i.e. a picture).

Table 7.8 displays comparisons between ALS patients and healthy controls on these three semantic tasks, all assessing receptive semantics to ensure that word retrieval deficits did not interfere with performance.

Table 7.8. Performance of ALS patients compared to healthy controls on modality-specific receptive semantic tasks.

Semantic Task		**ALS Patients** *M ± SD*	**Healthy Controls** *M ± SD*	**Intergroup differences**	
				t(df)	***p*[c]**
PALPA Spoken Word – Picture Matching	*Auditory input*	19.9 ± 0.35	19.9 ± 0.37	-0.25(211)[a]	.80
PALPA Written Word – Picture Matching	*Written input*	19.9 ± 0.36	19.8 ± 0.43	-1.66(193.7)[b]	.10
Pyramids & Palm Trees Test	*Visual input*	13.9 ± 0.23	13.9 ± 0.20	-0.18(213)[a]	.86

[a] Student t-test (t). Equal variances assumed, as per Levene's test.

[b] Welch's t-test (t). Equal variances not assumed, as per Levene's test.

[c] Bonferroni adjusted p-value for statistical significance: $p = .016$.

Results on Table 7.8 indicate that no significant differences between ALS patients and healthy controls exist on any modality of semantic processing. This is in concordance with our assumption of preserved semantic processing in ALS, at least in the early stages of the disease.

7.3.2.3. The Role of Word Access in Verbal Fluency

Another aspect we aimed to investigate was the extent by which verbal fluency deficits in ALS are of executive or linguistic nature. In accordance with the literature, impairment on verbal fluency measures in ALS is mostly caused by executive dysfunction. Correspondingly, in our third assumption we predicted poorer performance on phonemic in comparison to semantic paradigms, and the worst performance was anticipated for the restricted phonemic paradigm. Results on verbal fluency performance on our ALS sample are displayed in Table 7.9.

Table 7.9. Performance of the ALS sample on verbal fluency measures.

Verbal Fluency Paradigms	Mean Performance *M* ± *SD*[a]
FAS test	9.00 ± 2.13
Restricted Phonemic Fluency (letter C)	8.87 ± 2.26
Semantic Fluency (Animals)	9.38 ± 1.88

[a] VFI converted scores (range: 0 to 12).

Descriptive data confirms that the lowest score was obtained for restricted phonemic fluency followed by standard phonemic fluency, and the best performance was observed for semantic fluency. One-way repeated measures ANOVA analysis showed that there was a significant difference in performance between the three different verbal fluency paradigms within the ALS sample, $F(1.8,209.5) = 3.54$, $p = .03$, $\eta_G^2 = .01$. Post-hoc comparisons indicated that performance on semantic fluency (Animals) significantly differed from performance on both phonemic fluency paradigms, although this did not survive correction for multiple comparisons. How ALS patients perform in comparison to healthy controls is explored in section 7.4, when executive function in our ALS sample is analysed in detail.

As part of this third assumption, it was also predicted that, to a certain degree, verbal fluency deficits are caused by word retrieval, independent of executive dysfunction. To explore what proportion of variance in verbal fluency is solely explained by word retrieval, first-order partial correlations were used, controlling for the effect of executive function. Results are displayed in Table 7.10. Word retrieval was assessed by means of the Boston Naming Test (spontaneous responses), and the executive score selected for this purpose was backward digit span, as this was found to be one of the executive tasks that accounted for a higher degree of variance in verbal fluency tasks. Although the number of confirmed correct sorts from the Sorting Test also highly correlated with verbal fluency performance, backward digit span was chosen over this task given that the former also involves a language component (i.e. sorts must be accurately described) and therefore the latter is considered a purer executive task. The extent of unique variance in verbal fluency explained by word retrieval was explored for the three verbal fluency paradigms reported above.

Table 7.10. Partial correlations to explore the proportion of variance in verbal fluency performance solely explained by word retrieval abilities.

Verbal Fluency Paradigms	Backward Digit Span[a]			Boston Naming Test[b]		
	r	*p*	R^2	r	*p*	R^2
FAS test	.40	<.0001	.16	.25	.007	.06
Restricted Phonemic Fluency (letter C)	.34	.0002	.12	.22	.02	.05
Semantic Fluency (Animals)	.28	.002	.08	.37	<.0001	.14

[a] Zero-order correlations (Pearson's product-moment correlation coefficients).

[b] First-order partial correlations (effect of executive dysfunction held constant).

As can be seen in Table 7.10, executive function measured by means of backward digit span accounted for 16% of the variance in the FAS test, 12% of the variance in restricted phonemic verbal fluency, and 8% of the variance in semantic verbal fluency. When controlling for the effect that executive function has on verbal fluency, word retrieval accounted for 6% of the variance in the FAS test, 5% of the variance in restricted phonemic verbal fluency, and 14% of the variance in semantic fluency. Thus, whereas executive processes seem to influence phonemic verbal fluency performance to a higher degree compared to semantic verbal fluency, word retrieval has a greater influence on semantic verbal fluency performance compared to phonemic verbal fluency when controlling for the effect of executive function. In fact, word retrieval deficits alone explain a very small variance proportion of phonemic verbal fluency deficits in ALS. These results are concordant with the idea that phonemic verbal fluency paradigms are more executively mediated than semantic fluency paradigms, and that the latter rely more heavily on linguistic aspects such as semantic processing and word retrieval compared to phonemic verbal fluency.

7.3.2.4. Action Word Processing

Up to now, word retrieval in our ALS sample has been explored for nouns or object words. However, the processing of action words seem to extend beyond language networks and involve regions of the motor system, including the premotor cortex, and therefore it is important to also explore action word processing in ALS (see chapter 2).

The premotor cortex has been linked to action semantics, this being part of a broader structure of lexico-semantic representations of actions that extends to other semantic processing areas. Considering this, a higher degree of difficulties on action word processing was anticipated compared to processing objects or nouns in ALS. Accordingly, poorer performance of the patient sample in comparison to controls was predicted on an action confrontation naming task (i.e. the Action Naming Test) as well as on an action fluency task (i.e. the Action Fluency Task).

Regarding the Action Naming Test, ALS patients and healthy controls were first compared in terms of spontaneous response performance. Significantly lower performance was observed for the patient sample compared to controls (ALS M = 25.6, SD = 2.23; HC M = 26.3, SD = 1.68), $t(204.2) = 2.75$, $p = .007$, $\eta^2 = .03$. This lower performance can be due to word retrieval deficits or to semantic degradation, and therefore performance following the presentation of cues was analysed. Although the presentation of semantic cues did not improve performance of the ALS sample in comparison to controls (ALS M = 26.2, SD = 1.93; HC M = 26.8, SD = 1.47), $t(204.9) = 2.48$, $p = .01$, $\eta^2 = .03$, a significant difference between the two groups was observed after presentation of phonemic cues, but in this case ALS patients performed significantly better than healthy controls (ALS M = 27.8, SD = 0.48; HC M = 27.3, SD = 1.25), $t(124.4) = -4.02$, p =

.0001, η^2 = .07. These results indicate that ALS patients highly benefit from provision of phonemic cues and are concordant with those observed for object naming, thus showing that action naming deficits in ALS are due to word retrieval difficulties rather than impaired semantic representations.

ALS patients and healthy controls were also compared in terms of performance on the Action Fluency Task. Significant differences were observed, with poorer performance for the ALS sample (ALS *M* = 9.02, *SD* = 2.34; HC *M* = 10.1, *SD* = 1.57), *t*(202.4) = 3.89, p = .0001, η^2 = .07. These results further confirm action word retrieval deficits in ALS.

Further analyses were undertaken to compare object word retrieval versus action word retrieval in our ALS sample. Accordingly, performance on the Boston Naming Test was compared to performance on the Action Naming Test. Mean performance as well as percentage of impairment were considered. Results are depicted in Table 7.11.

Table 7.11. Performance on object word retrieval versus action word retrieval in the ALS sample.

Boston Naming Test[a]		**Action Naming Test**[a]		**Within-group differences**			
				Mean performance[c]		**% abnormal performance**[d]	
M ± *SD*[b]	Nº of Impaired (%)	*M* ± *SD*[b]	Nº of Impaired (%)	t(df)	*p*	X^2(df)	*p*
- 0.50 ± 1.17	18(16)	- 0.43 ± 1.33	23(21)	-0.92(111)	.36	0.94(1)	0.33

[a] Correct spontaneous responses.
[b] Results presented in Z scores to allow for direct comparisons between tasks.
[c] Paired-samples t-test.
[d] McNemar's test.

Results in Table 7.11 indicate that our ALS cohort performed at the same level of ability on object and action naming. In fact, object word retrieval and action word retrieval shared 56% of the variance (r = .75, p < .0001). Overall, these results indicate that while semantic knowledge is spared in early stages of ALS for both objects and actions, retrieval mechanisms are impaired, and these are equally impaired for both object and action words.

7.3.2.5. Word Spelling

According to our fifth assumption, postulating that ALS patients experience a decline on spelling abilities, Table 7.5 showed that ALS patients performed significantly poorer than healthy controls on word spelling, although these findings did not survive correction for multiple comparisons when included in a broader analysis considering overall language performance. Regardless, specific performance on spelling of our ALS sample considering regularity of the words was further analysed.

As part of our hypothesis regarding spelling performance in ALS, it was also postulated that ALS patients present with specific deficits on the lexical spelling route, with preserved ability

to spell through the non-lexical route (i.e. surface agraphia). Accordingly, we predicted that ALS patients would be able to accurately spell regular and pseudowords, but that they would have difficulties spelling irregular words, thus presenting with regularisation errors. The PALPA spelling paradigms utilised for this work allow for a specific assessment of the Dual-Route Model of spelling. Results on Table 7.12 show between-groups comparisons on spelling performance, considering the three types of words outlined.

Table 7.12. Performance of ALS patients compared to healthy controls on word spelling, considering word regularity.

PALPA Spelling	ALS Patients *M ± SD*	Healthy Controls *M ± SD*	Intergroup differences		
			t(df)	p^c	η^2
Regular Words	19.3 ± 1.21	19.7 ± 0.68	2.79(154.3)[a]	.006	.04
Irregular Words	17.4 ± 2.96	18.1 ± 2.57	1.57(197)[b]	.12	.01
Pseudoword	10.1 ± 1.95	10.1 ± 1.69	-0.05(196)[b]	.96	<.01

[a] Welch's t-test (t). Equal variances not assumed, as per Levene's test.
[b] Student t-test (t). Equal variances assumed, as per Levene's test.
[c] Bonferroni adjusted p-value for statistical significance: $p = .016$.

Contrary to our predictions, no significant difference between ALS patients and healthy controls was observed when spelling irregular words, but a significantly poorer performance of the ALS sample compared to healthy controls was found when spelling regular words. Regarding pseudoword spelling, no significant difference between groups was observed. This last finding indicates preserved phoneme-to-grapheme conversion rules in ALS, which is not concordant with findings relating to regular word spelling but which is in accordance with our prediction of preserved non-lexical spelling route in ALS.

To further elucidate this matter, a qualitative analysis of the types of errors committed when spelling both regular and irregular words was undertaken. These are described in Table 7.13.

Table 7.13. Most common errors committed by ALS patients on word spelling.

Regular Words		Irregular Words	
Target Word	**Errors**	**Target Word**	**Errors**
Cat		Aunt	
Jam		Lamb	
Pet		Egg	*Eeg*
Nest		Ghost	*Goast*, *Gost*, *Ghoast*
Bump	*Bomp*	Knock	*Nock*
Swim		Shoe	
Hold		Move	
Bird		Queen	*Quenn*
Tent		Sledge	*Sledgh*, *Sleidge*, *Sleigh*, *Sleegh*, *Slege*, *Sleg*
Frog		Yacht	*Yacth*, *Yatch*, *Yaght*, *Yaucht*, *Yauth*, *Yaught*, *Yought*
Wind		Watch	
Canal	*Cannal*, *Canall*, *Canel*, *Canell*, *Cannell*	Castle	*Castel*
		Giraffe	*Girafe*, *Girrafe*, *Girraffe*, *Giraff* , *Girraff*, *Geraffe*, *Geraff*, *Gerraff*, *Geraph*, *Jiraffe*, *Jiraff*, *Jeraff*, *Jeraf*
Robin	*Robbin*		

Table 7.13 (continued). Most common errors committed by ALS patients on word spelling.

Regular Words		Irregular Words	
Target Word	**Errors**	**Target Word**	**Errors**
Tiger		Squirrel	*Squirell*, *Squirll*, *Squirl*, *Squirle*, *Squirele*, *Squiral*, *Squirrl*, *Squril*, *Scurrle*
Potato[a]	*Patato*		
Sister		Sword	*Sord*
Spring		Soldier	*Soilder*, *Soldire*, *Soildger*, *Soldger*, *Solger*, *Solder*
Banana	*Banna*, *Bannana*, *Bananna*	Heart	*Hart*, *Hearth*
		Aeroplane[b]	*Airoplane*, *Aeroplain*, *Aerplane*, *Eroplane*, *Earplane*
Holiday	*Holliday*, *Holyday*	Photograph	*Photograf*, *Photographe*
Caravan	*Carvan*, *Carivan*	Elephant	*Elephent*, *Elefant*

[a] *Potatoe* also accepted.

[b] *Airplane* also accepted.

As seen in Table 7.13, most errors committed when spelling regular words consisted of doubling consonants, missing vowels or replacing graphemes by others with similar allophones, errors that do not change the actual pronunciation of the word. Therefore, the resulting spelling form still follows phoneme-to-grapheme conversion rules. This confirms spared non-lexical spelling route in ALS. Regarding the type of errors committed when spelling irregular words, two types of patterns are observed. On one hand, regularisation errors are evident (e.g. *jeraf* instead of 'giraffe'), and on the other hand, other errors committed seem to be more related to a difficulty remembering the visual form of the word and therefore the resulting error resembles the same but is not the accurate spelling form (e.g. *girrafe* instead of 'giraffe'). Although ALS patients performed poorer on irregular word spelling compared to healthy controls and an analysis of the type of errors committed show some difficulty when processing learned orthographic word forms, this difference in performance was not significant. Therefore, regardless any difficulties ALS patients may have when spelling through the lexical route, these are not significantly more frequent than those characteristic of the standard population.

7.3.2.6. Word Reading

Although there are no existing studies up to date looking at reading abilities in ALS, we hypothesised that these abilities are spared. Results in Table 7.5 showed that although ALS patients performed significantly poorer than healthy controls on word reading, these results did not survive correction for multiple comparisons, as was the case for word spelling. Similarly, performance when considering regularity of the words was also explored for reading.

As with spelling, the PALPA reading paradigms selected for this study also aimed to explore the ability of ALS patients to read regular, irregular and pseudowords in order to assess the two different reading routes that conform the Dual-Route Model. Table 7.14 displays between-group comparisons on the three aforementioned types of words.

Table 7.14. Performance of ALS patients compared to healthy controls on word reading, considering word regularity.

PALPA Reading	ALS Patients *M* ± *SD*	Healthy Controls *M* ± *SD*	Intergroup differences	
			t(df)	p^c
Regular Words	29.8 ± 0.73	29.9 ± 0.39	1.46(159.9)[a]	.15
Irregular Words	29.0 ± 1.43	29.3 ± 1.12	1.78(203)[b]	.08
Pseudoword	10.8 ± 1.31	10.8 ± 1.38	0.36(203)[b]	.72

[a] Welch's t-test (t). Equal variances not assumed, as per Levene's test.
[b] Student t-test (t). Equal variances assumed, as per Levene's test.
[c] Bonferroni adjusted p-value for statistical significance: $p = .016$.

No significant differences were found between patients and healthy controls on either regular, irregular or pseudoword reading. These results support our hypothesis of spared reading abilities in ALS.

Reading was further assessed using the PALPA Homophone Definition x Regularity paradigm. In accordance to our previous prediction, we also hypothesised that ALS patients would perform accurately on a homophone definition task, irrespectively of the words to read being regular or irregular. Results on this task are presented in Table 7.15.

Table 7.15. Performance of ALS patients compared to healthy controls on homophone definition and reading, considering word regularity.

PALPA Homophone Definition & Regularity		ALS Patients *M* ± *SD*	Healthy Controls *M* ± *SD*	Intergroup differences		
				t(df)	p^b	η^2
Definition	Regular	9.43 ± 1.04	9.64 ± 0.69	1.76(190.4)[a]	.08	.01
	Irregular	9.08 ± 1.56	9.44 ± 0.86	2.08(172.2)[a]	.04	.02
Reading	Regular	9.80 ± 0.51	9.92 ± 0.27	2.16(156.6)[a]	.03	.02
	Irregular	9.16 ± 1.36	9.55 ± 0.76	2.56(160.4)[a]	.01	.03

[a] Welch's t-test (t). Equal variances not assumed, as per Levene's test.
[b] Bonferroni adjusted p-value for statistical significance: $p = .025$.

Contrary to our expectations, the results from Table 7.15 show that ALS patients performed significantly poorer than healthy controls on regular and irregular word reading as well as on irregular word definition, although only the latter survived multiple comparisons correction. Focusing first on performance for regular words, the spared ability to define them indicates that ALS patients do not retrieve the meaning of homophones more often than healthy controls, which is concordant with our previous results indicating spared lexical reading route. ALS patients' significantly poorer performance on reading these words, although it did not survive significance level adjustment for multiple comparisons, was unanticipated. A qualitative look at the data showed that all the variance in performance of the ALS sample when reading regular words from this task was caused by an inability to accurately read two specific words (i.e. *Gait* and *Prophet*), and it is believed to be caused by unfamiliarity of these words. Thus, these words, despite being regular, contain combinations of graphemes (i.e. ⟨ai⟩, ⟨phe⟩) that can be more challenging to process from a grapheme-to-phoneme conversion approach. This could make

these words more prone to be processed from a lexical point of view, but unfamiliarity with the same would create difficulties in accessing them from the orthographic input lexicon.

Focusing on performance on irregular words, ALS patients performed significantly poorer compared to healthy controls when reading them, which caused, in turn, difficulties in defining such words. These results suggest that access to the input orthographic lexicon may be affected somehow in ALS, which subsequently causes deficits in accessing the meaning from the semantic system and the pronunciation of the word from the orthographic output lexicon. This would be concordant with the finding that some patients were unable to read the two aforementioned regular words. Further investigations on input orthographic processing are performed in the following section, where performance on visual lexical decision is analysed.

7.3.2.7. Lexical Processing

Phonological and orthographic lexical processing has not been comprehensively studied in ALS. According to our initial premise that no phonological lexical difficulties exist in ALS and that difficulties with orthographic processing are only at an output level (i.e. spelling), performance on lexical decision was predicted to be unimpaired for both auditory and written tasks. Table 7.16 shows results on the PALPA lexical decision tasks.

Table 7.16. Performance of ALS patients compared to healthy controls on auditory and visual lexical decision.

PALPA Lexical Decision	ALS Patients *M ± SD*	Healthy Controls *M ± SD*	Intergroup differences		
			t(df)	*p*	η^2
Auditory	71.6 ± 4.99	72.5 ± 5.84	1.20(214)[a]	.23	.01
Visual	57.3 ± 3.18	58.3 ± 2.54	2.63(212.9)[b]	.009	.03
PALPA Visual Lexical Decision					
True Positives	29.1 ± 1.67	29.7 ± 0.99	3.07(190.5)[b]	.002	.04
True Negatives	28.2 ± 2.43	28.7 ± 2.36	1.42(214)[a]	.16	.01
Type of words					
HF x HI	7.97 ± 0.23	7.91 ± 0.45	-1.12(140.6)[b]	.27	.01
HF x LI	8.89 ± 0.43	8.97 ± 0.22	1.79(177.1)[b]	.08	.01
LF x HI	5.92 ± 0.30	5.97 ± 0.17	1.46(187.6)[b]	.15	.01
LF x LI	6.32 ± 1.23	6.81 ± 0.46	3.99(151.6)[b]	.0001	.07

Abbreviations. HF: High Frequency, HI: High Imageability, LF: Low Frequency, LI: Low Imageability.

[a] Student t-test (t). Equal variances assumed, as per Levene's test.

[b] Welch's t-test (t). Equal variances not assumed, as per Levene's test.

Results in Table 7.16 indicate that although phonological lexical processing was spared in our ALS sample, significantly poorer performance was found when compared to healthy controls on visual lexical decision. In fact, a weak positive correlation was observed between auditory and visual lexical decision tasks ($r = .27$, $p = .004$), these only sharing 7% of variance.

Table 7.16 also displays further analysis on the visual lexical decision paradigm, which showed that difficulties do not lie in the number of true negatives, but instead lie in the number of true

positives recognised (i.e. ALS patients fail to recognise some orthographic word forms). Analysing in more detail the type of words that are missed by patients considering frequency and imageability, words that are infrequent and more abstract are those that are significantly missed.

These results confirm that orthographic processing deficits exist to some degree at an input level in ALS, which is concordant with results from the Homophone Definition task described in the previous section. In fact, visual lexical decision was found to share 53% of the variance with word spelling ($r = .73$, $p < .0001$) and 44% with word reading ($r = .66$, $p < .0001$). One-way ANCOVA considering word reading and word spelling as covariates indicated that no significant difference on performance on the Visual Lexical Decision task was observed between ALS patients and healthy controls when the effect of orthographic processing was controlled for, $F(1,185) = 0.35$, $p = .55$. A significant effect on visual lexical decision performance was observed for both word reading, $F(1,185) = 9.48$, $p = .002$, $\eta_p^2 = .05$, and word spelling, $F(1,185) = 44.9$, $p < .0001$, $\eta_p^2 = .20$.

7.3.2.8. Syntactic and Grammatical Processing

In the last of our assumptions regarding language performance in ALS we predicted that grammatical and syntactic comprehension deficits are present in ALS. Two sentence – picture matching tasks were implemented to assess this, the first task consisting of auditory sentences given by the examiner, and the second one involving written sentences that had to be read by the examinee. Table 7.17 displays results from both tasks.

Table 7.17. Performance of ALS patients compared to healthy controls on sentence – picture matching tasks.

PALPA Auditory Sentence – Picture Matching	**ALS Patients** *M ± SD*	**Healthy Controls** *M ± SD*	**Intergroup differences**		
			t(df)	***p***	**η^2**
Total Correct	27.0 ± 2.51	28.5 ± 1.99	4.95(208.7)[a]	<.0001	.10
Active	5.59 ± 0.65	5.85 ± 0.41	3.49(191.9)[a]	.0006	.05
Passive	5.31 ± 0.88	5.61 ± 0.68	2.81(207.5)[a]	.005	.04
Reversible	9.35 ± 0.90	9.76 ± 0.55	4.09(188.5)[a]	<.0001	.07
Non-Reversible	7.35 ± 1.11	7.58 ± 0.91	1.70(209.9)[a]	.09	.01
Gapped	7.28 ± 1.01	7.72 ± 0.55	3.97(177.2)[a]	.0001	.07
Converse Relations	3.04 ± 0.84	3.48 ± 0.85	3.83(211)[b]	.0002	.07
PALPA Written Sentence – Picture Matching	**ALS Patients** *M ± SD*	**Healthy Controls** *M ± SD*	**Intergroup differences**		
			t(df)	***p***	**η^2**
Total Correct	28.2 ± 1.87	29.1 ± 1.32	4.14(201.8)[a]	<.0001	.08
Active	5.59 ± 0.68	5.79 ± 0.56	2.33(209.9)[a]	.02	.03
Passive	5.64 ± 0.66	5.88 ± 0.36	3.41(176.9)[a]	.0008	.05
Reversible	9.26 ± 0.94	9.70 ± 0.66	4.01(200.6)[a]	<.0001	.07
Non-Reversible	7.84 ± 0.41	7.94 ± 0.24	2.18(182.9)[a]	.03	.02
Gapped	7.61 ±0.67	7.74 ± 0.48	1.62(202.8)[a]	.11	.01
Converse Relations	3.48 ± 0.66	3.72 ± 0.53	2.97(209.5)[a]	.0003	.04

[a] Welch's t-test (t). Equal variances not assumed, as per Levene's test.

[b] Student t-test (t). Equal variances assumed, as per Levene's test.

ALS patients performed significantly poorer in comparison to healthy controls on both auditory and written syntactic processing tasks, as well as on most types of sentences assessed in each task. These results suggest that syntactic/grammatical processing deficits exist in ALS for auditory as well as for written input. A significant strong positive correlation was observed between auditory and written sentence processing in ALS ($r = .70$, $p < .0001$).

Further explorations were undertaken to discern the influence that comprehension of words included in these tasks had on performance in the ALS sample. As described in the methods chapter (section 5.4.2.1), a task assessing comprehension of verbs and adjectives used on the two sentence processing tasks (i.e. PALPA Auditory Comprehension of Verbs and Adjectives) was administered. Although negligible or weak correlations were observed between performance on sentence processing and comprehension of adjectives (Auditory $r = .14$, $p = .15$; Written $r = .31$, $p = .001$), moderate correlations were observed with comprehension of verbs (Auditory $r = .58$, $p < .0001$; Written $r = .45$, $p < .0001$). These results are concordant with the premise that verbs are syntactically more complex than other types of words such as adjectives.

Another aspect that it is important to explore is the influence that reading had on written sentence processing performance. A moderate positive correlation was observed between the PALPA Written Sentence – Picture Matching and the PALPA Word Reading Paradigm ($r = .58$, $p < .0001$), thus meaning that they shared 34% of the variance. One-way ANCOVA was used to assess if significant differences between ALS patients and healthy controls were still present when controlling for the influence that reading had on performance. Although the effect of word reading on written sentence processing was significant, $F(1,200) = 69.7$, $p < .0001$, $\eta_p^2 = .26$, significantly lower performance of ALS patients in comparison to healthy controls on written sentence processing was still present even when correcting for the effect of word reading, $F(1,200) = 11.2$, $p = .001$, $\eta_p^2 = .05$.

The role that working memory has on auditory sentence processing is analysed later on in this chapter (section 7.4.2), when the influence that executive function has on language change is addressed.

7.4. The Role of Executive Dysfunction in Language Change in ALS

The second aim of this work intends to assess the relationship between the previously described language changes in ALS and executive dysfunction. Prior to investigating the contribution that executive dysfunction has on language change, performance of our ALS sample on executive tasks was evaluated.

7.4.1. Executive Function: Between-Groups Comparisons

One-way MANCOVA was employed to compare executive performance between our population-based ALS sample and the demographically-matched healthy control cohort. Mood and arterialised tissue capillary blood gas tensions were also considered as covariates.

Regarding MANCOVA assumptions, multivariate and univariate normality was not assumed in this case either. Mahalanobis distances indicated that deviations from normality were also due to skewness rather than extreme outliers (only three cases exceeded the critical value for extreme outliers, 27.88 in this case as per chi-square distribution table at an alpha value of .001 and 9 degrees of freedom). Univariate equality of variances was proven for semantic fluency (Animals), Inhibition and Inhibition/Switching paradigms from the Colour-Word Interference Test, the Sorting Test, and Conflicting Emotional Prosody. The assumption of homogeneity of variance – covariance matrices was not met, but greater variances were observed for the group with larger samples, which was the patient groups in most cases. No strong correlations were observed between variables thus ruling out multicollinearity, but in some cases low correlations were found between executive tasks, which needs to be considered when interpreting multivariate results. The assumption of homogeneity of regression slopes was met for all three covariates.

No significant difference was observed between patients and healthy controls on executive function as per MANCOVA multivariate results, $F(9,87) = 1.03$, $p = .43$, $V = .096$. This is most likely due to the lack of correlations between dependent variables, described above. Because of this, separate univariate ANOVAs were then performed to assess performance on each executive task. Moreover, MANCOVA results also indicated that none of the covariates had a significant effect on executive function performance: mood, $F(9,87) = 0.426$, $p = .92$, $V = .042$, $Sp0_2$ levels, $F(9,87) = 1.396$, $p = .20$, $V = .126$, and $PaC0_2$ levels, $F(9,87) = 0.630$, $p = .77$, $V = .061$. Therefore, no covariates were included in subsequent one-way ANOVAs.

Results from univariate tests are shown in Table 7.18. The proportion of impaired ALS patients compared to the proportion of impaired healthy controls on each executive task were explored, and results are also presented in Table 7.18.

Mean performance on executive tasks was lower for the patient group in comparison to healthy controls for all executive tasks except for Conflicting Emotional Prosody. However, one-way ANOVA results indicated that such lower performance on the patient group was only significant for some of the executive tasks, including the two phonemic verbal fluency paradigms as well as the number of correct sorts on the Sorting Test, with small effects in all cases. Semantic fluency and Reading the Mind in the Eyes task did not survive significance adjustments for multiple comparisons.

Table 7.18. Performance of ALS patients in comparison to healthy controls on executive function measures.

Executive Function Measure	ALS Patients n = 117		Healthy Controls n = 100		Intergroup differences					
					Mean performance[a]			% of impaired[b]		
	M ± *SD*	Nº of Impaired (%)[c]	*M* ± *SD*	Nº of Impaired (%)[c]	F(df)	*p*[f]	η^2	X^2(df)	*p*	φ
FAS test	9.00 ± 2.13	18 (16)	9.78 ± 1.42	4	10.2(1,201.6)[e]	.002	.04	6.58(1)[g]	.006	.19
Restricted Phonemic Fluency (letter C)	8.87 ± 2.26	17 (15)	9.70 ± 1.25	3	11.5(1,185.9)[e]	.0008	.05	7.24(1)[g]	.004	.20
Semantic Fluency (Animals)	9.38 ± 1.88	7 (6)	9.92 ± 1.42	4	5.44(1,215)	.02	.02	0.12(1)[g]	.55	.05
Digit Span Backward	4.71 ± 1.47	21 (19)	4.92 ± 1.16	9	1.28(1,206.4)[e]	.26	.006	3.27(1)	.07	.14
CWIT Inhibition – TIP[d]	1.33 ± 0.66	10 (10)	1.38 ± 0.52	6 (7)	0.37(1,186)	.54	.002	0.48(1)	.49	.07
CWIT Inhibition/Switching – TIP[d]	1.42 ± 0.67	9 (10)	1.47 ± 0.53	7 (8)	0.24(1,180)	.62	.001	0.02(1)	.90	.03
Sorting Test – Correct Sorts	7.25 ± 2.41	19 (18)	8.35 ± 2.22	5	11.4(1,203)	.0009	.05	6.75(1)	.009	.20
Reading the Mind in the Eyes	22.1 ± 5.54	20 (18)	23.5 ± 4.44	4	4.12(1,208.4)[e]	.04	.02	8.49(1)[g]	.002	.22
Conflicting Emotional Prosody	29.7 ± 5.47	5 (8)	29.0 ± 5.63	6	0.56(1,157)	.46	.004	0.08(1)	.78	.02

[a] One-way ANOVA.

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[c] Abnormal performance considered as 1.65 SD below the control mean, as per Revised Diagnostic Criteria (Strong et al., 2017).

[d] Higher scores indicate poorer performance.

[e] Welch's F-ratio.

[f] Bonferroni adjusted p-value for statistical significance: $p = .005$.

[g] Fisher's Exact Probability Test.

Regarding the proportion of impairment, a significantly higher proportion of patients were impaired on the three aforementioned executive tasks in comparison to controls (i.e. FAS test, restricted phonemic fluency, and the Sorting Test), thus confirming phonemic verbal fluency deficits as well as difficulties with abstract reasoning and/or problem-solving in ALS. Moreover, a significantly higher proportion of impairment in the patient group was also observed for the Reading the Mind in the Eyes Test, indicating that ALS patients are more frequently impaired on social cognition in comparison to healthy controls. Effect sizes for the percentages of impairment for executive tasks were small in all cases.

Further investigations on the Sorting Test were undertaken to better delineate the profile of dysfunction on this task. As described in Table 7.18, ALS patients generated a significantly lower number of correct sorts in comparison to healthy controls. These results can indicate difficulties in abstract reasoning and concept formation, but they can also be due to difficulties in problem-solving and goal-directed behaviour. To discern the nature of such deficits, performance on description scores were explored. Accordingly, the ability to identify conceptual relationships of sorts that were already given (i.e. Sort Recognition Description) in comparison to sorting and describing them freely (i.e. Free Sorting Description) was analysed. ALS patients performed significantly poorer compared to healthy controls on Free Sorting Description (ALS M = 27.1, SD = 9.80; HC M = 31.7, SD = 8.85), $t(203) = 3.54$, $p = .0005$, $\eta^2 = .06$, but no significant difference on performance was observed on Sort Recognition Description (ALS M = 32.2, SD = 9.88; HC M = 33.4, SD = 9.06), $t(196) = 0.93$, $p = .35$. Paired-samples analysis confirmed a significant improvement on Sort Recognition Description in comparison to Free Sorting Recognition in the patient group, $t(99) = -8.16$, $p < .0001$, $\eta^2 = .40$. These results indicate that deficits in Free Sorting in ALS are most likely due to a limited ability to generate sorts (i.e. problem-solving abilities), rather than an inability to identify and explain their conceptual relationship (i.e. concept formation and abstract reasoning).

The number of errors committed on different executive tasks was also inspected as a measure of self-monitoring. ALS patients committed more errors compared to healthy controls across all verbal fluency paradigms (ALS M = 5.87, SD = 3.95; HC M = 3.37, SD = 2.89), $t(215) = -5.24$, $p < .0001$[b], $\eta^2 = .11$. More specifically, ALS patients had a significantly higher number of both set-loss errors (ALS M = 3.24, SD = 2.88; HC M = 1.65, SD = 1.90), $t(202.9) = -4.86$, $p < .0001$, $\eta^2 = .10$), and repetition errors (ALS M = 2.63, SD = 2.52; HC M = 1.72, SD = 1.86), $t(210.9) = -3.06$, $p = .003$, $\eta^2 = .04$. Regarding the Colour-Word Interference Test, no significant differences were observed on the number of errors committed on both paradigms: Inhibition (ALS M = 1.95, SD = 3.75; HC M = 1.68, SD = 2.62), $t(186) = -0.56$, $p = .58$, and Inhibition/Switching (ALS M = 2.84, SD = 3.93; HC M = 2.32, SD = 3.35), $t(180) = -0.96$, $p = .34$. Finally, no significant difference was

[b] Bonferroni adjusted p-value for statistical significance: $p = .02$.

found on the number of non-target responses given on free sorting on the Sorting Test (ALS *M* = 1.08, *SD* = 1.35; HC *M* = 1.28, *SD* = 1.49), *t*(203) = 0.97, p = .34).

7.4.2. The Relationship between Executive and Language Dysfunction in ALS

We have shown that our incident ALS sample performed significantly lower than healthy controls on some measures of language and executive function, and that a significant proportion of ALS patients were actually impaired on those measures. In this section we intend to investigate how the aforementioned executive deficits relate to language change in our population-based incident ALS sample. To explore this aim, multiple regression is utilised.

We investigated the effect that executive dysfunction has on the following language domains: orthographic lexical processing, word spelling, word reading, word retrieval and syntactic/grammatical processing. We did not examine phonological lexical and semantic processing, as no evidence of impairment on these language measures was observed in our ALS sample. Regarding executive functions included as predictors, phonemic verbal fluency, problem-solving, cognitive flexibility and social cognition were considered. In order to identify the most contributing predictors for each model or language domain, the change in R^2 produced by each predictor when added to a model that already contained the other three predictors was calculated. This change in R^2 represents the unique contribution of that specific predictor to the model, thus the unique proportion of the variance that predictor variable explains beyond the other predictors.

Multiple regression assumptions were checked for the five models. The assumption of normality of the residuals was met for the orthographic lexical processing and the word retrieval models, but it was not met for the spelling, reading and syntactic/grammatical processing models due to the presence of outliers (i.e. 1 for spelling, 2 for reading and 1 for syntactic/grammatical processing models). However, Cook's distances indicated that none of these outliers was an influential observation. Only one value for the spelling model had a Di > 0.5, but < 1, and therefore this case was kept in the analysis. The assumption of linearity of residuals was met in all cases except for orthographic lexical processing, thus limiting the model's generalizability in this case. Homoscedasticity was not met in any of the five models, and therefore parameters were adjusted using sandwich heteroscedasticity corrected matrix estimators. The variance inflator factor was around 1 for all predictor variables in all models, thus confirming the absence of multicollinearity. Multiple regression results are displayed in Table 7.19.

Table 7.19. Regression models to predict the effect of executive dysfunction on language performance in ALS.

		β[e]	SEE[e]	t-test[e]	*p*[e]	R^2 [f]	F(df)	*p*	Unique contribution to R^2
Orthographic Lexical Processing	Phonemic Verbal Fluency[a]	0.36	0.195	1.84	.07	.37	13.0(4,87)	<.0001	.04
	Problem-solving[b]	0.14	0.140	1.03	.31				-.01
	Cognitive Flexibility[c]	-1.27	0.396	-3.20	.002				.09
	Social Cognition[d]	0.11	0.064	1.73	.09				.03
Word Spelling	Phonemic Verbal Fluency[a]	0.87	0.383	2.28	.03	.33	9.77(4,79)	<.0001	.14
	Problem-solving[b]	-0.14	0.187	-0.74	.46				-.01
	Cognitive Flexibility[c]	-1.32	0.617	-2.15	.03				.08
	Social Cognition[d]	0.12	0.098	1.26	.21				.02
Word Reading	Phonemic Verbal Fluency[a]	0.28	0.183	1.51	.13	.26	7.70(4,87)	<.0001	.07
	Problem-solving[b]	-0.08	0.085	-0.93	.36				-.01
	Cognitive Flexibility[c]	-0.66	0.295	-2.22	.03				.06
	Social Cognition[d]	0.07	0.043	1.63	.11				.03
Word Retrieval	Phonemic Verbal Fluency[a]	0.55	0.353	1.56	.12	.29	9.07(4,87)	<.0001	.04
	Problem-solving[b]	0.13	0.205	0.64	.52				-.01
	Cognitive Flexibility[c]	-0.51	0.636	-0.80	.42				.00
	Social Cognition[d]	0.21	0.094	2.25	.03				.05
Syntactic and Grammatical Processing	Phonemic Verbal Fluency[a]	0.87	0.336	2.58	.01	.49	20.6(4,87)	<.0001	.12
	Problem-solving[b]	0.24	0.175	1.37	.18				.02
	Cognitive Flexibility[c]	0.01	0.559	0.02	.98				-.02
	Social Cognition[d]	0.21	0.070	2.95	.004				.06

[a] A phonemic verbal fluency composite score was created by summing scores from the FAS test and restricted phonemic fluency (letter C), and dividing it by 2. Converted scores, which are equivalent, were employed to ensure that both variables had the same weight within the composite.

[b] Sorting Test, total confirmed correct sorts.

[c] Colour-Word Interference Test, Inhibition/Switching – Time Increase Proportion.

[d] Reading the Mind in the Eyes Test.

[e] Parameters obtained using sandwich heteroscedasticity corrected matrix estimators.

[f] R^2 is used to represent the proportion of the variance from the outcome variable explained by executive function in each model. R^2 is chosen here over Adjusted R^2 given that all models use the same predictors and therefore there is no need for adjustment.

Executive dysfunction was found to be a significant contributor to language deficits in the five domains assessed. The language process sharing the highest amount of variance with executive dysfunction was syntactic/grammatical processing (49%), followed by orthographic lexical processing (37%), word spelling (33%) and word retrieval (29%). Phonemic verbal fluency deficits accounted for the largest proportion of variance in most cases, and social cognition was also found to be a significant predictor for word retrieval and sentence processing. Moreover, cognitive flexibility was found to significantly predict performance on orthographic lexical processing, word reading, and spelling. Whereas these results confirm our hypothesis that language change in ALS is associated with executive dysfunction to a degree, they also prove that executive dysfunction does not explain the entirety of language change characteristic of ALS.

Another aspect we aimed to investigate was the role of working memory in auditory syntactic/grammatical processing. As part of Aim 2, we hypothesised that this executive function component would have an influence on auditory sentence processing performance. A moderate significant positive correlation was in fact observed between the PALPA Auditory Sentence – Picture Matching task and the longest backward digit-string recalled from the WAIS-IV Digit Span subtest ($r = .50$, $p < .0001$) in the patient group. Thus, these two tasks shared 25% of the variance. Simple linear regression analysis confirmed that working memory is a significant predictor of auditory syntactic/grammatical processing, $\beta = 0.84$, SEE = 0.16, $t(1,109) = 5.16$, $p < .0001$[c]. Correlations between the aforementioned working memory test and each type of sentence included in the PALPA task were also investigated. Results are displayed in Table 7.20.

Table 7.20. Correlations between auditory sentence processing and working memory measures in ALS.

Auditory Sentence – Picture Matching	Backward Digit Span		
	r[a]	*p*	R^2
Active	.33	.0005	.11
Passive	.35	.0002	.12
Reversible	.27	.005	.07
Non-Reversible	.30	.001	.09
Gapped	.36	.0001	.13
Converse Relations	.40	<.0001	.16

[a] Pearson's product-moment correlation coefficients.

As per results in Table 7.20, the type of sentence that share a higher degree of variance with working memory are sentences involving converse relations, followed by gapped and passive sentences.

[c] Parameters obtained using sandwich heteroscedasticity corrected matrix estimators.

Further investigations were undertaken to determine if auditory syntactic/grammatical processing difficulties that are independent of working memory deficits are present in ALS. One-way ANCOVA was performed to compare performance between ALS patients and healthy controls on the PALPA Auditory – Sentence Picture Matching task while controlling for the effect of working memory. Concordant with previous results, the effect of working memory on auditory sentence processing was significant, $F(1,206) = 7.62$, $p = .006$, $\eta_p^2 = .04$, although significant differences on performance were still observed between ALS patients and healthy controls after controlling for the effect of this executive component, $F(1,206) = 7.30$, $p = .007$, $\eta_p^2 = .03$. These results are concordant with our hypothesis that although working memory difficulties contribute to deficits in auditory sentence processing, pure grammatical and syntactic processing deficits for auditory information exist in ALS.

7.5. Population-Based Incidence of Frontotemporal Syndromes in ALS

This section addresses the third aim of this work, which intends to establish the incidence of the various frontotemporal syndromes of ALS on a representative population-based sample, based on revised diagnostic criteria (Strong et al., 2017).

7.5.1. Incidence of FTD

As described in chapter 5, all participants underwent comprehensive assessment that extended from the domains of interest of this work (see Appendix F, page 356). The administration of a broad battery that covered the whole cognitive spectrum along with behaviour permitted an accurate diagnosis of comorbid dementia in our ALS cohort.

Eighteen ALS patients met criteria for comorbid FTD. This represents 13% of our population-based incident ALS sample. The vast majority of these ALS-FTD patients (n = 15, 83%) met revised diagnostic criteria for bvFTD (Rascovsky et al., 2011). Two patients (11%) met criteria for svPPA and one (6%) for nfvPPA, according to diagnostic criteria by Gorno-Tempini et al. (2011). One of the ALS-bvFTD patients also met revised diagnostic criteria for possible AD with an etiologiacally mixed presentation (Appendix D, pages 350-351; McKhann et al., 2011).

Table 7.21 describes demographic and clinical characteristics of ALS-FTD patients in comparison to non-demented ALS patients. The ALS and ALS-FTD samples were overall equivalent. The only significant differences were encountered in the fact that none of the ALS-FTD patients were working in contrast to 24% of the ALS sample who were still employed, and that only 56% of ALS-FTD patients were taking Riluzole in contrast to 89% of ALS patients. ALS patients scored significantly lower on the ALSFRS-R limb sub-score compared to ALS-FTD patients, although no significant difference was observed on the total ALSFRS-R score.

Table 7.21. Demographic and clinical characteristics of the patient sample segregated by non-demented ALS and ALS patients meeting criteria for FTD.

		ALS n = 117	ALS-FTD n = 18	W / X^2(df)	*p*
Age *M±SD* (*Mdn*) years		62.4 ± 10.9 (64)	67.24± 7.67 (66)	805[a]	.11
Gender n(%)	Females Males	42 (36) 75 (64)	8 (44) 10 (56)	0.19(1)[b]	.66
Years of formal education *M±SD* (*Mdn*) years		14.4 ± 3.52 (14)	14.7 ± 4.27 (14)	1015[a]	.80
Currently working n(%)		28 (24)	0	4.08(1)[c]	.04
Marital Status n(%)	Single Married Widowed Separated	9 (8) 85 (73) 10 (9) 13 (11)	1 (5) 15 (85) 1 (5) 1 (5)	0.97(3)[d]	.81
Age at onset *M±SD* (*Mdn*) years		60.7 ± 10.9 (62)	65.5 ± 7.36 (64)	815[a]	.12
Site of onset n(%)	Spinal Bulbar Thoracic / Respiratory	79 (68) 32 (27) 6 (5)	12 (67) 6 (33) 0	1.12(2)[d]	.57
Age at diagnosis *M±SD* (*Mdn*) years		62.0 ± 11.0 (64)	67.3 ± 7.58 (66)	787[a]	.09
Diagnostic Delay *M±SD* (*Mdn*) months		16.5 ± 15.3 (12)	21.6 ± 17.05 (14)	824[a]	.14
Family History of ALS or ALS-FTD n(%)		25 (21)	5 (28)	0.09(1)[b]	.76
Family History of FTD n(%)		7 (6)	3 (16)	1.27(1)[c]	.13
Family History of other Neurological Conditions n(%)		62 (53)	7 (39)	0.74(1)[b]	.39
Family History of Psychiatric Conditions n(%)		49 (42)	8 (44)	0.00(1)[b]	.99
Riluzole use n(%)		104 (89)	10 (56)	10.8(1)[b]	.001
Caregiver Relationship n(%)	Spouse Child Other family mem./friend Hospice	83 (71) 18 (15) 15 (13) 1 (1)	12 (66) 3 (17) 3 (17) 0	0.38(3)[d]	.94
External homecare n(%)		15 (13)	0	1.46(1)[c]	.22
Use of NIV n(%)		26 (22)	1 (6)	1.77(1)[c]	.18
Enteral feeding tube in place n(%)		6 (5)	0	0.14(1)[c]	.99
SpO_2 *M±SD* (*Mdn*) %		97.1 ± 1.45 (97)	97.0 ± 1.05 (97)	648[a]	.50
$PaCO_2$ *M±SD* (*Mdn*) kPa		5.37 ± 0.56 (5.4)	5.44 ± 0.47 (5.4)	551[a]	.83
ALSFRS-R total score *M±SD* (*Mdn*) score		35.9 ± 7.23 (38)	*n = 12* 39.3 ± 3.23 (39.5)	531[a]	.17
ALSFRS-R bulbar sub-score *M±SD* (*Mdn*) score		9.69 ± 2.67 (10)	9.00 ± 2.59 (9.5)	847[a]	.23
ALSFRS-R limb sub-score *M±SD* (*Mdn*) score		16.3 ± 5.06 (16)	19.5 ± 3.50 (20)	440[a]	.03
ALSFRS-R respiratory sub-score *M±SD* (*Mdn*) score		9.92 ± 3.13 (12)	10.8 ± 2.04 (11.5)	663[a]	.73

[a] Mann-Whitney-Wilcoxon Test.

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[c] Fisher's Exact Probability Test.

[d] Pearson's Chi-square test for independence (X^2).

Two out of the three ALS patients with comorbid PPA presented with spinal onset (67%), and the distribution of bulbar/spinal disease onset in bvFTD patients was also similar (67% spinal, 33% bulbar). None of the ALS-FTD patients presented with respiratory onset.

Neuropsychological performance was compared between ALS and ALS-FTD patients, also considering behavioural change as well as mood. Results are displayed in Table 7.2 2.

Table 7.22. Neuropsychological performance of ALS-FTD patients compared to non-demented ALS patients.

