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Review Article

Lessons of ALS imaging: Pitfalls and future directions — A critical review

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ABSTRACT

Background: While neuroimaging in ALS has gained unprecedented momentum in recent years, little progress has been made in the development of viable diagnostic, prognostic and monitoring markers.

Objectives: To identify and discuss the common pitfalls in ALS imaging studies and to reflect on optimal study designs based on pioneering studies.

Methods: A "PubMed"-based literature search on ALS was performed based on neuroimaging-related keywords. Study limitations were systematically reviewed and classified so that stereotypical trends could be identified.

Results: Common shortcomings, such as relatively small sample sizes, statistically underpowered study designs, lack of disease controls, poorly characterised patient cohorts and a large number of conflicting studies, remain a significant challenge to the field. Imaging data of ALS continue to be interpreted at a group-level, as opposed to meaningful individual-patient inferences.

Conclusions: A systematic, critical review of ALS imaging has identified stereotypical shortcomings, the lessons of which should be considered in the design of future prospective MRI studies. At a time when large multicentre studies are underway a candid discussion of these factors is particularly timely.

1. Introduction

An exponential increase in high-impact imaging publications of ALS has been seen in recent years. However, the majority of recent systematic reviews on the topic are technique-based (Turner et al., 2012), classifying and discussing studies based on the specific imaging method utilised, rather than highlighting common themes and shared conclusions. Furthermore, comprehensive reviews of ALS imaging have focused primarily on the achievements of landmark studies, and are insufficiently critical of shortcomings, discussion of which may contribute to improved study designs.

ALS imaging has been relatively successful as a descriptive tool, characterising features of specific ALS phenotypes and genotypes (Chang et al., 2005; Stanton et al., 2009a; Bede et al., 2013a). Additionally, the anatomical bases of recent clinical observations, such as the concept of cortical focality, neuropsychological deficits, extrapyramidal dysfunction, and sensory deficits, have been elucidated. Imaging studies of ALS have also contributed to our understanding of active biological processes, such as confirmation of inflammatory mechanisms (Corcia et al., 2012), spread along functional connections (Verstraete et al., 2013), and dysfunction of inhibitory circuits (Douaud et al., 2011). Recent work has provided evidence of network degeneration as opposed to preferential, focal white and grey matter pathology (Douaud et al., 2011). Landmark studies of presymptomatic genetic variants such as *SOD-1* mutation carriers have highlighted structural and metabolic changes prior to symptom onset and have offered unprecedented insights into the presymptomatic phase of the disease (Ng et al., 2008; Carew et al., 2011). PET and fMRI studies have revealed compensatory processes, suggestive of an attempted functional adaptation in the face of relentless neurodegeneration (Schoenfeld et al., 2005).

However as in the case of Alzheimer's disease and multiple sclerosis, the development of viable diagnostic, prognostic and disease progression markers at an individual level remains as one of the primary aspirations of ALS. Despite years of research, progress on this front has been relatively slow, results inconsistent, and the outcomes

Abbreviations: AD, axial diffusivity; C9orf72, chromosome 9 open reading frame 72; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; MEG, magnetoencephalography; MRS, magnetic resonance spectroscopy; MUNE, motor unit number estimation; PET, positron emission tomography; PNS, peripheral nervous system; RD, radial diffusivity; ROI, region of interest; SPECT, single photon emission computed tomography; TMS, transcranial magnetic stimulation; VBM, voxel-based morphometry.

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not readily transferable to the clinic. The aims of this study are to explore the factors that have led to a large number of inconsistent results and to reflect on optimal study designs which could be utilised in future multi-centre studies.