Neuropsychological Measure	ALS n = 117	ALS-FTD n = 18	W[d]	*p*	*r*
Intellectual Ability					
	M ± *SD* (*Mdn*)[a]				
Premorbid Intellectual Ability	103 ± 13.4 (103)	96.1 ± 13.3 (96)	1044	.07	.16
Current Intellectual Function	96.7 ± 15.5 (97)	73.1 ± 20.7 (81)	1747	<.0001	.39
Language					
	M ± *SD* (*Mdn*)[b]				
PALPA Lexical Decision	129 ± 6.59 (130)	116 ± 14.2 (118)	1239	.0001[e]	.33
PALPA Word Spelling	36.7 ± 3.95 (38)	29.8 ± 8.41 (30)	1183	.0002[e]	.35
PALPA Word Reading	58.8 ± 1.70 (59)	55.9 ± 4.29 (57)	1134	.0006[e]	.32
PALPA Word – Picture Matching	39.8 ± 0.62 (40)	37.6 ± 2.87 (38.5)	1512	<.0001[e]	.55
PALPA Sentence – Picture Matching	55.2 ± 4.04 (56)	47.3 ± 5.43 (48)	1603	<.0001[e]	.44
Boston Naming Test	23.6 ± 4.37 (25)	14.4 ± 5.93 (13)	1740	<.0001[e]	.44
Pyramids and Palm Trees Test	14.0 ± 0.23 (14)	13.3 ± 1.20 (14)	1242	<.0001[e]	.45
Executive Function					
FAS test	9.00 ± 2.13 (10)	4.88 ± 3.86 (5)	1522	<.0001[f]	.42
Restricted Phonemic Fluency (letter C)	8.87 ± 2.26 (10)	5.33 ± 3.14(4)	1720	<.0001[f]	.43
Semantic Fluency (Animals)	9.38 ± 1.88 (10)	5.00 ± 3.31 (6)	1847	<.0001[f]	.47
Digit Span – backward span	4.71 ± 1.47 (5)	3.35 ± 0.86 (3)	1491	.0001[f]	.34
CWIT Inhibition – TIP[c]	1.33 ± 0.66 (1.17)	2.06 ± 1.15 (1.73)	357	.005[f]	.27
CWIT Inhibition/Switching – TIP[c]	1.42 ± 0.67 (1.31)	2.16 ± 1.17 (1.74)	320	.01[f]	.24
Sorting Test – Free Correct Sorts	7.25 ± 2.41 (7)	3.73 ± 2.20 (3)	1004	.0001[f]	.36
Sorting Test – Free Sorting Description	27.1 ± 9.80 (27)	13.6 ± 8.18 (12)	1000	.0001[f]	.35
Sorting Test –Recognition Description	32.2 ± 9.88 (33)	11.0 ± 6.50 (10)	858	<.0001[f]	.43
Reading the Mind in the Eyes Test	22.1 ± 5.54 (22)	11.8 ± 5.46 (10.5)	1832	<.0001[f]	.48
Conflicting Emotional Prosody Test	29.7 ± 5.47 (32)	12.8 ± 1.71 (12.5)	262	.001[f]	.39
Behaviour					
Beaumont Behavioural Inventory[c]	8.34 ± 9.61 (5)	25.9 ± 23.3 (15)	268	.0004	.36
Mood					
HADS-T[c]	7.14 ± 5.44 (5)	9.11 ± 6.53 (7)	316	.42	.08

[a] Standard Scores or IQ.

[b] Raw Scores.

[c] Higher scores indicate poorer performance.

[d] Mann-Whitney-Wilcoxon Test.

[e] Bonferroni adjusted p-value for statistical significance: $p = .007$

[f] Bonferroni adjusted p-value for statistical significance: $p = .005$

Results from Table 7.22 indicate that although no significant difference exists in terms of premorbid IQ between ALS and ALS-FTD patients, current intellectual functioning is significantly lower in ALS-FTD patients compared to non-demented ALS patients.

Regarding language and executive function, ALS patients with a comorbid diagnosis of FTD performed significantly poorer compared to non-demented ALS patients in all measures considered. The only exception was observed in the two Colour-Word Interference Test paradigms in terms of the time taken to complete them, which did not survive adjustments for multiple comparisons. However, looking at the number of errors committed, ALS-FTD patients committed a significantly higher number of errors in comparison to ALS patients in both paradigms, Inhibition (ALS $M = 1.95$, $SD = 3.75$, $Mdn = 1$; ALS-FTD $M = 11.93$, $SD = 12.3$, $Mdn = 5.5$), $W = 257$, $p < .0001$, $r = .37$, and Inhibition/Switching (ALS $M = 2.84$, $SD = 3.93$, $Mdn = 2$; ALS-FTD $M = 15.2$, $SD = 11.2$, $Mdn = 11$), $W = 133$, $p < .0001$, $r = .42$. This is characteristic of frontal dysfunction related to impulse control.

Regarding behaviour, ALS-FTD patients also scored significantly higher on the Beaumont Behavioural Inventory compared to ALS patients. Looking at descriptive data, we observe that the mean score for ALS patients is right above the cut-off of 7, indicative of behavioural change, and that the mean score for ALS-FTD is right above the cut-off of 23, highly sensitive to such diagnosis.

Finally, regarding mood, no significant differences were observed between ALS and ALS-FTD patients on the HADS-T.

7.5.2. Incidence of ALSci

The revised criteria for the diagnosis of frontotemporal syndromes in ALS (Strong et al., 2017) were used to investigate the incidence of ALSci in our population-based cohort. We examine cognitive status for the non-demented ALS sample in this section, and behavioural status is investigated in the next section. Subsequently, cognitive and behavioural classifications for the non-demented ALS sample are combined, and their incidence is also explored in relation to the presence of ALS-FTD cases in our population-based cohort.

Focusing on cognitive status for non-demented ALS patients, revised diagnostic criteria for ALSci along with the neuropsychological measures considered to assess participants on each cognitive domain are depicted in Table 7.23. Selection of neuropsychological measures and scores considered for classification purposes are based on analyses undertaken in sections 7.3 and 7.4. Details on this are specified at the bottom of Table 7.23.

Table 7.23. Revised diagnostic classification criteria for ALS with cognitive impairment (ALSci).

ALS with Cognitive Impairment (ALSci)				
Type of impairment	**Revised Diagnostic Criteria**	**Neuropsychological Measure**	**Score Considered**	**Cognitive Function Assessed**
ALS with EXECUTIVE IMPAIRMENT (ALSei)	*Impairment on phonemic verbal fluency (after controlling for motor/speech impairment)*	FAS Test	VFI Converted Score	Phonemic Verbal Fluency
		Restricted VF (letter C)		
	OR			
	Impairment on two other non-overlapping tests of executive function (may include social cognition)	Backward Digit Span	Longest Span	Working memory
		Sorting Test – Free Sorting – Confirmed Correct Sorts[a]	Correct sorts	Problem Solving
		Sorting Test – Sort Recognition – Description[a]	Total Score	Abstract Reasoning
		CWIT – Inhibition[b]	TIP or Errors[c]	Inhibitory Control
		CWIT – Inhibition/Switching[b]	TIP or Errors[c]	Cognitive Flexibility
		Reading the Mind in the Eyes Test	Correct answers	Social Cognition
ALS with LANGUAGE IMPAIRMENT (ALSli)	*Impairment on two non-overlapping language tests*	PALPA Auditory Lexical Decision[d]	Correct answers	Phonological Lexical Processing
		PALPA Word Spelling		Spelling
		PALPA Word Reading		Reading
		Boston Naming Test[e]		Word Retrieval
		Semantic Composite Score[f]		Semantic Processing
		PALPA Sentence – Picture Matching[g]		Syntactic / Grammatical Processing

[a] A strong positive correlation was found between the number of correct sorts on Free Sorting and the description score on Sort Recognition from the Sorting Test ($r = .82$, $p < .0001$). Given that these are considered overlapping tasks (i.e. impairment on number of correct sorts can also be due to deficits in abstract reasoning), impairment on Free Sorting – Confirmed Correct Sorts is only considered if the Sort Recognition Description condition is spared, as the former is then likely to represent a pure problem-solving deficit.

[b] A moderate positive correlation was found between Inhibition and Inhibition/Switching ($r = .62$, $p < .0001$). Given that these are considered overlapping tasks (i.e. impairment in Inhibition/Switching can also be due to deficits in inhibitory control), impairment in Inhibition/Switching is only considered if the Inhibition condition is spared, as the former is then likely to represent a pure cognitive flexibility deficit.

[c] Impairment in either the TIP or the number of errors committed is considered, to include those with a more impulsive profile who perform accurately in terms of reaction time but commit a high number of errors.

[d] Auditory Lexical Decision is considered uniquely as a measure of lexical processing, given the previously shown high overlap between orthographic lexical processing and reading and spelling abilities in our ALS sample.

[e] Considering results in section 7.3.2.1, the Boston Naming Test number of spontaneous responses are considered as a measure of word retrieval.

[f] A semantic composite score was created by adding up Z scores for Spoken Word – Picture Matching, Written Word – Picture Matching, and the Pyramids and Palm Trees Test, and divide it by three, aiming for this composite score to include the whole variance of modalities assessed in our ALS sample.

[g] The total score for Sentence – Picture Matching, composed by auditory and written sentence paradigms, is considered here. The rationale under this choice is to avoid considering isolated auditory deficits caused by working memory difficulties or isolated written deficits caused by reading difficulties.

It was not possible to classify 13 ALS patients and two healthy controls due to missing data. From the remaining 104 non-demented ALS patients, 34 (32%) were classified as impaired (i.e. ALSci), in comparison to 16% of healthy controls, $X^2(1) = 6.40$, $p = .01$, $\varphi = .19$.

The proportion of ALS patients in comparison to healthy controls who were impaired on the executive as well as on the language domain was also explored. Results are shown in Table 7.24. A significantly higher proportion of ALS patients presented with executive impairment, although no significant difference was observed for the percentage of language impairment encountered.

Table 7.24. Proportion of ALS patients and healthy controls that met criteria for executive and language impairment.

Cognitive Classification	ALS patients	Healthy Controls	$X^2(df)^a$	*p*	φ
Executive Impairment n(%)	*n = 109* 35 (32)	*n = 98* 11	11.8(1)	.0006	0.25
Language Impairment n(%)	*n = 108* 20 (19)	*n = 100* 13	0.81(1)	.37	0.08

[a] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

Focusing on the ALS cohort, three different cognitive classifications were considered for ALSci patients, determined by the presence of executive impairment in isolation (i.e. namely ALSei), the presence of language impairment in isolation (i.e. namely ALSli), or the presence of both executive and language impairment (i.e. namely ALSeli). 15 patients (14%) met criteria for ALSei, 16 patients (15%) met criteria for ALSeli, and only 3 patients (3%) met criteria for ALSli. 70 participants (68%) showed preserved cognitive function. These results are visually represented in Figure 7.2.

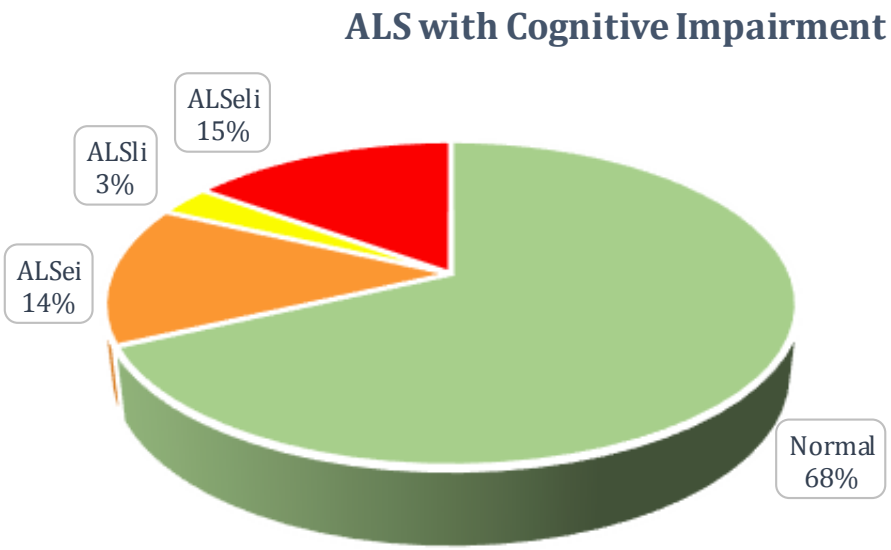

Figure 7.2. Cognitive classification of the non-demented ALS sample

ALSci patients were compared to cognitively unimpaired ALS patients in terms of demographic and clinical characteristics. Results are presented in Table 7.25.

Table 7.25. Demographic and clinical characteristics of the patient sample segregated by ALS with cognitive impairment (ALSci) and cognitively unimpaired ALS patients.

		ALS Normal n = 70	**ALSci** n = 34	**t(df) / W / X^2(df)**	***p***
Age *M±SD* (*Mdn*) years		60.6 ± 12.4 (62)	64.8 ± 8.00 (67)	1376[a]	.20
Gender n(%)	Females Males	20 (29) 50 (71)	16 (47) 18 (53)	2.69(1)[b]	.10
Years of formal education *M±SD* (*Mdn*) years		15.6 ± 3.23 (16)	12.7 ± 3.57 (12)	574[a]	<.0001
Premorbid Intellectual Ability *M±SD* (*Mdn*) IQ		n = 70 109 ± 11.1 (109.5)	n = 30 92.9 ± 11.8 (92)	311[a]	<.0001
HADS-T *M±SD* (*Mdn*) score		n = 52 6.13 ± 4.46 (5)	n = 25 9.12 ± 6.79 (8)	817[a]	.07
Age at onset *M±SD* (*Mdn*) years		58.8 ± 12.4 (60.5)	63.1 ± 7.81 (65)	2.14(95.2)[c]	.03
Site of onset n(%)	Spinal Bulbar Respiratory	49 (70) 17 (24) 4 (6)	23 (68) 9 (26) 2 (6)	0.06(2)[d]	.97
ALSFRS-R total score *M±SD* (*Mdn*) score		37.9 ± 6.50 (39.5)	34.7 ± 6.50 (34.5)	849[a]	.02
SpO_2 *M±SD* (*Mdn*) %		97.6 ± 1.11 (98)	96.8 ± 1.52 (97)	764[a]	.0006
$PaCO_2$ *M±SD* (*Mdn*) kPa		5.32 ± 0.55 (5.3)	5.44 ± 0.63 (5.4)	1233[a]	.50

[a] Mann-Whitney-Wilcoxon Test.

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[c] Welch's t-test (t). Equal variances not assumed, as per Levene's test.

[d] Pearson's Chi-square test for independence (X^2).

Significant differences were encountered between ALSn and ALSci patients in some of the aspects considered. Thus, ALSci patients had a significantly lower mean IQ, less years of formal education, lower levels of oxygen in blood, and were older at disease onset and more advanced in terms of motor progression.

Neuropsychological performance was then compared between ALSci, cognitively unimpaired ALS patients and healthy controls. ANCOVA was used for this purpose and the effect of education, disease severity and SpO_2 levels were controlled for. Given the strong correlation found between IQ and education ($r = .74$, $p < .0001$), the former was not included as a covariate. The rationale underlying this choice was that information on years of education was available for all participants, whereas IQ was not available for anarthric patients. Age at onset could not be considered as a covariate as this is not applicable to healthy controls. However, no significant difference was observed between cognitively impaired and cognitively unimpaired ALS patients on age at time of assessment. ANCOVA results are displayed in Table 7.26.

Table 7.26. Neuropsychological performance of ALSci patients compared to cognitively unimpaired ALS patients and healthy controls.

Neuropsychological Measures	Healthy Controls n = 100	ALS Normal n = 70	ALSci n = 34	Intergroup differences Mean performance		
	M ± *SD*[a]	*M* ± *SD*[a]	*M* ± *SD*[a]	**F(df)**	p[b]	η_p^2
Language						
PALPA Auditory Lexical Decision	-0.07 ± 1.19	0.04 ± 1.08	-0.25 ± 1.11	1.06(2,194)	.35	.01
PALPA Visual Lexical Decision	0.27 ± 1.39	-0.01 ± 1.08	-0.93 ± 1.28	20.9(2,190)	<.0001#†	.20
PALPA Word Spelling	0.11 ± 1.39	-0.04 ± 1.21	-1.33 ± 1.27	14.3(2,184)	<.0001#†	.13
PALPA Word Reading	0.14 ± 1.39	0.01 ± 1.25	-1.42 ± 1.24	18.8(2,190)	<.0001#†	.17
Boston Naming Test	0.15 ± 1.39	-0.26 ± 1.17	-0.92 ± 1.40	5.73(2,190)	.004#	.06
Semantic Composite Score	0.11 ± 0.99	0.15 ± 0.83	0.22 ± 0.93	15.0(2,192)	<.0001#†	.14
PALPA Auditory Sentence – Picture Matching	-0.14 ± 1.29	0.03 ± 1.08	-1.41 ± 1.28	11.4(2,192)	<.0001#†¥	.11
PALPA Written Sentence – Picture Matching	-0.15 ± 1.39	-0.02 ± 1.25	-1.47 ± 1.34	18.4(2,194)	<.0001#†	.16
Executive Function				**F(df)**	p[c]	η_p^2
FAS Test	-0.15 ± 1.39	0.23 ± 1.25	-2.00 ± 1.46	1.40(2,192)	.25	.01
Restricted Verbal Fluency (letter C)	-0.07 ± 1.68	0.12 ± 1.42	-2.16 ± 1.57	32.9(2,194)	<.0001#†	.25
Semantic Fluency (Animals)	0.06 ± 1.48	-0.01 ± 1.25	-1.18 ± 1.40	11.5(2,194)	<.0001#†	.11
Backward Digit Span	-0.14 ± 1.38	0.38 ± 1.25	-0.75 ± 1.30	12.3(2,191)	<.0001†	.11
Sorting Test – Free Sorting Correct Sorts	-0.07 ± 1.18	-0.07 ± 1.00	-0.96 ± 1.04	9.84(2,189)	<.0001#†	.09
Sorting Test – Sort Recognition Description	0.07 ± 1.18	0.13 ± 1.08	-0.62 ± 1.20	8.35(2,185)	.0003#†	.05
CWIT – Inhibition	-0.03 ± 1.43	0.44 ± 1.31	-0.57 ± 1.27	8.28(2,178)	.0004†	.09
CWIT- Inhibition/Switching	0.15 ± 1.40	0.22 ± 1.23	-0.85 ± 1.25	8.67(2,173)	.0003#†	.09
Reading the Eyes in the Mind Test	-0.02 ± 1.29	0.12 ± 1.17	-0.96 ± 1.24	11.2(2,192)	<.0001#†	.10

[a] Descriptive data presented as z scores. Adjusted means and standard deviations are presented. Adjusted standard deviations were obtained by multiplying the standard error by the square root of the sample size: $(s = \sigma_{\bar{x}}\sqrt{N})$.

[b] Bonferroni adjusted p-value for statistical significance: $p = .006$

[c] Bonferroni adjusted p-value for statistical significance: $p = .005$.

Post hoc pairwise comparisons by means of Tukey's Honest Significant Test (HDS): #Significant difference between ALSci and HC, †Significant difference between ALSci and ALSn, ¥Significant difference between ALSn and HC.

Results from Table 7.26 indicate that ALSci patients performed significantly lower compared to cognitively unimpaired ALS patients and healthy controls in most language domains, including orthographic lexical processing, word reading, word spelling, word retrieval, and syntactic/grammatical processing for both auditory and written information. In the case of word retrieval, no significant difference was observed between ALSci and ALS patients with no evidence of cognitive decline, but solely between ALSci and healthy controls. The only language measure where no significant difference was observed among groups was the PALPA Auditory Lexical Decision. Regarding the semantic composite, ALSci patients actually performed significantly better compared to the other two groups. Overall, these results are concordant with results reported in section 7.3, which indicated that phonological lexical processing and semantic processing are spared in ALS, at least in early stages of the disease. In contrast to results from Table 7.5, effect sizes for the between-group differences in this case are larger. As mentioned, small to medium effect sizes observed in Table 7.5 were due to the cognitive heterogeneity within the ALS sample, with a high proportion of patients performing within the normal range on language tests. In fact, no significant differences in performance were observed between cognitively unimpaired ALS patients and healthy controls on most language measures.

Regarding executive function performance, ALSci patients performed significantly lower compared to the other two groups on measures of phonemic verbal fluency (restricted paradigm), semantic verbal fluency, both Sorting Test paradigms, on the Colour Word Interference Test Inhibition/Switching paradigm, and on the Reading the Mind in the Eyes test, with medium to large effects. Performance on Backward Digit Span was significantly lower for ALSci compared to cognitively unimpaired patients, but no significant difference was observed between ALSci and healthy controls. No significant differences were observed between groups on the FAS test. In this case, the assumption of homogeneity of regression slopes was not met for the covariate 'years of education', and the interaction term was therefore kept in the model, this being significant ($F(2) = 4.90$, $p = .008$). Overall, the profile of executive dysfunction in our ALSci sample is also concordant to that reported in Table 7.18, but in this case significant results are also observed for semantic fluency, cognitive flexibility and social cognition.

7.5.3. Incidence of ALSbi

This section is concerned with the investigation of behavioural status in our ALS incident population-based sample. Behaviour is explored here in isolation, not considering the cognitive classifications above, and subsequently, in section 7.5.4, both cognitive and behaviour categorisations are combined.

The BBI is our selected measure to assess behaviour. Table 7.27 describes classification criteria for ALSbi, based on revised diagnostic criteria (Strong et al., 2017).

Table 7.27. Revised diagnostic classification criteria for ALS with behavioural impairment (ALSbi).

ALS with Behavioural Impairment (ALSbi)

Type of impairment	Revised Diagnostic Criteria (Strong et al., 2017)	Test	Behaviour Assessed		Endorsed Items
BEHAVIOURAL IMPAIRMENT	*Identification of apathy (with or without other behaviour change)*	BBI	Apathy or Inertia		▪ Has lost interest in previous interests and hobbies.
	OR				
	Meeting at least two non-overlapping supportive diagnostic features from bvFTD diagnostic criteria (Appendix A; Rascovsky et al., 2011)	BBI	Early behavioural disinhibition[a]	Socially inappropriate behaviour	▪ Seeks contact with other people much more than before; for example follows people around or calls them frequently. ▪ Acts inappropriately in public.
				Loss of manners or decorum	▪ Does not get embarrassed even in situations that cause embarrassment. ▪ Has developed new unusual toileting and grooming habits. ▪ Is less concerned about cleanliness than used to be and needs to be prompted to wash and change clothes. ▪ Has become more aggressive than before. ▪ There is a major increase in sexual interest.
				Impulsive, rash or careless actions	▪ If has an idea to do something, has to do it immediately, often without thinking it through.
			Early loss of sympathy or empathy	Diminished response to other people's needs and feelings	▪ Is much more selfish than before, has much less concern for others.
				Diminished social interest, interrelatedness or personal warmth	▪ Shows much less emotion than before. ▪ Avoids social contact with people.[b]

[a] Due to the high diversity of items that define this behavioural categorisation, it is required that at least two of them are endorsed or that, if only one item is endorsed, this involves a moderate or severe degree of change, to consider this a significant behavioural change.

[b] Endorsement of this item in isolation is not considered enough to classify as 'loss of sympathy or empathy', given that this can also be related to apathy, but endorsement of at least one of the other two items that define this behavioural classification must be endorsed too.

Table 7.27 (continued). Revised diagnostic classification criteria for ALS with behavioural impairment (ALSbi).

Behaviour Assessed		Endorsed Items
Early perseverative, stereotyped or compulsive/ ritualistic behaviour[a]	Simple repetitive movements	▪ Repeats certain behaviours over and over again, for example grunting, humming, sniffing, hand rubbing, foot tapping, singing, pacing in the same pattern, etc.
	Complex, compulsive or ritualistic behaviours	▪ Is constantly counting things. ▪ Constantly aligns or corrects furniture or insists on arranging things in a certain way. ▪ Has become overly concerned with neatness and cleanliness. ▪ Is constantly checking the clock or other things such as light switches. ▪ Has developed rituals that insists on, such as avoiding standing on cracks between paving stones.
	Stereotypy of speech	▪ Repeats word or phrases immediately after saying them. ▪ Repeats the same word or catchphrase again and again. ▪ Copies words or sentences said by other people.
Hyperorality and dietary changes[a]	Altered food preferences	▪ Has developed new preference for certain foods. ▪ Has become less picky about what he/she eats, would eat anything now.
	Binge eating, increased consumption of alcohol or cigarettes	▪ Eats much more than before, looks for extra food. ▪ Smokes more cigarettes than before.
	Oral exploration or consumption of inedible objects	▪ Is always putting things in her/his mouth.

[a] Due to the high diversity of items that define this behavioural categorisation, it is required that at least two of them are endorsed or that, if only one item is endorsed, this involves a moderate or severe degree of change, to consider this a significant behavioural change.

[b] Endorsement of this item in isolation is not considered enough to classify as 'loss of sympathy or empathy', given that this can also be related to apathy, but endorsement of at least one of the other two items that define this behavioural classification must be endorsed too.

Behavioural status was not available for 6 out of the 117 non-demented ALS patients, therefore behavioural results are based on information from 111 ALS patients. 43 ALS patients (39% of the non-demented ALS sample) met diagnostic criteria for the presence of apathy, 27 (24%) for behavioural disinhibition, 21 (19%) for loss of sympathy or empathy, 10 (9%) for early perseverative, stereotyped or compulsive/ritualistic behaviour, and 18 (16%) for hyperorality and dietary changes. Overall, 51 non-demented ALS patients (46%) met revised diagnostic criteria for ALSbi. This is represented graphically in Figure 7.3.

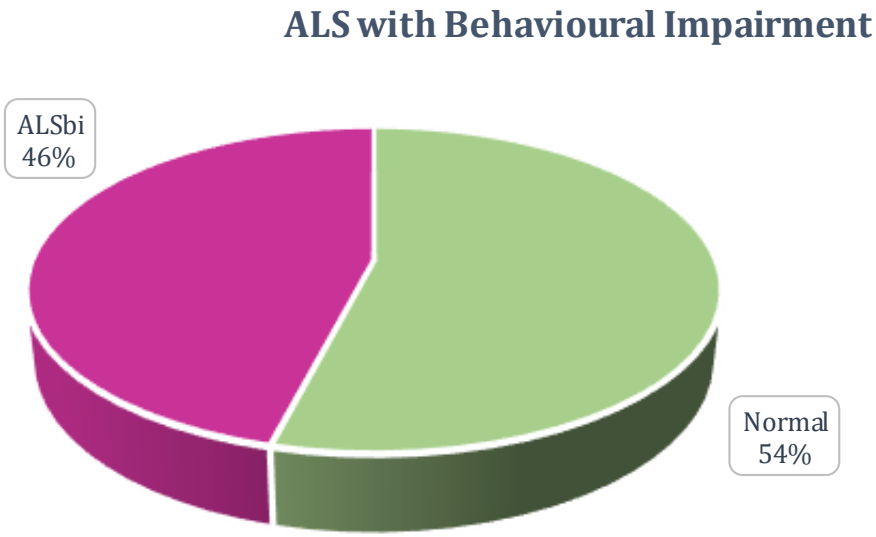

Figure 7.3. Behavioural classification of the non-demented ALS sample

We also evaluated diagnostic accuracy of the classification criteria for ALSbi employed in this work in comparison to published cut-off norms for the BBI, which have been validated against two gold standards, a general behavioural measure (Elamin et al., 2017) and another ALS-specific measure (Pinto-Grau, Costello, et al., 2017).

In comparison to 46% of the sample classified as ALSbi using the revised diagnostic criteria, 44 patients (40%) were classified as behaviourally impaired using the established cut-off of 7 for the BBI. Cohen's Kappa coefficient (k = .65) indicated moderate to good level of agreement, with 75% sensitivity, 90% specificity and 83% accuracy. Predictive powers were as follows: PPV = 86% and NPV = 81%. Lower sensitivity of the established BBI cut-off for impairment in comparison to the revised diagnostic criteria is given by the fact that the presence of apathy in isolation is considered enough to classify a patient as ALSbi in the latter.

Psychotic symptoms in our ALS sample were also investigated. Two items of the BBI explore psychotic symptoms: "Sometimes sees or hears things/people that are not there", which explores the presence of hallucinations, and "Has developed new bizarre beliefs and are fixed and not easy to change", which ascertains the presence of delusions. Only 7 non-demented ALS

patients (6%) reported the presence of psychotic symptoms, in comparison to 4 (22%) of the ALS-FTD patients, $X^2(1) = 3.20$, $p = .07$. The majority of non-demented ALS patients that reported psychotic symptoms (88%) did so in the context of broader behavioural change. Only one non-demented ALS patient who reported psychotic symptoms did not meet criteria for ALSbi.

7.5.4. Incidence of ALScbi

Cognitive and behavioural statuses characterised in the two previous sections are combined here to assess the joined incidence of both ALSci and ALSbi (i.e. ALScbi) in our non-demented population-based ALS sample. Results here are based on 100 ALS patients, given that cognitive status was not available for 11 patients, behavioural status was missing for 4 patients, and two patients did not have either cognitive or behavioural status.

20 non-demented ALS patients met criteria for ALScbi, 12 met criteria for ALSci but had normal behavioural status, and 24 met criteria for ALSbi with normal cognitive status. 44 patients were characterised by normal cognitive and behavioural statuses. These results are represented in Figure 7.4.

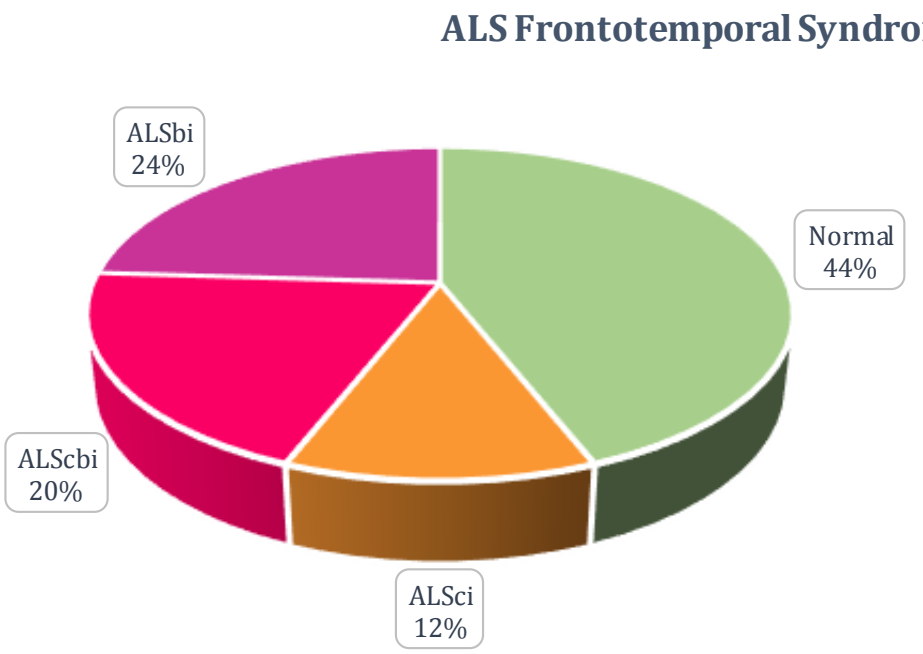

Figure 7.4. Frontotemporal syndromes in the non-demented ALS sample

Focusing solely on patients who met criteria for ALScbi, the pattern of cognitive impairment within them was also explored. Out of the 20 ALScbi patients, 9 (45%) met diagnostic criteria for ALSei and another 9 (45%) met criteria for ALSeli, and only 2 (10%) met criteria for language impairment alone.

7.5.5. Overall Incidence of ALS Frontotemporal Syndromes

Lastly, the global incidence of frontotemporal syndromes in our population-based ALS cohort, including ALS-FTD, is explored.

Starting with the cognitive domain-based classification, Figure 7.5 displays the incidence of each cognitive syndrome characteristic of ALS.

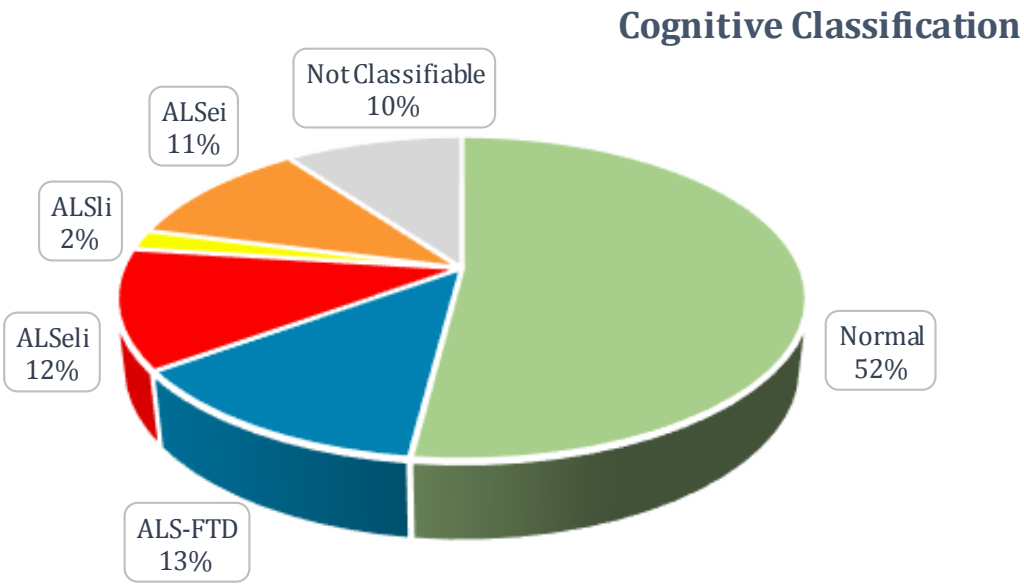

Figure 7.5. The incidence of cognitive syndromes in ALS

Regarding behaviour, Figure 7.6 displays the population-based incidence of behavioural change in ALS.

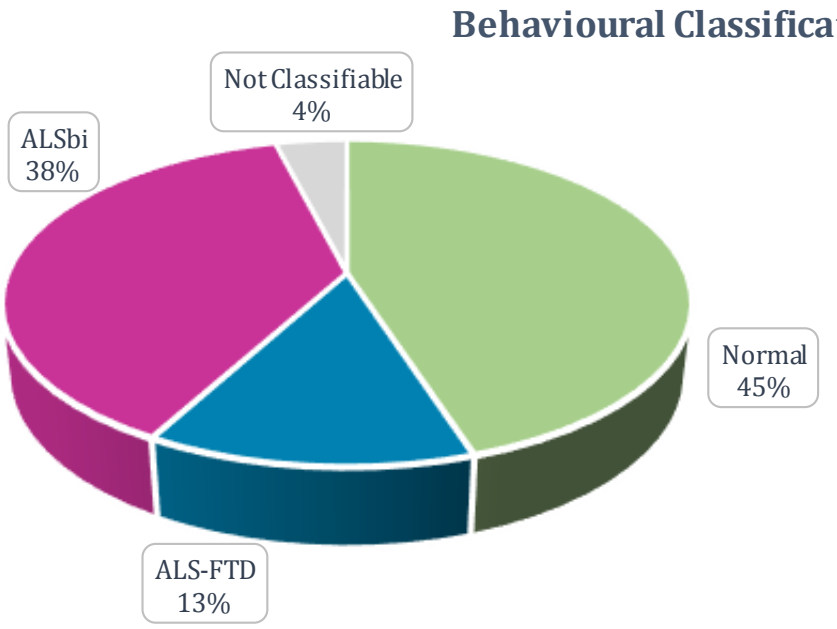

Figure 7.6. The incidence of behavioural syndromes in ALS

Finally, the frontotemporal spectrum disorder characteristic of ALS is represented in Figure 7.7. From our population-based incident ALS sample (n = 135), 12 patients (9%) met criteria for ALSci, 24 patients (18%) met criteria for ALSbi, 20 patients (15%) were classified as ALScbi, and 18 (13%) were diagnosed as ALS-FTD. 44 (33%) of our population-based sample showed no evidence of frontotemporal impairment.

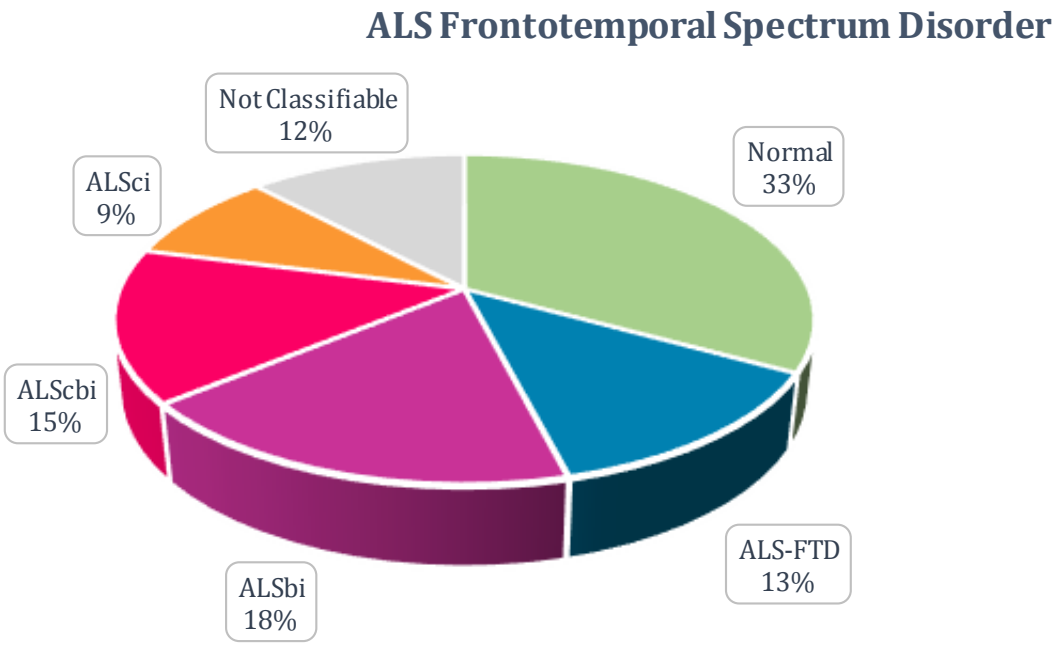

Figure 7.7. The incidence of frontotemporal syndromes in ALS

7.6. Summary of Findings

This results chapter has addressed the first three aims of this work, which intended: 1) to investigate the incidence and nature of language change in a large population-based cohort of incident ALS patients; 2) to assess the relationship between language change and executive dysfunction in this large population-based incident cohort; and 3) to establish the incidence of the various frontotemporal syndromes of ALS, considering revised diagnostic criteria (Strong et al., 2017). The main findings of this chapter are summarized below.

Population-based Sampling of an ALS Incident Cohort

The population-based incident sample recruited for this study consisted of 135 ALS patients. This represents 50% of all ALS cases diagnosed in the Republic of Ireland that attended the National Specialist MND Clinic at Beaumont Hospital during the period from December 2014 to August 2017. Mean age was 63 ± 10.7 years, gender rates were 37% females and 63% males,

mean age at symptom onset was 61.3 ± 10.6 years, and mean age at diagnosis was 62.7 ± 10.8 years, with a median diagnostic delay of 12 months. In terms of site of onset, 68% of the patients had spinal onset ALS, 28% bulbar onset, and 4% respiratory onset.

Demographic and clinical characteristics of our population-based incident sample were compared to those characteristics of non-participants (i.e. potential participants that were not captured or unsuitable for participation). No significant differences were encountered in terms of gender rates, age at onset, site of onset, age at diagnosis, and diagnostic delay. This confirms that our patient sample is representative of the true incident ALS population in Ireland, which ensures generalizability of our results.

Regarding survival, 53% of non-participants suffered from a more aggressive form of the disease that lead to death within the first year of diagnosis, compared to only 17% of participants dying within the first twelve months since diagnosis. When excluding these more aggressive cases, no significant differences in survival were found between ALS participants and non-participants a year post-finalisation of the recruitment period (i.e. August 2018).

Regarding other clinical characteristics of our population-based incident ALS sample, 24% had a family history of ALS and/or FTD (i.e. familial ALS), and 51% and 42% had a family history of other neurological and psychiatric conditions, respectively. Most patients (84%) were taking Riluzole, 11% had external homecare in place, 20% were using NIV, and 4% had enteral feeding tube in place. The mean score on the ALSFRS-R at recruitment time was 36.2 ± 7.02, out of 48 points. None of the ALS patients presented with hypoxaemia (i.e. oxygen saturation < 90%), and only 2% had pulse oximeter readings below 95%. Eleven patients (9%) showed evidence of CO_2 retention (i.e. $PaCO_2$ levels > 6.0 kPa).

Our population-based incident ALS sample (n = 135) was accurately matched for age, gender, handedness, years of formal education, and estimated premorbid intellectual ability to the population-based healthy control sample (n = 100) also recruited as part of this work.

The Incidence and Nature of Language Change in ALS

The incidence and nature of language change in ALS was investigated for patients not meeting criteria for dementia. Eighteen of the 135 ALS patients met criteria for comorbid FTD (i.e. ALS-FTD). Therefore, analyses on this section focused on performance of the remaining 117 non-demented ALS patients (i.e. ALS). This sub-sample was also matched by age, gender, handedness, years of formal education, premorbid intellectual ability, as well as current intellectual function to the healthy control sample. Baseline neuropsychological assessments occurred within the first year of diagnosis for all ALS patients (mean time from diagnosis to assessment: 3.91 ± 2.59 months).

The language domains assessed included lexical processing, word spelling, word reading, semantic processing, word naming, and syntactic/grammatical processing. MANCOVA analyses showed that, when language was taken as an overall construct, ALS patients performed significantly lower compared to healthy controls. Mood and arterialised tissue capillary blood gas tensions, included as covariates, showed not to be significant predictors of language performance in ALS.

Univariate contrasts indicated that language deficits in ALS are confined to word naming and syntactic/grammatical processing abilities. Although word reading and spelling abilities were also significantly poorer in ALS patients compared to healthy controls, this did not survive correction for multiple comparisons. The proportion of impaired ALS patients was significantly higher to that of healthy controls solely on measures of syntactic/grammatical processing, and at the threshold for significance for word naming measures, concordant with ANOVA results.

Further analyses on word naming difficulties in ALS showed that these were of retrieval nature rather than caused by semantic deficits, given that ALS patients significantly benefited from the presentation of cues, most notably from phonemic cueing. Deficits on action word processing in ALS were also shown to be of retrieval nature, with improved performance following the presentation of phonemic cues. In fact, ALS patients performed at the same level of ability on object and action naming.

Preserved access to semantic knowledge was further demonstrated for the three different input routes by which the semantic system can be accessed through: the phonological input lexicon, the orthographic input lexicon, and the visual recognition system. Receptive semantic tasks were used in all three modalities to control for the effect that word retrieval deficits may have on performance.

The extent to which word retrieval deficits contributed to verbal fluency deficits in ALS was also investigated. Thus, while executive processes influenced phonemic verbal fluency to a higher degree, word retrieval had a greater influence on semantic fluency. Accordingly, word retrieval explained 14% of unique variance (this means, independent from executive dysfunction) in semantic fluency, and only 5-6% of unique variance in phonemic fluency tasks.

The profile of spelling performance on our ALS sample indicated preserved phoneme-to-grapheme conversion rules and therefore spared non-lexical spelling. Although ALS patients performed significantly lower compared to healthy controls on regular word reading, the type of errors committed consisted of doubling consonants, missing vowels or replacing graphemes by similar allophones. These are errors that do not affect the pronunciation of the word and therefore still follow the phoneme-to-grapheme conversion rules. Regarding irregular word

spelling, regularisation errors as well as difficulties recalling visual word forms were observed, although ALS patients did not perform significantly different compared to healthy controls.

Performance on word reading indicated preserved lexical and non-lexical reading in ALS. However, further analyses of the processing of homophone words suggested that ALS patients may present with difficulties processing certain words from a lexical point of view, which was related to accessing the word form from the orthographic input lexicon, to then access its meaning from the semantic system and its pronunciation from the orthographic output lexicon. Further investigations on the ability of ALS patients to recognise orthographic word forms were undertaken by means of a visual lexical decision paradigm, and results confirmed that orthographic processing deficits in ALS also exist at an input level. More specifically, the type of words that ALS patients failed to recognise were those less frequent and more abstract. Contrarily, phonological lexical processing was preserved in ALS.

Syntactic/grammatical processing deficits in ALS were confirmed for both spoken and written information, and a significant strong positive correlation between them was found. The influence that reading abilities had on written sentence processing was also analysed, and it was found that although reading had a significant effect on written sentence processing (they shared 34% of the variance), sentence processing deficits for written information were still present after correcting for the effect of reading difficulties on performance.

Overall, these results confirm that incident language deficits are present in ALS, specifically in the domains of orthographic lexical processing, word retrieval and syntactic/grammatical processing.

The Role of Executive Dysfunction in Language Change in ALS

The executive domains assessed included phonemic and semantic verbal fluency, working memory, inhibitory control, cognitive flexibility, problem-solving and goal-directed behaviour, abstract reasoning and concept formation, and social cognition. MANCOVA analyses showed that, when executive function was taken as an overall construct, no significant differences were found between ALS patients and healthy controls, most likely explained by the lack of correlations encountered among executive tasks. Mood and arterialised tissue capillary blood gas tensions, included as covariates, showed not to be significant predictors of executive performance in ALS.

Univariate contrasts indicated that executive deficits in ALS are confined to phonemic verbal fluency, and problem solving and goal-directed behaviour. Although performance on semantic verbal fluency and social cognition was also significantly poorer in ALS patients compared to healthy controls, this did not survive correction for multiple comparisons. The proportion of

impaired ALS patients was significantly higher to that of healthy controls solely on measures of phonemic verbal fluency, problem-solving and social cognition, in accordance with previous ANOVA results.

Multiple linear regression analyses indicated that executive dysfunction was a significant contributor to language deficits in ALS. Specifically, syntactic/grammatical processing deficits in ALS shared 49% of the variance with executive dysfunction, orthographic lexical processing deficits 37%, word spelling deficits 33%, word retrieval deficits 29%, and word reading deficits 26%. The larger proportion of variance in language performance in ALS was explained by phonemic verbal fluency deficits. Moreover, social cognition was a significant predictor for word retrieval and sentence processing deficits, and cognitive flexibility significantly predicted orthographic lexical processing, word reading, and word spelling performance. Working memory was also found to be a significant predictor of auditory sentence processing in ALS, although syntactic/grammatical processing deficits were still observed in our ALS sample after controlling for the effect that this executive component has on performance.

Overall, these results confirm that although language impairment in ALS is associated with executive dysfunction to a degree, pure language deficits also exist.

Population-based Incidence of Frontotemporal Syndromes in ALS

In accordance to relevant diagnostic criteria, 13% of our population-based incident ALS sample received a diagnosis of comorbid FTD. Of these, 83% met criteria for bvFTD, 11% for semantic dementia, and 6% for nonfluent variant PPA. One ALS-bvFTD patient also met revised diagnostic criteria for possible AD with an etiologically mixed presentation.

No significant differences were observed between ALS and ALS-FTD patients on age at assessment, gender rates, years of formal education, age and site of onset, age at diagnosis, diagnostic delay, rate of familial ALS, family history of other neurological and psychiatric conditions, use of NIV, whether enteral feeding tube was in place, or on arterialised tissue capillary blood gas tensions. However, a significantly higher proportion of ALS patients were taking Riluzole (89%), in comparison to only 56% of ALS-FTD patients. Moreover, ALS patients scored significantly lower compared to ALS-FTD patients on the ALSFRS-R limb sub-score, although no significant difference was found on the total ALSFRS-R score.

On neuropsychological performance, no significant difference was observed between ALS and ALS-FTD patients on premorbid IQ, although ALS-FTD patients' current intellectual functioning was significantly lower. ALS-FTD patients performed significantly poorer compared to ALS patients on all measures of language and executive function, as well as on behavioural measures. No significant difference between groups was found on psychological distress.

From our population-based non-demented ALS sample, 32% met criteria for cognitive impairment (i.e. ALSci). Specifically, 14% met criteria for executive impairment (i.e. ALSei), 3% for language impairment (i.e. ALSli), and 15% for both executive and language impairment (i.e. ALSeli). 68% of ALS patients were cognitively unimpaired (i.e. ALSn). The proportion of ALS patients that met criteria for executive impairment (32%) was significantly higher to that of healthy controls (11%), but the proportion of ALS patients meeting criteria for language impairment (19%) was not significantly different to that of healthy controls (13%).

ALSci patients had a significantly lower premorbid IQ, fewer years of formal education, lower $Sp0_2$ levels, were older at diagnosis, and presented with more advanced motor decline in comparison to ALSn patients. No differences between groups were encountered in terms of age at assessment, gender rates, mood, site of onset and $PaC0_2$ levels.

ANCOVA was used to compare cognitive performance between ALSci, ALSn patients and healthy controls while accounting for the effect of education, disease severity and SpO_2 levels. Regarding language, ALSci patients performed significantly lower compared to ALSn patients and healthy controls on measures of orthographic lexical processing, word reading, word spelling, word retrieval, and syntactic/grammatical processing for both auditory and written information. No significant differences were observed between ALSn patients and healthy controls on most language measures. Concerning executive function, ALSci patients performed significantly lower compared to ALSn patients and healthy controls on measures of phonemic and semantic verbal fluency, problem-solving and goal-directed behaviour, abstract reasoning and concept formation, cognitive flexibility, and social cognition. Performance of ALSn patients and healthy controls did not significantly differ on any executive measure.

From our population-based non-demented ALS sample, 46% met criteria for behavioural impairment (i.e. ALSbi). Specifically, 39% of the sample met diagnostic criteria for the presence of apathy, 24% for behavioural disinhibition, 19% for loss of sympathy or empathy, 9% for early perseverative, stereotyped or compulsive/ritualistic behaviour, and 16% for hyperorality and dietary changes. Only 6% of the sample reported psychotic symptoms, and this was in the context of broader behavioural impairment in most cases.

The global incidence of frontotemporal syndromes in our population-based ALS sample was as follows: 13% met diagnostic criteria for ALS-FTD, 9% met criteria for ALSci, 18% met criteria for ALSbi, 15% met criteria for ALScbi, and 33% were cognitively and behaviourally unimpaired. 12% of the sample could not be classified due to missing data.

CHAPTER 8 Outline.

Results Part III:

Longitudinal Neuropsychological Change in ALS

CHAPTER 8.

Results Part III:

Longitudinal Neuropsychological Change in ALS

8.1. Introduction

This results chapter addresses aim 4 of this work, which focuses on longitudinal change in neuropsychological performance in ALS. Firstly, the evolution of frontotemporal decline in ALS is investigated by looking at between group differences across time in neuropsychological performance, as well as by examining significant change in individual scores. Moreover, the prevalence of frontotemporal syndromes in our population-based sample is also determined. To begin, longitudinal capture and attrition rates are described.

8.2. Longitudinal Study Design: Attrition and Capture Rates

As per longitudinal study design described in chapter 5, ALS patients not meeting criteria for FTD at diagnosis as well as healthy controls were approached every four months for another three points in time since first assessment to carry out follow-up neuropsychological assessments. Capture rates for each group at each time point are depicted in Table 8.1.

Table 8.1. Longitudinal patient and healthy control capture rates.

	Time 1 n(%)	**Time 2** n(%)	**Time 3** n(%)	**Time 4** n(%)
ALS Patients	117 (100)	79 (68)	64 (55)	46 (39)
Healthy Controls	100	79	68	61

As per figures in Table 8.1, capture rates for patients were maintained approximately at 70, 60 and 40 per cent at each time point, respectively. For healthy controls, capture rates were slightly higher, these being around 80, 70 and 60 per cent at each time point, respectively. These numbers are overall concordant with previous population-based studies carried out by the Irish National ALS Research Team, which reported attrition rates of 50 and 40 per cent after a year follow-up in ALS patients and healthy controls respectively (Crockford et al., 2017; Crockford et al., 2018), although these figures were slightly lower for the patient group in our case. The most marked difference between patients and healthy controls was observed at Time 4, where patient attrition rates experienced a considerable decline. Capture rates at each time point are visually represented in Figure 8.1.

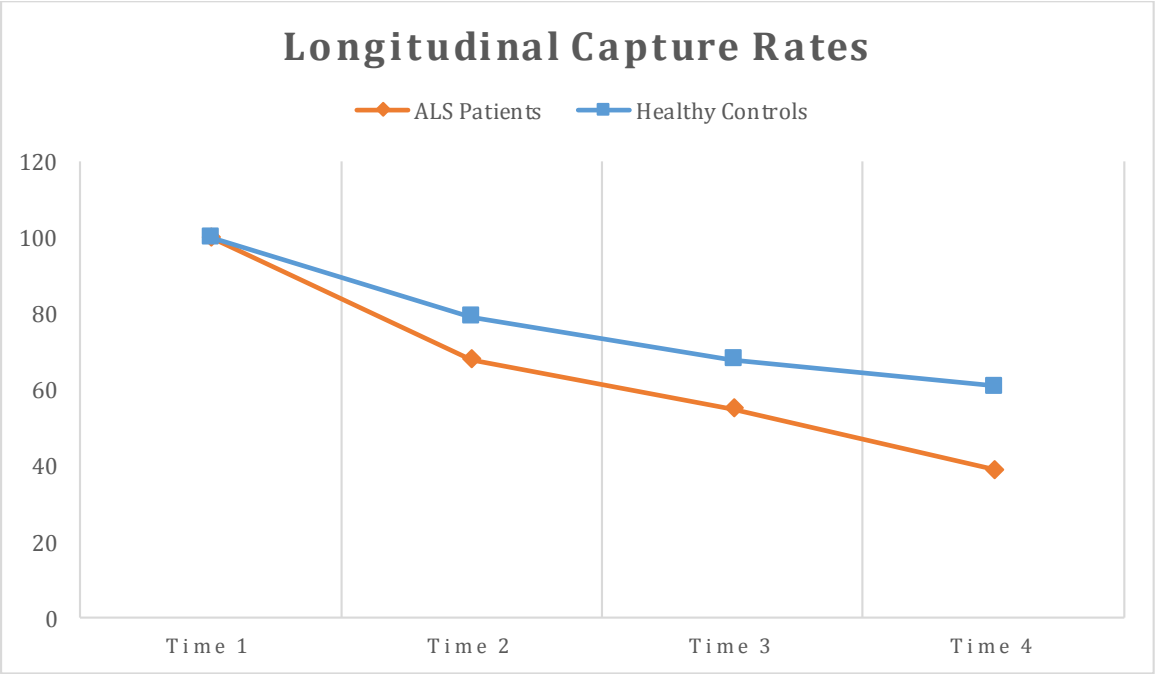

Figure 8.1. Longitudinal patient and healthy controls capture rates

Figure 8.1 shows that while the tendency in healthy control attrition is to stabilise with time, attrition for patients tended to continue growing over time due to the progressive and fatal nature of ALS. Reasons for patients and healthy control discontinuation of study participation were documented in all cases and are summarised in Table 8.2.

Table 8.2. Patient and healthy control frequency and reason for discontinuation of longitudinal follow-up at each time point.

	Reason for Discontinuation	T2	T3	T4
ALS Patients	▪ Decline of further involvement	n = 22	n = 8	n = 7
	▪ Development of disability that precluded further participation or of a medical condition that denoted an exclusion criterion	n = 8	n = 4	n = 4
	▪ Death	n = 8	n = 3	n = 7
Healthy Controls	▪ Decline of further involvement	n = 19	n = 9	n = 7
	▪ Development of a medical condition that denoted an exclusion criterion	n = 2	n = 1	n = 0
	▪ Death	n = 0	n = 1	n = 0

As described in Table 8.2, development of disability that precluded further participation and death were more commonly encountered within the patient sample compared to controls. In both groups, decline of further participation was the most common reason for discontinuation. The most marked drop out was seen between assessment one and first follow up.

Focusing solely on ALS patients, captured and non-captured rates at each time point for the various frontotemporal syndromes diagnosed at time 1 are described in Table 8.3. The former are also visually represented in Figure 8.2.

Table 8.3. Frequency of frontotemporal syndromes diagnosed at time 1 that were captured and not captured at each time point.

	ALS Normal n(%)	**ALSci** n(%)	**ALSbi** n(%)	**ALScbi** n(%)	**Unclassifiable**
Captured					
Time 1 n = 117	43 (37)	12 (10)	25 (21)	20 (17)	17
Time 2 n = 79	35 (44)	4 (5)	20 (25)	12 (15)	8
Time 3 n = 64	29 (45)	1 (2)	18 (28)	11 (17)	5
Time 4 n = 46	25 (54)	1 (2)	10 (22)	7 (15)	3
Not Captured					
Time 2 n = 38	8 (21)	8 (21)	5 (13)	8 (21)	9
Time 3 n = 15	6 (40)	3 (20)	2 (13)	1 (7)	3
Time 4 n = 18	4 (22)	0	8 (44)	4 (22)	2

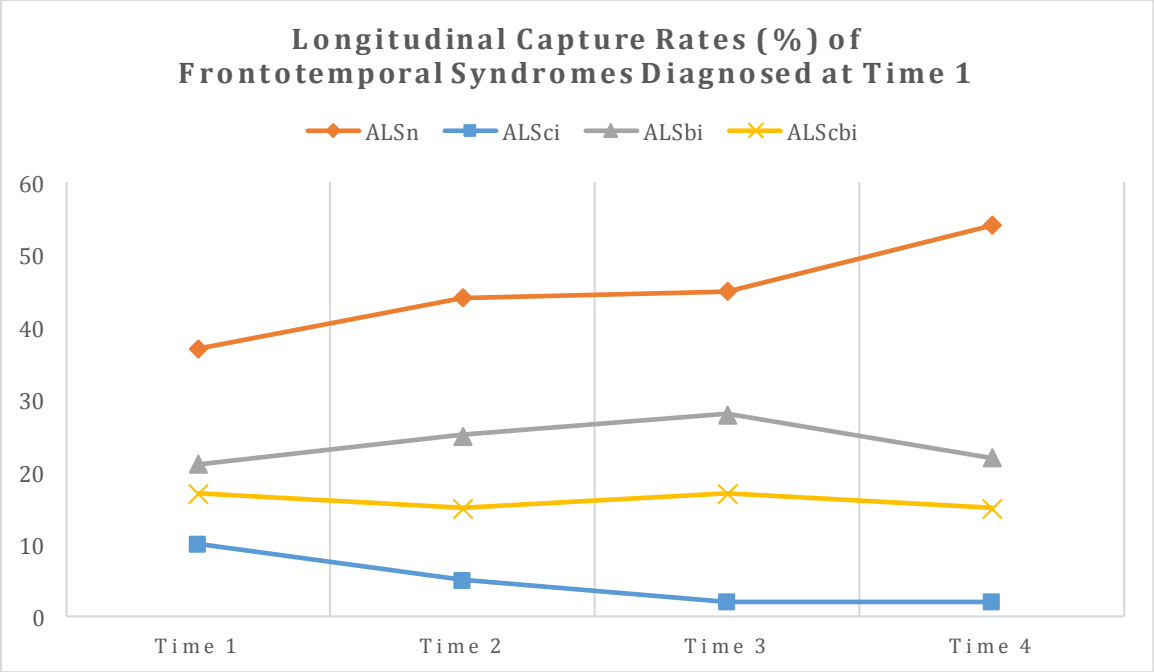

Figure 8.2. Longitudinal capture rates of frontotemporal syndromes diagnosed at time 1

While the proportion of ALSci progressively decreased from first to last assessment, the proportion of ALSbi and ALScbi patients at each time point was maintained relatively stable. The proportion of ALS patients not meeting criteria for cognitive and/or behavioural

impairment continued to grow within time points, and this group has the highest representation at time 4.

Predictors of patient discontinuation at each time point were evaluated using binary logistic regression. Predictors considered were: gender, education, age at onset, site of onset, ALSFRS-R score at baseline, and frontotemporal status at baseline. Total years of education, b = -0.26, z = -2.77, p = .006, and lower ALSFRS-R scores at baseline, b = -0.10, z = -2.25, p = .02, were significant predictors for discontinuation at first follow-up, $X^2(9) = 27.6$, p = .001, $R_N^2 = .33$. Regarding the 15 ALS patients that discontinued at 8 months, the only significant predictor was lower ALSFRS-R scores at baseline, b = -0.24, z = -2.41, p = .02, $X^2(9) = 24.6$, p = .003, $R_N^2 = .49$. Finally, significant predictors for discontinuation at month 12 included lower ALSFRS-R scores at baseline, b = -0.19, z = -2.29, p = .02, and bulbar onset, b = 2.82, z = 2.91, p = .004; $X^2(9) = 19.6$ p = .02, $R_N^2 = .40$. The assumptions of independence of errors and absence of multicollinearity between predictors were met in all cases. Regarding linearity of the logit, a significant interaction was found between years of education and discontinuation at first and second follow-up. Regardless, years of education can still be interpreted as a significant predictor of patient discontinuation at first follow-up.

Focusing on demographics, population and clinical characteristics of the patient sample at each time point are described in Table 8.4. Moreover, demographics of patient and healthy control samples at each time point were compared and results are presented in Table 8.5. At each follow-up time point, ALS patients and healthy controls were equivalent in terms of demographic characteristics including age, gender distribution, handedness and years of formal education. The two groups were also equivalent in terms of premorbid IQ and current intellectual functioning at the three follow-up time points. As expected, ALS patients had significantly lower peripheral capillary oxygen saturation levels and significantly higher carbon dioxide partial pressure levels for the three follow-up time points. ALS patients also scored significantly higher on mood screening at time 4, but no significant differences were observed at the other two time points. Regarding length of the retest intervals, although fixed timing (i.e. four months intervals) was set up for the longitudinal design of this study, participant availability caused for the time elapsed between assessment 2 and assessment 3 to be significantly longer for healthy controls than for patients. Time elapsed between assessment 1 and 2 and between assessment 3 and 4 were equivalent between groups. Such significant differences between ALS patients and healthy controls in respiratory measures as well as in time elapsed between repeat assessments are addressed when their neuropsychological performance is compared. Regarding the difference in the HADS score, given that this is only significant for one time point and that results are based on a smaller proportion of participants, this will not be considered on further analyses.

Table 8.4. Demographic and clinical characteristics of the ALS patient sample at each time point.

		Time 1 n = 117	**Time 2** n = 79	**Time 3** n = 64	**Time 4** n = 46
Age *M±SD* years		62.4 ± 10.9	62.5 ± 10.6	62.9 ± 10.6	62.9 ± 10.8
Gender n(%)	Females	42 (36)	28 (35)	25 (39)	18 (39)
	Males	75 (64)	51 (65)	39 (61)	28 (61)
Handedness n(%)	Right	105 (90)	70 (89)	56 (88)	39 (85)
	Left	12 (10)	9 (11)	8 (12)	7 (15)
Years of formal education *M±SD* years		14.4 ± 3.52	15.2 ± 3.48	15.2 ± 3.25	15.2 ± 3.33
Age at onset *M±SD* years		60.7 ± 10.9	60.3 ± 10.5	60.5 ± 10.5	60.1 ± 11.0
Site of onset n(%)	Spinal	79 (68)	54 (68)	46 (72)	37 (80)
	Bulbar	32 (27)	22 (28)	17 (26)	8 (17)
	Thoracic / Respiratory	6 (5)	3 (4)	1 (2)	1 (3)
Diagnostic Delay *M±SD* months		16.5 ± 15.3	17.9 ± 17.5	15.8 ± 13.5	16.1 ± 14.8
Familial ALS[a] n(%)		25 (21)	17 (22)	13 (20)	12 (26)
Riluzole use n(%)		104 (89)	68 (86)	56 (88)	45 (98)
External homecare n(%)		15 (13)	16 (20)	19 (30)	8 (17)
Use of NIV n(%)		26 (22)	18 (23)	20 (31)	11 (24)
Enteral feeding tube in place n(%)		6 (5)	0	4 (6)	5 (11)
ALSFRS-R total score *M±SD* score		35.9 ± 7.23	34.4 ± 8.37	32.2 ± 8.18	31.2 ± 8.04
ALSFRS-R bulbar sub-score *M±SD* score		16.3 ± 5.06	14.7 ± 6.05	13.2 ± 5.83	12.2 ± 5.99
ALSFRS-R limb sub-score *M±SD* score		9.69 ± 2.67	9.70 ± 2.62	9.08 ± 3.02	9.15 ± 3.34
ALSFRS-R respiratory sub-score *M±SD* score		9.92 ± 3.13	9.96 ± 3.05	9.94 ± 2.92	9.87 ± 3.07
Peripheral capillary oxygen saturation levels – $Sp0_2$ *M±SD* %		97.1 ± 1.45	97.1 ± 1.38	96.9 ± 1.38	96.8 ± 1.24
Carbon dioxide partial pressure – $PaC0_2$ *M±SD* kPa		5.37 ± 0.56	5.46 ± 0.68	5.49 ± 0.54	5.48 ± 0.46

[a] Familial ALS is defined with the presence of at least one biological relative within three generations diagnosed with ALS and/or FTD.

Table 8.5. Demographic characteristics comparison between ALS patients and healthy controls at each time point.

		Time 2				Time 3				Time 4			
		ALS n = 79	**Healthy Controls** n = 79	**t(df) / W X^2(df)**	***p***	**ALS** n = 64	**Healthy Controls** n = 68	**t(df) / W X^2(df)**	***p***	**ALS** n = 46	**Healthy Controls** n = 61	**t(df) / W X^2(df)**	***p***
Age *M±SD* (*Mdn*) years		62.5 ± 10.6	63.2 ± 10.4	-0.42(156)[a]	.67	62.9 ± 10.6	63.1 ± 10.2	-0.08(130)[a]	.94	62.9 ± 10.8 (64)	63.9 ± 10.3 (67)	1476 [b]	.65
Gender n(%)	Females	51 (65)	56 (71)	0.46(1)[c]	.50	39 (61)	48 (71)	0.97(1)[c]	.32	28 (61)	43 (70)	0.70(1)[c]	.40
	Males	28 (35)	23 (29)			25 (39)	20 (29)			18 (39)	18 (30)		
Handedness n(%)	Right	70 (89)	73 (92)	0.29(1)[c]	.59	56 (88)	62 (91)	0.16(1)[c]	.69	39 (85)	56 (90)	0.30(1)[c]	.59
	Left	9 (11)	6 (8)			8 (12)	6 (9)			7 (15)	6 (10)		
Years of formal education *M±SD* (*Mdn*) years		15.2 ± 3.48 (15)	15.2 ± 3.77 (14)	3051[b]	.81	15.2 ± 3.25 (15)	15.2 ± 3.75 (14)	2097[b]	.72	15.2 ± 3.33 (15)	15.2 ± 3.82 (14)	1360[b]	.79
Premorbid Intellectual Ability *M±SD* IQ		*n = 74* 106 ± 13.1	104 ± 12.0	0.85(151)[a]	.40	*n = 62* 105 ± 12.8	104 ± 12.2	0.61(128)[a]	.54	*n = 45* 105 ± 12.6	104 ± 12.3	0.45(104)[a]	.66
Current Intellectual Function[d] *M±SD* (*Mdn*) IQ		100 ± 15.3 (104)	103 ± 13.7 (104)	3356[b]	.33	101 ± 14.9 (104)	103 ± 14.0 (106)	2312[b]	.54	100 ± 17.0 (104)	104 ± 14.7 (110)	1608[b]	.15
$Sp0_2$ *M±SD* (*Mdn*) %		97.1 ± 1.38 (97)	98.1 ± 0.82 (98)	4227[b]	<.0001	96.9 ± 1.38 (97)	98.1 ± 0.93 (98)	3256[b]	<.0001	96.8 ± 1.24 (97)	98.1 ± 0.82 (98)	2061[b]	<.0001
$PaC0_2$ *M±SD* (*Mdn*) kPa		5.46 ± 0.68 (5.5)	5.13 ± 0.47 (5.2)	1708[b]	<.0001	5.49 ± 0.54 (5.4)	5.18 ± 0.38 (5.1)	3.71(128)[a]	.0003	5.48 ± 0.46 (5.4)	5.17 ± 0.38 (5.2)	754[b]	.001
HADS-T *M±SD* (*Mdn*) score		*n = 52* 6.65 ± 4.74 (6)	*n = 53* 5.04 ± 4.34 (4)	1073[b]	.05	*n = 34* 6.68 ± 4.95 (6)	*n = 43* 5.12 ± 4.78 (5)	567[b]	.09	*n = 29* 7.14 ± 5.06 (6)	*n = 36* 4.86 ± 4.55 (4)	351[b]	.02
Time since previous assessment *M±SD* (*Mdn*) months		4.44 ± 0.81 (4)	4.68 ± 1.03 (4)	3521[b]	.11	4.36 ± 0.70 (4)	4.78 ± 0.86 (5)	2812[b]	.001	4.39 ± 0.54 (4)	4.57 ± 0.76 (4)	1550 [b]	.29

[a] Student t-test (t). Equal variances were assumed in all cases, as per Levene's test.

[b] Mann-Whitney-Wilcoxon Test.

[c] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[d] Z scores on the Raven's Coloured Progressive Matrices were transformed to IQ Scores ($M = 100, SD = 15$) by applying the following formula: IQ score = [(Z score x 15) + 100].

8.3. The Evolution of Frontotemporal Decline in ALS

Aim 4, concerning the evolution of frontotemporal decline in ALS, is addressed in this section by looking at longitudinal neuropsychological change using three different approaches: (1) by investigating between-group differences across time points; (2) by examining significant change in individual scores using the Reliable Change Index (RCI) and standardised regression-based (SRB) methods; and (3) by determining the prevalence of frontotemporal syndromes at each time point and assessing how this changes over time. Each one of these approaches is addressed in subsequent sections (section 8.3.1, 8.3.2, and 8.3.3, respectively).

8.3.1. Between-Group Differences across Time Points

Between-group differences across time points in neuropsychological performance were assessed by employing a series of generalised linear mixed models implemented as multilevel models for each neuropsychological measure of interest. Within (Level 1; i.e. time) and between (Level 2; i.e. group) effects were evaluated, as well as the interaction between them, which examines if ALS patients perform significantly different than healthy controls over time. The use of a multilevel regression approach also permits the inclusion of additional predictors to the model to address the effect that these may have on the data. In this case, oxygen and carbon dioxide levels (i.e. $Sp0_2$ and $PaC0_2$) were relevant given that, as described in Table 8.5, ALS patients had significantly lower $Sp0_2$ and significantly higher $PaC0_2$ levels at each time point. Accordingly, $Sp0_2$ and $PaC0_2$ were added to the regression equation to account for the effect that their variation across time may have on neuropsychological performance. Moreover, as also described in Table 8.5, the time elapsed between assessment 2 and assessment 3 was significantly longer for healthy controls compared to ALS patients. Thus, the effect of the variation in the timing of data collection is also accounted for by including the length of the retest intervals in the regression equation.

The multilevel modelling implemented consisted of building five hierarchical models working up from a simple model with random coefficients to more complex models also considering fixed effects. Accordingly, a first basic random effects model was built which included random intercepts (i.e. allowing the intercepts to vary across participants to consider individual variation in baseline performance) and random slopes (i.e. allowing the effect of time to vary across participants enabling individual variation in the rate of change). Secondly, the term to model the covariance structure was added. In our case, given that we are analysing time series data, a first-order autoregressive covariance structure was modelled, which assumes higher correlations between data points that are closer in time. In the third model built we added the first fixed effect we are interested in: *group*. In this model, the other predictors we want to consider (i.e. arterialised tissue capillary blood gas tensions and retest intervals) were also

added. Subsequently, *time* as another fixed factor was added in model number 4, and finally, in model number 5, the interaction term *time x group* was included.

For each full model, regression assumptions were checked. No multicollinearity between predictors was observed for any of the models run. Although the assumption of normality of residuals was not met in most cases, no influential observations were present for any of the models. Moreover, no curvature or funnel-shape patters were observed for any of the plots of fitted values against residuals, which suggests linearity and homoscedasticity of the data.

Results from multilevel models are interpreted in two different ways. On the one hand, the full model or model number 5 (which includes the interaction term *time x group*) was compared to model number 4 (which includes fixed effects for time and group but does not include the interaction term) using chi-square likelihood ratio tests. These results, which assess the contribution of the interaction term to the fit of each model, are depicted in Table 8.6.

On the other hand, the coefficients for each fixed effect (i.e. *time*, *group* and *time x group*) on the full model were analysed. Results are described in Table 8.7. For each model, beta coefficients, t-values and significance levels are reported. In cases where other predictors included in the model such as respiratory levels or time elapsed between assessments have a significant effect, this is reported. Descriptive data on performance for each group and time point are as well depicted in Table 8.7 and are also visually represented in Figure 8.3.

Table 8.6. Goodness of fit and multilevel model comparisons.

Neuropsychological Measures	AIC Model 4	AIC Model 5	X^2 L. Ratio (df) [a]	*p*
Language				
PALPA Auditory Lexical Decision	3331.7	3332.7	4.95(3)	.18
PALPA Visual Lexical Decision	2528.1	2533.8	0.30(3)	.96
PALPA Word Spelling	2221.1	2223.2	3.96(3)	.27
PALPA Word Reading	1655.4	1653.7	7.73(3)	.05
Boston Naming Test	2667.9	2666.0	7.94(3)	.05
Semantic Composite Score	1149.9	1151.6	4.37(3)	.22
PALPA Auditory Sentence – Picture Matching	2371.9	2377.5	0.45(3)	.93
PALPA Written Sentence – Picture Matching	2003.3	2005.6	3.65(3)	.30
Executive Function				
FAS Test	2017.8	2023.3	0.50(3)	.92
Restricted Phonemic Fluency (letter C)	2152.2	2154.9	3.28(3)	.35
Semantic Fluency (Animals)	2067.1	2071.0	2.08(3)	.56
Backward Digit Span	1803.3	1807.2	2.11(3)	.55
Sorting Test – Free Sorting Correct Sorts	2210.0	2215.0	0.99(3)	.80
Sorting Test – Sort Recognition Description	3770.3	3773.3	3.05(3)	.38
CWIT – Inhibition TIP	674.8	679.2	1.66(3)	.65
CWIT– Inhibition/Switching TIP	812.0	809.1	8.87(3)	.03
Reading the Mind in the Eyes Test	3181.5	3182.8	4.64(3)	.20
Conflicting Emotional Prosody	2578.1	2579.4	4.74(3)	.19
Behaviour				
Beaumont Behavioural Inventory	2651.1	2646.9	10.2(3)	.02

[a] Degrees of freedom were obtained by subtracting the number of parameters in model 4 from the ones in model 5.
Abbreviations. AIC: Akaike's Information Criterion.

Table 8.7. Longitudinal neuropsychological performance of ALS patients compared to healthy controls: between-subjects, within-subjects and interaction effects.

Neuropsychological Measures[a]	ALS Patients *M ± SD*				Healthy Controls *M ± SD*				Between-subjects Effects Group			Within-subjects Effects Time			Interaction Effects Time x Group		
	T1 n = 117	**T2** n = 79	**T3** n = 64	**T4** n = 46	**T1** n = 100	**T2** n = 79	**T3** n = 68	**T4** n = 61	***b***	**t(df)**	***p***	Time point	***b***	**t(df)**	***p***	***b***	**t(df)**	***p***
Language																		
PALPA Auditory Lexical Decision	71.6 ± 4.99	73.4 ± 4.68	74.3 ± 3.80	74.1 ± 4.08	72.5 ± 5.84	75.3 ± 4.45	75.5 ± 4.16	74.9 ± 4.45	-0.75	-1.08(213)	.28	2	2.69	2.32(364)	.02	-1.38	-2.01(364)	.05
												3	2.82	2.37(364)	.02	-1.12	-1.53(364)	.13
												4	2.27	1.93(364)	.05	-0.37	-0.46(364)	.65
PALPA Visual Lexical Decision	57.3 ± 3.18	58.0 ± 2.98	58.1 ± 2.82	58.1 ± 2.42	58.3 ± 2.54	58.7 ± 1.91	58.8 ± 2.14	58.5 ± 2.54	-0.98	-2.41(213)	.02	2	0.30	0.56(364)	.58	-0.03	-0.08(364)	.94
												3	0.43	0.80(364)	.43	-0.16	-0.48(364)	.63
												4	0.20	0.37(364)	.71	0.01	0.02(364)	.98
PALPA Word Spelling	36.7 ± 3.95	36.6 ± 4.04	37.0 ± 3.91	37.2 ± 3.12	37.7 ± 2.95	37.7 ± 2.86	38.0 ± 2.59	38.0 ± 2.78	-0.99	-1.92(196)	.06	2	0.02	0.04(323)	.97	-0.39	-1.52(323)	.13
												3	0.21	0.47(323)	.64	-0.33	-1.17(323)	.24
												4	0.23	0.52(323)	.60	-0.55	-1.74(323)	.08
PALPA Word Reading	58.8 ± 1.70	59.2 ± 1.16	59.3 ± 1.09	59.3 ± 1.13	59.2 ± 1.29	59.3 ± 1.29	59.4 ± 1.22	59.0 ± 1.83	-0.33	-1.61(203)	.11[#]	2	0.31	1.10(344)	.27	-0.08	-0.45(344)	.65
												3	0.28	0.99(344)	.32	0.12	0.67(344)	.51
												4	-0.01	-0.01(344)	.99	0.46	2.33(344)	.02
Boston Naming Test – spontaneous responses	23.6 ± 4.37	25.4 ± 3.50	25.1 ± 3.59	25.5 ± 3.47	25.6 ± 3.54	25.9 ± 3.34	26.5 ± 3.14	26.7 ± 3.61	-1.73	-3.24(213)	.001[#]	2	0.13	0.24(359)	.81	0.86	2.67(359)	.008
												3	0.57	1.01(359)	.31	0.36	1.04(359)	.30
												4	0.70	1.24(359)	.22	0.67	1.75(359)	.08
Semantic Composite Score	0.10 ± 0.82	-0.08 ± 0.72	0.09 ± 0.49	0.08 ± 0.56	0.01 ± 0.70	-0.02 ± 0.55	-0.02 ± 0.68	-0.02 ± 0.70	0.15	1.47(212)	.14	2	0.01	0.02(361)	.98	-0.22	-1.91(361)	.06
												3	-0.04	-0.20(361)	.84	-0.01	-0.10(361)	.92
												4	-0.02	-0.09(361)	.93	-0.04	-0.28(361)	.78
PALPA Auditory Sentence – Picture Matching	27.0 ± 2.51	27.4 ± 2.97	27.7 ± 2.32	27.7 ± 2.56	28.5 ± 1.99	28.9 ± 1.42	29.0 ± 1.44	28.9 ± 1.55	-1.28	-4.08(210)	.0001[#]	2	-0.16	-0.30(361)	.76	-0.08	-0.26(361)	.79
												3	-0.14	-0.26(361)	.79	0.14	0.44(361)	.66
												4	-0.15	-0.27(361)	.79	0.04	0.11(361)	.91
PALPA Written Sentence – Picture Matching	28.2 ± 1.87	28.5 ± 1.82	28.7 ± 1.66	28.5 ± 2.24	29.1 ± 1.32	29.2 ± 1.13	29.1 ± 1.26	29.3 ± 1.04	-0.66	-2.90(210)	.004[#]	2	-0.05	-0.12(361)	.90	-0.05	-0.21(361)	.83
												3	-0.20	-0.51(361)	.61	0.30	1.24(361)	.21
												4	0.01	0.02(361)	.98	-0.19	-0.72(361)	.47
Executive Function																		
FAS Test	9.00 ± 2.13	9.37 ± 2.02	9.48 ± 1.73	9.52 ± 1.89	9.78 ± 1.42	9.85 ± 1.66	9.88 ± 1.09	9.93 ± 1.16	-0.61	-2.45(213)	.01[#]	2	-0.37	-1.03(363)	.30	-0.04	-0.21(363)	.83
												3	-0.40	-1.09(363)	.28	0.06	0.28(363)	.78
												4	-0.30	-0.82(363)	.41	-0.11	-0.42(363)	.67
Restricted Phonemic Fluency (letter C)	8.87 ± 2.26	9.22 ± 1.87	9.29 ± 1.99	9.57 ± 1.73	9.70 ± 1.25	9.80 ± 1.04	9.79 ± 1.26	9.63 ± 1.54	-0.66	-2.54(214)	.01	2	0.42	0.99(362)	.32	-0.01	-0.03(362)	.97
												3	0.39	0.90(362)	.37	-0.01	-0.03(362)	.98
												4	0.13	0.31(362)	.75	0.46	1.56(362)	.12

[a] Descriptive data presented as raw scores, except for the semantic composite, which is presented in z scores.

Note. Other predictors' significance level: [#]$Sp0_2$as a significant predictor, [†]$PaC0_2$as a significant predictor, [¥]Time elapsed between assessments as a significant predictor.

Table 8.7 (continued). Longitudinal neuropsychological performance of ALS patients compared to healthy controls: between-subjects, within-subjects and interaction effects.

Neuropsychological Measures[a]	ALS Patients *M ± SD*				Healthy Controls *M ± SD*				Between-subjects Effects Group				Within-subjects Effects Time			Interaction Effects Time x Group		
	T1 n = 117	**T2** n = 79	**T3** n = 64	**T4** n = 46	**T1** n = 100	**T2** n = 79	**T3** n = 68	**T4** n = 61	***b***	**t(df)**	***p***	Time point	***b***	**t(df)**	***p***	***b***	**t(df)**	***p***
Executive Function																		
Semantic Fluency (Animals)	9.38 ± 1.88	9.64 ± 1.74	9.57 ± 1.83	9.70 ± 1.58	9.92 ± 1.42	10.2 ± 1.15	9.85 ± 1.36	10.1 ± 1.33	-0.37	-1.54(214)	.12[#]	2	0.09	0.24(361)	.81	-0.23	-0.97(361)	.33
												3	-0.38	-0.91(361)	.36	0.14	0.53(361)	.59
												4	-0.03	-0.06(361)	.95	-0.05	-0.19(361)	.85
Backward Digit Span	4.71 ± 1.47	5.03 ± 1.39	5.23 ± 1.42	5.28 ± 1.53	4.92 ± 1.16	4.86 ± 1.24	5.10 ± 1.24	5.05 ± 1.25	-0.10	-0.53(208)	.60[#]	2	-0.56	-1.70(362)	.09	0.26	1.36(362)	.18
												3	-0.33	-1.00(362)	.32	0.17	0.81(362)	.42
												4	-0.24	-0.73(362)	.47	0.05	0.24(362)	.81
Sorting Test – Free Sorting Correct Sorts	7.25 ± 2.41	8.34 ± 2.45	8.59 ± 2.34	8.80 ± 2.36	8.35 ± 2.22	8.78 ± 2.06	9.02 ± 2.14	9.28 ± 2.27	-0.70	-2.14(205)	.03[#]	2	0.74	1.54(341)	.13	-0.01	-0.01(341)	.99
												3	0.84	1.69(341)	.09	0.25	0.82(341)	.41
												4	1.00	2.05(341)	.04	0.19	0.57(341)	.57
Sorting Test – Sort Recognition Description	32.2 ± 9.88	34.5 ± 9.53	34.2 ± 10.8	35.8 ± 9.44	33.4 ± 9.06	36.7 ± 9.69	36.7 ± 9.87	37.8 ± 11.1	-0.41	-0.28(199)	.78	2	1.66	0.73(329)	.47	-1.81	-1.36(329)	.18
												3	1.26	0.54(329)	.59	-1.58	-1.10(329)	.27
												4	2.65	1.17(329)	.24	-2.35	-1.49(329)	.14
CWIT – Inhibition TIP	1.33 ± 0.66	1.25 ± 0.68	1.21 ± 0.65	1.14 ± 0.51	1.38 ± 0.52	1.25 ± 0.44	1.24 ± 0.55	1.16 ± 0.41	-0.06	-0.70(189)	.48[†]	2	-0.01	-0.04(319)	.97	0.05	0.65(319)	.51
												3	0.02	0.13(319)	.89	-0.04	-0.43(319)	.67
												4	-0.07	-0.48(319)	.63	-0.06	-0.62(319)	.54
CWIT– Inhibition/Switching TIP	1.42 ± 0.67	1.36 ± 0.58	1.21 ± 0.52	1.21 ± 0.61	1.47 ± 0.53	1.55 ± 0.76	1.52 ± 0.67	1.49 ± 0.69	-0.08	-0.79(187)	.43[†¥]	2	0.49	2.94(310)	.004	-0.13	-1.38(310)	.17
												3	0.48	2.81(310)	.005	-0.28	-2.77(310)	.006
												4	0.43	2.59(310)	.01	-0.24	-2.12(310)	.03
Reading the Mind in the Eyes	22.1 ± 5.54	24.2 ± 5.49	23.4 ± 5.63	23.3 ± 5.04	23.5 ± 4.44	23.8 ± 4.65	24.4 ± 5.03	24.4 ± 4.92	-1.07	-1.47(209)	.14	2	-0.24	-0.26(362)	.80	0.94	1.66(362)	.10
												3	0.23	0.23(362)	.82	-0.08	-0.13(362)	.89
												4	0.37	0.38(362)	.70	-0.29	-0.43(362)	.66
Conflicting Emotional Prosody	29.7 ± 5.47	31.1 ± 4.98	30.1 ± 5.36	29.9 ± 6.01	29.0 ± 5.63	30.4 ± 5.17	31.4 ± 4.95	32.4 ± 2.68	0.19	0.22(177)	.82[#]	2	0.81	0.73(269)	.47	0.06	0.08(269)	.94
												3	1.30	1.13(269)	.26	-0.87	-1.17(269)	.24
												4	1.92	1.68(269)	.09	-1.44	-1.79(269)	.07
Behaviour																		
Beaumont Behavioural Inventory	8.34 ± 9.61	10.5 ± 11.8	10.4 ± 12.9	12.2 ± 13.1	4.08 ± 6.51	3.98 ± 7.54	3.88 ± 6.44	3.23 ± 6.17	3.03	1.83(162)	.07	2	-5.35	-1.76(203)	.08	3.79	2.40(203)	.02
												3	-4.69	-1.51(203)	.13	3.69	2.09(203)	.04
												4	-4.36	-1.36(203)	.18	5.47	2.74(203)	.007

[a] Descriptive data are presented in raw scores, except for the semantic composite, which is presented in z scores.

Note. Other predictors' significance level: [#]$Sp0_2$as a significant predictor, [†]$PaC0_2$as a significant predictor, [¥]Time elapsed between assessments as a significant predictor.

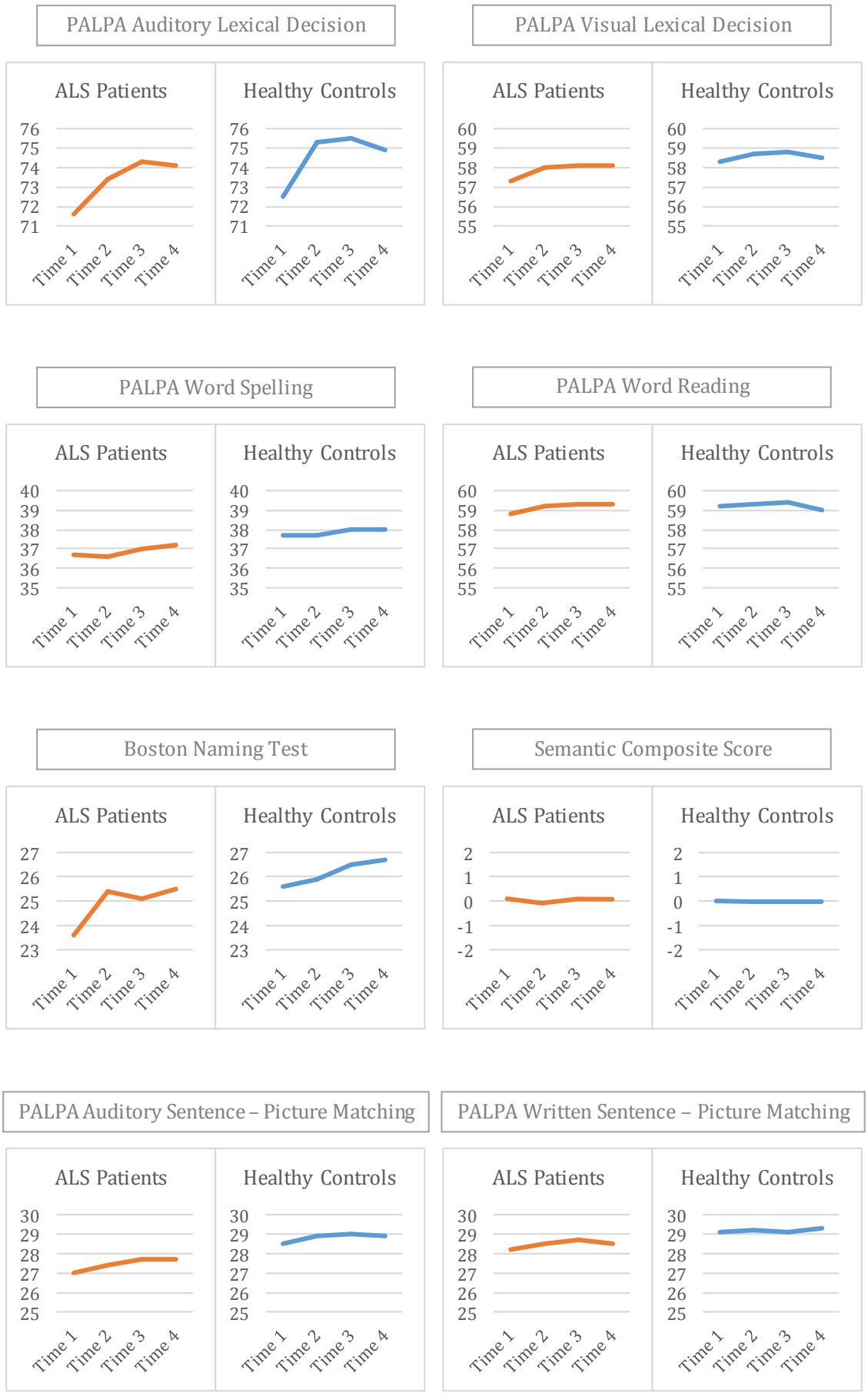

Figure 8.3. Longitudinal neuropsychological performance comparison between ALS patients and healthy controls

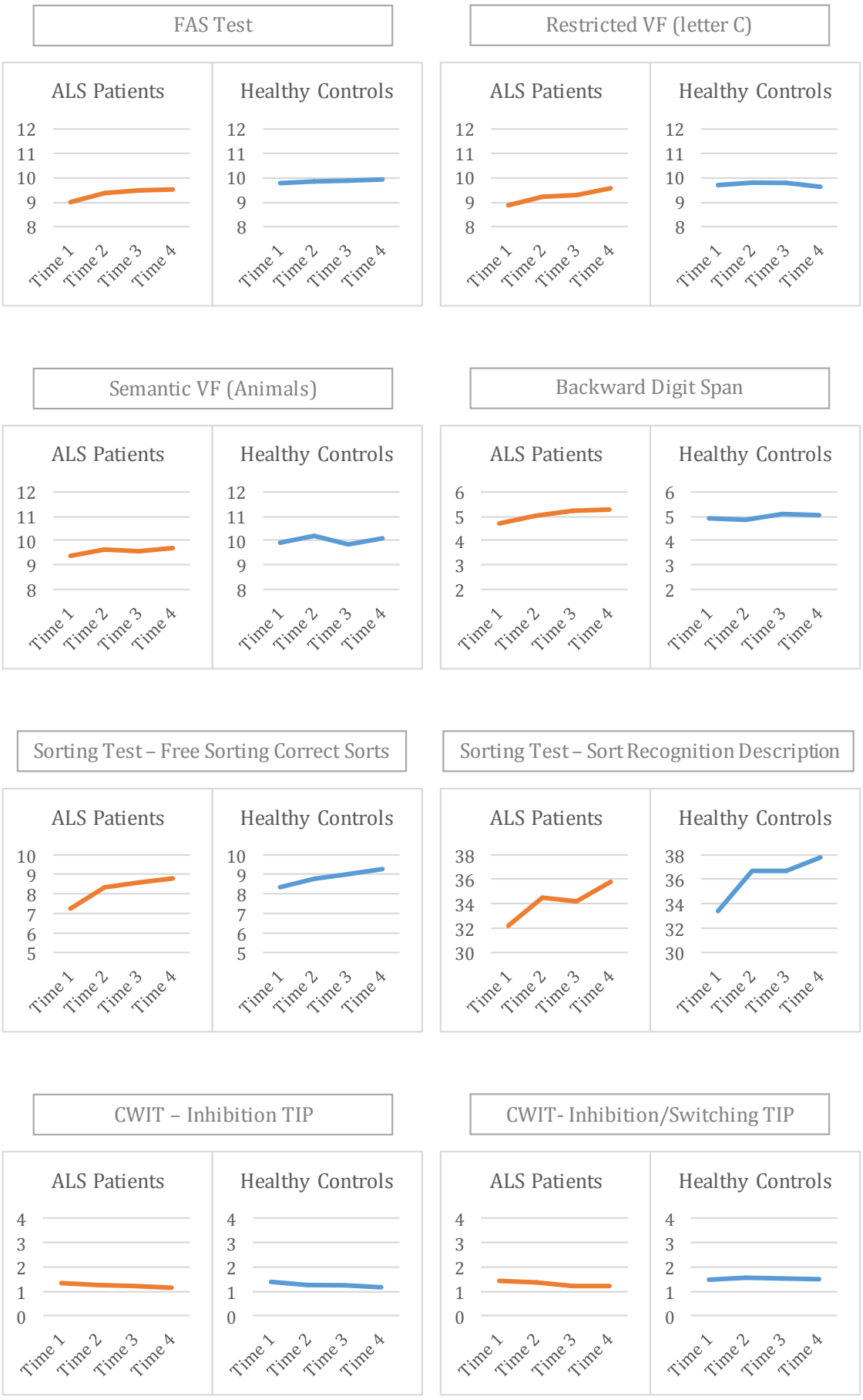

Figure 8.3 (continued). Longitudinal neuropsychological performance comparison between ALS patients and healthy controls

Figure 8.3 (continued). Longitudinal neuropsychological performance comparison between ALS patients and healthy controls

Results on Table 8.6 show that adding the interaction term to the model improved goodness of fit (i.e. decreased AICs) for only four of the neuropsychological measures: the PALPA Word Reading, the Boston Naming Test, the Inhibition/Switching condition from the Colour-Word Interference Test, and the Beaumont Behavioural Inventory. Out of these four cases, the interaction term significantly contributed to the fit of the model solely for the latter two, the two language measures being at the threshold for significance. No significant contribution of the interaction term to the fit of the model was observed for any other neuropsychological measure considered. Specific results on the coefficients for the interaction effect (i.e. *time x group*), presented in Table 8.7 and discussed below, give a better insight on the different patterns of performance of ALS patients in comparison to healthy controls over time.

Table 8.7 presents results on the coefficients for each fixed effect on the full model. Between-subjects effects are first discussed, followed by within-subjects and interaction effects. Thus, regarding between-subjects, ALS patients performed significantly poorer compared to healthy controls on the following neuropsychological measures: PALPA Visual Lexical Decision (r = .16), Boston Naming Test – spontaneous responses (r = .22), PALPA Spoken Sentence – Picture Matching (r = .27), PALPA Written Sentence – Picture Matching (r = .20), FAS Test (r = .17), Restricted VF- letter C (r = .17), and the Sorting Test – Free Sorting Correct Sorts (r = .15). In

all significant cases, effects sizes were small. These results are concordant with the pattern of incident neuropsychological deficits characteristic of ALS patients described in chapter 7, which exhibited difficulties in orthographic processing, word naming, syntactic/grammatical processing, phonemic verbal fluency and problem-solving abilities.

Within-subjects effects were significant for the following neuropsychological measures and time points: PALPA Auditory Lexical Decision Time 2 (r = .12), Time 3 (r = .12) and Time 4 (r = .10); Sorting Test – Free Sorting Correct Sorts Time 4 (r = .11); and CWIT- Inhibition/Switching TIP Time 2 (r = .16), Time 3 (r = .16) and Time 4 (r = .15). Size effects were also small in all cases. These results indicate variation within individual performance across time in the aforementioned tasks. Looking at Figure 8.3, performance tends to improve across time points for all three measures described, and therefore it can be presumed that these significant changes over time likely represent learning effects. In fact, significant effects of prior exposure for the PALPA Auditory Lexical Decision task were already described in chapter 6.

Finally, interaction effects were significant for the following measures and time points: PALPA Word Reading Time 4 (r = .12); Boston Naming Test Time 2 (r = .14); CWIT-Inhibition/Switching TIP Time 2 (r = .16) and Time 3 (r = .12); and the Beaumont Behavioural Inventory Time 2 (r = .17), Time 3 (r = .12) and Time 4 (r = .19); with small effect sizes in all cases. These results are concordant with results presented in Table 8.6. These significant effects are analysed in detail, also focusing on descriptive data visually represented in Figure 8.3. Regarding the PALPA Word Reading, the significant difference at Time 4 is due to a decrease in performance for the healthy control group which is not observed for the patient group. Performance on the Boston Naming Test also experiences a remarkable increase from Time 1 to Time 2 on the ALS sample, compared to a more subtle increase in performance occurring in the case of healthy controls. Concerning performance on the Inhibition/Switching condition from the Colour-Word Interference Test, it can be observed that while ALS patients' TIP decrease with time, indicating improved performance, performance on the healthy control group is maintained relatively stable over time. In all three cases, the significant interaction effects observed are caused by a variation in the pattern of performance over time between ALS patients and healthy controls with better performance in the former group, and in any instance is the case that these effects represent a decrease in cognitive performance of the ALS sample. However, when focusing on results from the Beaumont Behavioural Inventory, a significant increase of behavioural change is reported for the ALS sample over time, while scores on the healthy control group significantly decreased across time points.

Overall, these results indicate that although the pattern of neuropsychological deficits present at first year of diagnosis is maintained over the course of the disease in ALS, no significant decrease in performance of the ALS sample compared to healthy controls is observed over time

on cognitive measures, although a significant increase in behavioural change occurs. The specific pattern of behavioural change over time is explored in section 8.3.3.2, when the prevalence of behavioural change in ALS is explored.

8.3.1.1. Further Investigations into Longitudinal Semantic Processing

In the previous section, longitudinal performance on all language domains studied in this project have been investigated. However, semantic processing requires further investigation. As demonstrated in chapter 7, sematic processing deficits are not significantly present in incident ALS patients. However, based on results from the systematic review presented in chapter 3, which indicated that a proportion of prevalent ALS patients present with semantic processing deficits, it was hypothesised that these develop during the course of the disease in some patients.

Results presented in Table 8.7 showed no significant effects between ALS patients and healthy controls on the semantic composite, and no significant effects were found either when considering time or the interaction between time and group. These results indicate that semantic processing deficits neither appear nor progress over time in ALS patients. However, to further explore this matter, the proportion of impaired ALS patients compared to healthy controls on the semantic composite across time points is also investigated. As per results in Table 8.8, the proportion of ALS patients and healthy controls that present with impairment on semantic processing is very low, and no significant differences are observed between the two groups at any of the time points.

Table 8.8. Proportion of ALS patients compared to healthy controls that are impaired on the semantic composite score.

	No of impaired (%)[a]		X^2(df) [b]	*p*	*φ*
	ALS Patients	**Healthy Controls**			
Time 2	*n = 78* 2 (3)	*n = 79* 1 (1)	0.0001	.62 [c]	.05
Time 3	*n = 63* 0	*n = 67* 4 (6)	2.14	.12 [c]	.17
Time 4	*n = 44* 2 (5)	*n = 58* 5 (9)	0.17	.70 [c]	.08

[a] Abnormal performance considered as 1.65 SD below the control mean, as per Revised Diagnostic Criteria (Strong et al., 2017).

[b] Pearson's Chi-square test for independence (X^2), with Yates' continuity correction.

[c] Fisher's Exact Probability Test.

To further investigate semantic processing in prevalent ALS cases, performance on the Boston Naming Test after cueing was analysed. As previously noted in this work, difficulties on spontaneous recall on this task can be of retrieval nature or of degradation of semantic knowledge. Cross-sectional results presented in chapter 7 indicated that incident ALS patients had difficulties with naming that were of retrieval nature as performance improved following

the presentation of semantic and, most notably, phonemic cues. In terms of longitudinal performance, results from Table 8.7 showed that ALS patients performed significantly poorer than healthy controls on the number of spontaneous responses given on the Boston Naming Test across all time points, although a tendency for performance to improve over time was observed for both groups. Again, such poorer performance of ALS patients in comparison to healthy controls across time points can be caused by a deficit of retrieval, but it can also represent an emerging semantic deficit. Longitudinal performance on post-cueing responses on the Boston Naming Test is investigated next to address this matter.

Mean performance for each group at each time point on post-cueing performance was as follows: Semantic Cue – *Time 1* (ALS patients: $M = 24.1$, $SD = 3.98$; healthy controls: $M = 25.9$, $SD = 3.25$), *Time 2* (ALS patients: $M = 25.6$, $SD = 3.32$; healthy controls: $M = 26.3$, $SD = 2.89$), *Time 3* (ALS patients: $M = 25.3$, $SD = 3.46$; healthy controls: $M = 26.7$, $SD = 2.84$), *Time 4* (ALS patients: $M = 25.7$, $SD = 3.20$; healthy controls: $M = 26.9$, $SD = 3.31$); Phonemic Cue – *Time 1* (ALS patients: $M = 28.2$, $SD = 2.12$; healthy controls: $M = 27.7$, $SD = 2.83$), *Time 2* (ALS patients: $M = 28.9$, $SD = 1.23$; healthy controls: $M = 27.9$, $SD = 2.30$), *Time 3* (ALS patients: $M = 28.9$, $SD = 1.27$; healthy controls: $M = 28.6$, $SD = 2.03$), *Time 4* (ALS patients: $M = 28.8$, $SD = 1.57$; healthy controls: $M = 28.5$, $SD = 2.56$). These data are visually represented in Figure 8.3.

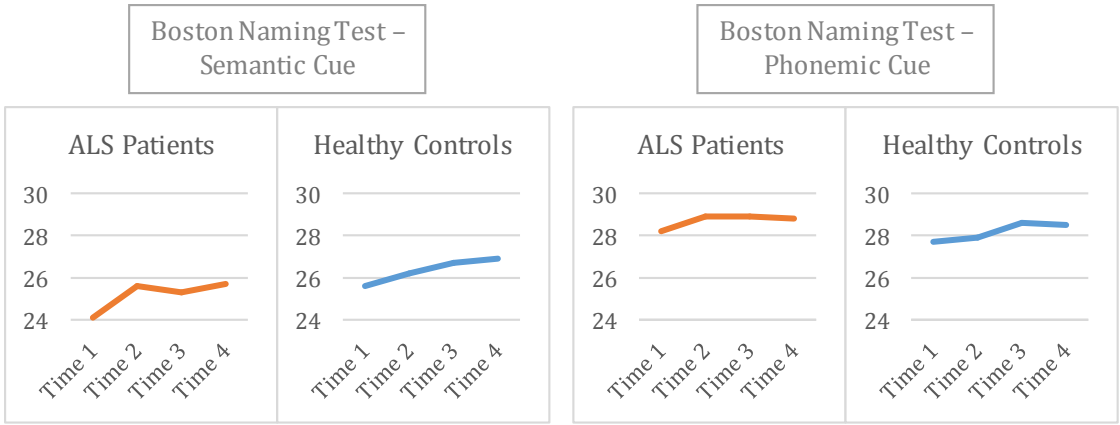

Figure 8.4. Longitudinal performance comparison between ALS patients and healthy controls on the Boston Naming Test post-cueing responses

A generalised linear mixed model for each Boston Naming Test post-cueing condition was built following the same procedure utilised for all other models run in this section and previously outlined. Assumptions were checked in both cases and no significant violations were found. When considering post-semantic cueing responses, a significant between-subjects effect was found ($b = -1.50$, $t(213) = -3.08$, $p = .002$), which indicates that ALS patients performed significantly lower compared to healthy controls, although the effect of time or the interaction time x group was not significant for any of the time points (within-subjects effects: *Time 2*, $b = 0.20$, $t(359) = 0.37$, $p = .71$; *Time 3*, $b = 0.54$, $t(359) = 0.96$, $p = .34$; *Time 4*, $b = 0.69$, $t(359) =$

1.23, p = .22. Interaction effects: *Time 2*, *b* = 0.63, t(359) = 1.96, p = .05; *Time 3*, *b* = 0.18, t(359) = 0.51, p = .61; *Time 4*, *b* = 0.48, t(359) = 1.26, p = .21). Looking at the 'Semantic Cue' graphs in Figure 8.4, it can be seen that healthy controls' performance is higher compared to ALS patients across the four time points, but in both cases performance increases with time. These results are similar to those observed when considering performance on total spontaneous responses and indicate that the provision of semantic cue does not contribute differently between groups.

On the contrary, when considering responses following provision of phonemic cues, a significant effect of groups was observed (*b* = 0.66, t(213) = 2.10, p = .04), but this time ALS patients performed significantly better than healthy controls (Figure 8.4). Within-subjects effects were significant for Time 3 and Time 4 (*Time 2*, *b* = 0.32, t(359) = 0.71, p = .48; *Time 3*, *b* = 1.00, t(359) = 2.15, p = .03; *Time 4*, *b* = 0.95, t(359) = 2.05, p = .04), but no significant interaction effects were observed (*Time 2*, *b* = 0.19, t(359) = 0.72, p = .47; *Time 3*, *b* = -0.45, t(359) = -1.59, p = .11; *Time 4*, *b* = -0.30, t(359) = -0.96, p = .34). These results indicate that although both groups improve performance following the presentation of phonemic cue compared to their performance after semantic cueing (as it can be seen in Figure 8.4), ALS patients benefit from phonemic cue more strongly than healthy controls.

Overall, these results, which indicate that ALS patients benefit from the presentation of cues and most notably from the presentation of phonemic cues, are in accordance with the hypothesis that deficits observed on spontaneous responses given on the Boston Naming Test are of access or retrieval nature, rather than of semantic nature. To confirm if such improvement on performance following cueing is significant, performance of the ALS sample across Boston Naming Test conditions at each time point was compared, and results are depicted in Table 8.9 for both mean performance and percentage of impairment.

Table 8.9. Longitudinal performance of the ALS sample on the Boston Naming Test, considering post-cueing responses (mean performance and percentage of impairment).

	Mean performance *M* ± *SD*						
	Spontaneous responses	**Semantic cue**	**Phonemic cue**	**F(df)**[a]	**ε**	***p***	η_G^2
Time 2	25.4 ± 3.50	25.6 ± 3.32	28.9 ± 1.23	121.7 (1,80.1)	0.520	<.0001	.24
Time 3	25.1 ± 3.59	25.3 ± 3.46	28.9 ± 1.27	93.01 (1,58.6)	0.514	<.0001	.25
Time 4	25.5 ± 3.47	25.7 ± 3.20	28.8 ± 1.57	76.1 (1.1,45.9)	0.534	<.0001	.22
	Nº of impaired (%)						
	Spontaneous responses	**Semantic cue**	**Phonemic cue**	**Q(df)**[b]	***p***	η_Q^2	
Time 2	8 (10)	11 (14)	0	17.6(2)	.0001	.11	
Time 3	11(18)	13(21)	1(2)	20.7(2)	<.0001	.17	
Time 4	7(16)	6(14)	1(2)	10.3(2)	.006	.12	

[a] One-way repeated measures ANOVA, with Greenhouse-Geisser correction.

[b] Cochran's Q test.

Focusing first on mean performance, results on Table 8.9 indicate that this increased by two tenths following the presentation of semantic cue and by 3 points following the presentation of phonemic cue for the three follow-up time points. One-way repeated measures ANOVA revealed a significant difference across Boston Naming Test conditions at each time point and pairwise comparisons indicated that, although these were also significant between spontaneous responses and semantic cueing at first and second follow up (Spontaneous vs Semantic: *Time 2*, p = .0006; *Time 3*, p = .02; *Time 4*, p = .13), significantly improved performance was mainly present when comparing performance following phonemic cueing to the other two conditions for all time points (Spontaneous vs Phonemic: *Time 2*, p = <.0001; *Time 3*, p = <.0001; *Time 4*, p = <.0001. Semantic vs Phonemic: *Time 2*, p = <.0001; *Time 3*, p = <.0001; *Time 4*, p = <.0001).

Considering percentage of impairment, Cochran's Q test also revealed a significant difference between Boston Naming Test conditions across time points. Specifically, pairwise comparisons indicated that these significant differences did not exist when comparing percentage of impairment between spontaneous responses and following semantic cueing (Spontaneous vs Semantic: *Time 2*, p = .25; *Time 3*, p = .47; *Time 4*, p = .95), but that these were present mostly when performance following phonemic cueing was compared to the other two conditions (Spontaneous vs Phonemic: *Time 2*, p = .01; *Time 3*, p = .005; *Time 4*, p = .04. Semantic vs Phonemic: *Time 2*, p = .003; *Time 3*, p = .002; *Time 4*, p = .08).

Overall, results in Table 8.9 show that performance of the ALS sample significantly improved following the presentation of cues, more remarkably phonemic cues. These results support the view that longitudinal deficits on spontaneous recall on the Boston Naming Test are of access nature. As per Table 8.9, the percentage of ALS patients that remained impaired on the Boston Naming Test following presentation of phonemic cues is minimal and, contrary to our assumption, confirms that no prevalent semantic deficits are present within our ALS sample.

8.3.1.2. Findings on Longitudinal Action Word Processing

Preserved semantic knowledge in prevalent ALS cases has been proven so far for objects, but not for actions. In chapter 7, action word processing was also investigated, with results showing that while action semantics was preserved in incident ALS cases, these presented with retrieval deficits for action words similar to those observed when asked to name objects. Here, longitudinal performance on the Action Naming Test is also analysed to assess if semantic deficits for the processing of action words appear at later stages of the disease in ALS.

Mean performance for each group at each time point on the Action Naming Test was as follows: Spontaneous Responses – *Time 1* (ALS patients: *M* = 25.6, *SD* = 2.23; healthy controls: *M* = 26.3, *SD* = 1.68), *Time 2* (ALS patients: *M* = 26.1, *SD* = 2.04; healthy controls: *M* = 26.5, *SD* = 1.47),

Time 3 (ALS patients: *M* = 26.2, *SD* = 2.00; healthy controls: *M* = 26.5, *SD* = 1.74), *Time 4* (ALS patients: *M* = 26.0, *SD* = 2.06; healthy controls: *M* = 26.6, *SD* = 1.98). Semantic Cue – *Time 1* (ALS patients: *M* = 26.2, *SD* = 1.93; healthy controls: *M* = 26.7, *SD* = 1.47), *Time 2* (ALS patients: *M* = 26.6, *SD* = 1.61; healthy controls: *M* = 26.8, *SD* = 1.40), *Time 3* (ALS patients: *M* = 26.6, *SD* = 1.73; healthy controls: *M* = 26.9, *SD* = 1.48), *Time 4* (ALS patients: *M* = 26.4, *SD* = 1.73; healthy controls: *M* = 27.0, *SD* = 1.68). Phonemic Cue – *Time 1* (ALS patients: *M* = 27.8, *SD* = 0.48; healthy controls: *M* = 27.3, *SD* = 1.25), *Time 2* (ALS patients: *M* = 27.9, *SD* = 0.34; healthy controls: *M* = 27.6, *SD* = 0.68), *Time 3* (ALS patients: *M* = 27.9, *SD* = 0.30; healthy controls: *M* = 27.6, *SD* = 0.95), *Time 4* (ALS patients: *M* = 27.9, *SD* = 0.33; healthy controls: *M* = 27.6, *SD* = 1.05). These data are visually represented in Figure 8.5.

Figure 8.5. Longitudinal performance comparison between ALS patients and healthy controls on the Action Naming Test

Visual data on Figure 8.5 suggests that the longitudinal pattern of performance on the Action Naming Test is very similar to that observed for the Boston Naming Test. Thus, lower performance of the ALS sample compared to healthy controls across time points is observed for spontaneous responses given as well as for post-semantic cueing responses, but a reverse pattern is observed following phonemic-cueing. Generalised linear mixed models for each response condition were built, again following the same procedure outline in section 8.3.1.1, with no significant violations of the main assumptions observed. Between-subjects effects

confirmed that while ALS patients performed significantly poorer compared to healthy controls across time points on the number of spontaneous responses given (b = -0.56, t(209) = -2.02, p = .04), ALS patients performed significantly better compared to healthy controls across time points following provision of phonemic cues (b = 0.60, t(209) = 5.41, p = <.0001). No significant difference on performance between groups was observed following provision of semantic cues (b = -0.39, t(209) = -1.66, p = .10), and no significant effects of time nor the interaction between time and group were observed for any of the three conditions, except for a significant interaction effect at Time 2 following phonemic cueing (Spontaneous responses – Within-subjects effects: *Time 2*, b = 0.42, t(358) = 1.17, p = .24; *Time 3*, b = 0.39, t(358) = 1.05, p = .29; *Time 4*, b = 0.48, t(358) = 1.31, p = .19. Spontaneous responses – Interaction effects: *Time 2*, b = -0.03, t(358) = -0.14, p = .89; *Time 3*, b = 0.22, t(358) = 0.97, p = .33; *Time 4*, b = -0.03, t(358) = -0.10, p = .92. Semantic cue – Within-subjects effects: *Time 2*, b = 0.14, t(358) = 0.44, p = .66; *Time 3*, b = 0.21, t(358) = 0.62, p = .54; *Time 4*, b = 0.35, t(358) = 1.06, p = .29. Semantic cue – Interaction effects: *Time 2*, b = 0.17, t(358) = 0.91, p = .36; *Time 3*, b = 0.17, t(358) = 0.81, p = .42; *Time 4*, b = -0.11, t(358) = -0.50, p = .62. Phonemic cue – Within-subjects effects: *Time 2*, b = 0.13, t(358) = 0.60, p = .55; *Time 3*, b = 0.16, t(358) = 0.71, p = .48; *Time 4*, b = 0.23, t(358) = 1.05, p = .30. Phonemic cue – Interaction effects: *Time 2*, b = -0.29, t(358) = -2.20, p = .03; *Time 3*, b = -0.26, t(358) = -1.89, p = .06; *Time 4*, b = -0.30, t(358) = -1.94, p = .05).

Performance of the ALS sample across Action Naming Test conditions was also compared (Table 8.10), and results confirm that performance improved following the provision of both semantic and phonemic cues (Pairwise comparisons: Spontaneous vs Semantic – *Time 2*, p = <.0001; *Time 3*, p = <.0001; *Time 4*, p = .003. Spontaneous vs Phonemic – *Time 2*, p = <.0001; *Time 3*, p = <.0001; *Time 4*, p = <.0001. Semantic vs Phonemic – *Time 2*, p = <.0001; *Time 3*, p = <.0001; *Time 4*, p = <.0001). Overall, these results are concordant with those observed for the Boston Naming Test and indicate that action naming deficits in ALS are also of retrieval nature and that no action semantic impairments are present in prevalent ALS cases.

Table 8.10. Longitudinal performance of the ALS sample on the Action Naming Test, considering post-cueing responses (mean performance).

	Mean performance *M ± SD*						
	Spontaneous responses	**Semantic cue**	**Phonemic cue**	**F(df)**[a]	**ε**	***p***	**η_G^2**
Time 2	26.1 ± 2.04	26.6 ± 1.61	27.9 ± 0.34	58.9 (1.2,88.8)	0.592	<.0001	.20
Time 3	26.2 ± 2.00	26.6 ± 1.73	27.9 ± 0.30	45.1 (1.2,69.2)	0.577	<.0001	.19
Time 4	26.0 ± 2.06	26.4 ± 1.73	27.9 ± 0.33	36.0 (1.3,53.8)	0.626	<.0001	.22

[a] One-way repeated measures ANOVA, with Greenhouse-Geisser correction.

Finally, action word retrieval deficits in ALS were further investigated by comparing longitudinal performance on the Action Fluency Test between patients and healthy controls.

Mean performance for each group at each time point were as follows: *Time 1* (ALS patients: *M* = 9.02, *SD* = 2.34; healthy controls: *M* = 10.1, *SD* = 1.57), *Time 2* (ALS patients: *M* = 9.21, *SD* = 2.47; healthy controls: *M* = 10.2, *SD* = 1.27), *Time 3* (ALS patients: *M* = 9.64, *SD* = 1.88; healthy controls: *M* = 10.3, *SD* = 0.96), *Time 4* (ALS patients: *M* = 9.48, *SD* = 1.76; healthy controls: *M* = 10.4, *SD* = 1.09). Between-subjects effects were significant (*b* = -0.69, t(213) = -2.59, p = .01), which indicates that ALS patients performed significantly poorer than healthy controls across time points, although no effects of time or interaction effects were found (Within-subjects effects: *Time 2*, *b* = -0.14, t(361) = -0.33, p = .74; *Time 3*, *b* = -0.06, t(361) = -0.14, p = .89; *Time 4*, *b* = -0.01, t(361) = -0.02, p = .98. Interaction effects: *Time 2*, *b* = -0.09, t(361) = -0.35, p = .72; *Time 3*, *b* = 0.21, t(361) = 0.77, p = .44; *Time 4*, *b* = 0.09, t(361) = 0.32, p = .75). These results further confirm the presence of action word retrieval deficits in prevalent ALS cases.

8.3.2. Significant Individual Change on Neuropsychological Performance

The second approach used to evaluate longitudinal performance in our ALS sample focuses on detecting significant individual change on neuropsychological performance. To do so, two RCI and two SRB methods were employed. Regarding the first, Jacobson and Truax RCI and Chelune RCI were used, the former solely correcting for the effect of measurement error and the latter accounting for both measurement error and practice effects. Concerning SRB methods, simple and complex models were run, which account for regression to the mean effects as well as any other moderating effects included in the regression equation (see section 5.7.2.6 for details).

Data from the healthy control group was used to calculate the RCIs, including the mean (M_1) and standard deviation (s_1) at baseline and the mean (M_2) and standard deviation (s_2) at the follow-up time point of interest. Test-retest reliability (r_{xx}) between the two measurements (i.e. baseline and follow-up time point) was also obtained from healthy control data using ICCs, specifically a mean-rating, consistency, two-way fixed-effects model (Koo & Li, 2016).

Potential moderating factors explored to be included in the complex SRB models included age, IQ, retest interval and $Sp0_2$ levels. A significant correlation was required between a potential moderating variable and the outcome variable for this to be included in the model. Moreover, for both simple and complex SRB methods, the presence of significant influential observations was investigated and cases with D_i values above 1 were excluded.

As described in chapter 5, the cut-off for significant decline is usually considered at z = -1.645, with 5% of cases expected to fall below it (two-tailed 90% confidence interval, α = .10; one-tailed 95% confidence interval, α = .05). However, according to revised diagnostic criteria of frontotemporal syndromes in ALS (Strong et al., 2017), a decline of at least 1.5 standard deviations from baseline is considered significant (one-tailed 93% confidence interval, α = .07). Both cut-offs are explored, and results are presented in Tables 8.11 to 8.13 for each time point.

Table 8.11. RCI and SRB methods for individual reliable change at Time 2, including thresholds for significant decline and percentage of ALS patients who presented with significantly deteriorated performance considering two different cut-offs: z = -1.645 (one tailed α = .05) and z = -1.5 (one tailed α = .07).

Neuropsychological Measures	Method 1 Jacobson & Truax's RCI (measurement error)				Method 2 Chelune's RCI (plus practice effects)				Method 3 Simple SRB Approach (regression to the mean)				Method 4 Complex SRB Approach (plus other predictors)			
	Cut-off: <-1.645		Cut-off: <-1.5		Cut-off: <-1.645		Cut-off: <-1.5		Cut-off: <-1.645		Cut-off: <-1.5		Cut-off: <-1.645		Cut-off: <-1.5	
	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline
Language																
PALPA Auditory Lexical Decision[#†ϕ]	*-8.03*	0	*-7.32*	0	*-4.34*	8	*-3.71*	12	*-5.33*	6	*-4.86*	10	*-4.90*	8	*-4.47*	10
PALPA Visual Lexical Decision[†]	*-3.65*	0	*-3.33*	0	*-2.82*	8	*-2.54*	8	*-2.75*	8	*-2.51*	8	*-2.80*	6	*-2.55*	8
PALPA Word Spelling[†]	*-1.68*	24	*-1.53*	24	*-1.66*	24	*-1.52*	24	*-3.09*	5	*-2.82*	5	*-3.14*	5	*-2.87*	5
PALPA Word Reading[†]	*-1.22*	1	*-1.11*	1	*-1.10*	1	*-1.00*	22	*-1.30*	4	*-1.19*	4	*-1.30*	1	*-1.19*	3
Boston Naming Test[†ϕ]	*-2.60*	0	*-2.37*	0	*-2.23*	0	*-2.01*	0	*-2.30*	4	*-2.10*	4	*-2.34*	4	*-2.13*	5
Semantic Composite Score	*-1.37*	12	*-1.25*	12	*-1.28*	12	*-1.17*	12	*-0.74*	14	*-0.68*	14	*-0.74*	14	*-0.68*	14
PALPA Auditory Sentence – Picture Matching[#†ϕ]	*-2.63*	12	*-2.40*	12	*-1.87*	17	*-1.67*	17	*-3.60*	5	*-3.29*	6	*-3.37*	5	*-3.08*	6
PALPA Written Sentence – Picture Matching[†ϕ]	*-1.53*	17	*-1.40*	17	*-1.33*	17	*-1.21*	17	*-2.39*	5	*-2.18*	5	*-2.12*	5	*-1.94*	12
Executive Function																
FAS Test[†]	*-1.51*	9	*-1.38*	9	*-1.58*	9	*-1.43*	9	*-2.34*	3	*-2.13*	5	*-2.19*	4	*-2.00*	4
Restricted Phonemic Fluency[†]	*-2.19*	5	*-2.00*	18	*-1.91*	18	*-1.73*	18	*-2.25*	6	*-2.06*	6	*-2.52*	8	*-2.30*	8
Semantic Fluency (Animals)[†]	*-1.91*	25	*-1.74*	25	*-1.45*	25	*-1.30*	25	*-2.07*	3	*-1.89*	3	*-2.52*	1	*-2.30*	1
Backward Digit Span[†ϕ]	*-1.81*	6	*-1.65*	6	*-1.94*	6	*-1.77*	6	*-1.65*	4	*-1.50*	4	*-1.61*	3	*-1.47*	3
Sorting Test – Free Sorting Correct Sorts[#†ϕ]	*-2.42*	3	*-2.21*	3	*-1.91*	14	*-1.70*	14	*-2.80*	3	*-2.55*	3	*-2.50*	0	*-2.28*	3
Sorting Test – Sort Recognition Description[#†ϕ]	*-11.5*	1	*-10.5*	1	*-8.70*	6	*-7.60*	7	*-10.6*	1	*-9.63*	4	*-9.56*	3	*-8.72*	4
CWIT – Inhibition TIP	*+0.61*	3	*+0.56*	3	*+0.43*	15	*+0.38*	17	*+0.43*	9	*+0.39*	9	*+0.43*	9	*+0.39*	9
CWIT– Inhibition/Switching TIP[#]	*+0.56*	12	*+0.51*	12	*+0.75*	5	*+0.70*	6	*+0.81*	3	*+0.74*	5	*+0.77*	3	*+0.71*	5
Reading the Mind in the Eyes[†¥ϕ]	*-4.26*	5	*-3.89*	10	*-4.06*	5	*-3.68*	10	*-5.71*	6	*-5.21*	8	*-5.59*	3	*-5.10*	3
Conflicting Emotional Prosody[#†ϕ]	*-5.23*	2	*-4.77*	4	*-3.63*	7	*-3.19*	7	*-4.15*	11	*-3.78*	11	*-4.21*	4	*-3.84*	4
Behaviour																
Beaumont Behavioural Inventory	*+6.23*	19	*+5.69*	25	*+6.66*	19	*+6.07*	19	*+13.3*	6	*+12.1*	8	*+13.3*	6	*+12.1*	8

Note. Moderating factors included in the model: [#]Age, [†]IQ, [¥]Retest interval, [ϕ]$Sp0_2$ levels.

Table 8.12. RCI and SRB methods for individual reliable change at Time 3, including thresholds for significant decline and percentage of ALS patients who presented with significantly deteriorated performance considering two different cut-offs: z = -1.645 (one tailed α = .05) and z = -1.5 (one tailed α = .07).

Neuropsychological Measures	**Method 1 Jacobson & Truax's RCI** (measurement error)				**Method 2 Chelune's RCI** (plus practice effects)				**Method 3 Simple SRB Approach** (regression to the mean)				**Method 4 Complex SRB Approach** (plus other predictors)			
	Cut-off: <-1.645		**Cut-off: <-1.5**		**Cut-off: <-1.645**		**Cut-off: <-1.5**		**Cut-off: <-1.645**		**Cut-off: <-1.5**		**Cut-off: <-1.645**		**Cut-off: <-1.5**	
	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline
Language																
PALPA Auditory Lexical Decision[†]	*-7.45*	3	*-6.80*	3	*-3.46*	10	*-2.90*	11	*-4.97*	11	*-4.53*	11	*-4.75*	10	*-4.34*	10
PALPA Visual Lexical Decision[†]	*-3.70*	3	*-3.38*	3	*-2.91*	5	*-2.61*	5	*-2.78*	5	*-2.54*	5	*-2.83*	3	*-2.58*	5
PALPA Word Spelling[†]	*-2.29*	6	*-2.09*	6	*-1.84*	12	*-1.65*	12	*-2.91*	4	*-2.66*	4	*-2.99*	4	*-2.73*	4
PALPA Word Reading[†]	*-1.53*	2	*-1.40*	2	*-1.30*	2	*-1.17*	2	*-1.35*	4	*-1.23*	9	*-1.35*	2	*-1.23*	2
Boston Naming Test[#†]	*-3.19*	2	*-2.91*	7	*-2.11*	7	*-1.85*	11	*-3.11*	8	*-2.84*	10	*-2.99*	7	*-2.73*	7
Semantic Composite Score[†]	*-1.33*	2	*-1.22*	2	*-1.35*	2	*-1.23*	2	*-0.46*	5	*-0.42*	5	*-0.49*	5	*-0.45*	6
PALPA Auditory Sentence – Picture Matching[†]	*-2.70*	11	*-2.46*	11	*-1.85*	19	*-1.65*	19	*-2.88*	6	*-2.63*	6	*-2.65*	6	*-2.42*	6
PALPA Written Sentence – Picture Matching[†]	*-1.65*	10	*-1.50*	10	*-1.61*	10	*-1.47*	10	*-2.22*	5	*-2.03*	5	*-2.20*	3	*-2.01*	3
Executive Function																
FAS Test[†]	*-1.50*	13	*-1.37*	13	*-1.22*	13	*-1.10*	13	*-2.42*	3	*-2.21*	3	*-2.35*	2	*-2.15*	2
Restricted Phonemic Fluency[†]	*-2.04*	5	*-1.86*	16	*-1.98*	16	*-1.80*	16	*-1.83*	5	*-1.67*	13	*-1.81*	6	*-1.65*	10
Semantic Fluency (Animals)[#†]	*-2.19*	5	*-2.00*	31	*-2.21*	5	*-2.02*	5	*-2.73*	5	*-2.49*	5	*-2.30*	8	*-2.10*	8
Backward Digit Span[#†]	*-1.68*	8	*-1.53*	8	*-1.56*	8	*-1.41*	8	*-1.76*	5	*-1.61*	5	*-1.69*	3	*-1.55*	3
Sorting Test – Free Sorting Correct Sorts[#†¥]	*-2.98*	5	*-2.72*	5	*-2.24*	5	*-1.99*	9	*-2.86*	5	*-2.61*	5	*-2.53*	5	*-2.31*	5
Sorting Test – Sort Recognition Description[#†¥]	*-13.5*	6	*-12.3*	8	*-10.8*	8	*-9.60*	9	*-13.1*	8	*-12.0*	8	*-10.6*	4	*-9.63*	9
CWIT – Inhibition TIP	*+0.74*	2	*+0.68*	2	*+0.63*	2	*+0.57*	4	*+0.53*	6	*+0.48*	6	*+0.53*	6	*+0.48*	6
CWIT– Inhibition/Switching TIP[#†]	*+0.63*	0	*+0.57*	2	*+0.77*	0	*+0.71*	0	*+0.49*	8	*+0.45*	8	*+0.48*	6	*+0.44*	8
Reading the Mind in the Eyes[#†¥]	*-3.26*	11	*-2.97*	20	*-2.59*	20	*-2.29*	20	*-5.64*	5	*-5.15*	5	*-5.05*	5	*-4.61*	8
Conflicting Emotional Prosody[#†]	*-6.42*	9	*-5.85*	11	*-3.64*	11	*-3.11*	11	*-6.61*	6	*-6.03*	9	*-6.37*	6	*-5.81*	6
Behaviour																
Beaumont Behavioural Inventory[†ϕ]	*+4.79*	52	*+4.37*	52	*+4.57*	26	*+4.15*	26	*+10.7*	6	*+9.75*	10	*+10.1*	6	*+9.18*	6

Note. Moderating factors included in the model: [#]Age, [†]IQ, [¥]Retest interval, [ϕ]$Sp0_2$ levels.

Table 8.13. RCI and SRB methods for individual reliable change at Time 4, including thresholds for significant decline and percentage of ALS patients who presented with significantly deteriorated performance considering two different cut-offs: z = -1.645 (one tailed α = .05) and z = -1.5 (one tailed α = .07).

Neuropsychological Measures	Method 1 Jacobson & Truax's RCI (measurement error)				Method 2 Chelune's RCI (plus practice effects)				Method 3 Simple SRB Approach (regression to the mean)				Method 4 Complex SRB Approach (plus other predictors)			
	Cut-off: <-1.645		Cut-off: <-1.5		Cut-off: <-1.645		Cut-off: <-1.5		Cut-off: <-1.645		Cut-off: <-1.5		Cut-off: <-1.645		Cut-off: <-1.5	
	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline	Thres-hold	% Decline
Language																
PALPA Auditory Lexical Decision†	*-9.00*	0	*-8.21*	0	*-5.61*	2	*-4.91*	4	*-5.05*	9	*-4.61*	9	*-4.89*	4	*-4.46*	4
PALPA Visual Lexical Decision†	*-3.65*	2	*-3.33*	2	*-3.44*	2	*-3.12*	2	*-2.22*	7	*-2.03*	13	*-2.19*	7	*-2.00*	7
PALPA Word Spelling†	*-1.53*	16	*-1.40*	16	*-1.20*	16	*-1.07*	16	*-2.83*	6	*-2.58*	9	*-2.93*	6	*-2.67*	6
PALPA Word Reading†	*-1.17*	3	*-1.07*	3	*-1.63*	3	*-1.51*	3	*-1.15*	18	*-1.05*	18	*-1.32*	5	*-1.20*	5
Boston Naming Test#†	*-2.47*	5	*-2.25*	5	*-1.40*	11	*-1.18*	11	*-3.29*	7	*-3.00*	7	*-3.14*	7	*-2.87*	7
Semantic Composite Score	*-1.30*	5	*-1.19*	7	*-1.35*	5	*-1.23*	7	*-0.76*	11	*-0.69*	11	*-0.76*	11	*-0.69*	11
PALPA Auditory Sentence – Picture Matching†	*-2.65*	11	*-2.42*	11	*-1.99*	18	*-1.78*	18	*-3.21*	7	*-2.93*	11	*-3.14*	9	*-2.87*	9
PALPA Written Sentence – Picture Matching†	*-2.35*	9	*-2.15*	9	*-1.92*	18	*-1.74*	18	*-3.24*	2	*-2.96*	2	*-3.11*	2	*-3.84*	2
Executive Function																
FAS Test	*-1.58*	7	*-1.44*	7	*-1.30*	7	*-1.17*	7	*-1.37*	4	*-1.25*	4	*-1.37*	4	*-1.25*	4
Restricted Phonemic Fluency	*-2.32*	4	*-2.12*	4	*-2.69*	4	*-2.46*	4	*-2.83*	4	*-2.58*	4	*-2.83*	4	*-2.58*	4
Semantic Fluency (Animals)#	*-1.96*	28	*-1.79*	28	*-1.71*	28	*-1.55*	28	*-2.37*	4	*-2.16*	4	*-2.14*	11	*-1.95*	13
Backward Digit Span#	*-2.09*	2	*-1.91*	11	*-2.04*	2	*-1.85*	11	*-1.89*	7	*-1.73*	9	*-1.79*	2	*-1.64*	4
Sorting Test – Free Sorting Correct Sorts#	*-2.63*	8	*-2.40*	8	*-1.73*	13	*-1.50*	13	*-3.08*	10	*-2.81*	10	*-2.71*	8	*-2.48*	8
Sorting Test – Sort Recognition Description#	*-13.3*	0	*-12.2*	0	*-10.5*	5	*-9.20*	5	*-9.61*	5	*-8.76*	5	*-8.73*	3	*-7.97*	5
CWIT – Inhibition TIPϕ	*+0.74*	0	*+0.68*	0	*+0.44*	5	*+0.38*	5	*+0.67*	5	*+0.62*	8	*+0.63*	3	*+0.57*	5
CWIT– Inhibition/Switching TIP#ϕ	*+0.61*	5	*+0.56*	5	*+0.73*	3	*+0.67*	5	*+0.64*	5	*+0.59*	5	*+0.54*	5	*+0.50*	5
Reading the Mind in the Eyes†	*-3.72*	15	*-3.39*	15	*-3.03*	15	*-2.69*	20	*-5.41*	7	*-4.94*	7	*-5.51*	4	*-5.03*	7
Conflicting Emotional Prosody#†	*-7.17*	3	*-6.54*	3	*-2.23*	20	*-1.73*	27	*-6.23*	3	*-5.69*	3	*-5.31*	3	*-4.85*	3
Behaviour																
Beaumont Behavioural Inventory†ϕ	*+8.70*	28	*+7.94*	28	*+7.62*	28	*+6.88*	36	*+18.8*	8	*+17.1*	8	*+17.8*	12	*+16.2*	12

Note. Moderating factors included in the model: #Age, †IQ, ¥Retest interval, ϕ$Sp0_2$ levels.

When interpreting results from Tables 8.11 to 8.13, RCI methods are addressed first, followed by SRB methods. Thus, when Method 1 and Method 2 are compared it can be seen that in some cases results from Method 2, which accommodates for learning effects, are characterised by lower thresholds for significant decline (and therefore narrower prediction intervals), hence a higher number of patients are classified as having deteriorated. This is the case for some tasks across the three times points, including the PALPA Auditory Lexical Decision, PALPA Auditory Sentence – Picture Matching, both conditions from the Sorting Test, and Conflicting Emotional Prosody. This suggests that these measures are more susceptible to learning effects and therefore, when correcting for the improvement in performance observed within the healthy control sample due to repeat exposure, which is not observed within the patient sample, a higher number of ALS patients are classified as having deteriorated. On the contrary, tasks that are not as susceptible to learning effects have more stable thresholds for significant decline and percentages of patients classified as having deteriorated across time points are less variable across Method 1 and Method 2. This is the case for the Semantic Composite Score, the three Verbal Fluency conditions, Digit Span and the Reading the Mind in the Eyes test. The other measures show variable effects of repeated exposure across time points.

Regarding SRB methods, when Method 3 and Method 4 are compared, it can be seen that in some cases the percentage of patients that significantly deteriorated considerably varies from one method to another. These are cases where the moderating variables included in the model in Method 4 have a more significant effect. In some instances, the percentage is reduced, whereas in other instances this is increased. For example, the percentage of patients that deteriorated decreased for Conflicting Emotional Prosody and the Reading the Mind in the Eyes Test at time 2, the PALPA Written Sentence – Picture Matching at time 3, or the PALPA Auditory Lexical Decision task at time 4. Conversely, the percentage of patients that declined increased when correcting for moderating factors on verbal fluency tasks in some cases, specifically for Restricted Verbal Fluency at time 2 and for Semantic Verbal Fluency at time 3 and time 4. PALPA Word Reading and Backward Digit Span showed a constant pattern across time points with decreased percentage of patients classified as having deteriorated after correcting for the effect of moderating variables. In most cases however, moderating factors did not have such a significant effect and the thresholds for significant decline and percentage of patients classified as having deteriorated remained relatively stable when comparing Method 3 to Method 4.

Differences between RCI and SRB methods are also evident in some instances. In the majority of cases where this is observed, thresholds for significant decline are lower for RCI methods compared to SRB methods, and therefore the percentages of patients that deteriorated are higher for the former. This is relevant to measures such as the PALPA Word Spelling, both PALPA Sentence – Picture Matching tasks, Verbal Fluency measures and the Reading the Mind

in the Eyes test, with variability across time points within them. Moreover, the difference between RCI and SRB methods is substantial on behavioural change across the three time points. Thus, the percentage of patients that present with significantly deteriorated behaviour ranges from 19% to 52% when considering RCI methods, whereas this ranges from 6% to 12% for SRB methods. It is worth reminding readers that whilst RCI methods are based on performance from a reference sample (in our case the healthy control sample), SRB methods are based on predictions from patients' baseline performance. Accordingly, RCI methods treat the parameters obtained from this reference sample (i.e. standard deviations and test-retest reliability coefficients) as fixed or measured without error, but these are actually subject to sampling error, especially when sample sizes are small (Crawford & Garthwaite, 2006). In our case, our healthy control sample from baseline to follow up assessments was reduced from a hundred to 79, 68 and 61 respectively, and therefore this is an issue that must be considered.

Acknowledging the above, results from SRB methods are considered a more accurate estimate of individual reliable change in our ALS sample. Specifically, from the two SRB methods employed, results from the complex SRB approach are interpreted as the most precise estimation of the percentage of ALS patients that significantly declined compared to their baseline performance, as these further correct for other moderating factors. Thus, results obtained using this approach show that the percentage of patients that present with significant decline in neuropsychological performance is low for most measures and time points. Only a few neuropsychological measures have percentages of deterioration of 10% or greater, including the PALPA Auditory Lexical Decision, Semantic Composite Score, the PALPA Written Sentence – Picture Matching, Restricted Verbal Fluency, Semantic Verbal Fluency and the Beaumont Behavioural Inventory, and these are not consistently higher across time points.

Still focusing on results from the complex SRB method, when the two cut-offs for significant decline are compared (i.e. -1.645sd vs -1.5sd from baseline), no difference in the percentage of patients classified as having deteriorated is observed in most cases, or a very small difference of 1% or 2% more cases classified as having deteriorated is seen when using the less stringent cut-off. Neuropsychological measures where the percentage difference is higher (although still lower than 10%) include: the PALPA Written Sentence – Picture Matching at time 2 (7%), the number of correct free sorts from the Sorting Test at time 2 (3%), Restricted Verbal Fluency at time 3 (4%), the Sort Recognition Description score from the Sorting Test at time 3 (5%), and the Reading the Mind in the Eyes Test at time 3 (3%) and at time 4 (3%).

Individual reliable change was also explored separating the ALS sample by patients diagnosed with a cognitive syndrome and patients classified as cognitively unimpaired at baseline, to investigate how these progress. For each group, the proportion of patients that significantly declined on each cognitive measure at each follow-up time point was obtained (Table 8.14).

Table 8.14. Percentage of ALS patients (ALS Normal vs ALS with Cognitive Impairment at baseline) that presented with significant deterioration on cognitive performance at each follow-up time point, considering results on the complex SRB approach and the cut-off for reliable change at -1.5 standard deviations.

Neuropsychological Measures	ALS – Normal			ALS – Cognitive Impairment		
	Time 2 n = 56	**Time 3** n = 49	**Time 4** n = 36	**Time 2** n = 17	**Time 3** n = 12	**Time 4** n = 8
Language	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
PALPA Auditory Lexical Decision	3 (5)	5 (10)	2 (6)	4 (24)	1 (9)	0
PALPA Visual Lexical Decision	2 (4)	2 (4)	1 (3)	3 (18)	0	1 (13)
PALPA Word Spelling	2 (4)	1 (3)	1 (4)	1 (8)	1 (13)	1 (33)
PALPA Word Reading	2 (4)	0	2 (6)	0	1 (10)	0
Boston Naming Test	1 (2)	1 (2)	2 (6)	2 (12)	2 (18)	1 (13)
Semantic Composite Score	8 (15)	2 (4)	4 (12)	3 (18)	1 (8)	1 (13)
PALPA Auditory Sentence – Picture Matching	3 (5)	3 (6)	4 (12)	1 (6)	1 (8)	0
PALPA Written Sentence – Picture Matching	6 (11)	1 (2)	0	2 (12)	1 (8)	1 (13)
Executive Function	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
FAS Test	0	0	2 (6)	3 (19)	1 (9)	0
Restricted Phonemic Fluency (letter C)	2 (4)	4 (8)	1 (3)	3 (19)	2 (18)	1 (13)
Semantic Fluency (Animals)	0	4 (9)	3 (8)	0	1 (9)	3 (38)
Backward Digit Span	2 (4)	2 (4)	1 (3)	0	0	0
Sorting Test – Free Sorting Correct Sorts	2 (4)	2 (4)	2 (6)	0	1 (10)	1 (14)
Sorting Test – Sort Recognition Description	3 (6)	4 (9)	1 (3)	0	1 (13)	1 (14)
CWIT – Inhibition TIP	4 (8)	1 (2)	1 (3)	2 (14)	2 (22)	1 (13)
CWIT– Inhibition/Switching TIP	1 (2)	4 (10)	2 (7)	2 (14)	0	0
Reading the Mind in the Eyes	1 (2)	2 (4)	2 (6)	0	3 (25)	1 (13)
Conflicting Emotional Prosody	1 (3)	2 (7)	1 (4)	1 (17)	0	0

Note. Each percentage was calculated considering the total number of patients that had completed that specific task, not the total number of subjects included in that group, bearing in mind that missing data was present, specifically in those tasks with higher motor requirements.

Results presented in Table 8.14 aim to investigate the progression of ALS patients that do not present with cognitive impairment at baseline assessment compared to those that do meet criteria for cognitive impairment. The percentage of cognitively unimpaired patients at baseline that significantly deteriorate is very low (less than 10% in most cases) across all three follow-up time points. Although the absolute frequency of individuals that further declined in the impaired group is not much higher compared to that of unimpaired patients, the relative frequency actually is, with proportions ranging mostly from 10% to 25%, although these vary across neuropsychological measures and time points. These results indicate that although it is not common for unimpaired ALS patients at baseline to decline over time, further deterioration in some patients that present with initial impairment can be observed. However, this is not the case for most impaired ALS patients, who seem to maintain a relatively stable performance. The next section addresses how frontotemporal syndromes evolve across time points and explores the presence of newly diagnosed cognitive syndromes in patients that were initially unimpaired, which further elucidates results presented in this section, concerned with the progression of cognitively unimpaired ALS patients at baseline.

8.3.3. Population-Based Prevalence of Frontotemporal Syndromes in ALS

The third approach used to assess the progression of neuropsychological change in our ALS population-based sample consisted in determining the prevalence of frontotemporal syndromes at four, eight and twelve months post-initial assessment. To this aim, revised criteria presented in chapter 7 for the diagnostic of ALSci (Table 7.22) and ALSbi (Table 7.26) were utilised to reclassify each ALS participant that underwent repeat assessment at each time point. Cognitive results are presented first, followed by behavioural status and then, combined results.

8.3.3.1. Prevalence of ALSci

To undergo cognitive classifications, raw scores were converted into Z scores using equivalent healthy control data at each time point to adjust for practice effects that occur as a result of repeat exposure to neuropsychological tests. Cognitive classifications were not possible for some ALS patients due to missing data. Specifically, 13% of ALS patients could not be classified at time 2, 16% at time 3, and 15% at time 4. These proportions are similar to those encountered for Time 1 assessment, where cognitive status could not be obtained for 11% of ALS patients.

First, the proportion of ALS patients that were impaired on executive function and language at each time point (including Time 1) are presented in Table 8.15, and the proportion of ALS patients diagnosed with each cognitive syndrome (i.e. ALSei, ALSli and ALSeli) at each time point is represented in Figure 8.6.

Table 8.15. Proportion of ALS patients that met criteria for executive and language impairment at each time point.

Cognitive Classification	Time 1	Time 2	Time 3	Time 4
Executive Impairment	*n = 109*	*n = 72*	*n = 57*	*n = 41*
n(%)	35 (32)	22 (31)	16 (28)	7 (17)
Language Impairment	*n = 108*	*n = 74*	*n = 58*	*n = 42*
n(%)	20 (19)	15 (20)	11 (19)	7 (17)

Results in Table 8.15 indicate that the percentage of patients that present with executive impairment is maintained at around 30% for the first three time points, but this drops to around 20% at the last assessment. On the contrary, the proportion of ALS patients meeting criteria for language impairment is maintained at around 20% for all four time points.

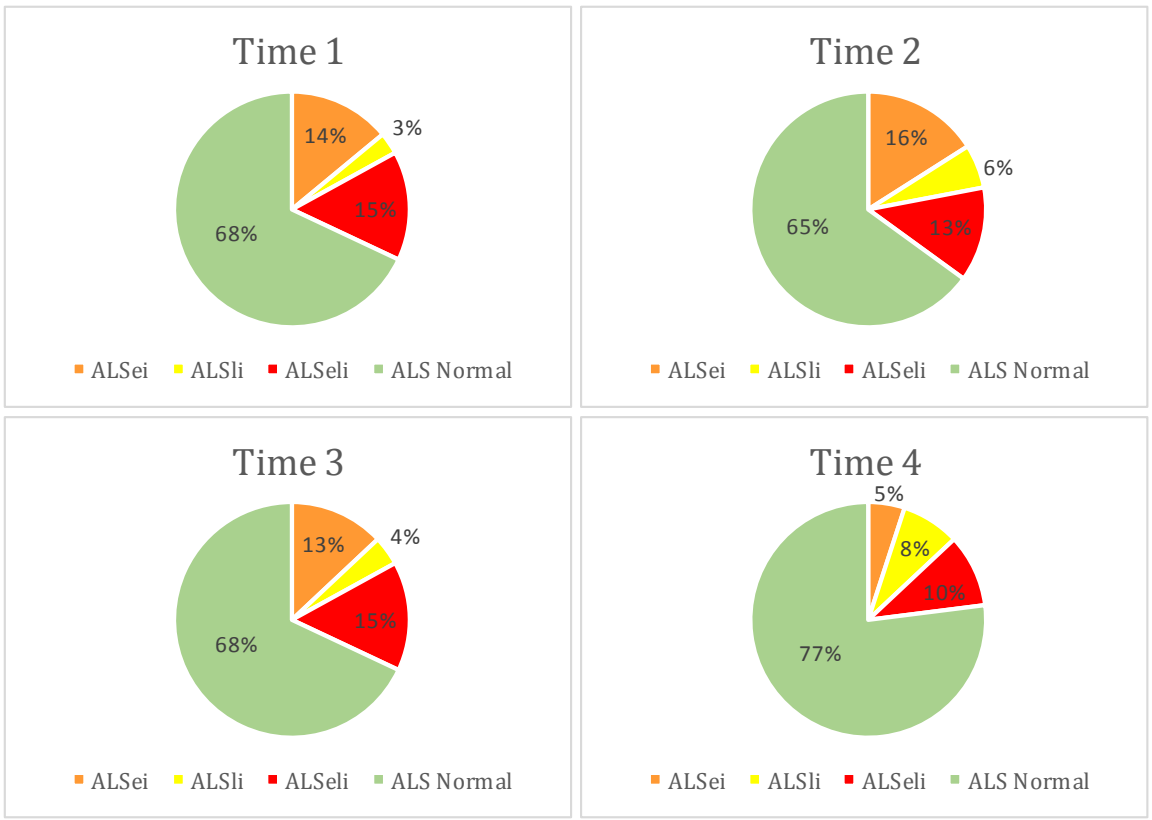

Figure 8.6. Cognitive classifications at each assessment time point

Focusing on the prevalence of the various ALS cognitive syndromes across time points, it can be observed in Figure 8.6 that the proportion of ALS patients that meet criteria for cognitive impairment is maintained at around 32-35% for the first three time points, although this decreases to 23% at Time 4. This is caused by a decrease in the proportion of patients that present with executive impairment, which decreases from around 15% to 5% on patients solely meeting diagnostic criteria for ALSei and form 15% to 10% in ALSeli patients. In contrast, the proportion of patients diagnosed with ALSli slightly increases at Time 4 compared to the other three time points.

This increase in the number of patients diagnosed with ALSli at time 4 is given however as the relative frequency of occurrence in our ALS sample is considered. If we look at the absolute frequency of occurrence of each cognitive syndrome at each time point (Figure 8.7), we can see that the number of ALSli patients actually remains stable across time points, whereas the number of patients meeting criteria for ALSei and ALSeli progressively decreases over time.

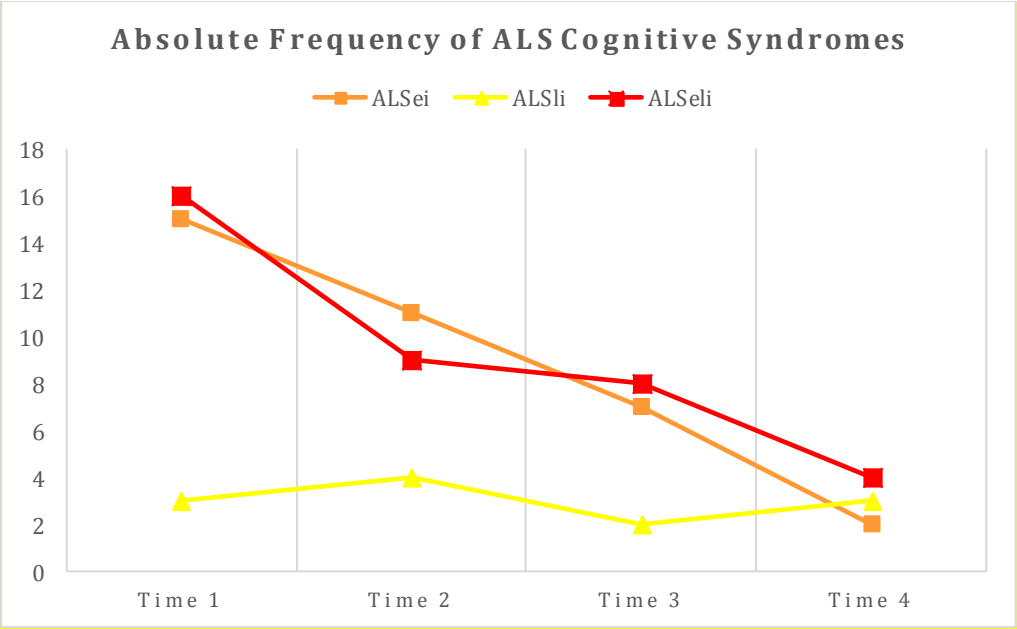

Figure 8.7. Absolute frequencies of ALS cognitive syndromes at each time point

Tendencies for withdrawals and new diagnoses across time points are depicted in Figure 8.8.

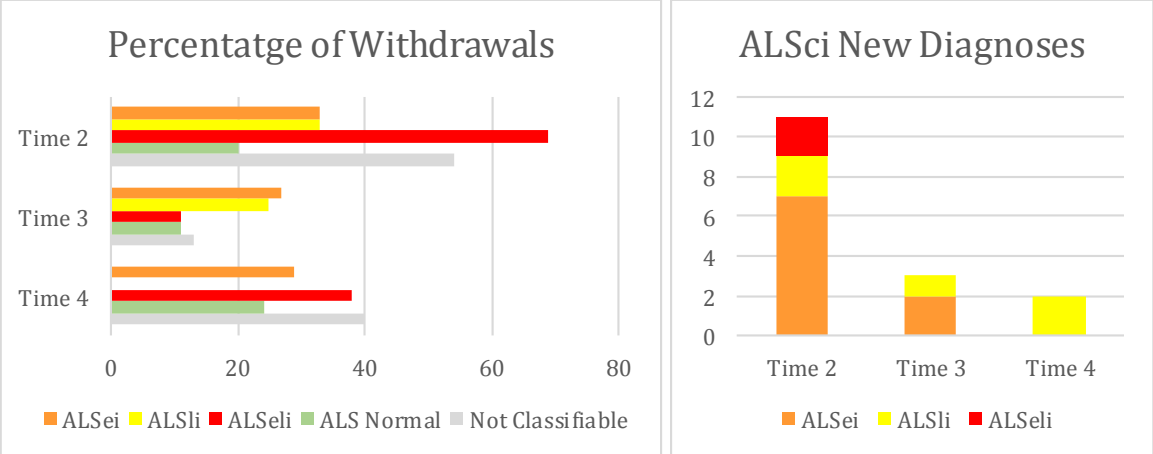

Figure 8.8. Percentage of withdrawals and number of new diagnoses at each follow-up time point

Results indicate that patients meeting criteria for ALSei and ALSeli as well as patients that could not be classified are those who withdrew more frequently, although these patterns varied across time points. Accordingly, ALSeli and non-classifiable ALS patients discontinued more frequently at Time 2, ALSei at Time 3, and the three groups were those who most

frequently discontinued at Time 4. Moreover, the number of new diagnoses of ALSei and ALSeli progressively declined across time points. Thus, although there are a few new ALSei diagnoses at Time 2, these decrease at Time 3 and none are present at Time 4. The same pattern is observed for ALSeli diagnoses, with only two new ones observed at Time 2 and none at Time 3 and Time 4. Regarding ALSli, around 25% and 35% discontinued at Time 2 and Time 3 respectively, but none discontinued at Time 4. Moreover, the number of new ALSli diagnoses at each time point remains stable (between 1 and 2) across time points. This explains the increased percentage of ALSli at Time 4 compared to previous time points. Finally, ALS patients not meeting criteria for cognitive impairment discontinued participation least frequently.

Overall, these results indicate that patients meeting criteria for executive impairment are more likely to withdraw and that the rates of patients that develop executive impairment during the study timeline also progressively decrease, possibly because they are not captured. Contrarily, ALSli patients withdrew less frequently and the rates of new diagnoses across time points are maintained relatively stable, although the frequency of occurrence of language impairment in isolation is very small. The aforementioned reduction in the number of ALS patients meeting criteria for executive impairment across time points causes the overall prevalence of cognitive syndromes in ALS to decrease at time 4, and therefore the prevalence of ALS patients not meeting criteria for cognitive impairment increases (77%). However, it is believed that this estimation does not represent an accurate estimate of the actual prevalence of unimpaired ALS patients a year post-initial assessment, but it is rather a consequence of a higher number of cognitively impaired patients discontinuing research.

This raises the question whether ALS patients meeting criteria for executive impairment discontinue research more frequently because they experience a faster progression of the motor symptoms that precludes further participation and/or is accompanied by a more rapid death, or if it is the executive impairment per se that causes them to withdraw. To further investigate this matter, the reasons for discontinuation for each ALS cognitive status were recorded and are depicted in Table 8.16.

Table 8.16. Frequency and reasons for longitudinal patient discontinuation for each ALS cognitive status.

Reason for Discontinuation	**ALS Normal** n(%)	**ALSei** n(%)	**ALSli** n(%)	**ALSeli** n(%)	**Unclassifiable** n(%)
Decline of further involvement	16 (57)	7 (70)	1 (50)	8 (53)	5 (31)
Non- Suitability	7 (25)	2 (20)	1 (50)	3 (20)	3 (19)
RIP	5 (18)	1 (10)	0	4 (27)	8 (50)

In the majority of cases, ALSci patients as well as ALS patients not meeting criteria for cognitive impairment voluntarily declined further participation. For ALS Normal, ALSei and ALSli, the second most common reason for discontinuation was non-suitability (mostly due to motor impairment), and the least number of those patients passed away during the course of the study. In ALSeli patients the opposite pattern was observed, with a higher number of patients passing away during the study than having to discontinue because of non-suitability. Finally, most ALS patients that could not be classified due to missing data, and therefore that presented with more severe motor symptoms, passed away during the course of the disease. These results could indicate that ALS patients presenting with more severe forms of cognitive impairment (i.e. ALSeli) may progress and die more rapidly than patients with less severe forms of cognitive impairment, although this assumption is only hypothetical. The relationship between ALS cognitive syndromes and survival is further explored in chapter 9, where the clinical and genetic characterisation of ALS frontotemporal syndromes is addressed.

Finally, individual reliable change was explored for those patients that remained cognitively unimpaired at follow-up. This aimed to explore if cognitive unimpaired ALS patients, even if not progressing to meet criteria for impairment, significantly declined from baseline assessment. Results are shown in Table 8.17.

Table 8.17. Percentage of cognitively unimpaired ALS patients at follow-up that presented with significant deterioration on cognitive performance, according to the complex SRB approach and considering a cut-off for reliable change at -1.5 standard deviations.

Neuropsychological Measures	ALS Normal		
	Time 2 n = 45	**Time 3** n = 37	**Time 4** n = 30
Language	n(%)	n(%)	n(%)
PALPA Auditory Lexical Decision	2 (5)	4 (11)	0
PALPA Visual Lexical Decision	2 (5)	3 (8)	1 (3)
PALPA Word Spelling	1 (3)	1 (3)	2 (9)
PALPA Word Reading	0	0	1 (4)
Boston Naming Test	0	1 (3)	1 (3)
Semantic Composite Score	5 (11)	1 (3)	2 (7)
PALPA Auditory Sentence – Picture Matching	2 (5)	0	2 (7)
PALPA Written Sentence – Picture Matching	5 (11)	0	0
Executive Function	n(%)	n(%)	n(%)
FAS Test	0	0	0
Restricted Phonemic Fluency (letter C)	0	3 (8)	0
Semantic Fluency (Animals)	0	1 (3)	1 (3)
Backward Digit Span	2 (5)	1 (3)	0
Sorting Test – Free Sorting Correct Sorts	1 (2)	1 (3)	1 (3)
Sorting Test – Sort Recognition Description	1 (2)	4 (11)	1 (3)
CWIT – Inhibition TIP	4 (10)	1 (3)	1 (4)
CWIT– Inhibition/Switching TIP	0	1 (3)	2 (7)
Reading the Mind in the Eyes	1 (2)	2 (5)	2 (7)
Conflicting Emotional Prosody	2 (6)	0	0

Note. Each percentage was calculated considering the total number of patients that had completed that specific task, not the total number of subjects included in that group, bearing in mind that missing data was present, specifically in those tasks with higher motor requirements.

Concordant with what was already described in Table 8.14, results in Table 8.17 show that only a small proportion (less than 10% in most cases) of non-impaired ALS patients present with significant cognitive decline. These results, in conjunction with those reported in Figure 8.8, which showed that very few unimpaired ALS patients at baseline progressed to developed cognitive impairment (i.e. eleven at time 2, three at time 3, and two a time 4), indicate that a high proportion of ALS patients do not develop cognitive impairment, at least up to the first two years of the disease.

8.3.3.2. Prevalence of ALSbi

The behavioural status at each follow-up time point was investigated considering revised classification criteria presented in Table 7.26. Behavioural data was available for 68% of the ALS sample at Time 2, 53% at Time 3, and 63% at Time 4.

The frequency of ALS patients meeting criteria for ALSbi at each time point, including Time 1, is presented in Figure 8.9.

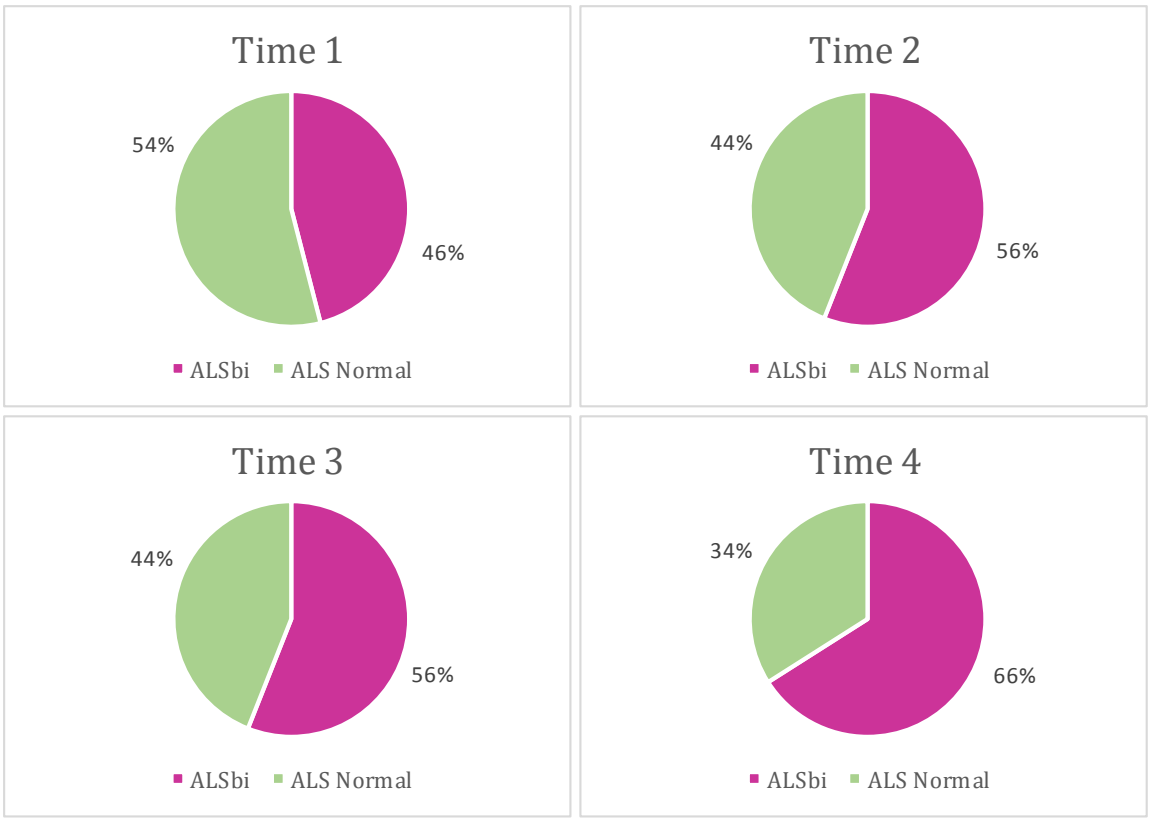

Figure 8.9. Frequency of behavioural impairment across time points

Contrary to what was observed for cognition, behavioural change becomes more prevalent in ALS as the disease progresses, with the percentage of patients meeting criteria for behavioural impairment increasing from 46% to 66% from time 1 to time 4.

The frequency of each behavioural feature that support the diagnosis of behavioural impairment according to bvFTD diagnostic criteria (Rascovsky et al., 2011) considered in revised ALS-FTSD criteria (Strong et al., 2017) was also scrutinised. These include apathy, behavioural disinhibition, loss of sympathy or empathy, perseverative, stereotyped or compulsive/ritualistic behaviour, and hyperorality or other dietary changes. Results are presented in Figure 8.10.

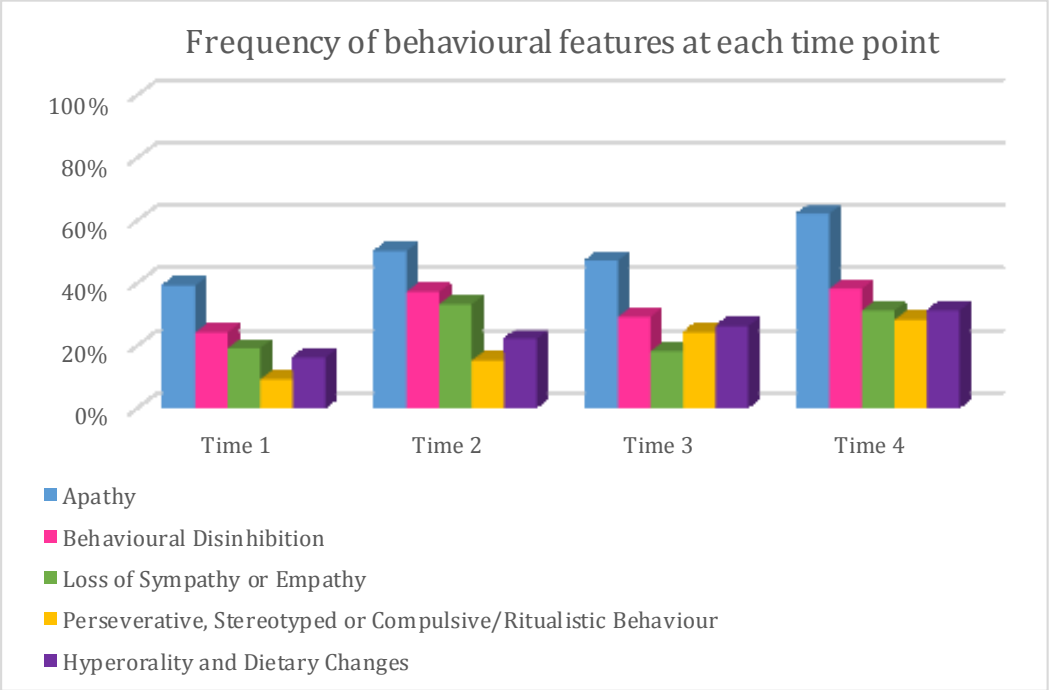

Figure 8.10. Frequency of behavioural features present at each time point

As can be observed in Figure 8.10, the most frequent behavioural change observed across time points is apathy, with an increasing prevalence over time. Thus, 39% of ALS patients presented with apathy at time 1, and this increased to 62% at time 4. The second most prominent behavioural change reported is behavioural disinhibition, which also increases in occurrence from time 1 to time 4 (from 24% to 38%). The frequency of carers reporting loss of sympathy or empathy varied across time points, but this also increased when comparing time 1 to time 4 (from 19% to 31%). The last two behavioural features (i.e. hyperorality and dietary changes, and perseverative or compulsive behaviours) are the least frequent behaviours observed, respectively. In both cases, however, its prevalence also increased over time (hyperorality and dietary changes: from 9% to 28%, time 1 to time 4; and perseverative or compulsive behaviours: from 16% to 31%, time 1 to time 4).

Overall, these results demonstrate that the increased prevalence of behavioural change with disease progression is general to all behavioural features, although some, like apathy, are characterised by a more marked increased.

8.3.3.3. Prevalence of ALScbi

Cognitive and behavioural classifications were combined to obtain the prevalence of ALS patients meeting criteria for both cognitive and behavioural impairment longitudinally. Complete data to allow for cognitive and behavioural classifications were available for 62% of the ALS sample at Time 2, 46% at Time 3, and 52% at time 4. The frequency of ALS patients meeting criteria for ALSci, ALSbi and ALScbi is represented in Figure 8.11. The percentage of patients that could not be classified because of missing data is also incorporated, given that this is quite significant.

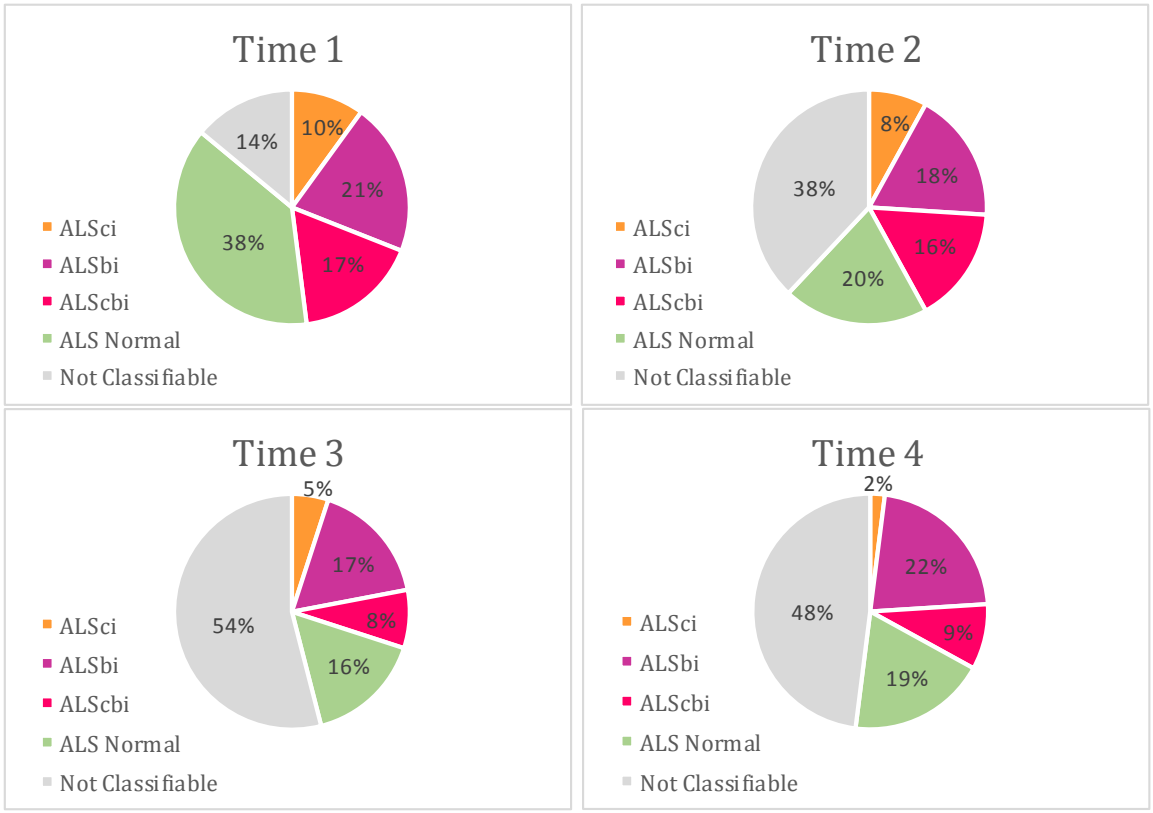

Figure 8.11. Prevalence of frontotemporal syndromes at each time point

Results in Figure 8.11 show that the prevalence of ALS patients meeting criteria for a frontotemporal syndrome progressively declines over time. Specifically, the prevalence of ALSci tends to decrease with time, which is in accordance to what has been described in section 8.3.3.1, whereas the prevalence of ALSbi remains stable. Regarding ALScbi, its prevalence also tends to decrease across time points, most likely due to the aforementioned higher drop out of patients meeting criteria for cognitive impairment. The prevalence of patients not meeting criteria for frontotemporal impairment also decreases over time. These results, however, must be interpreted with caution as the number of patients that could not be classified because of missing data is very high, and therefore the final estimates are based on a limited number of participants. On a final note, no ALS patients developed FTD on longitudinal follow-up.

8.4. Summary of Findings

This results chapter has addressed the fourth aim of this work, which intended to assess the evolution of frontotemporal decline in ALS and to establish the prevalence of frontotemporal syndromes as disease progresses, considering revised diagnostic criteria (Strong et al., 2017). The main findings of this chapter are summarized below.

Longitudinal Study Design: Attrition and Capture Rates

Longitudinal capture rates of this study were maintained at approximately 70, 60 and 40 per cent for patients, and at 80, 70 and 60 per cent for healthy controls at each follow-up time point, respectively. Whereas healthy control attrition grew at a stable tendency, patient attrition experienced a marked increase at time 4 given the progressive and fatal nature of ALS.

Among reasons for discontinuation, development of disability that precluded further participation and death were more common within the patient sample compared to controls, which is concordant with the progressive and fatal nature of the disease. Decline of further participation was the most common reason for discontinuation for both groups across time points.

ALSci patients were the ones who discontinued most frequently, whereas the proportion of patients that met criteria for ALSbi and ALScbi at baseline remained relatively stable across time points. ALS patients not meeting diagnostic criteria for cognitive and/or behavioural impairment were the ones who discontinued least frequently and therefore they have the highest representation at time 4.

Total years of education and lower ALSFRS-R scores at baseline were significant predictors of discontinuation at first follow-up, lower ALSFRS-R scores at baseline also significantly predicted discontinuation at second follow-up, and these as well as bulbar onset were significant predictors of discontinuation at last follow-up.

ALS patients and healthy controls were equivalent in terms of demographic characteristics at each follow-up time point, including age, gender distribution, handedness and years of formal education. They were also equivalent in terms of premorbid IQ and current intellectual ability. However, ALS patients had significantly lower $Sp0_2$ levels and higher $PaC0_2$ levels compared to healthy controls at all follow-up time points. Moreover, although retest intervals between assessment 1 and 2 and between assessment 3 and 4 were equivalent between ALS patients and healthy controls, participant availability caused for the time elapsed between assessment 2 and assessment 3 to be significantly longer for healthy controls than for patients.

The Evolution of Frontotemporal Decline in ALS

The evolution of frontotemporal decline in our ALS sample was investigated using three different approaches: (1) by investigating between-group differences across time points using generalised linear mixed models implemented as multilevel modes, (2) by examining significant change in individual scores using SRB and RCI methods, and (3) by determining the prevalence of frontotemporal syndromes at each follow-up time point.

Generalised Linear Mixed Models

$Sp0_2$ and $PaC0_2$ levels as well as the length of the retest intervals were included as predictors in the generalised linear mixed models to account for the effect that their variation across time may have on neuropsychological performance.

Regarding between-subjects effects, significant differences were observed between ALS patients and healthy controls on orthographic lexical processing, word naming, syntactic/grammatical processing, phonemic verbal fluency and problem-solving abilities, with poorer performance on the former case, concordant with findings described in chapter 7.

Concerning within-subjects effects, significant improvements on performance over time were observed consistently in all follow-up time points for phonological lexical processing and cognitive flexibility measures. The former is concordant with findings described in chapter 6.

In relation to interaction effects, although a significant improvement in performance of the ALS sample compared to a more stable performance of the healthy control sample was observed for cognitive measures of word reading, word naming and cognitive flexibility, in any case a decrease in cognitive performance of the ALS sample was observed. On the contrary, a significant increase on behavioural change was observed in the ALS sample.

Further investigations into the pattern of longitudinal word naming deficits encountered in ALS showed that these are of retrieval nature for both objects and actions. No impairments on semantic processing was developed by our ALS sample at follow-up assessments.

Overall, these results indicate that the pattern of neuropsychological change characteristic of ALS at diagnosis is maintained relatively stable over a year follow-up period, whereas behavioural change significantly increases over time.

RCI and SRB Methods

Focusing on results from RCI methods, results indicated that when accommodating for learning effects that occur in the normative sample, those cognitive measures that are more susceptible to effects of prior exposure have lower thresholds for significant decline. Therefore, those ALS patients who present with stable performance are classified as having deteriorated.

Accordingly, the RCI method that corrects for learning effects classified a higher percentage of ALS patients as having deteriorated compared to the RCI method that solely controls for measurement error. Contrarily, cognitive measures that are not prone to learning effects have thresholds for significant decline that are more stable across the two RCI methods and the percentage of patients classified as having deteriorated are less variable between them.

Regarding SRB methods, the thresholds for significant decline and percentage of patients classified as having deteriorated remained relatively stable among the two methods, except in cases where the moderating factors included in the latter model had a more significant effect.

When comparing RCI to SRB methods, the former tended to have lower thresholds for significant decline and therefore higher percentages of ALS patients classified as having deteriorated. Considering that RCI methods are subject to sampling error and that the size of our normative sample considerably decreased across time points, SRB methods were considered a more accurate estimate of individual reliable change in our ALS sample, specifically the one correcting for additional moderating factors (i.e. complex SRB method).

Results from complex SRB methods showed that the percentage of ALS patients that presented with significant decline in neuropsychological performance was below 10% in most cases, and for those measures where the percentage exceeded 10% at any time point, this decline was not consistent over time. Moreover, no substantial differences were observed in the percentage of patients classified as having deteriorated when comparing the two considered cut-offs for significant decline (i.e. -1.645 sd vs -1.5 sd from baseline). The percentages of ALS patients meeting criteria for cognitive impairment at baseline that further declined significantly ranged mostly from 10% to 25%, whereas the proportions of cognitively unimpaired ALS patients at baseline that significantly declined were below 10% in most cases.

Overall, these results indicate that although cognitively impaired ALS patients at baseline tended to deteriorate more often than cognitively unimpaired ALS patients, most ALS patients presented with relatively stable cognitive performance over time.

The Prevalence of Frontotemporal Syndromes in ALS

The proportion of ALS patients that met criteria for ALSci longitudinally was around 32 -35% for the first two follow-up time points, but a decrease to 23% was observed at Time 4. This decrease at Time 4 was caused by a drop in the proportion of patients meeting criteria for executive impairment (including ALSei and ALSeli), who were shown to be more likely to discontinue participation. The number of ALS patients diagnosed with a new onset executive impairment at follow-up progressively declined across time points, most likely due to the fact that these cases were not captured. For both ALSei and ALSeli cases, the main reason for discontinuation was a decline of further participation. However, the second reason for

discontinuation for ALSei patients was non-suitability, whereas for ALSeli patients this was death, which could indicate that ALS patients that present with more severe forms of cognitive impairment present with a more rapid form of the disease.

The number of patients meeting criteria for ALSli remained relatively stable across time points, with about 20% of patients being diagnosed with language impairment across time points. However, the frequency of language impairment occurring in isolation (without the presence of executive impairment) was very small.

ALS patients not meeting criteria for cognitive impairment discontinued less frequently, which explains the increased representation of this group at Time 4. Only a very small proportion (less than 10% in most cases) of cognitively unimpaired ALS patients presented with significant cognitive decline at follow-up, and the number of ALS patients that developed a new onset cognitive syndrome at follow-up was very small (i.e. eleven at time 2, three at time 3, and two a time 4).

Contrastingly, behavioural change did become more prevalent as disease progressed given the percentage of patients meeting criteria for behavioural impairment at follow-up, which increased from 46% to 66% from time 1 to time 4. Apathy was the most frequently observed behavioural change across time points, followed by behavioural disinhibition and loss of sympathy of empathy, in all cases with an increasing prevalence over time. Hyperorality and dietary changes as well as perseverative or compulsive behaviours were less frequently reported although its prevalence also increased over time. No ALS patients developed comorbid FTD on longitudinal follow-up.

CHAPTER 9 Outline.

Results Part IV:

Clinical and Genetic Characterisation of ALS Frontotemporal Syndromes

CHAPTER 9.

Results Part IV:

Clinical and Genetic Characterisation of ALS Frontotemporal Syndromes

9.1. Introduction

This final results chapter focuses on the fifth and sixth aim described in chapter 4. Aim five intends to investigate how incident and prevalent ALS frontotemporal syndromes relate to clinical and demographic features. Moreover, prognostic implications of frontotemporal dysfunction in ALS are also investigated, specifically its relationship to motor disease progression and survival. Finally, in relation to aim six, the C9orf72 genotype is characterised from a neuropsychological perspective, and the influence that a positive family history of ALS and/or FTD in the absence of an identified genetic mutation have on cognition and behaviour in our ALS sample is also explored.

9.2. Clinical Characterisation of ALS Frontotemporal Syndromes

This section is concerned with the relationship between a diagnosis of an ALS frontotemporal syndrome and demographic and clinical characteristics, which is the fifth aim of this work. To start with, demographic and clinical characteristics of incident frontotemporal syndromes categorised in chapter 7 are considered, and longitudinal data are examined next.

9.2.1. Characterisation of Incident ALS Frontotemporal Syndromes

Clinical and demographic characteristics were compared among the different incident frontotemporal syndromes identified in chapter 7. Demographic characteristics such as age and gender were explored, as well as disease characteristics, including age and site of onset, diagnostic delay, family history and disease severity, among others. Moreover, mood was also examined across ALS frontotemporal syndromes, as well as caregiver burden.

According to our hypotheses outlined in chapter 4, no relationship with age was expected, although female gender and bulbar-onset ALS were predicted to be related to a higher risk of developing cognitive and behavioural change. Disease severity at early stages was also predicted to be independent from cognitive and behavioural change, concordant with selective patterns of brain disease at onset. Results are represented in Table 9.1.

Table 9.1. Demographic and clinical characteristics of the patient sample segregated by incident frontotemporal syndromes.

		ALS n = 44	**ALSci** n = 12	**ALSbi** n = 24	**ALScbi** n = 20	**ALS-FTD** n = 18	**F(df)/ X^2(df)**	***p***
Age *M±SD* years		59.5 ± 12.8	64.6 ± 8.86	62.6 ± 12.0	65.3 ± 7.72	67.4 ± 7.67	2.38(4,45.1)[b,c]	.07
Gender n(%)	Females	14 (32)	7 (58)	6 (25)	8 (40)	8 (44)	4.85(4)[d]	.30
	Males	30 (68)	5 (42)	18 (75)	12 (60)	10 (56)		
Age at onset *M±SD* years		58.0 ± 13.0	62.9 ± 8.71	60.4 ± 11.6	63.5 ± 7.50	65.5 ± 7.36	2.26(4,45.3)[b,c]	.08
Site of onset n(%)	Spinal	29 (66)	7 (58)	17 (71)	15 (75)	12 (67)	5.06(8)[d]	.75
	Bulbar	11 (25)	4 (33)	7 (29)	4 (20)	6 (33)		
	Thoracic / Respiratory	4 (9)	1 (9)	0	1 (5)	0		
Diagnostic Delay *M±SD* (*Mdn*) months		13.7 ± 12.6 (9.5)	15.1 ± 10.4 (13.5)	22.8 ± 24.7 (14.5)	16.9 ± 11.1 (11.5)	21.6 ± 17.1 (14)	6.10(4)[e]	.19
Familial ALS[a] n(%)		4 (9)	3 (25)	6 (25)	10 (50)	6 (33)	13.4(4)[d]	.009
Family History of other Neurological Conditions n(%)		28 (64)	7 (58)	13 (54)	8 (40)	7 (39)	4.94(4)[d]	.29
Family History of Psychiatric Conditions n(%)		22 (50)	4 (33)	10 (42)	8 (40)	8 (44)	1.38(4)[d]	.85
Use of NIV n(%)		9 (20)	5 (42)	4 (17)	4 (20)	1 (6)	6.14(4)[d]	.19
Enteral feeding tube in place n(%)		0	3 (25)	0	3 (15)	0	18.5(4)[d]	.001
ALSFRS-R total score *M±SD* (*Mdn*) score		38.9 ± 6.56 (39.6)	32.9 ± 7.29 (33)	35.4 ± 5.84 (36.5)	35.4 ± 6.16 (34.5)	*n = 12* 39.3 ± 3.23 (39.5)	13.5(4)[e]	.009
ALSFRS-R bulbar sub-score *M±SD* (*Mdn*) score		10.4 ± 2.04 (11)	8.25 ± 3.31 (9)	10.2 ± 2.08 (11)	9.30 ± 3.36 (10.5)	9.00 ± 2.59 (9.5)	7.85(4)[e]	.10
ALSFRS-R limb sub-score *M±SD* (*Mdn*) score		18.2 ± 4.16 (18)	16.1 ± 3.80 (16.5)	15.3 ± 3.73 (15)	15.9 ± 5.77 (15.5)	19.5 ± 3.50 (20)	11.4(4)[e]	.02
ALSFRS-R respiratory sub-score *M±SD* (*Mdn*) score		10.3 ± 3.15 (12)	8.75 ± 3.55 (10.5)	9.88 ± 3.49 (12)	10.4 ± 2.62 (12)	10.8 ± 2.04 (11.5)	4.55(4)[e]	.34
HADS-T		n = 35	n = 6	n = 18	n = 18	n = 9	3.30(4)[b,c]	.03
M±SD score		4.97 ± 2.97	7.67 ± 4.72	8.33 ± 5.86	9.83 ± 7.5	9.11 ± 6.53		
The Zarit Burden Interview		n = 27	n = 4	n = 11	n = 11	n = 7		
M±SD (*Mdn*) score		10.9 ± 8.94 (9)	11.0 ± 7.07 (11.5)	22.2 ± 14.3 (21)	17.8 ± 10.5 (14)	28.9 ± 18.2 (29)	12.1(4)[e]	.02
n(%) of burned out caregivers		3 (11)	0	5 (46)	4 (36)	5 (71)	13.9(4)[d]	.008

[a] Familial ALS is defined with the presence of at least one biological relative within three generations diagnosed with ALS and/or FTD.

[b] One-way ANOVA.

[c] Welch's F-ratio.

[d] Pearson's Chi-square test for independence (X^2).

[e] Kruskal-Wallis H Test.

As per results in Table 9.1, significant differences between ALS frontotemporal syndromes were observed for the presence of familial ALS, the presence of enteral feeding tube in place, disease severity, mood, and caregiver burden. No significant differences were observed for other clinical aspects explored nor for demographic characteristics (i.e. age and gender). These results are explored in more detail below.

Regarding age, no significant difference was observed among groups. This is concordant with our prediction that the presence of cognitive and behavioural change in ALS is not age related. Regarding gender, the proportion of ALSci patients is higher for females than males, a pattern that is opposite to that observed for other frontotemporal syndromes, although this does not represent a significant difference. Therefore, contrary to our predictions, gender was not related to the presence of frontotemporal syndromes in ALS, and neither was the type of disease onset. Other disease characteristics that were not related to the presence of frontotemporal syndromes in ALS were age at onset, diagnostic delay, use of NIV or severity of respiratory status.

The rates of familial ALS were significantly different among groups, and post hoc tests indicated that two of the groups were significantly different from the others. The rate of 9% observed for ALS patients not meeting criteria for the diagnosis of a frontotemporal syndrome was significantly lower than the rates observed for the other groups. Also, the rate of familial ALS for ALScbi patients, 50% of whom had a positive family history of ALS and/or FTD, was significantly higher compared to all other groups. The rates of family history of other neurological or psychiatric conditions were not significantly different among groups.

Regarding the significant finding relating to the presence of an enteral feeding tube inserted, post hoc tests indicated that this was significant for ALSci and ALScbi patients in comparison to all other groups. Although no significant difference was observed among groups on the ALSFRS-R bulbar score, this finding indicates that a higher proportion of patients with bulbar symptoms that progressed rapidly (thus requiring enteral feeding tube insertion during first year of diagnosis) present with cognitive impairment. Exploring the profile of cognitive change in incident patients with enteral feeding tube in place in more detail, a significantly higher proportion of executive impairment was observed (i.e. ALSei) compared to patients with no enteral feeding tube in place, $X^2(1) = 10.3$, $p = .0008$, $\varphi = .31$, but language was not more frequently affected, $X^2(1) = 2.26$, $p = .08$.

A significant difference was observed among ALS frontotemporal syndromes on mood. Post hoc tests indicated that ALScbi patients had significantly higher scores compared to ALS patients not meeting criteria for cognitive nor behavioural impairment.

Regarding caregiver burden, 17 (28%) out of the 60 ALS carers for whom this information was available showed evidence of burden associated with caring for a relative diagnosed with ALS. A significant difference was found between frontotemporal syndromes on caregiver burden, for both Zarit total score and percentage of caregivers experiencing burn-out. Although this did not survive correction for multiple comparison in the former case, post hoc tests in the latter case indicated that a significantly higher proportion of carers of ALS-FTD patients presented with caregiver burden in comparison to all other groups.

In terms of motor disease severity, the total ALSFRS-R score was significantly different among frontotemporal syndromes, driven by a significant difference on the spinal ALSFRS-R subscore which did not survive multiple comparisons adjustment on post hoc tests. To further explore the relationship between ALS frontotemporal syndromes and motor disease severity, the rate of motor progression from symptom onset to baseline assessment was calculated and compared between frontotemporal diagnoses. A previously published method was used to calculate the rate of motor progression at baseline (Elamin et al., 2013; Kimura et al., 2006), estimated by obtaining the rate of decline from presumed normal function prior to the development of ALS-related motor symptoms (i.e. maximum ALSFRS-R score) to level of function at the time of assessment. Accordingly, rate of decline for limb, bulbar and respiratory functions as well as the overall decline rate at baseline were calculated as follows:

$$\text{Overall rate of decline at baseline} = \frac{48 - \text{ALSFRS}_{\text{total score}} \text{ at assessement}}{\text{Disease duration at baseline assessment}}$$

$$\text{Spinal rate of decline at baseline} = \frac{24 - \text{ALSFRS}_{\text{limb subscore}} \text{ at assessement}}{\text{Disease duration at baseline assessment}}$$

$$\text{Bulbar rate of decline at baseline} = \frac{12 - \text{ALSFRS}_{\text{bulbar subscore}} \text{ at assessement}}{\text{Disease duration at baseline assessment}}$$

$$\text{Respiratory rate of decline at baseline} = \frac{12 - \text{ALSFRS}_{\text{respiratory subscore}} \text{ at assessement}}{\text{Disease duration at baseline assessment}}$$

, where disease duration is expressed in months and 48, 24, 12 and 12 are the maximum ALSFRS-R scores for each category above respectively, and therefore represents normal function for that motor category.

Between-group comparisons on rate of motor progression from symptom onset to baseline assessment are displayed in Table 9.2. No significant differences were observed among ALS frontotemporal syndromes on the rate of motor progression for any of the ALSFRS-R scores considered. These findings are concordant with our hypothesis that motor disease severity is not related to cognitive and behavioural dysfunction in ALS in early stages of the disease.

Table 9.2. Rate of motor progression from symptom onset to assessment of the patient sample segregated by frontotemporal syndromes.

	ALS n = 44	**ALSci** n = 12	**ALSbi** n = 24	**ALScbi** n = 20	**ALS-FTD** n = 12	**F(df)**[a]	***p***
Overall Decline Rate *M*±*SD* (*Mdn*) score	0.67 ± 0.53 (0.56)	1.03 ± 0.90 (0.68)	0.75 ± 0.61 (0.56)	0.73 ± 0.47 (0.52)	0.61 ± 0.42 (0.44)	3.33(4)	.50
Spinal Decline Rate *M*±*SD* (*Mdn*) score	0.43 ± 0.37 (0.34)	0.60 ± 0.68 (0.34)	0.50 ± 0.42 (0.42)	0.42 ± 0.37 (0.31)	0.29 ± 0.24 (0.25)	2.82(4)	.59
Bulbar Decline Rate *M*±*SD* (*Mdn*) score	0.15 ± 0.24 (0.04)	0.26 ± 0.28 (0.18)	0.12 ± 0.19 (0.02)	0.20 ± 0.32 (0.06)	0.24 ± 0.24 (0.16)	6.82(4)	.15
Respiratory Decline Rate *M*±*SD* (*Mdn*) score	0.09 ± 0.17 (0)	0.17 ± 0.19 (0.12)	0.13 ± 0.21 (0)	0.09 ± 0.15 (0)	0.08 ± 0.14 (0.02)	4.61(4)	.33

[a] Kruskal-Wallis H Test.

9.2.2. Characterisation of Prevalent ALS Frontotemporal Syndromes

This section aims to investigate longitudinal predictors of frontotemporal impairment. Accordingly, possible predictors of the presence of a frontotemporal syndrome at each follow-up time point were examined using binary logistic regression. Potential predictors included gender, age at onset, site of onset, family history of ALS and/or FTD, ALSFRS-R score at each specific time point, and use of NIV and whether enteral feeding tube was in place at the time of assessment. The assumptions of independence of errors, absence of multicollinearity between predictors and linearity of the logit were met in all cases. No significant predictors of frontotemporal impairment were encountered at any of the follow-up time points, although the fit of the model improved across time points, *Time 2*, $X^2(7) = 11.0$, $p = .14$, $R_N^2 = .28$; *Time 3*, $X^2(8) = 12.3$, $p = .14$, $R_N^2 = .48$; *Time 4*, $X^2(7) = 15.6$, $p = .03$, $R_N^2 = .65$. Accordingly, the abovementioned predictors explained 28% of the variance at time 2, 48% at time 3, and 65% at time 4.

9.3. Frontotemporal Syndromes and Prognostic Implications in ALS

This section addresses the second part of aim 5, which intends to evaluate the relationship between frontotemporal impairment and motor decline in ALS, and the influence that the former has on survival.

First, multiple linear regression was used to investigate demographic and clinical predictors of motor disease severity at each time point. Possible predictors included age at symptom onset, gender, site of onset and diagnostic delay. Results are presented in Table 9.3. Multiple linear regression assumptions were checked and met in all cases.

Table 9.3. Regression models to predict the effect of clinical and demographic characteristics on longitudinal ALSFRS-R scores.

		β	SEE	t-test	*p*	R^2 [a]	F(df)	*p*
ALSFRS-R total score – Time 1	Age at onset	-0.08	0.06	-1.29	.20	.03	1.10 (4,124)	.36
	Gender	-0.43	1.30	-0.33	.74			
	Site of onset	-0.89	1.08	-0.82	.41			
	Diagnostic delay	-0.05	0.04	-1.19	.24			
ALSFRS-R total score – Time 2	Age at onset	-0.04	0.09	-0.45	.65	.04	0.82 (4,74)	.52
	Gender	-2.54	2.00	-1.27	.21			
	Site of onset	-1.52	1.75	-0.87	.39			
	Diagnostic delay	-0.01	0.05	-0.26	.80			
ALSFRS-R total score – Time 3	Age at onset	-0.06	0.10	-0.60	.55	.01	0.14 (4,59)	.96
	Gender	-0.75	2.25	-0.33	.74			
	Site of onset	0.51	2.19	0.23	.82			
	Diagnostic delay	-0.01	0.08	-0.05	.96			
ALSFRS-R total score – Time 4	Age at onset	-0.03	0.12	-0.30	.77	.01	0.06 (4,41)	.99
	Gender	-0.78	2.70	-0.29	.78			
	Site of onset	0.20	2.78	0.07	.94			
	Diagnostic delay	-0.01	0.09	-0.10	.92			

[a] R^2 is used to represent the proportion of the variance from the outcome variable explained by executive function in each model. R^2 is chosen here over Adjusted R^2 given that all models use the same predictors and therefore there is no need for adjustment.

Results from Table 9.3 indicate that none of the demographic and clinical characteristics considered are significant predictors of motor dysfunction at diagnosis or during the first year post-diagnosis. We next explore the relationship between frontotemporal impairment and motor decline and survival.

9.3.1. Frontotemporal Dysfunction and Progressive Motor Decline in ALS

This section focuses on investigating the effect that a diagnosis of a frontotemporal syndrome has on motor decline. To do so, the progressive rate of motor decline was obtained by calculating the slope in ALSFRS-R scores between baseline and follow-up assessments using a previously published formula (Elamin et al., 2013):

$$\text{Overall rate of decline} = \frac{\text{ALSFRS}_{\text{total}} \text{ at baseline} - \text{ ALSFRS}_{\text{total}} \text{ at follow} - \text{up}}{\text{Time between visits}}$$

, where time between visits is in months. Accordingly, an estimate of the rate of decline per month on ALSFRS-R scores is obtained. This was obtained for ALSFRS-R total scores (i.e. overall rate of decline) and for each ALSFRS-R sub-score (i.e. spinal, bulbar and respiratory).

Simple linear regression was used first to investigate if the presence of frontotemporal dysfunction predicts a more rapid motor decline. The presence of a frontotemporal syndrome,

irrespective of this involving cognitive or behavioural dysfunction, or both, was considered as the predictor variable, and the overall rate of decline at each follow-up time point was the outcome variable. Simple linear regression assumptions were checked and met in all cases. Results from regression analyses are presented in Table 9.4.

Table 9.4. Regression models to predict the effect that a diagnosis of a frontotemporal syndrome has on overall motor decline.

	β	SEE	t-test	*p*
Overall rate of decline – Time 1 to Time 2	-0.04	0.223	-0.17	.87
Overall rate of decline – Time 1 to Time 3	-0.31	0.470	-0.65	.52
Overall rate of decline – Time 1 to Time 4	-0.32	0.569	-0.56	.58

Results from Table 9.4 indicate that although the slopes are negative, thus indicating an increase in the rate of decline for ALS patients meeting criteria for a frontotemporal syndrome, this was not a significant predictor of overall motor decline at any of the time points.

A more detailed analysis of the overall rate of motor dysfunction for each specific frontotemporal diagnosis at each time point was performed. To do so, the overall rate of decline as well as the rate of decline for spinal, bulbar and respiratory scores were compared among the different frontotemporal syndromes at each time point. Results are presented in Table 9.5.

Table 9.5. Rate of overall, spinal, bulbar and respiratory motor decline in the ALS sample segregated by frontotemporal syndromes at each time point.

Decline from T1 to T2 (in months)	**ALS**	**ALSci**	**ALSbi**	**ALScbi**	**X^2(df)/ F(df)**	***p***
	n = 16	n = 6	n = 14	n = 13		
Overall Rate of Decline *M±SD* (*Mdn*) score	0.58 ± 0.68 (0.5)	0.74 ± 1.07 (0.38)	0.37 ± 0.74 (0.32)	0.63 ± 0.62 (0.5)	0.58(3)[a]	.90
Spinal Rate of Decline *M±SD* (*Mdn*) score	0.27 ± 0.38 (0.22)	0.25 ± 0.45 (0.12)	0.39 ± 0.51 (0.32)	0.50 ± 0.53 (0.50)	0.68(3,45)[b]	.57
Bulbar Rate of Decline *M±SD* (*Mdn*) score	0.24 ± 0.34 (0.10)	0.12 ± 0.13 (0.10)	0 ± 0.16 (0)	0.12 ± 0.21 (0)	5.48(3)[a]	.14
Respiratory Rate of Decline *M±SD* (*Mdn*) score	0.06 ± 0.34 (0)	0.38 ± 0.92 (0)	-0.02 ± 0.33 (0)	0.01 ± 0.15 (0)	0.64(3)[a]	.89
Decline from T1 to T3 (in months)	**ALS**	**ALSci**	**ALSbi**	**ALScbi**	**X^2(d)/ F(df)**	***p***
	n = 10	n = 3	n = 11	n = 5		
Overall Rate of Decline *M±SD* (*Mdn*) score	1.57 ± 1.36 (1.25)	2.23 ± 1 (2.20)	1.07 ± 1.22 (1)	1.10 ± 0.74 (1)	3.76(3)[a]	.29
Spinal Rate of Decline *M±SD* (*Mdn*) score	0.77 ± 0.52 (0.75)	0.83 ± 0.52 (1)	1.05 ± 0.71 (1.20)	0.75 ± 0.50 (1)	0.52(3,25)[b]	.68
Bulbar Rate of Decline *M±SD* (*Mdn*) score	0.42 ± 0.43 (0.5)	0.73 ± 0.64 (1)	0.14 ± 0.20 (0)	0.2 ± 0.33 (0.25)	4.83(3)[a]	.18
Respiratory Rate of Decline *M±SD* (*Mdn*) score	0.38 ± 0.86 (0)	0.67 ± 1.15 (0)	-0.12 ± 0.64 (0)	0.15 ± 0.22 (0)	2.69(3)[a]	.44

[a] Kruskal-Wallis H Test.

[b] One-way ANOVA.

Table 9.5 (continued). Rate of overall, spinal, bulbar and respiratory motor decline in the ALS sample segregated by frontotemporal syndromes at each time point.

Decline from T1 to T4 (in months)	**ALS**	**ALSci**	**ALSbi**	**ALScbi**	**X^2(df)/ F(df)**	***p***
	n = 9	n = 1	n = 10	n = 4		
Overall Rate of Decline *M*±*SD* (*Mdn*) score	2.12 ± 1.55 (1.75)	0.2 ± 0 (0.2)	1.34 ± 0.74 (1.35)	3.38 ± 0.66 (3.25)	8.69(3)[a]	.03
Spinal Rate of Decline *M*±*SD* (*Mdn*) score	1.03 ± 0.82 (1)	0.2 ± 0 (0.2)	1.22 ± 0.82 (1.25)	1.75 ± 0.61 (1.62)	4.67(3)[a]	.20
Bulbar Rate of Decline *M*±*SD* (*Mdn*) score	0.62 ± 0.54 (0.5)	0 ± 0 (0)	0.12 ± 0.26 (0)	1.19 ± 0.55 (1.25)	10.6(3)[a]	.01
Respiratory Rate of Decline *M*±*SD* (*Mdn*) score	0.46 ± 0.62 (0.25)	0 ± 0 (0)	0 ± 0.42 (0)	0.44 ± 0.31 (0.5)	6.52(3)[a]	.09

[a] Kruskal-Wallis H Test.

[b] One-way ANOVA.

Results in Table 9.5 indicate that no significant differences were present among groups on the rate of motor decline at time 2 and at time 3, but a significant difference was observed at time 4 on overall motor rate of decline and, more precisely, on bulbar rate of decline. Post hoc tests indicated that this significant difference existed between ALScbi and ALSbi patients, with the former showing a more rapid rate of decline. These results are consistent with our hypothesis that the presence of both cognitive and behavioural impairment represents a more aggressive type of syndrome, characterised by a more rapid decline of bulbar motor function. How frontotemporal dysfunction in ALS relates to survival is explored next.

9.3.2. Frontotemporal Dysfunction and Survival in ALS

This section explores survival in our population-based incident ALS sample and how this relates to frontotemporal dysfunction. Of the 135 incident ALS patients recruited for this study, 90 (67%) were deceased by the end of June 2019, fifty-five months after the recruitment period was commenced. Mean survival time (i.e. time from symptom onset to death) in months was as follows: *M* = 35.0, *SD* = 14.4, *Mdn* = 33.5.

Clinical and demographic factors related to shorter survival were explored using multiple linear regression. Potential predictors considered included age at onset, gender, site of onset, diagnostic delay, and the overall rate of motor decline at baseline assessment. Mean survival time (in months) was considered as the outcome variable. Multiple regression assumptions were checked and met in all cases. Results in Table 9.6 indicate that while age at onset, gender or site of onset were not significant predictors of survival, diagnostic delay and the rate of motor decline at baseline assessment were. Specifically, longer diagnostic delay was associated with longer survival, and a higher rate of decline at first assessment was related to shorter survival.

Table 9.6. Regression models to investigate potential significant predictors of shorter survival in ALS.

		β	SEE	t-test	*p*	R^2 [a]	F(df)	*p*
Mean Survival Time	Age at onset	-0.15	0.10	-1.53	.13	.64	28.7 (5,82)	<.0001
	Gender	0.74	1.89	0.39	.70			
	Site of onset	-2.26	1.43	-1.58	.12			
	Diagnostic Delay	0.69	0.11	6.48	<.0001			
	Rate of decline at baseline [a]	-7.09	1.53	-4.63	<.0001			

[a] This represents the overall rate of decline from presumed normal function prior to the development of ALS-related motor symptoms to level of function at the time of baseline assessment, calculated considering total ALSFRS-R score at first assessment.

The impact that a diagnosis of an incident frontotemporal syndrome has on survival in ALS was also explored. Thus, survival rates were also investigated considering frontotemporal diagnoses at baseline. Percentages of deceased patients and mean survival times categorised by incident frontotemporal syndromes are depicted in Table 9.7.

Table 9.7. Survival rates of the ALS incident population-based sample by the 30th of June 2019.

	ALS	ALSci	ALSbi	ALScbi	ALS-FTD	Unclassifiable
	n = 44	n = 12	n = 24	n = 20	n = 18	n = 17
Percentage of deceased n(%)	21 (48)	9 (75)	16 (67)	18 (90)	12 (67)	14 (82)
Mean survival time *M±SD* (*Mdn*) score	33.2 ± 9.58 (30)	32. 9 ± 10.8 (34)	34.4 ± 11.7 (34)	35.9 ± 13.1 (36)	43.5 ± 24.3 (41)	31.1 ± 14.9 (28)

The highest rates of death were observed for ALScbi patients, followed by patients who could not be classified and ALSci patients. The highest rate of survival in this study was for ALS patients not meeting criteria for a frontotemporal diagnosis, with 52% of them remaining alive by the time point of interest. However, looking at the mean survival time for each group, ALS patients not meeting criteria for frontotemporal impairment showed a shorter survival time compared to ALS patients with evidence of frontotemporal dysfunction. This indicates that, although showing the lowest rate of mortality, those ALS patients with no frontotemporal impairment who died more quickly, had a more rapid progression compared to ALS patients with cognitive and behavioural decline. Finally, unclassifiable patients showed the lowest mean survival, which is concordant with the fact that they presented with more advanced motor disease that prevented them to be able to fully engage in testing.

The Kaplan-Meier plot of survival probabilities was obtained to characterise survival curves among the different incident frontotemporal syndromes. Survival probabilities for each frontotemporal syndrome are detailed in Table 9.8, and the Kaplan-Meier plot is displayed in Figure 9.1. Log-rank test results (*p = .28*) indicate that no significant differences were observed in terms of survival curves among frontotemporal syndromes.

Table 9.8. Survival probabilities for each incident frontotemporal syndrome.

	Time[a]	n. Risk[b]	n. Event[c]	Survival[d]	SE[e]	95% CI[f]
ALS	18	21	1	0.95	0.047	[0.87,1.00]
	19	20	1	0.91	0.064	[0.79,1.00]
	20	19	1	0.86	0.076	[0.72,1.00]
	28	18	2	0.76	0.093	[0.60,0.97]
	29	16	4	0.57	0.108	[0.39,0.83]
	30	12	2	0.48	0.109	[0.30,0.75]
	32	20	1	0.43	0.108	[0.26,0.70]
	34	9	1	0.38	0.106	[0.22,0.66]
	35	8	1	0.33	0.103	[0.18,0.61]
	38	7	3	0.19	0.086	[0.08,0.46]
	42	4	1	0.14	0.076	[0.05,0.41]
	46	3	1	0.10	0.064	[0.03,0.36]
	49	2	1	0.05	0.047	[0.01,0.32]
	56	1	1	0.00	n/a	n/a
ALSci	15	9	1	0.89	0.105	[0.71,1.00]
	17	8	1	0.78	0.139	[0.55,1.00]
	31	7	1	0.67	0.157	[0.42,1.00]
	32	6	1	0.56	0.166	[0.31,0.99]
	34	5	1	0.44	0.166	[0.21,0.92]
	38	4	1	0.33	0.157	[0.13,0.84]
	39	3	1	0.22	0.139	[0.07,0.75]
	44	2	1	0.11	0.105	[0.02,0.71]
	46	1	1	0.00	n/a	n/a
ALSbi	16	16	1	0.94	0.061	[0.83,1.00]
	20	15	1	0.88	0.083	[0.73,1.00]
	23	14	1	0.81	0.098	[0.64,1.00]
	24	13	1	0.75	0.108	[0.57,0.99]
	25	12	1	0.69	0.116	[0.49,0.96]
	29	11	2	0.56	0.124	[0.37,0.87]
	32	9	1	0.50	0.125	[0.31,0.82]
	36	8	2	0.38	0.121	[0.20,0.71]
	39	6	1	0.31	0.116	[0.15,0.65]
	42	5	1	0.25	0.108	[0.11,0.58]
	43	4	1	0.19	0.100	[0.07,0.52]
	48	3	1	0.13	0.083	[0.03,0.46]
	53	2	1	0.06	0.061	[0.01,0.42]
	55	1	1	0.00	n/a	n/a
ALScbi	18	18	1	0.94	0.054	[0.84,1.00]
	19	17	1	0.89	0.074	[0.76,1.00]
	20	16	2	0.78	0.100	[0.61,0.99]
	30	14	3	0.61	0.115	[0.42,0.88]
	33	11	1	0.56	0.117	[0.37,0.84]
	35	10	1	0.50	0.118	[0.32,0.79]
	37	9	1	0.44	0.117	[0.27,0.75]
	38	8	3	0.28	0.106	[0.13,0.59]
	41	5	1	0.22	0.098	[0.09,0.53]
	46	4	1	0.17	0.088	[0.06,0.47]
	51	3	1	0.11	0.074	[0.03,0.41]
	55	2	1	0.06	0.054	[0.01,0.37]
	67	1	1	0.00	n/a	n/a

[a] Time point (in months) at which an event (death) occurs.

[b] Number of ALS patients at risk before the time point.

[c] Number of ALS patients who die before the time point.

[d] Proportion of ALS patients that survive after that time point.

[e] Standard error of the estimated survival.

[f] 95% confidence intervals for the estimated survival.

Table 9.8 (continued). Survival probabilities for each incident frontotemporal syndrome.

	Time[a]	n. Risk[b]	n. Event[c]	Survival[d]	SE[e]	95% CI[f]
ALS-FTD	15	12	1	0.92	0.080	[0.77,1.00]
	22	11	1	0.83	0.108	[0.65,1.00]
	23	10	1	0.75	0.125	[0.54,1.00]
	24	9	1	0.67	0.136	[0.45,0.99]
	25	8	1	0.58	0.142	[0.46,0.94]
	34	7	1	0.50	0.144	[0.28,0.88]
	48	6	1	0.42	0.142	[0.21,0.81]
	51	5	1	0.33	0.136	[0.15,0.74]
	53	4	1	0.25	0.125	[0.09,0.67]
	62	3	1	0.17	0.108	[0.05,0.59]
	68	2	1	0.08	0.080	[0.01,0.54]
	97	1	1	0.00	n/a	n/a
Not Classifiable	9	14	1	0.93	0.069	[0.80,1.00]
	16	13	1	0.86	0.094	[0.69,1.00]
	18	12	1	0.79	0.110	[0.60,1.00]
	19	11	1	0.71	0.121	[0.51,0.99]
	21	10	1	0.64	0.128	[0.44,0.95]
	22	9	1	0.57	0.132	[0.36,0.90]
	28	8	2	0.43	0.132	[0.23,0.79]
	41	6	3	0.21	0.110	[0.08,0.58]
	43	3	1	0.14	0.094	[0.04,0.52]
	45	2	1	0.07	0.069	[0.01,0.47]
	63	1	1	0.00	n/a	n/a

[a] Time point (in months) at which an event (death) occurs.

[b] Number of ALS patients at risk before the time point.

[c] Number of ALS patients who die before the time point.

[d] Proportion of ALS patients that survive after that time point.

[e] Standard error of the estimated survival.

[f] 95% confidence intervals for the estimated survival.

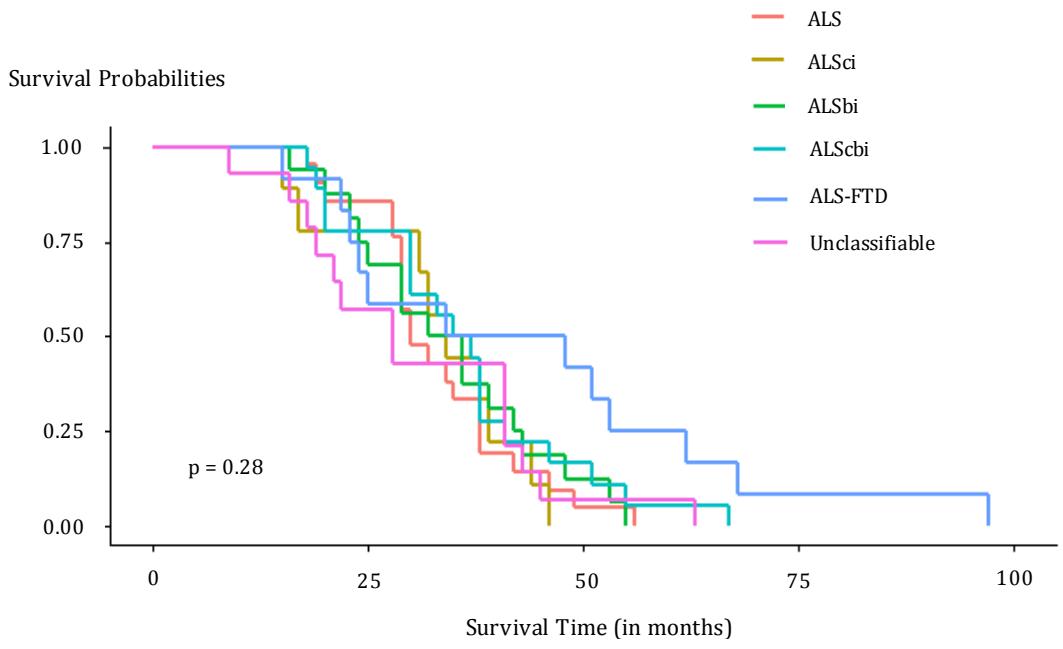

Figure 9.2. Kaplan-Meier plot of survival probabilities

A Cox proportional-hazard model was also fit to adjust for the effect that clinical and demographic characteristics may have on survival. Thus, along with frontotemporal diagnosis at baseline assessment, other clinical and demographic variables considered included age at onset, gender, site of onset, diagnostic delay, and the overall rate of motor decline at baseline assessment. Results from Cox proportional-hazard regression are depicted in Figure 9.2.

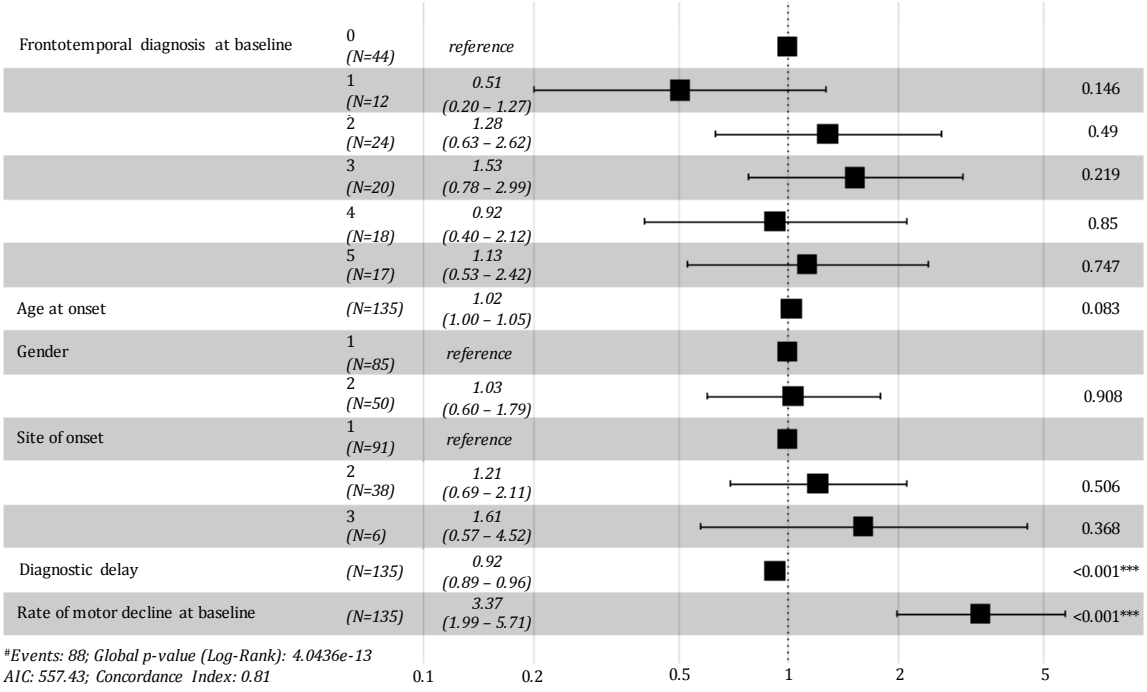

Figure 9.2. Cox proportional-hazard model

Overall, the model was statistically significant, log-rank test = 90.3, df = 11, p<.0001. Considering specific predictors, two of the variables considered significantly influenced survival: diagnostic delay, hazard ratio HR = 0.92, 95% CI [0.89,0.96], z = -4.21, p <.0001, and the overall rate of motor decline at baseline, hazard ratio HR = 3.37, 95% CI [1.99,5.71], z = 4.51, p <.0001. In accordance to previous results, frontotemporal diagnosis at baseline, age at onset, gender and site of onset did not significantly affect survival.

9.4. Neuropsychological Characterisation of the ALS C9orf72 Genotype

This section addresses aim 6, which intends to investigate the relationship between the C9orf72 hexanucleotide repeat expansion and the presence of frontotemporal syndromes in ALS. Moreover, the association between familial ALS in the absence of an identified genetic mutation and frontotemporal dysfunction is also explored.

Genetic screening for the C9orf72 mutation was carried out in 133 out of the 135 ALS patients (99%), 12 of whom (9%) were positive for the pathogenic C9orf72 hexanucleotide repeat expansion in chromosome 9 (i.e. C9orf72+: above 23 repeats; Byrne et al., 2012; Byrne, Heverin, Elamin, Walsh, & Hardiman, 2014; DeJesus-Hernandez et al., 2011). 58% of C9orf72 positive patients were classified as familial ALS, and from all familial ALS cases, 22% carried the C9orf72 repeat expansion. Binary logistic regression analysis indicated that the presence of a family history of ALS and/or FTD (i.e. Familial ALS) is a significant predictor of being a C9orf72 repeat expansion carrier, $b = 1.68$, z = 2.68, p = .007, odds = 1.68, 95% CI [1.59, 19.6], $X^2(1) = 7.19$, p = .007, $R_N^2 = .12$.

Before investigating the relationship between frontotemporal dysfunction and the C9orf72 hexanucleotide repeat expansion, clinical characteristics of C9orf72 positive patients were compared to those of familial ALS cases with no genetic mutation identified and sporadic ALS cases. Results are displayed in Table 9.9.

Table 9.9. Demographic and clinical characteristics of the patient sample segregated by the presence of the C9orf72 repeat expansion (C9orf72+), the presence of a family history with no known genetic mutation (FHx ALS), and the absence of both a known genetic mutation and a family history (Sporadic ALS).

		C9orf72+ n = 12	FHx ALS n = 25	Sporadic ALS n = 96	X^2(df)	*p*
Age *M±SD* (*Mdn*) years		58.6 ± 7.66 (58)	61.4 ± 10.8 (62)	63.9 ± 10.9 (67)	6.01(2)[a]	.05
Gender n(%)	Females	9 (75)	7 (28)	32 (33)	8.90(2)[b]	.01
	Males	3 (25)	18 (72)	64 (67)		
Age at onset *M±SD* (*Mdn*) years		57.2 ± 8.33 (57)	59.5 ± 10.3 (61)	62.2 ± 10.9 (65)	5.64(2)[a]	.06
Site of onset n(%)	Spinal	8 (67)	22 (88)	61 (64)	6.67(4)[b]	.15
	Bulbar	4 (33)	3 (12)	29 (30)		
	Thoracic/Respiratory	0	0	6 (6)		
Diagnostic Delay *M±SD* (*Mdn*) months		10.8 ± 15.2 (6)	19.9 ± 12.6 (19)	16.7 ± 16.3 (12)	9.68(2)[a]	.008
Family History of other Neurological Conditions n(%)		6 (50)	9 (36)	53 (55)	2.94(2)[b]	.23
Family History of Psychiatric Conditions n(%)		7 (58)	9 (36)	41 (43)	1.65(2)[b]	.44
Use of NIV n(%)		3 (25)	6 (24)	17 (18)	0.75(2)[b]	.69
Enteral feeding tube in place n(%)		3 (25)	0	2 (2)	16.7(2)[b]	.0002
ALSFRS-R total score *M±SD* (*Mdn*) score		34.6 ± 6.12 (32)	35.3 ± 7.26 (38)	36.8 ± 6.81 (38)	2.09(2)[a]	.35

[a] Kruskal-Wallis H Test.

[b] Pearson's Chi-square test for independence (X^2).

According to results in Table 9.9, age was at the borderline level of significance, with C9orf72 positive patients being younger compared to the other two groups, although no significant difference was found on post hoc analyses. Regarding gender, a significantly higher proportion

of females was observed in the C9orf72 positive group. Diagnostic delay was also significantly shorter for C9orf72 patients compared to familial ALS patients with no identified genetic mutation, and there was a significantly higher proportion of patients with the C9orf72 repeat expansion that had enteral feeding tube in place compared to the other two groups. No significant differences were observed among groups on age or site of onset, family history of other neurological or psychiatric conditions, use of NIV, or motor disease progression.

Concerning the relationship between the C9orf72 repeat expansion and the diagnosis of an ALS frontotemporal syndrome, 10 out of 11 C9orf72 positive patients (91%) met criteria for a frontotemporal diagnosis at baseline (one C9orf72 positive patient could not be classified due to missing data), compared to 62 out of 105 of C9orf72 negative patients (59%), although this difference did not reach statistical significance, $X^2(1) = 3.05$, $p = .08$. When comparing the incidence of frontotemporal syndromes in C9orf72 positive patients (91%) to that of familial ALS patients with no identified genetic mutation (81%) and that of sporadic cases (54%), this did reach statistical significance, $X^2(2) = 9.64$, $p = .008$, but did not survive correction for multiple comparisons on post hoc tests.

The incidence of each specific ALS frontotemporal syndrome in each of these three groups is displayed in Table 9.10.

Table 9.10. Incidence of ALS frontotemporal syndromes in the patient sample stratified by the presence of the C9orf72 repeat expansion (C9orf72+), the presence of a family history of ALS with no known genetic mutation (FHx ALS), and the absence of both a known genetic mutation and a family history (Sporadic ALS).

	C9orf72+ n = 11	**FHx ALS** n = 21	**Sporadic ALS** n = 84	***X²(df)***[a]	***p***
ALS n(%)	1 (10)	4 (19)	39 (46)	9.64(2)	.008
ALSci n(%)	2 (18)	1 (5)	8 (10)	1.52(2)	.47
ALSbi n(%)	2 (18)	5 (24)	17 (20)	0.18(2)	.92
ALScbi n(%)	3 (27)	7 (33)	10 (12)	6.26(2)	.04
ALS-FTD n(%)	3 (27)	4 (19)	10 (12)	2.23(2)	.33

[a] Pearson's Chi-square test for independence (X^2).

Results in Table 9.10 show that there was a significantly higher proportion of sporadic ALS cases that did not meet criteria for the diagnosis of a frontotemporal dysfunction. Moreover, a significantly higher proportion of C9orf72 positive patients and familial ALS cases with no identified genetic mutation presented with evidence of both cognitive and behavioural impairment (i.e. ALScbi). No significant differences were observed in the rates of ALSci, ALSbi and ALS-FTD among the three groups. Regarding ALS-FTD patients, all three C9orf72 positive patients met criteria for bvFTD. No language-variants were observed within the ALS-FTD cohort.

9.5. Summary of Findings

This results chapter has addressed the fifth and sixth aims of this work, which intended: 1) to investigate the relationship between cognitive/behavioural phenotypes and demographic and clinical features, as well as motor progression and survival in ALS; and 2) to assess if the presence of the C9orf72 hexanucleotide repeat expansion is associated with a higher incidence of frontotemporal syndromes in ALS. The main findings of this chapter are summarized below.

Clinical Characterisation of ALS Frontotemporal Syndromes

No significant differences were observed among incident frontotemporal syndromes in terms of demographic characteristics such as age and gender. However, a higher proportion of females met criteria for ALSci at diagnosis compared to males, an opposite pattern to that observed for the rest of frontotemporal syndromes, although this did not represent a significant finding.

Clinical characteristics such as age at onset, site of onset, diagnostic delay, use of NIV, or severity of respiratory status were not significantly different among incident frontotemporal syndromes. However, the rate of familial ALS was significantly higher for ALScbi patients and significantly lower for ALS patients not meeting criteria for the diagnosis of a frontotemporal syndrome at baseline, compared to other frontotemporal syndromes. The rates of family history of other neurological or psychiatric conditions were not significantly different among frontotemporal syndromes.

Although no significant difference was observed among groups on the severity of bulbar symptoms, a higher proportion of patients diagnosed with cognitive impairment (ALSci and ALScbi) required enteral feeding tube insertion within the first year of diagnosis, and therefore these may represent a subgroup of patients with bulbar symptoms that progressed rapidly. These patients presented with significantly higher rates of executive dysfunction, but not language impairment.

No significant differences among ALS frontotemporal syndromes were observed on the rate of motor progression for spinal, bulbar nor respiratory scores, which supports the idea that motor disease severity is not related to frontotemporal dysfunction in early stages of ALS. ALScbi patients had significantly higher scores on a mood measure compared to ALS patients not meeting criteria for cognitive nor behavioural impairment. Also, a higher proportion of carers of ALS-FTD patients presented with caregiver burden compared to carers of patients meeting criteria for any other ALS frontotemporal syndrome. In total, 28% of ALS caregivers presented with significant caregiver burden.

No demographic or clinical characteristics were found to be significant predictors for the development of frontotemporal dysfunction at follow-up.

Frontotemporal Syndromes and Prognostic Implications in ALS

The overall rate of decline of spinal, bulbar and respiratory dysfunction was not significantly different among incident frontotemporal diagnoses at time 2 and time 3. Likewise, spinal and respiratory rates of decline at time 4 were not significantly different among incident frontotemporal syndromes. However, the rate of bulbar decline was significantly more rapid for ALScbi patients.

In terms of survival, 67% of our population-based incident ALS sample was deceased by June 2019. Mean survival time was 35.0 ± 14.4 months. Diagnostic delay and the rate of motor decline at baseline assessment were significant predictors of shorter survival, with longer diagnostic delays associated with longer survival and higher rates of decline at first assessment related to shorter survival. Age at onset, gender or site of onset were not significant predictors of survival.

ALScbi patients had the lowest rates of survival, followed by patients who could not be classified due to missing data and ALSci patients, and ALS patients that did not meet criteria for cognitive nor behavioural impairment showed the highest survival rates. However, survival analyses indicated that no significant differences existed among incident frontotemporal syndromes on survival curves.

Neuropsychological Characterisation of the ALS C9orf72 Genotype

Genetic testing indicated that 9% of our incident ALS sample were positive for the pathogenic C9orf72 hexanucleotide repeat expansion in chromosome 9. Of these, 58% had familial ALS, and 22% of all familial ALS cases were C9orf72 repeat expansion carriers. A positive family history of ALS and/or FTD was in fact a significant predictor for the presence of a pathogenic C9orf72 hexanucleotide repeat expansion.

No significant differences were observed among C9orf72 positive patients, familial ALS patients with no genetic mutation identified and sporadic ALS cases on age or site of onset, family history of other neurological or psychiatric conditions, use of NIV, or motor disease progression. However, a significantly higher proportion of females were positive for the C9orf72 repeat expansion, and a significantly higher proportion of C9orf72 positive patients had enteral feeding tube in place. Diagnostic delay was significantly shorter for C9orf72 repeat expansion carriers compared to familial ALS patients that had no identified genetic mutation.

From all C9orf72 repeat expansion carriers, 91% met criteria for the diagnosis of a frontotemporal syndrome at baseline, compared to 81% of familial ALS cases with no genetic mutation identified and 54% of sporadic ALS cases. More specifically, a significantly higher proportion of C9orf72 positive patients and of familial ALS patients with no identified genetic mutation met criteria for the diagnosis of ALScbi, compared to sporadic ALS patients. Moreover, a significantly higher proportion of sporadic ALS cases presented with preserved cognitive and behavioural function, compared to familial ALS cases (both C9orf72 repeat expansion carriers and cases with no identified genetic mutation). No significant differences were observed among the three groups on the rates of ALSci, ALSbi or ALS-FTD, although in the latter case, the proportion of C9orf72 positive patients was higher than that of familial ALS cases with no identified genetic mutation and sporadic ALS cases. All ALS-FTD patients who carried the C9orf72 repeat expansion (17%) met criteria for bvFTD.

CHAPTER 10 Outline.

Summary of Findings and Discussion, Limitations, Conclusions and Future Directions

CHAPTER 10.

Summary of Findings and Discussion, Limitations, Conclusions and Future Directions

This final chapter analyses the results of this work and discusses them relative to existing evidence. Moreover, study limitations are considered. Finally, the overall conclusions are deliberated as well as perspectives for future research, particularly in the areas of disease phenotyping and disease management in ALS.

10.1. Summary of Findings and Discussion

10.1.1. Aim 1 – The Incidence and Nature of Language Change in ALS

This study is the first to recruit an incident population-based sample to characterise the occurrence and nature of language change in newly diagnosed ALS patients. A demographically matched population-based healthy control sample was also recruited to adequately characterise the incidence of language change in ALS relative to that of the general population.

Considering language as an integral cognitive construct, significantly lower performance of the ALS sample compared to demographically matched healthy controls was observed. A closer analysis of performance on specific language measures indicated that incident language deficits in ALS are confined to the domains of word naming and syntactic/grammatical processing, as well as orthographic lexical processing. The incidence of word naming deficits in ALS was 18%, the incidence of syntactic/grammatical processing deficits was 20%, the incidence of word spelling deficits was 14%, and the incidence of word reading deficits was 16%. Phonological lexical processing as well as semantic processing were spared at early stages in ALS.

Orthographic processing in our ALS sample was explored by analysing performance on the recognition, reading and spelling of three different types of words that differed on the presence or absence of regularity in phoneme-to-grapheme/grapheme-to-phoneme correspondences (i.e. regular, irregular and pseudowords). Although the processing of regular versus irregular utterances in ALS has been studied in Japanese populations by analysing spelling of kana and kanji characters, no analogue studies had been previously performed in English, as per systematic review carried out in chapter 2.

The pattern of non-lexical spelling performance observed in our ALS sample was characterised by a spared ability to spell pseudowords, which follow the phoneme-to-grapheme conversion rules, although lower performance of ALS patients on regular word spelling was observed. The type of errors committed, however, did not break the phoneme-to-grapheme conversion rules but consisted of slight alterations of word forms characterised by omissions, replacements or repetitions of graphemes which did not affect word pronunciations. Results on regular word and pseudoword reading paradigms also indicated spared grapheme-to-phoneme conversion rules. These findings support spared non-lexical word processing.

Regarding orthographic processing via the lexical route, the presence of regularisation errors and difficulties recalling the accurate word forms were observed in ALS when spelling irregular words, although performance of the patient sample was not significantly lower to that of healthy controls. However, performance on a homophone processing task and on a visual lexical decision task showed that ALS patients presented with significantly more difficulties compared to healthy controls in processing certain word forms from a lexical point of view. Accordingly, ALS patients had difficulties accessing irregular word forms from the orthographic input lexicon which, in turn, caused difficulties accessing the meaning and pronunciation of the word form from the orthographic output lexicon. Orthographic processing deficits in ALS were thus demonstrated from an input level. Specifically, these deficits were more prone for those words that are infrequent and more abstract.

Our results on orthographic processing in English are concordant with some ALS Japanese spelling reports, which described impairments in the processing of kanji characters (Ichikawa et al., 2008; Satoh et al., 2009; Tsuji-Akimoto et al., 2010). These are considered equivalent to irregular words in English given that they also consist of learned visual characters, and difficulties processing them are related to image recall deficits. Also concordant with our results, errors on kana characters (equivalent to regular words in English as these follow sound-to-script correspondence rules) have also been described, including omissions, misplacements and substitutions (Tsuji-Akimoto et al., 2010). These were found to significantly correlate with bilateral anterior cingulate dysfunction, with mild right predominance, and were related to attention deficits (Yabe et al., 2012). This is concordant with the pattern of errors observed in our ALS sample when spelling regular words. Our work is the first to assess orthographic processing from an input point of view by using word reading and visual lexical decision paradigms.

Word naming difficulties were also evident in our ALS sample based on performance on confrontation naming for both nouns and action words. Reduced performance on the number of spontaneous responses given on confrontation naming can be explained by difficulties of access/retrieval, or by degradation of semantic knowledge. Significantly improved

performance after the presentation of semantic and phonemic cues was observed in our ALS sample, with a major influence of phonemic cueing in performance. This finding is concordant with preserved semantic knowledge and indicates that word naming deficits in ALS are of an access/retrieval nature. Performance of our ALS sample on receptive semantic tasks, which was preserved, further confirms that semantic processing is spared in ALS, at least in early stages of the disease. As described in the systematic review performed in chapter 2, existing literature on semantic processing in ALS supports this finding, although some reports have shown semantic deficits in a small proportion of their prevalent samples (Cobble, 1998; Leslie et al., 2015; Taylor et al., 2013). Longitudinal follow-up of our incident sample, addressed later, investigated this matter.

Syntactic and grammatical processing deficits in ALS were found for auditory and also for written stimuli. Sentence processing tasks are complex and require sufficient primary information-processing abilities in order to tap on higher syntactic and grammatical processes. Accordingly, the role of working memory on auditory sentence processing and the role of word reading on written sentence processing was analysed. Although these factors significantly influenced performance, pure syntactic/grammatical processing deficits were proven in ALS for both auditory and written information. Written sentence processing had not been previously assessed in ALS, but our finding of impaired auditory syntactic/grammatical processing is concordant with previous reports looking at auditory sentence comprehension performance in ALS. These results were, however, drawn from prevalent samples (Cobble, 1998; Kamminga et al., 2016; Rakowicz & Hodges, 1998; Taylor et al., 2013; Tsermentseli et al., 2015; Yoshizawa et al., 2014). Moreover, ours is the first study to explicitly assess the influence of working memory on auditory sentence processing in ALS, although Ash et al. (2015) had looked at the influence of executive dysfunction on syntactic processing on discourse production, and also encountered grammatical deficits that were independent from executive impairment.

10.1.2. Aim 2 – The Role of Executive Dysfunction in Language Change in ALS

The degree to which executive dysfunction influences language change in ALS has long been speculated. One report assessed the influence of executive dysfunction to grammatical processing in discourse production (Ash et al., 2015), and another examined the overall effect of executive dysfunction on language change in a prevalent ALS sample (Taylor et al., 2013). However, this is the first report to assess the influence of executive dysfunction on language change in a population-based incident ALS sample, while evaluating each language domain shown to be affected in ALS.

The presence of incident executive dysfunction in ALS, which has previously been established (Montuschi et al., 2015; Phukan et al., 2012), has been further confirmed by our results,

specifically on the domains of phonemic verbal fluency and problem-solving/goal-directed behaviour, as well as on semantic verbal fluency and social cognition to a lesser degree. Our results also confirmed that language change is associated with executive dysfunction to a degree in ALS, although this does not explain the entirety of language deficits characteristic of this disease. Thus, pure deficits of linguistic nature exist in ALS at diagnosis. This is concordant with results from a study on the prevalence of language change in ALS that reported that language and executive impairment shared 44% of variance (Taylor et al., 2013). More specifically on the relationship between language impairment and executive dysfunction in our ALS sample, the amount of shared variance between executive dysfunction and language impairment was 49% for syntactic/grammatical processing deficits, 37% for orthographic lexical processing deficits, 33% for spelling deficits, 29% for word retrieval deficits, and 26% for word reading.

The larger proportion of variance in language performance in our ALS sample was explained by phonemic verbal fluency deficits. These have been shown to be a very sensitive marker of frontostriatal dysfunction in ALS given the substantial demands this task places on various executive processes, which makes it very sensitive to any damage affecting the integrity of such frontal circuits (Phukan et al., 2012; Strong et al., 2017). Moreover, the anatomical regions recruited for verbal fluency performance also extend to inferior frontal and temporal centres of language processing (Baldo et al., 2006; Weiss et al., 2003). This was corroborated by our findings that demonstrated that verbal fluency deficits in ALS are related to difficulties of word access to a degree, which is concordant with some neuroimaging reports that confirmed the involvement of inferior frontal and superior temporal areas related to word retrieval processes in phonemic verbal fluency in ALS (Abrahams et al., 2004; Wicks et al., 2008). The contribution of retrieval deficits on verbal fluency were higher for semantic compared to phonemic paradigms in our ALS sample.

10.1.3. Aim 3 – The Incidence of Frontotemporal Syndromes in ALS

This is the first report to establish the incidence of frontotemporal syndromes in a population-based sample of ALS patients, based on revised diagnostic criteria (Strong et al., 2017). The population-based design reduced the risk of selective case ascertainment. Clinical and demographic characteristics of our patient sample were compared to those of patients that represented incident cases diagnosed within the recruitment period but that were uncaptured or unsuitable for research participation, and no significant differences were encountered between them. Therefore, it can be assumed that our captured sample embodies a true representation of the incident ALS population in Ireland. Moreover, clinical characteristics of our population-based sample were similar to those reported in previous population-based studies carried out in Ireland (Galvin et al., 2017; O'Toole et al., 2007; Phukan et al., 2007), and

the gender ratio and site of onset distributions in our ALS cohort represented the usual frequencies encountered in ALS (Al-Chalabi & Hardiman, 2013; Hardiman et al., 2011).

Our results support the notion that frontotemporal syndromes in ALS represent a spectrum of presentations. Accordingly, a proportion of ALS patients (9%) presented with cognitive impairment alone, single behavioural change was characteristic of 18% of newly diagnosed ALS patients, and another 15% met criteria for both cognitive and behavioural impairment. Consistent with previous incident population-based studies in ALS, we found that 13% of newly diagnosed ALS cases also met criteria for comorbid FTD (Montuschi et al., 2015; Phukan et al., 2012), and 33% of our incident sample had preserved cognitive function and behaviour. The dissociation between cognitive and behavioural impairment in ALS has been previously demonstrated (Burke et al., 2017; Crockford et al., 2018).

The frequencies of the different types of FTD encountered in our population-based sample were also consistent with those reported in previous incident population-based studies, with most ALS-FTD patients meeting criteria for the behavioural-variant subtype, and only a very small proportion of them presenting with language-variants (Montuschi et al., 2015; Phukan et al., 2012).

These previous ALS population-based studies had investigated the incidence of executive dysfunction in newly diagnosed ALS patients (Montuschi et al., 2015; Phukan et al., 2012), but the incidence of language dysfunction in ALS had not been previously established. Our results showed that while 14% of non-demented incident ALS patients met criteria for executive impairment and 15% met criteria for both executive and language impairment, only 3% of the non-demented sample met criteria for language impairment in isolation. Accordingly, the presence of language impairment alone was not frequent in our incident ALS sample. Moreover, the frequency of language impairment in non-demented ALS patients was not significantly higher to that of healthy controls. This is in accordance with results from Phukan et al. (2012), who showed that, in the absence of executive dysfunction, the frequency of language impairment (assessed using the Boston Naming Test) in non-demented ALS patients was not significantly higher in comparison to healthy controls. However, it has been earlier shown that a high variation in language dysfunction in our ALS sample occurred independently of executive dysfunction and therefore language impairment that uniquely contribute to the profile of cognitive impairment in ALS exists. This may indicate that the presence of language impairment in ALS represents a more widespread frontotemporal disease that extends beyond those areas involved in executive control.

ALS patients that presented with incident cognitive impairment had significantly lower premorbid IQs, fewer formal years of education, and were older at symptom onset compared to cognitively intact ALS patients. This is concordant with results from the previous incident

population-based study on cognition performed in Ireland (Phukan et al., 2012). Age and IQ are known to be significant predictors of cognitive performance (Strauss et al., 2006), and intelligence, education and occupational attainment are significant determinants of cognitive reserve (Borroni et al., 2009; R. F. Kaplan et al., 2009; Nucci, Mapelli, & Mondini, 2012). This would explain why older patients with lower premorbid IQs and lower levels of education performed lower on cognitive tests. However, significant differences between cognitively impaired and intact ALS patients were still observed after accounting for the effect of these demographic factors, and therefore these did not fully explain the patterns of impairment observed in ALSci patients. Regardless, the degree to which cognitive reserve protects ALS patients from more aggressive neurodegenerative processes, or how much older age makes them more vulnerable, is unknown.

The incidence of behavioural change in our population-based ALS sample was 46%. Other studies have reported the rates of behavioural change in clinic-based prevalent samples (Z. C. Gibbons, Richardson, Neary, & Snowden, 2008; A. B. Grossman, Woolley-Levine, Bradley, & Miller, 2007; Lillo, Mioshi, Zoing, Kiernan, & Hodges, 2011; Meier, Charleston, & Tippett, 2010) and one report investigated a population-based prevalent sample (Burke et al., 2017). However, to our knowledge, this is the first population-based study to assess its incidence. Moreover, ours is one of the first studies to apply the revised diagnostic classification for ALS with behavioural impairment (Strong et al., 2017). Another large population-based multicentre study (including ours) recently applied it, and reported that 40% of ALS patients met criteria for behavioural impairment (Crockford et al., 2018). This study involved, however, a mix of prevalent and incident cases.

In accordance with existing literature (Crockford et al., 2018; Z. C. Gibbons et al., 2008; A. B. Grossman et al., 2007; Lomen-Hoerth et al., 2003), apathy was the most frequently reported behavioural feature in our ALS sample, with 39% of patients endorsing it. This was followed by behavioural disinhibition (24%) and loss of sympathy or empathy (19%). Early perseverative, stereotyped or compulsive/ritualistic behaviour (9%) and hyperorality and dietary changes (16%) were less frequently reported. Psychotic symptoms were endorsed by only 6% of our ALS sample, and these symptoms were mainly present in the context of broader behavioural change.

10.1.4. Aim 4 – The Evolution of Frontotemporal Decline in ALS

This study is also the first to establish the evolution of frontotemporal change in an incident sample considering all relevant neuropsychological domains in ALS: executive function, language and behaviour. The extant longitudinal research in ALS is characterised by inconsistent results confounded by high attrition rates and therefore limited sample sizes at follow-up, recruitment of clinic-based prevalent rather than population-based incident

samples, missing data, and the underrepresentation of patients with more aggressive forms of the disease at follow-up assessments (Abrahams, Leigh, et al., 2005; Gordon et al., 2010; Kilani et al., 2004; Moretti et al., 2002; Robinson et al., 2006; Schreiber et al., 2005; Strong et al., 1999). There is only one other ALS longitudinal report that recruited a large population-based incident sample, although this did not comprehensively assess language and behavioural change, but mainly focused on executive function (Elamin et al., 2013).

Our results indicated that there was no significant decline on cognitive measures overall, but a significant increase in behavioural impairment was observed. This translated into a decrease in the prevalence of cognitively impaired patients over time and an increase in the prevalence of behavioural change. The percentage of ALS patients that cognitively declined was higher for those patients that already presented with cognitive dysfunction at baseline, but cognitive performance was maintained relatively stable for most ALS patients over time.

When interpreting our longitudinal results, however, it must be considered that cognitively impaired patients at baseline tended to discontinue more frequently. Specifically, ALS patients meeting criteria for executive impairment discontinued more frequently whereas the prevalence of language impairment remained stable across time points. As a consequence, there is an overrepresentation of ALS patients that were cognitively and behaviourally intact at baseline at time 4. Accordingly, those patients that present with faster rates of cognitive decline, and therefore meet criteria for impairment at first year of diagnosis, are not representatively captured at longitudinal follow-ups. The prevalence of cognitive decline in our ALS sample therefore embodies an underestimate of the true prevalence within a population-based sample.

Moreover, ALSFRS-R scores at baseline were significant predictors of discontinuation at all follow-up time points, meaning that those cases that were more physically impaired were the ones that were lost at longitudinal follow-up. It could be the case that those ALS patients that physically decline more rapidly and are, therefore, not captured longitudinally are the same patients that also present with significant cognitive deterioration. In fact, ALS patients that met criteria for cognitive impairment at baseline presented with more advanced motor decline in comparison to cognitively intact ALS patients. Moreover, Crockford et al. (2018) and Trojsi et al. (2016) demonstrated the relationship between neuropsychological deficits and disease stage in ALS, with more advanced stages in terms of motor function being related to higher rates of neuropsychological impairment. Elamin et al. (2013) also found that cognitive impairment was significantly associated with higher attrition rates and a more rapid motor progression. The underrepresentation of ALS patients with more marked forms of cognitive as well as motor impairment at follow-up time points is one of the main limitations of longitudinal research in ALS.

Bearing in mind the above, our results replicate the findings of the previous Irish longitudinal population-based study, which showed that most patients who are cognitively intact at baseline remain as such over time (Elamin et al., 2013). In our case, we performed three follow-up assessments every four months, which represent a year follow up from baseline assessment. Elamin et al. (2013), on the other side, performed three follow-up assessments every six months, which represents a year and a half follow-up period. In conjunction, these results confirm that there is a subgroup of ALS patients that present with spared frontotemporal function at diagnosis that is maintained relatively stable over the first year or two in the course of the disease. Longitudinal studies with longer follow-up periods are required to confirm whether this subgroup of patients remain cognitively intact over the whole course of the disease or whether they represent a slower progressing subgroup that develops frontotemporal involvement at later stages.

In relation to longitudinal language change, the prevalence of language impairment remained relatively stable and in most cases this was present in conjunction with executive impairment. In fact, the presence of language impairment in isolation was small. This is in accordance with our cross-sectional results, which indicated that the presence of language impairment in isolation is not characteristic of ALS but that this rather represents a more severe form of the disease involving widespread frontotemporal pathology. In our sample, the proportion of ALSeli patients that were deceased by the end of the study was higher to that of ALS patients meeting criteria for executive or language impairment in isolation. This suggests that this more severe form of the disease characterised by widespread frontotemporal involvement may also be accompanied by a more marked motor involvement that progresses more rapidly.

Other longitudinal research has suggested that language is especially vulnerable to disease progression (Abrahams, Leigh, et al., 2005; Elamin et al., 2013; Gordon et al., 2010). Moreover, some cross-sectional studies recruiting ALS prevalent samples have demonstrated semantic processing deficits in ALS (Cobble, 1998; Taylor et al., 2013). Taylor et al. (2013) also reported the prevalence of language impairment in ALS to be higher than that of executive dysfunction. Our longitudinal results do not confirm the presence of semantic deficits in ALS that develop over time nor the particular vulnerability of other language processes to disease progression. Again, this could be explained by the fact that patients with more severe forms of cognitive impairment are mostly lost to attrition.

Regarding longitudinal behavioural change, the increased prevalence over time was translated into an increased frequency of all five behavioural features evaluated. Apathy was characterised by the most marked increase. Thus, apathy was present in 39% of patients from our incident sample, and its frequency augmented to 62% after a year follow-up. This is concordant with the literature, where it has been reported that apathy can be present in up to

70% of ALS patients (Strong et al., 2017). Greater behavioural change has been reported in patients in more advanced stages of the disease (Burke et al., 2017; Crockford et al., 2018). Regardless, research discontinuation was not as prominent in patients meeting criteria for behavioural impairment in comparison to patients meeting criteria for cognitive impairment. This may be because a proxy measure was used to evaluate behavioural change.

No ALS patients developed comorbid FTD during the course of our longitudinal study. The rate of new onset dementia in the previous Irish population-based longitudinal study was also very low; only one C9orf72 negative patient, who presented with executive dysfunction affecting various domains at baseline, developed bvFTD during the course of the study (Elamin et al., 2013). Again, we cannot disregard the impact that the higher attrition observed in non-demented ALS patients with more severe frontotemporal presentations most likely had on these results.

Two RCI and two SRB methods were employed to assess significant individual change on neuropsychological performance over time: Jacobson and Truax RCI, which corrects for the effect of measurement error; Chelune RCI, which additionally accounts for practice effects; simple SRB methods, which additionally accounts for regression to the mean effects, and complex SRB methods, which additionally accounts for other moderating effects included in the regression equation, in this case age, IQ, retest interval and $Sp0_2$ levels. A comparison of all methods indicated that complex SRB methods were the most accurate in assessing reliable change over time, given that they account for a major number of confounding variables. On reflection, the use of all four methods was unnecessary, given that SRB methods have been shown to be more robust than RCI methods as they are based on predictions from the same sample, rather than based on performance from a reference sample like in RCI methods, which is subject to sampling error (Crawford & Garthwaite, 2006), especially for small samples, which is the case here due to attrition.

Finally, regarding cognitive classifications, it must be highlighted that a small proportion (6%) of ALS patients across all time points had been classified as impaired at a previous time point and returned to normal at follow-up. In most of these cases, the difference between being impaired and returning to normal at follow-up was discriminated by performance on one single task, in most cases this being within the borderline range of impairment (i.e. between 1.645 and 1.96 standard deviations below the control mean). The less stringent cut-off for impairment used, instead of the most commonly used one (i.e. 1.96 standard deviations below the mean), caused a higher proportion of healthy controls to fall within the impaired range on cross-sectional cognitive classifications. A detailed evaluation of the sensitivity and specificity of the revised diagnostic criteria (Strong et al., 2017) is beyond the scope of this work. However, we know that individual neuropsychological performance fluctuates across time and

that external factors such as fatigue, which is very common in ALS due to hypoxemia and hypercarbia, can also affect performance. Therefore, longitudinal follow-ups are crucial along the course of the disease to monitor changes and avoid misleading cognitive classifications that may be confounded by other factors, especially in those cases that present with borderline forms of impairment.

10.1.5. Aim 5 – Clinical Characterisation of Frontotemporal Dysfunction in ALS

No differences were observed among the different frontotemporal syndromes in terms of age and site of onset, diagnostic delay, nor in respiratory status and use of NIV. A higher proportion of females met criteria for ALSci in comparison to males, whilst the reverse pattern was observed for all other frontotemporal syndromes as well as for unimpaired ALS patients. However, no significant difference was observed among groups. ALS females have been reported to more frequently suffer from bulbar-onset ALS (McCombe & Henderson, 2010), which has been related to cognitive dysfunction in some reports (Abrahams et al., 1997; Lomen-Hoerth et al., 2003; Montuschi et al., 2015; Schreiber et al., 2005). Moreover, Palmieri et al. (2015) reported that ALS females were more vulnerable to develop executive dysfunction, a finding that was unrelated to the site of onset. Our finding of a significantly higher proportion of females being diagnosed with ALSci, although non-significant, could indicate a trend that is underpowered by the small sample size of patients meeting criteria for cognitive impairment in isolation.

Regarding family history, no significant differences among frontotemporal syndromes were observed on the frequency of family history of neurological or psychiatric conditions other than ALS and/or FTD in our sample. However, significantly higher rates of familial ALS were encountered in ALScbi patients, and the occurrence of a positive family history of ALS and/or FTD was significantly lower for those ALS patients with no evidence of frontotemporal dysfunction. This can indicate a relationship between genetic contributors and a more marked frontotemporal pathology in ALS. In fact, the pathogenic C9orf72 hexanucleotide repeat expansion in chromosome 9 has been associated with more widespread frontotemporal pathology (Bede, Bokde, Byrne, et al., 2013; Cistaro et al., 2014). The influence of this genetic defect and frontotemporal syndromes in our ALS sample is discussed below.

Concerning psychological distress, ALScbi patients presented with significantly higher scores on measures of negative affectivity compared to ALS patients not meeting criteria for cognitive nor behavioural impairment. A recent study showed an increased risk of developing cognitive impairment in ALS patients that had suffered from depression in the past, which was also related to shorter survival (De Marchi et al., 2019). These authors speculate on the possibility of depression being another marker of neurodegeneration, although this postulation requires

further examination. Regardless, accounting for the effect that mood has on neuropsychological performance when assessing cognition and behaviour in ALS is essential.

Regarding caregiver burden, carers of ALS patients meeting criteria for comorbid FTD experienced significantly more burden than carers of ALS patients meeting criteria for other frontotemporal syndromes or ALS patients with no evidence of cognitive and behavioural impairment. Although caregiver burden was significantly higher only for carers of ALS-FTD patients, non-demented ALS patients meeting criteria for behavioural impairment (including ALSbi and ALScbi) also had higher levels of burden compared to neuropsychological intact patients or ALS patients solely meeting criteria for cognitive impairment. This is consistent with existing evidence establishing the strong relationship between caregiver burden and neuropsychological deficits in ALS, especially behavioural change (Burke, Elamin, Galvin, Hardiman, & Pender, 2015; Chiò et al., 2010; Lillo, Mioshi, & Hodges, 2012; Tremolizzo et al., 2016; Watermeyer et al., 2015).

The relationship between bulbar onset ALS and cognitive dysfunction has been shown by some studies (Abrahams et al., 1997; Lomen-Hoerth et al., 2003; Montuschi et al., 2015; Schreiber et al., 2005), though this is not a consistent finding (Gordon et al., 2010; Kew et al., 1993; Ringholz et al., 2005; Rippon et al., 2006). Although site of onset was not related to incident frontotemporal dysfunction in our ALS sample, there was a significantly higher proportion of ALS patients meeting criteria for cognitive impairment at baseline (including ALSci and ALScbi) that required early insertion of enteral feeding tube. These results suggest that it is not the bulbar site of onset but the presence of a more aggressive bulbar presentation that is related to cognitive impairment in ALS. This is in accordance with recent results from Crockford et al. (2018), who showed that the presence of bulbar involvement but not bulbar site of onset was related to more severe neuropsychological presentations. Previous studies had already suggested that cognitive dysfunction in ALS is not associated with bulbar site of onset but to the degree of bulbar involvement (Massman et al., 1996; Sterling et al., 2010).

The anatomical proximity between prefrontal regions and the frontal regions involved in the corticobulbar tract (i.e. the rostral part of the precentral gyrus, in the primary motor cortex) are likely to explain the association between bulbar involvement and cognitive dysfunction in ALS. Neuroimaging evidence suggesting the relationship between a more widespread involvement of the frontal cortex and more severe bulbar dysfunction exists (Kiernan & Hudson, 1994), and this was further related to executive dysfunction in ALS, particularly to phonemic verbal fluency deficits and the dorsolateral prefrontal cortex (Abrahams et al., 1997). In our study, executive dysfunction but not language impairment was related to a more aggressive bulbar presentation.

The severity of the motor symptoms at baseline or the rate of progression from disease onset to baseline assessment was not significantly different among frontotemporal syndromes, which suggests that neuropsychological dysfunction at baseline is somewhat independent from motor impairment, thus representing different patterns of disease depositions in the brain at early stages of the disease. However, a significantly faster rate of bulbar decline at time 4 was encountered for ALScbi patients. This is concordant with our previous statement that ALS cases that present with faster progressing frontal pathology develop a more aggressive bulbar presentation as well as more severe neuropsychological deficits. Moreover, bulbar onset was a significant predictor for discontinuation at time 4, and we have previously reported that those patients that presented with significant cognitive deterioration were more likely to discontinue. Elamin et al. (2013), in another longitudinal population-based study carried out in Ireland, also found that the presence of frontotemporal dysfunction at baseline significantly predicted a more rapid decline in bulbar function.

Regarding survival, mean survival time in our ALS sample was 35 months, with 67% of our incident population-based sample being deceased fifty-five months post-beginning of the recruitment period. A previous population-based study carried out in Ireland reported a percentage of 63% of the sample being deceased four years post-commencement of recruitment (Elamin et al., 2011).

Diagnostic delay and the rate of motor progression from onset to baseline assessment were significant predictors of survival. Accordingly, faster progression rates were associated with shorter survival, and longer diagnostic delays were related to longer survival. Shorter diagnostic delays have been shown to have a negative impact on survival by a substantial number of studies (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). This is believed to indicate that patients with more aggressive forms of the disease seek earlier medical attention in the course of the illness and are therefore diagnosed more promptly (Chiò et al., 2009). Gender was not a significant prognostic indicator in our ALS sample, which is in line with most evidence (Chiò et al., 2009).

Bulbar onset has typically been considered a negative prognostic indicator in ALS (Chiò et al., 2009), but in some cases this has been related to older age in those patients that first develop bulbar signs (Eisen, Schulzer, MacNeil, Pant, & Mak, 1993; Haverkamp, Appel, & Appel, 1995; Jablecki, Berry, & Leach, 1989; Marti-Fabregas, Pradas, & Illa, 1996; Norris et al., 1993). In our study, neither age nor site of onset were significant predictors of survival, which is not in line with most evidence (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016). Given our finding that faster motor progression rates at diagnosis significantly influenced survival, it may not be the specific bulbar site of onset that it is related to faster progression, but the presence of fast progressing bulbar symptoms. An Italian population-

based study found in fact that the presence of bulbar involvement at diagnosis was a significant prognostic factor (Chiò et al., 2002).

Respiratory onset ALS is also usually associated with a poorer prognosis (Chiò et al., 2009), a finding that was not characteristic of our sample. This could be explained by the fact that all respiratory onset ALS patients from our sample were promptly started on NIV after diagnosis, and the use of NIV has been shown to significantly improve survival (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016; Shoesmith, Findlater, Rowe, & Strong, 2007).

In our sample, ALScbi patients had the lowest survival rates, followed by ALS patients that could not be classified due to missing data (more severely impaired from a physical perspective) and ALSci patients. The highest rates of survival were observed for those patients that were cognitively and behaviourally intact. Nevertheless, no significant differences were encountered among frontotemporal syndromes in terms of survival curves. This is discordant with other population-based ALS studies which have shown that frontotemporal dysfunction had a significant negative effect on survival (Elamin et al., 2011; Montuschi et al., 2015; Oh et al., 2014). Our survival analysis is likely to be underpowered given the small sample sizes obtained when ALS patients were segregated by the different frontotemporal diagnoses. However, the lower survival rates observed in ALS patients meeting criteria for frontotemporal dysfunction in our sample are believed to indicate the presence of a more aggressive disease with more widespread frontotemporal pathology.

In the aforementioned studies (Elamin et al., 2011; Montuschi et al., 2015; Oh et al., 2014), ALS-FTD patients had the shortest survival, compared to non-demented ALS patients, probably related partly to the more rapid progression of neurodegenerative processes and partly to their difficulty to adhere to life-prolonging interventions (Chiò et al., 2012). However, this was not the case in our ALS-FTD sample, which had the highest mean survival times compared to all other frontotemporal diagnoses and one of the lowest percentages of deceased at time of analysis. The reason behind this is not completely understood, although it is hypothesised that our ALS-FTD sample is biased towards a more severe neuropsychological presentation with less severe motor dysfunction. In fact, ALS-FTD patients scored significantly higher on the ALSFRS-R limb sub-score compared to non-demented ALS patients at baseline assessment, thus indicating more preserved motor involvement.

Finally, it must be highlighted that most analyses undertaken in this section considered incident frontotemporal diagnoses rather than neuropsychological status at follow-up. The reason for this is twofold: the development of new onset frontotemporal dysfunction at follow-up time points was rare in our sample, and including all incident cases increased the power of such analyses.

10.1.6. Aim 6 – The C9orf72 Genotype and Frontotemporal Decline in ALS

The percentage of ALS patients from our incident population-based sample that were positive for the pathogenic C9orf72 hexanucleotide repeat expansion was 9%. This is concordant with results from a previous Irish study, which reported that the percentage of C9orf72 positive carriers from a large population-based sample of 435 ALS patients was also 9% (Byrne et al., 2012). In our sample, most C9orf72 positive patients (58%) were familial ALS, and 22% of all familial ALS cases carried the C9orf72 repeat expansion. The significant relationship encountered between the presence of a pathogenic C9orf72 hexanucleotide repeat expansion and the occurrence of a positive family history of ALS and/or FTD is in line with existing literature (Byrne et al., 2013; Saberi et al., 2015; van Es et al., 2017).

Female gender was significantly more frequent within C9orf72 positive patients, and a significantly higher proportion of these had enteral feeding tube in place, this suggesting rapidly progressing bulbar involvement, which has been previously related to a higher incidence of neuropsychological impairment.

In relation to frontotemporal dysfunction, a significantly higher proportion of ALS patients carrying the C9orf72 repeat expansion mutation and familial ALS patients with no genetic mutation identified presented with ALScbi, whereas a significantly higher proportion of sporadic ALS patients presented with preserved cognitive and behavioural function. This results indicate an increased incidence of both cognitive and behavioural dysfunction in patients carrying a genetic mutation, this being the C9orf72 repeat expansion or another unidentified mutation. These results support existing evidence showing that the hexanucleotide repeat expansion in the C9orf72 gene is associated with more extensive frontotemporal pathology (Bede, Bokde, Byrne, et al., 2013; Cistaro et al., 2014; Floeter & Gendron, 2018). In our sample, this has been translated into a higher proportion of C9orf72 patients meeting criteria for both cognitive and behavioural impairment. The presence of cognitive or behavioural presentations in isolation however was not found to be associated with the C9orf72 repeat expansion. Familial ALS patients with no identified genetic mutation also presented with a significantly higher frequency of cognitive and behavioural impairment, which suggests the presence of some still unidentified genetic mutation/s that are also related to a higher degree of frontotemporal involvement in ALS.

The higher frequency of comorbid FTD in C9orf72 positive ALS patients is also acknowledged in the literature (Byrne et al., 2012; Irwin et al., 2012; Montuschi et al., 2015; Snowden et al., 2013). However, no significant differences were observed in the frequency of ALS-FTD patients carrying the C9orf72 repeat expansion and C9orf72 negative ALS-FTD patients in our sample. These results may be underpowered given the small sample size of patients meeting criteria for ALS-FTD in our study. However, looking at the proportion of C9orf72 positive patients

versus sporadic ALS cases, 27% of C9orf72 positive patients were diagnosed with ALS-FTD, and only 12% of sporadic ALS cases met criteria for comorbid FTD. All C9orf72 positive ALS-FTD patients in our sample met criteria for bvFTD, and no language-variants were observed, which is in accordance with the literature (Boeve & Graff-Radford, 2012).

10.2. Study Limitations

This study has addressed some of the methodological limitations that have characterised the study of language in ALS to date by recruiting an incident rather than a prevalent sample as well as by employing a population-based design and thus representing the whole spectrum of non-demented ALS patients. The incident design of this study reduced survival bias and the population-based design, referral and selection bias. Moreover, a carefully-matched healthy control sample, as required by Strong et al. (2017) diagnostic criteria, was recruited for both cross-sectional and longitudinal studies, in order to characterise the incidence and prevalence of frontotemporal dysfunction in ALS. In longitudinal analyses, the use of matched healthy controls at each follow-up time point allowed for the effect of repeated testing on performance to be accounted for. Other strengths of this study include the adaptation of neuropsychological measures to correct for the influence of motor impairment on performance, as well as the accounting of other confounding variables such as mood or altered respiratory function, both proven to be related to reduced cognitive performance (S.-M. Kim et al., 2007; Lezak, 2004; Newsom-Davis, Lyall, Leigh, Moxham, & Goldstein, 2001; Raaphorst et al., 2010; Strauss et al., 2006; Strutt et al., 2012).

Regardless the evident strengths of the current study, there are some limitations that must be highlighted. In the first place, relating to the study design, although captured ALS participants were equivalent to non-captured ALS patients in terms of demographic and clinical characteristics, a difference in survival was observed driven by a high proportion of non-captured patients that suffered from a more aggressive form of the disease and died within the first year of diagnosis. Although our incident population-based ALS sample is considered a reasonably true representation of the Irish population, this has evident implications on the rate of neuropsychological impairment in ALS, which could be higher if we consider the most likely existing relationship between the rate of motor progression and frontotemporal dysfunction in ALS.

Regarding the language assessment protocol, some limitations need to be highlighted. At early stages of the disease, output orthographic processing deficits in ALS were not found to be significantly more frequent than in the general population. It appeared that tasks assessing input orthographic processing utilizing low frequent and more abstract words were more

sensitive to deficits in orthographic lexical processing in ALS. However, word reading and word spelling tasks were the ones considered for the classification of language impairment according to the revised diagnostic criteria for ALSci. This decision was based on the rationale that reading and writing paradigms are more frequently used to assess orthographic processing. However, the use of these tasks may have resulted in an underestimation of the incidence of orthographic lexical processing deficits in our ALS sample.

The PALPA, like other language batteries such as the BDAE or the FAB, is a test of aphasia and as such, people with no severe language impairments have minimal or no difficulty performing at it. This is reflected by the low ceiling that characterises the normative data presented in Chapter 6. As a consequence, it may be argued that the PALPA is not sufficiently sensitive in order to identify language dysfunction in those presentations that are milder in nature. This has been observed in our ALS sample. The PALPA was sensitive to detect language impairment in those ALS patients that presented with comorbid dementia, but when assessing language change in non-demented ALS, results weren't as discernible. Thus, ALS-FTD patients performed significantly lower than ALS patients, with medium to large effect sizes and scores that differed by several units, as seen in Table 7.22 (page 215). When comparing non-demented ALS patients to healthy controls, significant results were observed for some of the language tasks, but in this case effect sizes were small to medium, as seen in Table 7.5 (page 194). This was expected, given the high heterogeneity that characterises this patient group, which includes a high proportion of ALS patients that present with spared cognition. However, in some instances, significant differences on the PALPA were observed in cases where the difference in scores was minimal (e.g. Table 7.12, page 201), and therefore the clinical meaningfulness of such findings is questionable.

The above raises concerns regarding the clinical utility of the PALPA to detect subtle changes in those patients whose presentations are mild. An example of this has been given, when we highlighted that the PALPA Word Reading and Word Spelling paradigms were not sensitive to detect orthographic processing deficits that were, in fact, detected using a lexical decision task that included low frequent and more abstract words. The limited use of aphasia batteries to detect mild forms of language change is not restricted to the PALPA. For instance, the WAB-R demonstrated good diagnostic accuracy in aphasic patients, but not in a group of nonaphasic patients suffering from varied conditions involving diffuse brain damage affecting language (Kertesz, 2007), this proving that this tool is not sensitive to milder forms of language impairment. Therefore, language paradigms of increased difficulty, which reduce the ceiling effects observed in the normal population, and are therefore more sensitive to subtler forms of impairment, need to be developed and employed to assess language change in non-demented ALS patients.

Another limitation relating to the language assessment protocol concerns the assessment of action word processing, which was evaluated in our sample by means of confrontation naming and word fluency with the aim to assess word retrieval versus semantic processing of action words in ALS. Although we evaluated the semantic component of action word processing in ALS, its syntactic component was not addressed in this work. The involvement of motor-related cortical areas in the processing of action words has been demonstrated in ALS (Cousins et al., 2017; M. Grossman et al., 2008; York et al., 2014). However, other hypotheses exist to explain action word processing deficits, including the higher syntactical complexity of verbs, its abstractness or its higher executive component (Vigliocco et al., 2011; York et al., 2014). Our assessment of action word processing was therefore very basic. Moreover, we found that our ALS sample presented with word retrieval deficits for both objects and actions, but we cannot make any assumptions regarding the underlying cause of such deficits; whether these are both caused by the same underlying mechanics involving superior temporal and inferior frontal areas implicated in lexical retrieval or whether deficits in action word processing are caused by wider damage also involving motor-associated areas, as it has been previously shown (M. Grossman et al., 2008). Given that the possible dissociated nature of action versus object word retrieval deficits in ALS was not elucidated as part of this work, the former was not included in the classification criteria for ALSci. However, this may need to be reviewed in line of further evidence that action word processing deficits represent a separate impairment to that observed for nouns in ALS.

Moreover, we have not assessed verbal expressive language and, as per systematic review carried out in chapter 3, deficits have been reported (Ash et al., 2014; Ash et al., 2015; Gallassi et al., 1985; Roberts-South et al., 2012; Strong et al., 1999; Tsermentseli et al., 2015). The rationale for not including a measure of expressive language as part of our broad neuropsychological battery was to keep it concise, to minimise patient fatigue. Moreover, the assessment of verbal expressive language in those ALS patients that present with speech impediments is challenging. Nonetheless, we acknowledge the need to further investigate language production in ALS, including sentence organisation and discourse planning. Moreover, the study of pragmatics and its relationship to social cognition also needs consideration, as deficits have been reported in ALS (Bambini et al., 2016).

We included a task of emotional prosody as part of our assessment, with no significant differences observed between ALS patients and healthy controls. The psychometric characteristics of the Florida Affect Battery have not been thoroughly studied (Bowers et al., 1998), and its sensitivity to emotional prosody deficits in Irish population is unknown. Moreover, a task of cognitive theory of mind has also been considered, but no analyses on the relationship between these deficits and executive dysfunction in ALS have been performed.

Although this goes beyond the scope of this work, it is important to investigate the specific relationship when including such task for classification purposes of executive impairment.

The behavioural proxy measure used in this study was developed for the use in ALS population and it therefore intends to correct for the effect of motor dysfunction on behaviour (Elamin et al., 2017). In fact, the BBI has been validated against another ALS specific measure (i.e. the ALS-FTD-Q; Pinto-Grau, Costello, et al., 2017). However, there are several limitations that need to be considered as a consequence of retrofitting data from the BBI to the revised classification criteria for ALSbi in our sample, the first being the lack of comparative normal data. The presence of an impaired behaviour was considered if that was endorsed by proxy, but we did not determine the presence of behavioural change in our ALS sample in comparison to that of the general population. Moreover, apathy was only assessed through one item related to lack of motivation or interest. Apathy is known, however, to have various facets, also including emotional and executive dimensions (Radakovic et al., 2017). This could have underestimated the actual frequency of apathy symptoms in our ALS sample, and the multidimensional nature of apathy needs to be considered in the future when assessing this behavioural feature in ALS. Likewise, lack of insight and psychotic symptoms are not comprehensively assessed on the BBI. This is primarily relevant when considering the diagnosis of ALS-dementia, and highlights the lack of sensitivity of the BBI to detect the whole range of behavioural deficits characteristic of the ALS-FTSD. Furthermore, the validity of the BBI to assess behavioural change over time also requires examination. No studies to date have investigated the reliability of the BBI to assess behaviour over time and the effects that repeated exposure to the questionnaire have on the informant's answers. Accordingly, the increased prevalence of behavioural change reported in our ALS sample over time could represent an increased reporting rather than a true increase.

The lack of sensitivity of the BBI to the whole spectrum of behavioural change characteristic of the ALS-FTSD as well as the unknown validity of repeating this informant questionnaire over time are limitations that are not only characteristic of the BBI, but that also apply to other frequently employed ALS-specific behavioural assessments, such as the ALS-FTD-Q or the ECAS behavioural screen (Abrahams et al., 2014; Raaphorst et al., 2012). Therefore, there is a need to revise current behavioural proxy measures in ALS to improve its diagnostic accuracy to the spectrum of behavioural change characteristic of this disease, as well as to assess its reliability to repeatedly assess behaviour over time.

Finally, regarding sample sizes, there are some important aspects that need to be raised. Although minimum sample sizes estimated in our a priori sample size calculations were achieved for all cross-sectional analyses, 12% of our incident population-based sample could not be classified due to missing cognitive and/or behavioural data. This percentage considerably increases at longitudinal follow-up, which imply that longitudinal frontotemporal

classifications must be interpreted cautiously. Although the percentage of patients missing cognitive longitudinal data is comparable to that of cross-sectional data, a very high percentage of patients lacked longitudinal behavioural data. This is due to the fact that proxy measures were not completed in a high number of occasions (the questionnaires were not posted back to the researcher). In the future, a different approach to gathering behavioural data must be considered.

Another important issue is the substantial attrition observed in the patient group, which turned out to be 60% rather than 50% as was predicted when a priori sample size calculations were performed. This difference is due to the fact that predicted attrition was calculated based on a preliminary estimate from a study recruiting a population-based prevalent sample (Crockford et al., 2018), rather than an incident sample. As a consequence of such high attrition, the minimum sample size estimated to be necessary at time 4 was not achieved. As previously stated, patient attrition is an expected challenge to face in longitudinal ALS research due to the rapid, progressive and fatal nature of the disease. However, in our case, a high number of patients declined further involvement due to reasons that were not death or the development of further disability that precluded participation.

The experience of testing, which was long, could have had an impact on the drop out observed due to 'decline of further involvement', especially from T1 to T2. Although this was probably true in some cases, all methods were put in place to ensure patient comfort while completing the assessment. Thus, participants were offered breaks throughout, and were also encouraged to inform the researcher if they wished to skip any part of the assessment or discontinue at any stage, and this was seldom the case. Moreover, participants were offered the option of home-based assessments, which the vast majority of participants peferred. Despite every effort being made to ensure patients were able to engage in the research, there are likely multiple factors which contributed to drop out, such as the anticipated mental fatigue from completing neuropsychological tests, the emotional burden that might be associated with declining cognition, or simply the physical strain of performing an assessment with declining functionality. The lower rate of attrition in patients with behavioural impairment may have been due to apathy, affecting their initiative to discontinue.

Another aspect that could have contributed to the high attrition is the short length of the interval between repeat assessments, which was set at 4 months. Such as short retest interval was chosen to allow for meaningful longitudinal data to be collected at middle time points, given the high attrition rates that characterise longitudinal ALS research after a year follow up. It may be argued that if the retest interval had been longer, the testing experience could have been less tedious and therefore attrition could have been reduced. However, a previous longitudinal population-based study carried out in Ireland with retest intervals set at 6 months

reported 75% attrition rate after a year follow-up (Elamin et al., 2013). Therefore, longer retest intervals did not seem to improve longitudinal capture rates.

Regardless of the reasons for discontinuation, the high attrition rate observed in our sample, especially at time 4, have a significant impact on the interpretation of our longitudinal findings. Patients lost to attrition are those that present with more severe cognitive and motor presentations, and therefore there is a bias in the representation of our incident sample longitudinally. Moreover, the small sample sizes obtained when our ALS sample was segregated by frontotemporal syndromes as well as the small number of ALS patients that carried the C9orf72 mutation have most likely limited the power of our analyses to detect more subtle differences among groups. Given the adequate size of our incidence sample, which represents 50% of all ALS patients diagnosed within the recruitment period, and the fact that the percentage of C9orf72 positive patients within this sample is in line with the actual frequency of this genetic defect within the ALS population, studies with larger samples are needed to further characterise the clinical and genetic aspects of the various frontotemporal syndromes.

10.3. General Discussion, Conclusions and Future Directions

This is the first population-based study that characterises the entire spectrum of neuropsychological change characteristic of incident ALS cases. Despite the limitations stated above, we have achieved to determine the incidence and nature of language change in ALS, its relationship to executive dysfunction, and we have also established the incidence of frontotemporal syndromes in ALS according to revised diagnostic criteria (Strong et al., 2017). Moreover, the longitudinal evolution of neuropsychological change in our ALS incident sample has also been characterised. Finally, clinical and genetic characterisations of the various frontotemporal syndromes have also been accomplished.

Our findings support the notion that the neuropsychological profile in ALS falls along a spectrum of frontotemporal involvement (Strong et al., 2017). Thus, we have demonstrated the presence of incident frontotemporal syndromes that are relatively independent from each other. While some ALS patients do not develop cognitive nor behavioural deficits along with the motor symptoms at diagnosis, isolated cognitive or behavioural impairment can be present, as well as a more widespread frontotemporal dysfunction affecting both and a more severe dementia presentation. This most likely represents specific patterns of pathological depositions across frontostriatal and frontotemporal networks at initial stages of the disease.

The dissociation between cognitive and behavioural impairment in ALS most likely reflects distinct involvement of frontostriatal circuits, specifically those that encompass dorsolateral

prefrontal regions versus ventral prefrontal areas, respectively. The former are related to cognitive processes of executive function, whereas the latter are involved in emotional and behavioural self-regulation (Stuss & Levine, 2002). Thus, the dorsolateral prefrontal cortex is related to executive processes such as task setting, monitoring and manipulation of online-held information, rule detection, planning, reasoning and problem-solving, as well as switching and sustaining attention. The ventromedial or orbitofrontal cortex, on the other hand, is involved in processes of inhibitory control and self-regulation, self-awareness and reward/risk processing. Its connections to the limbic system also make it fundamental for emotional processing. Moreover, ventromedial areas are also involved in the processing of mental states, attitudes and beliefs in oneself and others, which relates to the ability to empathise and make social judgements. Finally, the anterior cingulate cortex, in the medial prefrontal cortex, is also involved in selective attentional control, error monitoring and self-correction, as well as on initiation and self-motivation.

The dissociation between executive and language deficits in ALS is also likely to represent specific patterns of frontotemporal involvement that, in the case of language change, extend to language centres such as the inferior frontal cortex, the anterior superior temporal cortex and the fusiform gyrus. Inferior frontal and superior temporal regions are implicated in lexical retrieval as well as in grammatical and syntactic processing (Fridriksson et al., 2018; Thompson & Kielar, 2014), and the left posterior middle temporal gyrus, also known as fusiform gyrus, have been implicated in the retrieval of orthographic lexical representations of words (Jobard et al., 2003).

Different patterns of disease spread are likely to determine the presence of distinct disease phenotypes in ALS (M. Grossman, 2019). Our results further support this idea. Thus, there appears to be a subgroup of ALS patients that suffer from a more aggressive form of the disease that involve wider and more rapid spread of pathology across frontal areas and their connections to other relevant cortical and subcortical regions. These patients present with more severe forms of frontotemporal involvement that cause more generalised cognitive presentations including executive dysfunction and language impairment, along with behavioural change. They are also characterised by a more rapid progression of motor symptoms, especially bulbar function, and shorter survival. On the other hand, there also seems to be a purer motor phenotype characterised by slower and more contained pathological spread. Whether this represents a pure ALS phenotype with no frontotemporal involvement or whether it represents a very slow progressive phenotype with cognitive and behavioural changes occurring at later stages requires further investigation. In accordance with the latter, evidence exists to suggest the sequential spread of TDP-43 pathology from the motor system to prefrontal and temporal regions in ALS (Brettschneider et al., 2013). This

needs further confirmation by combining clinical, neuropsychological, neuroradiologocal and pathological data.

The link between the C9orf72 ALS genotype and different mechanisms of pathological propagation are also further supported by our results. Thus, our data suggest that different ALS genotypes may distinctly determine the pattern and speed of disease spread in ALS. Thus, ALS patients carrying the C9orf72 hexanucleotide repeat expansion or some other unidentified genetic mutation were characterised by a more extensive propagation of ALS pathology also affecting cognitive and behavioural function, whereas sporadic ALS patients more frequently presented with less aggressive forms of disease spread.

Neuropsychological status at early stages of the disease in ALS, in conjunction with specific clinical and genotypic presentations, are therefore relevant phenotypic markers that inform disease progression. Accordingly, it is important for clinical trials to include neuropsychological status as a stratification parameter for prognostication purposes. In fact, the revised diagnostic criteria for frontotemporal syndromes in ALS recommend that an assessment moderate in depth (Level II) is carried out with this aim when ALS patients are enrolled in clinical trials (Strong et al., 2017).

The accurate diagnosis of cognitive and behavioural impairment in ALS also has important implications related to the management of the disease. As already stated, neuropsychological dysfunction in ALS is associated with reduced engagement, adherence and compliance with life-prolonging interventions, which affect disease course and survival. There are also some safety concerns to consider in patients with cognitive and behavioural deficits, such an increased risk of falls or choking episodes. Moreover, cognitive and behavioural deficits also interfere with the patient's capacity to make informed care related and end-of-life decisions. Therefore, knowledge about the neuropsychological status of a patient is crucial for safety awareness as well as for informed decisions to be made regarding disease management by healthcare professionals and by patients and their families. In some cases, the patient may lack capacity to make informed decisions and a third person may need to be appointed to make these on his/her behalf.

Neuropsychological evaluations should therefore be considered part of the routine clinical care in ALS. Tools for the screening of cognitive and behavioural change in ALS have been developed, and it is highly recommended that these are employed in clinical settings to identify those cases that may require further neuropsychological input (*Motor Neurone Disease: assessment and management. NICE guideline*, 2016; Strong et al., 2017). Moreover, it is important to monitor neuropsychological symptoms across the course of the disease to adapt the interventions as required. It is also important to explain to ALS patients and their families

why the need to screen for cognition and behaviour in ALS as well as to give appropriate feedback regarding any symptoms that may be relevant to them (Wicks & Albert, 2018).

No evidence-based studies exist up to date that assess the efficacy of non-pharmacological interventions to manage cognitive and behavioural change in ALS, although some evidence exists supporting the effectiveness of behavioural interventions and environmental management strategies in bvFTD patients, which can be cautiously extrapolated to ALS (Caga et al., 2019). Cognitive and behavioural change, especially the latter, are also related to caregiver burden. Thus, prompt and comprehensive interventions are crucial not only to better manage cognitive and behavioural symptoms in ALS, but also to prevent further strain and distress on the caregivers (Merrilees, Klapper, Murphy, Lomen-Hoerth, & Miller, 2010). Therefore, psychoeducation for family members of ALS patients to provide them with adequate information regarding the nature, implications and management of cognitive and behavioural impairment in ALS are also vital.

It is also important to examine how specific cognitive scores translate into real-life deficits, by complementing neuropsychological measures with operationalised functional indicators (Duff, 2012). The consequences that severe cognitive and behavioural presentations as well as comorbid dementia have on ALS patients and their families are acknowledged. However, further research is required to assess how milder forms of impairment in ALS affect their functional outcomes, to inform the development of tailored interventions and supports.

Further research is also required to continue elucidating the nature of language change in ALS. Some aspects have already been mentioned earlier, including the need to further explore language change in non-demented ALS patients using paradigms that are more sensitive to mild forms of impairment, to assess the processing of action words, verbal expressive language, discourse and pragmatics and how these relate to social cognition, as well as the interference that apathy may have on language output in ALS.

Memory dysfunction in ALS also needs further investigation. This cognitive domain is excluded from the revised diagnostic criteria for ALS with cognitive impairment given the lack of consensus regarding the nature of memory deficits in ALS (Strong et al., 2017). For this reason, memory function has not been analysed as part of this work. Nevertheless, deficits in encoding and retrieval as well as in retention and recognition processes have been reported (Beeldman et al., 2016; Strong et al., 2017). The former are subserved by frontal-subcortical circuits whilst the latter are related to medial temporal lobe function (Eichenbaum, Yonelinas, & Ranganath, 2007; Nyberg, Cabeza, & Tulving, 1996; Sarazin et al., 2010). The actual nature of memory deficits in ALS and whether more generalised memory impairments represent more aggressive forms of the disease that further extend to medial temporal areas require further investigation.

Finally, the relationship between language impairments in non-demented ALS patients and language-variant FTD developing alongside ALS also needs further consideration. As already discussed in chapter 3, evidence exists suggesting that the occurrence of PPA alongside ALS is significantly lower than that of the non-ALS population, and that the ALS-FTD presentation may represent a separate phenotype associated with mixed behavioural and language impairments (Saxon, Harris, et al., 2017; Saxon, Thompson, et al., 2017). Further studies are needed that investigate the profile of neuropsychological change in ALS-FTD patients in comparison to that of pure FTD syndromes.

In conclusion, this study contributes to the characterisation of the heterogeneous neuropsychological profile of ALS and demonstrates the importance of evaluating the entire spectrum of deficits that result from frontotemporal dysfunction. Neuropsychological status in ALS has been proven to be an important disease marker with significant implications for disease management and prognosis.

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Appendices

Appendix A

Revised Diagnostic Criteria for Behavioural Variant FTD (Rascovsky et al., 2011)

I. Neurodegenerative Disease
The following symptom must be present to meet criteria for bvFTD:

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD
Three of the following behavioural/cognitive symptoms (A-F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early[a] behavioural disinhibition [one of the following symptoms (A.1 – A.3) must be present]:
   A.1. Socially inappropriate behaviour
   A.2. Loss of manners or decorum
   A.3. Impulsive, rash or careless actions
B. Early apathy or inertia [one of the following symptoms (B.1 – B.2) must be present]:
   B.1. Apathy
   B.2. Inertia
C. Early loss of sympathy or empathy [one of the following symptoms (C.1 – C.2) must be present]:
   C.1. Diminished response to other people's needs and feelings
   C.2. Diminished social interest, interrelatedness or personal warmth
D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1 – D.3) must be present]:
   D.1. Simple repetitive movements
   D.2. Complex, compulsive or ritualistic behaviours
   D.3. Stereotypy of speech
E. Hyperorality and dietary changes [one of the following symptoms (E.1 – E.3) must be present]:
   E.1. Altered food preferences
   E.2. Binge eating, increased consumption of alcohol or cigarettes
   E.3. Oral exploration or consumption of inedible objects
F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1 – F.3) must be present]:
   F.1. Deficits in executive tasks
   F.2. Relative sparing of episodic memory
   F.3. Relative sparing of visuospatial skills

III. Probable bvFTD
All of the following symptoms (A-C) must be present to meet criteria.

A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaires scores)
C. Imaging results consistent with bvFTD [one of the following (C.1 – C.2) must be present]:
   C.1. Frontal and/or anterior temporal atrophy on MRI or CT
   C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. bvFTD with definite FTLD pathology
Criterion A and either criterion B or C must be present to meet criteria:

A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD on biopsy or at post-mortem
C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorder
B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

[a] As a general guideline 'early' refers to symptom presentation within the first 3 years

Appendix B

Diagnostic Classification of Primary Progressive Aphasia (Gorno-Tempini et al., 2011)

Inclusion and exclusion criteria for the diagnosis of PPA:

I. Inclusion:

Criteria 1-3 must be answered positively:

1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficits at symptom onset and for the initial phases of the disease

II. Exclusion:

Criteria 1-4 must be answered negatively:

1. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
4. Prominent initial behavioural disturbance

Diagnostic features for the nonfluent/agrammatic variant PPA:

I. Clinical diagnosis of nonfluent/agrammatic variant PPA

At least one of the following core features must be present:

1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

At least 2 of 3 of the following other features must be present:

1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

II. Imaging-supported nonfluent/agrammatic variant diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant left posterior fronto-insular atrophy on MRI, or
   b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

III. Nonfluent/agrammatic variant PPA definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Diagnostic criteria for the semantic variant PPA

I. Clinical diagnosis of semantic variant PPA

Both of the following core features must be present:

1. Impaired confrontation naming
2. Impaired single-word comprehension

At least 3 of the following other diagnostic features must be present:

1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

II. Imaging-supported semantic variant PPA diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one of more of the following results:
   a. Predominant anterior temporal lobe atrophy

b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

III. Semantic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of semantic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Diagnostic criteria for logopenic variant PPA

I. Clinical diagnosis of logopenic variant PPA

Both the following core features must be present:

1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases

At least 3 of the following other features must be present:

1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism

II. Imaging-supported logopenic variant diagnosis

Both criteria must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
   a. Predominant left posterior perisylvian or parietal atrophy on MRI
   b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

III. Logopenic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Appendix C

Clinical Diagnostic Criteria for Frontotemporal Lobar Degeneration (Neary et al., 1998)

Clinical diagnostic features of FTD: Clinical profile

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

I. Core diagnostic features:
- A. Insidious onset and gradual progression
- B. Early decline in social interpersonal conduct
- C. Early impairment in regulation of personal conduct
- D. Early emotional blunting
- E. Early loss of insight

II. Supportive diagnostic features
- A. Behavioural disorder
  1. Decline in personal hygiene and grooming
  2. Mental rigidity and inflexibility
  3. Distractibility and impersistence
  4. Hyperorality and dietary changes
  5. Perseverative and stereotyped behaviour
  6. Utilization behaviour
- B. Speech and language
  1. Altered speech output
     - a. Aspontaneity and economy of speech
     - b. Press of speech
  2. Stereotypy of speech
  3. Echolalia
  4. Perseveration
  5. Mutism
- C. Physical signs
  1. Primitive reflexes
  2. Incontinence
  3. Akinesia, rigidity, and tremor
  4. Low and labile blood pressure
- D. Investigations
  1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder
  2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
  3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

Clinical diagnostic features of progressive nonfluent aphasia: Clinical profile

Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.

I. Core diagnostic features:
- A. Insidious onset and gradual progression
- B. Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia

II. Supportive diagnostic features:
- A. Speech and language
  1. Stuttering or oral apraxia
  2. Impaired repetition
  3. Alexia, agraphia
  4. Early preservation of word meaning
  5. Late mutism
- B. Behaviour

1. Early preservation of social skills
2. Late behavioural changes similar to FTD

C. Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor
D. Investigations
1. Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder
2. Electroencephalography: normal or minor asymmetric slowing
3. Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere

Clinical diagnostic features of semantic aphasia and associative agnosia (SD): Clinical profile

Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant features initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well preserved.

I. Core diagnostic features:
A. Insidious onset and gradual progression
B. Language disorder characterised by
1. Progressive, fluent, empty spontaneous speech
2. Loss of word meaning, manifest by impaired naming and comprehension
3. Semantic paraphasias, and/or

C. Perceptual disorder characterised by
1. Prosopagnosia: impaired recognition of identity of familiar faces, and/or
2. Associative agnosia; impaired recognition of object identity

D. Preserved perceptual matching and drawing reproduction
E. Preserved single-word repetition
F. Preserved ability to read aloud and write to dictation orthographically regular words

II. Supportive diagnostic features:
A. Speech and language
1. Press of speech
2. Idiosyncratic word usage
3. Absence of phonemic paraphasias
4. Surface dyslexia and dysgraphia
5. Preserved calculation

B. Behaviour
1. Loss of sympathy and empathy
2. Narrowed preoccupations
3. Parsimony

C. Physical signs
1. Absent or late primitive reflexes
2. Akinesia, rigidity, and tremor

D. Investigations
1. Neuropsychology
a. Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
b. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing
2. Electroencephalography: normal
3. Brain imaging (structural and/or functional): predominant anterior temporal abnormality (symmetric or asymmetric)

Features common to clinical syndromes of FTLD (extension of list 1 through 3)

III. Supportive features:
A. Onset before 65 years: positive family history of similar disorder in a first degree relative
B. Bulbar palsy, muscular weakness and wasting, fasciculations (associated motor neuron disease present in a minority of patients)

IV. Diagnostic exclusion features:
A. Historical and clinical
1. Abrupt onset with ictal events
2. Head trauma related to onset
3. Early, severe amnesia
4. Spatial disorientation

5. Logoclonic, festinant speech with loss of train of thought
6. Myoclonus
7. Corticospinal weakness
8. Cerebellar ataxia
9. Choreoathetosis

B. Investigations
1. Brain imaging: predominant postcentral structural or functional deficit; multifocal lesions on CT or MRI
2. Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS, and herpes simplex encephalitis

V. Relative diagnostic exclusion features
A. Typical history of chronic alcoholism
B. Sustained hypertension
C. History of vascular disease (e.g. angina, claudication)

Appendix D

Revised Diagnostic Criteria for Alzheimer's Disease (McKhann et al., 2011)

I. Core clinical criteria for all-cause dementia

Dementia is diagnosed when there are cognitive or behavioural (neuropsychiatric) symptoms that:

A. Interfere with the ability to function at work or at usual activities; and
B. Represent a decline from previous levels of functioning and performing; and
C. Are not explained by delirium or major psychiatric disorder;
D. Cognitive impairment is detected and diagnosed through a combination of:
    1. History-taking from the patients and a knowledgeable informant, and
    2. An objective cognitive assessment, either "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
E. The cognitive and behavioural impairment involves a minimum of two of the following domains:
    1. Impaired ability to acquire and remember new information – symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
    2. Impaired reasoning and handling of complex tasks, poor judgement – symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
    3. Impaired visuospatial abilities – symptoms include: inability to recognise faces or common objects or to find object in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
    4. Impaired language functions (speaking, reading, writing) – symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
    5. Changes in personality, behaviour, or comportment – symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviours, socially unacceptable behaviours.

II. Probable AD dementia: Core Clinical Criteria

Meets core clinical criteria for all-cause dementia, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
    1. Amnestic presentation: Is it the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
    2. Nonamnestic presentations:
        a. Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
        b. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
        c. Executive dysfunction: The most prominent deficits are impaired reasoning, judgement, and problem solving. Deficits in other cognitive domains should be present.
D. The diagnosis of probable AD dementia should not be applied when there is evidence of:
    1. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
    2. Core features of Dementia with Lewy Bodies other than the dementia itself; or

3. Prominent features of bvFTD; or
4. Prominent features of semantic variant PPA or nonfluent/agrammatic variant PPA; or
5. Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

III. Probable AD dementia with increased level of certainty

A. Probable AD dementia with documented decline:
Defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardised mental status examinations.
Documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology.

B. Probable AD dementia in a carrier of a causative AD genetic mutation:
Evidence of a causative genetic mutation (in *APP*, *PSEN1*, or *PSEN2*), increases the certainty that the condition is caused by AD pathology. Carriage of the ε4 allele of the apolipoprotein E gene is not sufficiently specific to be considered in this category.

IV. Possible AD dementia: Core Clinical Criteria

A diagnosis of possible AD dementia should be made in either of the following circumstances:

A. Atypical course:
Meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline; or

B. Etiologically mixed presentation:
Meets all core clinical criteria for AD dementia but has evidence of:
1. Concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
2. Features of Dementia with Lewy Bodies other than the dementia itself; or
3. Evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

V. Probable AD dementia with evidence of the AD pathophysiological process

In persons who meet the core clinical criteria for probable AD dementia, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, the use of AD biomarker tests for routine diagnostic purposes is no advocated at the present time.

VI. Possible AD dementia with evidence of the AD pathophysiological process

For persons who meet clinical criteria for a non-AD dementia but who have either biomarker evidence of AD pathophysiological process, or meet the neuropathological criteria for AD. This diagnosis does not preclude the possibility that a second pathophysiological condition is also present.

VII. Pathophysiologically proved AD dementia

If the patient meets the clinical and cognitive criteria for AD dementia outlined earlier in the text, and the neuropathological examination demonstrates the presence of the AD pathology.

VIII. Dementia unlikely to be due to AD

In cases where:

A. Clinical criteria for AD dementia is not met; or

B. When:
1. Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington's disease, or others that rarely, if ever, overlap with AD.
2. Regardless of meeting clinical criteria for possible AD dementia, both Aβ and neuronal injury biomarkers are negative.

Appendix E

The Study of Language in the ALS-FTSD: A Systematic Review Protocol

1. Introduction

1.1 Rationale for the review

Amyotrophic Lateral Sclerosis (ALS), the most common form of Motor Neurone Disease (MND), is a heterogeneous disease associated with cognitive and behavioural changes that involve frontotemporal and frontostriatal circuits (Tsermentseli et al., 2012). Cognitive changes are present in up to 50% of newly diagnosed ALS patients and approximately 14% also meet criteria for the diagnosis of comorbid Frontotemporal Dementia (FTD: Phukan et al., 2012).

The magnitude and nature of cognitive impairment in ALS seems to vary within patients. Executive dysfunction has been widely studied in ALS and it has been described as the most common form of impairment (Goldstein & Abrahams, 2013). Although, as per consensus criteria, language is not considered a core symptom for the diagnosis of frontotemporal cognitive and behavioural syndromes in ALS (Strong et al., 2009), current reports suggest that language impairment is also present (Beeldman et al., 2016). In fact, language is considered one of the ALS-specific cognitive domains assessed on the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), a multi-domain cognitive screen specifically developed for the use in ALS population (Abrahams et al., 2014; Niven et al., 2015). Nevertheless, it has been suggested that although language changes have been long suspected and sporadically shown in ALS, the study of such cognitive domain has been relatively neglected and lacks systematic study (Abrahams, 2013).

One of the studies up to date that comprehensively evaluates language in ALS suggests that language impairment could be as prevalent as executive dysfunction (Taylor et al., 2013). However, this conclusion is based on findings from a prevalent ALS sample, and it is the case that the characteristics of cognitive impairment in ALS depend on whether incident or prevalent samples are being studied. There are other methodological factors which are also crucial to consider when evaluating results from cognitive studies in ALS such as sample size, referral bias, inclusion of comparative control groups and accommodation for motor disability, among others. Thus, not only the presence but also the methodological robustness of the studies evaluating language in ALS needs to be evaluated.

1.2 Objectives

The objectives of this systematic review are twofold:

(1) To review the literature to identify neuropsychological findings of language changes in ALS.
(2) To evaluate methodological characteristics of such studies, to determine the accuracy of the results.

2. Methods

2.1 Search strategy and information sources

A search of the following electronic databases will be conducted: MEDLINE (via PubMed), PsychINFO (via EBSCOhost) and Science Direct. Search terms will include the population of interest in the title (Amyotrophic Lateral Sclerosis or Motor Neurone Disease), as well as the condition of interest in the title and/or abstract (neuropsychological or cognitive deficits/changes, language deficits/changes, or aphasia). The same search strategy will be used for the three databases consulted, with appropriate adaptations for each database interface. Medical Subject Headings and truncation of search terms will be employed, where appropriate. Refer to Table 1 for specific details of the search strategy.

Table 1. Details of search strategy

Search item:
1. ("Amyotrophic Lateral Sclerosis" OR "ALS" OR "Motor Neurone Disease" OR "MND")
2. ("Neuropsycho*" OR "Cogniti*" OR "Language" OR "Aphasia")

Additional searches will also consider (1) backward & forward reference searching, (2) "snowball" searching, and (3) identification of "grey" literature such as conference abstracts or Google Scholar. Results from these additional searches will only be considered if they present new relevant information. The search time frame will extend from January 1975 to August 2017.

2.2 Eligibility Criteria

Predefined criteria for eligibility of the studies will be as follows:

2.2.1 Types of participants/population:

Participants of interest are those with a diagnosis of ALS, also called MND in some areas. Studies evaluating disorders of the family of the motor neuron diseases other than ALS, such as Primary Lateral Sclerosis (PLS) or Progressive Muscular Atrophy (PMS), will not be included.

The main population of study will be ALS patients with no comorbid diagnosis of Frontotemporal Dementia (FTD) or any other type of dementia. However, studies including both non-demented ALS patients and ALS patients with comorbid dementia will also be considered.

2.2.2 Type of study design:

Quantitative observational studies of both cross-sectional and longitudinal nature will be included. Case studies will also be considered. No minimum sample size restrictions or geographical constraints will be applied, but only studies published in English will be included.

2.2.3 Types of assessments:

Included studies will focus on neuropsychological performance of the population of interest assessed by means standardised measures of cognitive functioning. Studies employing non-standardised measures

will only be considered if they present relevant new information and if some kind of normative data is presented (e.g. comparative healthy control group). Studies restricted to the use of screening tools will not be included.

2.2.4 Types of outcome measures

Language is the outcome of interest, measured in terms of performance on the following subdomains: (1) verbal expressive language, (2) verbal fluency, (3) confrontation naming, (4) semantic processing, (5) auditory comprehension, (6) action verb processing vs object noun processing, and (7) reading and writing.

2.2.5 Exclusion criteria

Exclusion criteria will be as follows: (1) qualitative studies, (2) studies that assess a linguistic aspect not considered above, (3) studies that solely assess ALS patients meeting criteria for the diagnosis of Frontotemporal Dementia (FTD) or any other dementia type, (4) other reviews or meta-analysis, or (5) studies published in a language other than English.

2.3 Study records

After completion of the electronic searches and removal of duplicates, the selection process will start. At the screening stage, all titles, abstracts, and methods sections where necessary, will be screened. Full articles that move to the eligibility stage will then be examined for suitability as per outlined criteria. For any excluded article, reason for the same will be recorded. Articles meeting eligibility criteria will be included in the systematic review. All this process will be documented in a PRISMA flow diagram (Liberati et al., 2009).

Data extraction will be based on a data extraction form which will include the following information: (1) authors, (2) title, (3) year, (4) study design, (5) patient sample size, (6) incident vs prevalent sample, (7) clinic-based vs population-based sample, (8) inclusion of control group, and sample size of the same where appropriate, (9) number of language tests included and details of the same, and (10) utilisation of corrections for motor disability.

2.4 Planned critical appraisal

As per best practice, the development of this protocol is based on the reporting guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols (PRISMA-P: Moher et al., 2015), and PRISMA guidelines (Liberati et al., 2009) will be employed to report the systematic review.

Risk of bias within and across individual studies will be evaluated and reported, considering factors relating to study design, selection of participants, data sources, quantitative variables and statistical methods. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be used to guide the identification of potential study bias (Von Elm et al., 2014).

2.5 Data synthesis

A systematic narrative synthesis of the findings will be presented in an article format, which will be submitted for publication to a peer reviewed journal. The findings will be structured around the eight outcome measures outlined above, and a table will also be incorporated to synthetize the most relevant methodological aspects of each study. Due to the expected heterogeneity of the outcome measures and other methodological factors of the studies of interest, a meta-analysis is not considered an appropriate method of synthesis of this work.

2.6 Timeline

Anticipated completion date is September 2017.

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Appendix F

Supplementary Neuropsychological Measures

Memory and visuospatial measures included as part of the broader battery, which allowed for the diagnosis of comorbid-dementia cases:

Memory

1. **Rey Auditory Verbal Learning Test (RAVLT: Schmidt, 1996).**

   Assesses encoding and acquisition of new information, retention, susceptibility to retroactive and proactive interference, spontaneous recall and recognition of the information.

2. **Logical Memory subtest from the Wechsler Memory Scale, fourth edition (WMS-IV: Wechsler, 2009).**

   Examines the ability to recall and recognise multiple elements from sequences forming logical stories.

3. **Rey Complex Figure Test (RCFT: Meyers & Meyers, 1995), recall.**

   Evaluates the ability to recall and recognise visual elements from a previously copied complex figure.

Visuospatial Abilities

1. **Rey Complex Figure Test (RCFT), copy.**

   Assesses visuoconstructive abilities through the copy of a complex figure.

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Appendix G

Validation and Standardisation of the PALPA: Supplementary Material

Table 1. Lexical Decision Tasks Items

Auditory Lexical Decision				Visual Lexical Decision			
Item number on original form	**Item**	**Word / Nonword**	**Frequency / Imageability**	**Item number on original form**	**Item**	**Word / Nonword**	**Frequency / Imageability**
1	Episode	*Word*	*LF, LI*	61	Effort	*Word*	*HF, LI*
2	Theory	*Word*	*HF, LI*	62	Fire	*Word*	*HF, LI*
3	Elbow	*Word*	*LF, HI*	63	Tribute	*Word*	*HF, LI*
4	Minner	*Nonword*		64	Vallige	*Nonword*	
5	Hotel	*Word*	*HF, HI*	65	Fact	*Word*	*HF, LI*
6	Potato	*Word*	*LF, HI*	66	Dend	*Nonword*	
7	Wembow	*Nonword*		67	Valour	*Word*	*LF, LI*
8	Puct	*Nonword*		68	Idea	*Word*	*HF, LI*
9	Church	*Word*	*HF, HI*	69	Funnel	*Word*	*LF, HI*
10	Clenth	*Nonword*		70	Purpise	*Nonword*	
11	Plen	*Nonword*		71	Gramy	*Nonword*	
12	Folly	*Word*	*LF, LI*	72	Tractor	*Word*	*LF, HI*
13	Reash	*Nonword*		73	Length	*Word*	*HF, LI*
14	Sutire	*Nonword*		74	Plea	*Word*	*LF, LI*
15	Gravity	*Word*	*LF, LI*	75	Pheory	*Nonword*	
16	Slape	*Nonword*		76	Ragio	*Nonword*	
17	Trenson	*Nonword*		77	Manner	*Word*	*HF, LI*
18	Irony	*Word*	*LF, LI*	78	Itony	*Nonword*	
19	Dunkey	*Nonword*		79	Pupit	*Nonword*	
20	Foaster	*Nonword*		80	Realm	*Word*	*LF, LI*
21	Fide	*Nonword*		81	Pisture	*Nonword*	
22	Tanacco	*Nonword*		82	Slope	*Word*	*LF, HI*
23	Crisis	*Word*	*HF, LI*	83	Merly	*Nonword*	
24	Prath	*Nonword*		84	Shality	*Nonword*	
25	Battle	*Word*	*HF, HI*	85	Window	*Word*	*HF, HI*
26	Clue	*Word*	*LF, LI*	86	Treason	*Word*	*LF, LI*
27	Concept	*Word*	*HF, LI*	87	Drister	*Nonword*	
28	Spider	*Word*	*LF, HI*	88	Drum	*Word*	*LF, HI*
29	Village	*Word*	*HF, HI*	89	Cart	*Word*	*LF, HI*
30	Deed	*Word*	*LF, LI*	90	Halocle	*Nonword*	
31	Gravy	*Word*	*LF, HI*	91	Boncept	*Nonword*	
32	Fict	*Nonword*		92	Miracle	*Word*	*LF, LI*
33	Dogma	*Word*	*LF, LI*	93	Hospital	*Word*	*HF, HI*
34	Idia	*Nonword*		94	Nirth	*Nonword*	
35	Weast	*Nonword*		95	Pell	*Nonword*	
36	Opinion	*Word*	*HF, LI*	96	Crasis	*Nonword*	
37	Afe	*Nonword*		97	Binus	*Nonword*	
38	Alcohol	*Word*	*LF, HI*	98	Pib	*Nonword*	
39	Fannel	*Nonword*		99	Audience	*Word*	*HF, HI*
40	Trantor	*Nonword*		100	Attitude	*Word*	*HF, LI*
41	Picture	*Word*	*HF, HI*	101	Settion	*Nonword*	
42	Calt	*Nonword*		102	Wrath	*Word*	*LF, LI*
43	Pline	*Nonword*		103	Letter	*Word*	*HF, HI*

Abbreviations. LF: Low Frequency, HF: High Frequency, LI: Low Imageability, HI: High Imageability.
Note. Higher frequency of a word facilitates lexical access, and an effect of imageability may indicate that the subject is helping the decision by accessing its meaning too (Kay et al., 1992).

Table 1 (continued). Lexical Decision Tasks Items

Auditory Lexical Decision				Visual Lexical Decision			
Item number on original form	**Item**	**Word / Nonword**	**Frequency / Imageability**	**Item number on original form**	**Item**	**Word / Nonword**	**Frequency / Imageability**
44	Drim	*Nonword*		104	Opunion	*Nonword*	
45	Thought	*Word*	*HF, LI*	105	Felly	*Nonword*	
46	Mercy	*Word*	*LF, LI*	106	Pitaro	*Nonword*	
47	Radio	*Word*	*HF, HI*	107	Principle	*Word*	*HF, LI*
48	Prisciple	*Nonword*		108	Prought	*Nonword*	
49	Pupil	*Word*	*LF, HI*	109	Apisade	*Nonword*	
50	Stadent	*Nonword*		110	Plane	*Word*	*HF, HI*
51	Onion	*Word*	*LF, HI*	111	Student	*Word*	*HF, HI*
52	Mimber	*Nonword*		112	Moment	*Word*	*HF, LI*
53	Loment	*Nonword*		113	Slurch	*Nonword*	
54	Purpose	*Word*	*HF, LI*	114	Otion	*Nonword*	
55	Quality	*Word*	*HF, LI*	115	Feather	*Word*	*LF, HI*
56	School	*Word*	*HF, HI*	116	Hetal	*Nonword*	
57	Sammer	*Nonword*		117	Pact	*Word*	*LF, LI*
58	System	*Word*	*HF, LI*	118	Mother	*Word*	*HF, HI*
59	Elephant	*Word*	*LF, HI*	119	Sprool	*Nonword*	
60	Mither	*Nonword*		120	Grivity	*Nonword*	
61	Hopsitle	*Nonword*					
62	Pig	*Word*	*LF, HI*				
63	Antitude	*Nonword*					
64	Trabite	*Nonword*					
65	Session	*Word*	*HF, LI*				
66	Dalour	*Nonword*					
67	Andience	*Nonword*					
68	Night	*Word*	*HF, HI*				
69	Baranter	*Nonword*					
70	Voe	*Nonword*					
71	Marriage	*Word*	*HF, HI*				
72	Luttter	*Nonword*					
73	Thing	*Word*	*HF, LI*				
74	Bonus	*Word*	*LF, LI*		-		
75	Hend	*Nonword*					
76	Affort	*Nonword*					
77	Minacle	*Nonword*					
78	Coffee	*Word*	*HF, HI*				
79	Pill	*Word*	*LF, HI*				
80	Analogy	*Word*	*LF, LI*				

Abbreviations. LF: Low Frequency, HF: High Frequency, LI: Low Imageability, HI: High Imageability.
Note. Higher frequency of a word facilitates lexical access, and an effect of imageability may indicate that the subject is helping the decision by accessing its meaning too (Kay et al., 1992).

Table 2. Spelling and Reading Tasks Items

Spelling to dictation			Oral Reading		
Words (Regularity)		**Nonwords**	**Words (Regularity)**		**Nonwords**
Item	**Regular / Irregular**	**Item**	**Item**	**Regular / Irregular**	**Item**
Elephant	*Irregular*	Bem	Effort	*Regular*	Ked
Aunt	*Irregular*	Cug	Pretty	*Irregular*	Nar
Egg	*Irregular*	Lat	Middle	*Regular*	Fon
Squirrel	*Irregular*	Boak	Barge	*Regular*	Shid
Bump	*Regular*	Birl	Break	*Irregular*	Doop
Sword	*Irregular*	Soaf	Envy	*Regular*	Dusp

Table 2 (continued). Spelling and Reading Tasks Items

Spelling to dictation			Oral Reading		
Words (Regularity)		Nonwords	Words (Regularity)		Nonwords
Item	**Regular / Irregular**	**Item**	**Item**	**Regular / Irregular**	**Item**
Hold	*Regular*	Hance	Blood	*Irregular*	Snite
Bird	*Regular*	Smode	Bowl	*Irregular*	Hoach
Giraffe	*Irregular*	Grest	Plank	*Regular*	Glope
Spring	*Regular*	Squate	Navy	*Regular*	Dringe
Wind	*Regular*	Thease	Ceiling	*Irregular*	Churse
Canal	*Regular*	Pretch	Iron	*Irregular*	Shoave
Soldier	*Irregular*		Cough	*Irregular*	
Tiger	*Regular*		Context	*Regular*	
Potato	*Regular*		Rub	*Regular*	
Sister	*Regular*		Routine	*Irregular*	
Cat	*Regular*		Bury	*Irregular*	
Photograph	*Irregular*		Yacht	*Irregular*	
Lamb	*Irregular*		Flannel	*Regular*	
Caravan	*Regular*		Tail	*Regular*	
Knock	*Irregular*		Wolf	*Irregular*	
Holiday	*Regular*		Island	*Irregular*	
Jam	*Regular*		Wedding	*Regular*	
Ghost	*Irregular*		Chicken	*Regular*	
Pet	*Regular*		Colonel	*Irregular*	
Shoe	*Irregular*		Luck	*Regular*	
Move	*Irregular*		Smog	*Regular*	
Queen	*Irregular*		Nerve	*Regular*	
Sledge	*Irregular*		Sew	*Irregular*	
Yacht	*Irregular*		Sword	*Irregular*	
Watch	*Irregular*		Shoe	*Irregular*	
Castle	*Irregular*		Bouquet	*Irregular*	
Tent	*Regular*		Castle	*Irregular*	
Nest	*Regular*		Brandy	*Regular*	
Swim	*Regular*		Pint	*Irregular*	
Robin	*Regular*		Check	*Regular*	
Heart	*Irregular*		Mist	*Regular*	
Aeroplane	*Irregular*		Stench	*Regular*	
Banana	*Regular*		Tomb	*Irregular*	
Frog	*Regular*		Peril	*Regular*	
			Choir	*Irregular*	
			Come	*Irregular*	
			Cult	*Regular*	
			Plant	*Regular*	
			Gauge	*Irregular*	
			Sure	*Irregular*	
			Friction	*Regular*	
			Debt	*Irregular*	
			Free	*Regular*	
			Curb	*Regular*	
			Marsh	*Regular*	
			Market	*Regular*	
			Pump	*Regular*	
			Cord	*Regular*	
			Brooch	*Irregular*	
			Take	*Regular*	
			Mortgage	*Irregular*	
			Answer	*Irregular*	
			Soul	*Irregular*	
			Quay	*Irregular*	

Table 3. Word – Picture Matching Tasks Items

Spoken Word – Picture Matching

Item number on original form	Item	Close Semantic Distractor [a]	Distant Semantic Distractor	Visually Related Distractor [b]	Unrelated Distractor [b]
1	Carrot	*Cabbage*	*Lemon*	*Saw*	*Chisel*
3	Hosepipe	*Bucket*	*Well*	*Snake*	*Frog*
5	Axe	*Hammer* (sv)	*Scissors*	*Flag*	*Kite*
7	Canoe	*Yacht* (sv)	*Lifebelt*	*Bowl*	*Bottle*
9	Television	*Radio* (sv)	*Record-player*	*Toaster*	*Frying-pan*
11	Apple	*Orange* (sv)	*Grapes*	*Ring*	*Necklace*
13	Button	*Zip*	*Bow*	*Coin*	*Banknote*
15	Syringe	*Stethoscope*	*Tablet*	*Screwdriver*	*Hinge*
17	Cobweb	*Spider*	*Ladybird*	*Wheel*	*Wagon*
19	Lobster	*Crab* (sv)	*Fish*	*Spanner*	*Nut*
21	Cow	*Horse* (sv)	*Chicken*	*Cradle*	*Bed*
23	Comb	*Brush*	*Mirror*	*Centipede*	*Ant*
25	Rake	*Hoe* (sv)	*Scarecrow*	*Fork*	*Salt*
27	Underpants	*Vest*	*Tie*	*Flowerpot*	*Watering-can*
29	Paintbrush	*Palette*	*Easel*	*Knife*	*Kettle*
31	Dart	*Spear* (sv)	*Bow*	*Toothbrush*	*Razor*
33	Pipe	*Cigar* (sv)	*Ashtray*	*Saucepan*	*Rolling-pin*
35	Needle	*Thimble*	*Spinning-wheel*	*Nailfile*	*Tweezers*
37	Bell	*Whistle*	*Trumpet*	*Lightbulb*	*Battery*
39	Mug	*Cup* (sv)	*Spoon*	*Drum*	*Harp*

Written Word – Picture Matching

Item number on original form	Item	Close Semantic Distractor	Distant Semantic Distractor	Visually Related Distractor	Unrelated Distractor
2	Belt	*Braces*	*Shirt*	*Watch*	*Clock*
3	Parachute	*Balloon* (sv)	*Plane*	*Umbrella*	*Puddle*
7	Moon	*Star*	*Planet*	*Horseshoe*	*Anvil*
8	Thumb	*Finger* (sv)	*Leg*	*Pipe*	*Cigarette*
10	Stamp	*Envelope*	*Pen*	*Picture*	*Paint*
11	Sword	*Shield*	*Gun*	*Anchor*	*Chain*
14	Stirrup	*Saddle*	*Bridle*	*Hanger*	*Jacket*
15	Ladder	*Steps* (sv)	*Rope*	*Ruler*	*Satchel*
16	Hat	*Coat*	*Sock*	*Iron*	*Ironing Table*
17	Stool	*Table* (sv)	*Sofa*	*Plug*	*Switch*
20	Dog	*Cat* (sv)	*Kangaroo*	*Beetle*	*Butterfly*
21	Pram	*Baby*	*Teddy*	*Bath*	*Towel*
23	Candle	*Match* (sv)	*Lamp*	*Lipstick*	*Glove*
24	Eye	*Ear*	*Hair*	*Football*	*Bat*
25	Hammock	*Cot*	*Pillow*	*Banana*	*Cherry*
28	Key	*Lock*	*Knob*	*Leaf*	*Flower*
29	Shoe	*Boot* (sv)	*Trousers*	*Peanut*	*Monkey*
30	Wall	*Fence* (sv)	*House*	*Chest*	*Rocking Chair*
33	Crown	*Tiara* (sv)	*Gown*	*Cake*	*Bread*
38	Nail	*Screw* (sv)	*Pliers*	*Pencil*	*Letter*

Abbreviations. (SV) semantic plus visual distractor.

Note. Cole-Virtue and Nickels (2004) found that most semantic distractors are also associated with the target words. Word associations are lexically driven, and therefore a lexical association between words rather than a semantic effect could confound distractor choice. Matched sets for sematic similarity of the target word to their close semantic distractor are presented by these authors, also matched by word frequency, imageability and association to control for the effect that these lexical characteristics may have on semantic choice. When assigning each item to the corresponding spoken and written paradigms, care was taken that half of the items from each category (high/low semantic similarity) were assigned to each paradigm.

Table 4. Sentence – Picture Matching Tasks Items

Auditory Sentence – Picture Matching				
Item number on original form	**Sentence**	**Type of Sentence**		**Type of Distractors**
1	The horse is kicking the man	*RN*	Active, Reversible	*lv, r*
2	The girl is taller than the dog	*RC*	Reversible	*r, ls*
3	The cat is carried by the horse	*NP*	Passive, Non-reversible	*ls, lv*
4	The cat is licking the man	*NA*	Active, Non-reversible	*lo, lv*
5	This man has got more chickens	*NC*	Non-reversible	*ca ,lo*
7	The man is wondering what to eat	*GS*	Gapped	*lv, ls*
8	The girl is buying the cat	*CR*	Converse Relations	*ls, lv*
9	The man is demonstrating what to do	*GO*	Gapped	*lv, ls*
10	The horse is moved by the man	*RNP*	Passive, Reversible	*lv, r*
13	The horse is likely to kick	*AS*	Gapped	*la, ls*
14	The dog is approaching the girl	*RD*	Active, Reversible	*lv, r*
16	The horse is chased by the girl	*RDP*	Passive, Reversible	*lv, r*
17	The cat is easy to bite	*AO*	Gapped	*ls, la*
19	This man has got less horses to watch	*NCT*	Non-reversible	*lo, ca*
24	The girl is accepting the cup	*CR*	Converse Relations	*lv, ls*
31	The girl is selling the cat	*CR*	Converse Relations	*ls, ls*
32	The cat is eager to bite	*AS*	Gapped	*ls, la*
33	The dog is frightened by the girl	*RNP*	Passive, Reversible	*lv, r*
34	This horse has got less chickens to scare	*NCT*	Non-reversible	*ca, lo*
36	The chicken is nice to feed	*AO*	Gapped	*la, ls*
37	The girl is approached by the dog	*RDP*	Passive, Reversible	*lv, r*
38	The horse is carrying the cat	*NA*	Active, Non-reversible	*lv, lo*
39	This man has got less horses	*NC*	Non-reversible	*lo, ca*
40	The man is puzzling what to do	*GS*	Gapped	*lv, ls*
43	The chicken is higher than the man	*RC*	Reversible	*r, ls*
44	The horse is pulling the man	*RD*	Active, Reversible	*r, ls*
45	The chicken is watching the girl	*RN*	Active, Reversible	*r, lv*
48	The man is receiving the money	*CR*	Converse Relations	*ls, lv*
52	The man is explaining what to eat	*GO*	Gapped	*ls, lv*
54	The man is licked by the cat	*NP*	Passive, Non-reversible	*lv, ls*

Abbreviations. RD: Reversible Directional Active Verb / RDP: Reversible Directional Passive Verb / RN: Reversible Non-directional Active Verb / RNP: Reversible Non-directional Passive / RC: Reversible Comparative Adjective / NA: Non-reversible Active Verb / NP: Non-reversible Passive Verb / NC: Non-reversible Comparative Adjective (to-complement) / GS: Gapped after Verb, gap as Subject / GO: Gapped after Verb, gap not as Subject / AS: Gapped after Adjective, gap as Subject / AO: Gapped after Adjective, gap no as Subject / CR: Converse Relations.

Table 4 (continued). Sentence – Picture Matching Tasks Items

Written Sentence – Picture Matching				
Item number on original form	**Sentence**	**Type of Sentence**		**Type of Distractors**
1	The man is offering the money	*CR*	Converse Relations	*ls, lv*
4	The man is thinner than the horse	*RC*	Reversible	*r, ls*
5	The girl is frightening the dog	*RN*	Active, Reversible	*lv, r*
10	The dog is washed by the girl	*NP*	Passive, Non-reversible	*ls, lv*
16	The man is keen to see	*AS*	Gapped	*la, ls*
17	The man is giving the prize	*CR*	Converse Relations	*ls, lv*
18	The girl is watched by the chicken	*RNP*	Passive, Reversible	*r, lv*
19	The girl is suggesting what to eat	*GO*	Gapped	*lv, ls*
20	This dog has got more cats to chase	*NCT*	Non-reversible	*ca, lo*
21	The man is kicking the chicken	*NA*	Active, Non-reversible	*lo, lv*
23	The horse is hard to kick	*AO*	Gapped	*la, ls*
24	This girl has got less dogs	*NC*	Non-reversible	*lo, ca*
25	The man is pulled by the horse	*RDP*	Passive, Reversible	*r, lv*
26	The girl is considering where to go	*GS*	Gapped	*ls, lv*
28	The man is following the dog	*RD*	Active, Reversible	*lv, r*
31	The man is difficult to see	*AO*	Gapped	*la, ls*
35	This girl has got more horses to feed	*NCT*	Non-reversible	*ca, lo*
36	The man is kicked by the horse	*RNP*	Passive, Reversible	*r, lv*
42	The girl is awarding the cup	*CR*	Converse Relations	*ls, lv*
47	The man is moving the horse	*RN*	Active, Reversible	*lv, r*
48	The girl is asking what to eat	*GS*	Gapped	*ls, lv*
49	The chicken is kicked by the man	*NP*	Passive, Non-reversible	*ls, lv*
50	The dog is smaller than the girl	*RC*	Reversible	*ls, r*
51	This girl has got more cats	*NC*	Non-reversible	*lo, ca*
52	The girl is indicating where to go	*GO*	Gapped	*lv, ls*
54	The girl is washing the dog	*NA*	Active, Non-reversible	*lv, lo*
56	The man is taking the prize	*CR*	Converse Relations	*ls, lv*
57	The chicken is anxious to feed	*AS*	Gapped	*ls, la*
58	The girl is chasing the horse	*RD*	Active, Reversible	*r, lv*
60	The dog is followed by the man	*RDP*	Passive, Reversible	*lv, r*

Abbreviations. RD: Reversible Directional Active Verb / RDP: Reversible Directional Passive Verb / RN: Reversible Non-directional Active Verb / RNP: Reversible Non-directional Passive / RC: Reversible Comparative Adjective / NA: Non-reversible Active Verb / NP: Non-reversible Passive Verb / NC: Non-reversible Comparative Adjective (to-complement) / GS: Gapped after Verb, gap as Subject / GO: Gapped after Verb, gap not as Subject / AS: Gapped after Adjective, gap as Subject / AO: Gapped after Adjective, gap no as Subject / CR: Converse Relations.

References

Cole-Virtue, J., & Nickels, L. (2004). Spoken word to picture matching from PALPA: A critique and some new matched sets. *Aphasiology, 18*(2), 77-102.

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Table 5. Scaled Scores for each PALPA subtest (all ages)

Scaled Score	Auditory Lexical Decision						Visual Lexical Decision						Auditory Comprehension of Verbs	Auditory Comprehension of Adjectives	Scaled Score
	Total Correct	Correct True Positives (HI_HF)	Correct True Positives (HI_LF)	Correct True Positives (LI_HF)	Correct True Positives (LI_LF)	Correct True Negatives	Total Correct	Correct True Positives (HI_HF)	Correct True Positives (HI_LF)	Correct True Positives (LI_HF)	Correct True Positives (LI_LF)	Correct True Negatives			
1	1-55	1-9	1-9	1-9	1-9	1-16	1-51	1-6	1-5	1-8	1-5	1-22	1-24	1-12	1
2	56-57	-	-	-	-	17-18	-	-	-	-	-	-	-	-	2
3	58-59	-	-	-	-	19	52	-	-	-	-	23	-	13	3
4	60-61	-	-	-	-	20-21	53	7	-	-	-	24	25	-	4
5	62-63	-	-	-	-	22-23	54	-	-	-	6	25	-	-	5
6	64-65	-	-	-	-	24-25	55	-	-	-	-	-	-	-	6
7	66-67	-	-	-	-	26-27	56	-	-	-	-	26	-	-	7
8	68-69	-	-	-	-	28-29	57	-	-	-	-	27	26	-	8
9	70-71	-	-	-	-	30-31	-	-	-	-	-	28	-	-	9
10	72-73	10	10	10	-	32-33	58	-	-	9	-	29	-	-	10
11	74-75				10	34-35	59	8	6		7	-	27	14	11
12	76-77					36-37	60					30			12
13	78-79					38-39									13
14	80					40									14
15															15
16															16
Mean ± SD	72.5 ± 5.84	10 ± 0	10 ± 0	10 ± 0	9.91 ± 0.29	32.6 ± 5.82	58.3 ± 2.54	7.91 ± 0.45	5.97 ± 0.17	8.97 ± 0.22	6.81 ± 0.46	28.7 ± 2.35	26.7 ± 0.89	13.9 ± 0.40	**Mean ± SD**

Abbreviations. HI: High Imageability, HF: High Frequency, LI: Low Imageability, LF: Low Frequency.

[a] Sentences included in each Sentence – Picture Matching sub-score: Active (RD+RN+NA), Passive (RDP+RNP+NP), Reversible (RD+RDP+RN+RNP+RC), Non-reversible (NA+NP+NC+NCT), Gapped (GS+GO+AS+AO), and Converse Relations (CR).

Table 5 (continued). Scaled Scores for each PALPA subtest (all ages)

Scaled Score	Homophone Definition - Definition			Homophone Definition - Reading			Word Spelling			Non-Word Spelling	Word Reading			Non-Word Reading	Scaled Score
	Total Correct	Correct Regular	Correct Irregular	Total Correct	Correct Regular	Correct Irregular	Total Correct	Correct Regular	Correct Irregular		Total Correct	Correct Regular	Correct Irregular		
1	1-15	1-7	1-7	1-17	1-9	1-7	1-29	1-17	1-10	1-5	1-55	1-28	1-26	1-6	1
2	-	-	-	-	-	-	30	-	11	-	56	-	-	7	2
3	16	8	-	-	-	-	31	18	12	6	-	29	-	-	3
4	-	-	-	-	-	8	32	-	13	7	-	-	27	8	4
5	17	-	8	18	-	-	33	-	14	-	57	-	-	-	5
6	-	-	-	-	-	-	34	-	15	8	-	-	28	9	6
7	18	9	-	-	-	-	35	19	-	-	58	-	-	-	7
8	-	-	9	19	-	9	36	-	16	9	-	-	-	10	8
9	-	-	-	-	-	-	37	-	17	-	-	-	29	-	9
10	19	-	-	-	-	-	38	-	18	10	59	-	-	11	10
11	-	-	-	-	10	-	39	20	19	-	-	30	-	-	11
12	20	10	10	20		10	40		20	11	60		30	-	12
13										12				12	13
14															14
15															15
16															16
Mean	19.1	9.64	9.44	19.5	9.92	9.55	37.7	19.7	18.1	10.1	59.2	29.9	29.3	10.8	**Mean**
± SD	± 1.27	± 0.69	± 0.85	± 0.83	± 0.27	± 0.75	± 2.94	± 0.68	± 2.56	± 1.68	± 1.28	± 0.39	± 1.11	± 1.38	**± SD**

Abbreviations. HI: High Imageability, HF: High Frequency, LI: Low Imageability, LF: Low Frequency.

[a] Sentences included in each Sentence – Picture Matching sub-score: Active (RD+RN+NA), Passive (RDP+RNP+NP), Reversible (RD+RDP+RN+RNP+RC), Non-reversible (NA+NP+NC+NCT), Gapped (GS+GO+AS+AO), and Converse Relations (CR).

Table 5 (continued). Scaled Scores for each PALPA subtest (all ages)

Scaled Score	Word – Picture Matching		Auditory Sentence – Picture Matching [a]							Written Sentence – Picture Matching [a]							Scaled Score
	Spoken	Written	Total Correct	Correct Active	Correct Passive	Correct Reversible	Correct Non-Reversible	Correct Gapped	Correct Converse Relations	Total Correct	Correct Active	Correct Passive	Correct Reversible	Correct Non-Reversible	Correct Gapped	Correct Converse Relations	
1	1-18	1-18	1-22	1-4	1-3	1-8	1-5	1-6	1	1-25	1-4	1-4	1-7	1-7	1-6	1-2	1
2	-	-	23	-	-	-	-	-	-	-	-	5	8	-	-	-	2
3	19	-	24	-	4	-	-	-	-	26	-	-	-	-	-	-	3
4	-	19	-	5	-	-	-	-	-	-	-	-	-	-	-	-	4
5	-	-	25	-	-	-	6	-	2	27	-	-	-	-	7	-	5
6	-	-	26	-	-	9	-	7	-	-	5	-	-	-	-	3	6
7	-	-	-	-	5	-	-	-	-	-	-	-	9	-	-	-	7
8	-	-	27	-	-	-	7	-	3	28	-	-	-	-	-	-	8
9	-	-	28	-	-	-	-	-	-	-	-	-	-	-	-	-	9
10	-	-	-	-	-	-	-	-	-	29	-	-	-	-	-	-	10
11	20	20	29	6	-	10	8	-	-	-	6	6	10	8	-	-	11
12			30		6			8	4	30					8	4	12
13																	13
14																	14
15																	15
16																	16
Mean ± SD	19.9 ± 0.37	19.8 ± 0.43	28.5 ± 1.99	5.85 ± 0.41	5.61 ± 0.68	9.76 ± 0.55	7.58 ± 0.91	7.72 ± 0.55	3.48 ± 0.84	29.1 ± 1.32	5.79 ± 0.55	5.88 ± 0.35	9.70 ± 0.66	7.94 ± 0.24	7.74 ± 0.48	3.72 ± 0.53	**Mean ± SD**

Abbreviations. HI: High Imageability, HF: High Frequency, LI: Low Imageability, LF: Low Frequency.

[a] Sentences included in each Sentence – Picture Matching sub-score: Active (RD+RN+NA), Passive (RDP+RNP+NP), Reversible (RD+RDP+RN+RNP+RC), Non-reversible (NA+NP+NC+NCT), Gapped (GS+GO+AS+AO), and Converse Relations (CR).

Table 6. Predicted PALPA raw scores from estimated premorbid FSIQ (all ages)

TOPF FSIQ	Auditory Lexical Decision	Visual Lexical Decision	Homophone Definition - Definition	Homophone Definition - Reading	Auditory Comprehension of Verbs	Auditory Comprehension of Adjectives	Word Spelling	Non-word Spelling	Word Reading	Non-word Reading	Spoken Word – Picture Matching	Written Word – Picture Matching	Auditory Sentence – Picture Matching	Written Sentence – Picture Matching	TOPF FSIQ
75	56-77	51-60	15-19	17-19	24-27	12-14	28-38	6-12	55-59	6-11	18-20	18-20	22-29	25-30	75
76	56-77	51-60	15-19	17-19	24-27	12-14	29-38	6-12	55-59	6-11	18-20	18-20	23-29	25-30	76
77	56-78	51-60	15-19	17-20	24-27	12-14	29-38	6-12	55-59	6-11	18-20	18-20	23-29	25-30	77
78	57-78	51-60	15-19	17-20	24-27	12-14	29-38	6-12	55-59	6-11	18-20	18-20	23-29	25-30	78
79	57-78	51-60	15-19	17-20	24-27	12-14	29-38	6-12	55-60	7-11	18-20	18-20	23-30	25-30	79
80	57-78	51-60	15-19	17-20	24-27	12-14	29-38	6-12	55-60	7-11	18-20	18-20	23-30	25-30	80
81	57-78	51-60	15-19	17-20	24-27	12-14	29-39	6-12	55-60	7-11	18-20	18-20	23-30	25-30	81
82	57-78	51-60	15-19	17-20	24-27	12-14	29-39	6-12	55-60	7-11	18-20	18-20	23-30	25-30	82
83	57-79	51-60	15-19	17-20	24-27	12-14	30-39	6-12	55-60	7-11	18-20	18-20	23-30	25-30	83
84	58-79	52-60	15-19	17-20	24-27	12-14	30-39	6-12	55-60	7-11	19-20	18-20	23-30	25-30	84
85	58-79	52-60	15-20	17-20	24-27	12-14	30-39	6-12	56-60	7-12	19-20	18-20	23-30	25-30	85
86	58-79	52-60	15-20	17-20	24-27	12-14	30-39	6-12	56-60	7-12	19-20	18-20	23-30	25-30	86
87	58-79	52-60	16-20	17-20	24-27	12-14	30-39	6-12	56-60	7-12	19-20	18-20	23-30	25-30	87
88	58-80	52-60	16-20	17-20	24-27	12-14	30-40	6-12	56-60	7-12	19-20	18-20	23-30	25-30	88
89	59-80	52-60	16-20	17-20	24-27	13-14	30-40	6-12	56-60	7-12	19-20	18-20	23-30	26-30	89
90	59-80	52-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	7-12	19-20	18-20	24-30	26-30	90
91	59-80	52-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	7-12	19-20	18-20	24-30	26-30	91
92	59-80	52-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	7-12	19-20	18-20	24-30	26-30	92
93	59-80	52-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	7-12	19-20	18-20	24-30	26-30	93
94	59-80	52-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	7-12	19-20	18-20	24-30	26-30	94
95	60-80	53-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	7-12	19-20	18-20	24-30	26-30	95
96	60-80	53-60	16-20	17-20	24-27	13-14	31-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	96
97	60-80	53-60	16-20	17-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	97
98	60-80	53-60	16-20	17-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	98
99	60-80	53-60	16-20	17-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	99
100	61-80	53-60	16-20	17-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	100
101	61-80	53-60	16-20	17-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	101
102	61-80	53-60	16-20	17-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	18-20	24-30	26-30	102
103	61-80	53-60	16-20	18-20	24-27	13-14	32-40	6-12	56-60	8-12	19-20	19-20	24-30	26-30	103
104	61-80	53-60	17-20	18-20	24-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	24-30	26-30	104
105	62-80	53-60	17-20	18-20	24-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	25-30	26-30	105

Table 6 (continued). Predicted PALPA raw scores from estimated premorbid FSIQ (all ages)

TOPF FSIQ	Auditory Lexical Decision	Visual Lexical Decision	Homophone Definition - Definition	Homophone Definition - Reading	Auditory Comprehension of Verbs	Auditory Comprehension of Adjectives	Word Spelling	Non-word Spelling	Word Reading	Non-word Reading	Spoken Word – Picture Matching	Written Word – Picture Matching	Auditory Sentence – Picture Matching	Written Sentence – Picture Matching	TOPF FSIQ
106	62-80	53-60	17-20	18-20	24-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	25-30	26-30	106
107	62-80	54-60	17-20	18-20	25-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	25-30	26-30	107
108	62-80	54-60	17-20	18-20	25-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	25-30	26-30	108
109	62-80	54-60	17-20	18-20	25-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	25-30	26-30	109
110	62-80	54-60	17-20	18-20	25-27	13-14	33-40	6-12	57-60	8-12	19-20	19-20	25-30	26-30	110
111	63-80	54-60	17-20	18-20	25-27	13-14	33-40	7-12	57-60	8-12	19-20	19-20	25-30	27-30	111
112	63-80	54-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	8-12	19-20	19-20	25-30	27-30	112
113	63-80	54-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	9-12	19-20	19-20	25-30	27-30	113
114	63-80	54-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	9-12	19-20	19-20	25-30	27-30	114
115	63-80	54-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	9-12	19-20	19-20	25-30	27-30	115
116	64-80	54-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	9-12	19-20	19-20	25-30	27-30	116
117	64-80	54-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	9-12	19-20	19-20	25-30	27-30	117
118	64-80	55-60	17-20	18-20	25-27	13-14	34-40	7-12	57-60	9-12	19-20	19-20	25-30	27-30	118
119	64-80	55-60	17-20	18-20	25-27	13-14	35-40	7-12	57-60	9-12	19-20	19-20	26-30	27-30	119
120	64-80	55-60	17-20	18-20	25-27	13-14	35-40	7-12	57-60	9-12	19-20	19-20	26-30	27-30	120
121	64-80	55-60	18-20	18-20	25-27	13-14	35-40	7-12	57-60	9-12	19-20	19-20	26-30	27-30	121
122	65-80	55-60	18-20	18-20	25-27	13-14	35-40	7-12	57-60	9-12	19-20	19-20	26-30	27-30	122
123	65-80	55-60	18-20	18-20	25-27	13-14	35-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	123
124	65-80	55-60	18-20	18-20	25-27	13-14	35-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	124
125	65-80	55-60	18-20	18-20	25-27	13-14	35-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	125
126	65-80	55-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	126
127	66-80	55-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	127
128	66-80	55-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	128
129	66-80	56-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	9-12	19-20	19-20	26-30	27-30	129
130	66-80	56-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	10-12	19-20	19-20	26-30	27-30	130
131	66-80	56-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	10-12	19-20	19-20	26-30	27-30	131
132	66-80	56-60	18-20	18-20	25-27	13-14	36-40	7-12	58-60	10-12	19-20	19-20	26-30	28-30	132
133	67-80	56-60	18-20	19-20	25-27	13-14	37-40	7-12	58-60	10-12	19-20	19-20	26-30	28-30	133
134	67-80	56-60	18-20	19-20	25-27	13-14	37-40	7-12	58-60	10-12	19-20	19-20	27-30	28-30	134
135	67-80	56-60	18-20	19-20	25-27	13-14	37-40	7-12	58-60	10-12	19-20	19-20	27-30	28-30	135

Appendix H

Parallel Short Forms of the ANT: Supplementary Material

Table 1. Items composing Form A and Form B of the ANT

Item number	ANT Form A	ANT Form B
1	Writing	Reading
2	Running	Fishing
3	Sitting	Eating
4	Flying	Swimming
5	Sleeping	Cutting
6	Smoking	Crying
7	Pointing	Sailing
8	Shaking	Drinking
9	Climbing	Throwing
10	Swinging	Saluting
11	Painting	Sweeping
12	Diving	Sawing
13	Pouring	Ironing
14	Skiing	Bowling
15	Brushing	Milking
16	Parachuting	Rowing
17	Knitting	Conducting
18	Boxing	Bowing
19	Peeling	Lassoing
20	Floating	Kneeling
21	Raking	Typing
22	Dripping	Fencing
23	Juggling	Shovelling
24	Surfing	Winking
25	Curtsying	Operating
26	Proposing	Petting
27	Weightlifting	Erupting
28	Knighting	Winning