2. Methods

A formal literature review was conducted on PubMed with the individual search terms 'Imaging', 'Neuroimaging', 'Magnetic resonance imaging', 'Positron emission tomography', 'Single photon emission computed tomography', 'Diffusion tensor imaging', 'Voxel-based morphometry', 'Spectroscopy' in combination with 'ALS' and 'Motor neuron disease' separately. Publications were searched during a 2 month period between November 2013 and December 2013. Both original contributions and review papers (Turner et al., 2009, 2012, 2013; Bede et al., 2012; Bowser et al., 2011; Turner and Modo, 2010; Foerster et al., 2013b; Wang et al., 2011; Agosta et al., 2010a; Pradat and Dib, 2009; van der Graaff et al., 2009; Dengler et al., 2005; Kalra and Arnold, 2003; Karitzky and Ludolph, 2001; Comi et al., 1999; Kollewe et al., 2012; Kassubek et al., 2012; Prell and Grosskreutz, 2013) were selected, but only articles published in English were reviewed. Where relevant, references of identified papers were also evaluated. Based on the above search criteria, a total of 184 original research papers and 21 review papers were identified (Supplementary Table 1). Each original contribution was individually reviewed for author-reported and reviewer-identified study limitations, based on which distinct trends of common methodological shortcomings were observed. An additional objective was to identify reports of seemingly inconsistent results or potentially contradicting conclusions. Thirdly, constructive examples of innovative methods were sought in response to the identified stereotypical pitfalls, so that recommendations for optimised ALS study designs can be presented.

3. Results

3.1. Common methodological limitations

While disease heterogeneity is an inherent challenge of the field, common methodological study limitations can also be identified across individual studies, such as small sample sizes, lack of disease controls, suboptimal patient characterisation, technique-driven rather than clinical problem-driven studies, lenient statistical models and insufficient discussion of laterality and symmetry of pathology (Table 1). In addition to the methodological shortcomings of single studies, fairly well-defined gaps in the ALS imaging literature as a whole can also be observed, indicating pressing, yet promising research opportunities (Table 1).

3.2. Inconsistencies of conclusions

The above factors are likely to have contributed to the inconsistencies of various studies, particularly in the degree of extra-motor involvement, laterality of pathology and the extent of brain changes in lower motor neuron dominant conditions. Many studies have highlighted right precentral gyrus changes (Kassubek et al., 2005; Grossman et al., 2008; Agosta et al., 2007; Grosskreutz et al., 2006), while others have demonstrated bilateral motor cortex pathology (Chang et al., 2005; Filippini et al., 2010; Verstraete et al., 2012; Thivard et al., 2007; Bede et al., 2013c). . Unilateral left (Bede et al., 2013c) and right (Mezzapesa et al., 2007) parahippocampal pathologies have both been reported. Similar discrepancies can be observed in studies of specific phenotypes. For example, relative sparing of corticospinal tract integrity has been reported in progressive muscle atrophy by some studies (Cosottini et al., 2005b), while others have identified extensive diffusivity changes in the brain, concluding that widespread CNS involvement occurs (Prudlo et al., 2012). And while some drug-response studies have captured a Riluzole effect (Kalra et al., 2006), others failed to replicate this (Bradley et al., 1999). Accounts of extra-motor grey matter pathology also show considerable variation ranging from limited frontotemporal pathology to widespread occipital, parietal and subcortical changes. This wide range of inconsistent findings may reflect true disease heterogeneity, but is more likely to be a function of small sample size, inadequate power, and consequent over-interpretation of findings.

3.3. Sample size and statistical analysis

The challenges of recruiting large patient cohorts in ALS imaging studies are obvious due to disease-specific factors such as orthopnoea, dyspnoea, and sialorrhoea. Yet, despite these recognised limitations, formal power calculations are seldom carried out. Methods for power calculations depend on the specific imaging technique utilised. Recent evidence suggests that the number of foci reported in small VBM studies and even in meta-analyses with few studies may often be exaggerated (Fusar-Poli et al., 2013). In contrast, whole-brain meta-analyses of large sample sizes identify fewer foci than single studies (Fusar-Poli et al., 2013). Region of interest (ROI) based studies, on the other hand, are susceptible to strong reporting bias (Ioannidis, 2011). Methods for bias-corrected power calculations have been specifically developed for diffusion tensor imaging (Lauzon and Landman, 2013). Sample size and power calculations for fMRI studies are relatively well established (Mumford, 2012; Desmond and Glover, 2002). Several commercial software packages also exist for power calculations of imaging studies (Joyce and Hayasaka, 2012).

The number of ALS patients included in SPECT studies varies between n= 14 (Waldemar et al., 1992) and n= 26 (Abe et al., 1997), and those in PET studies varies between n= 7 (Hoffman et al., 1992) and n= 32 (Cistaro et al., 2012). Single-centre morphometric studies of ALS also show considerable variation in sample size; from n= 12 (Minnerop et al., 2009) to n= 45 (Verstraete et al., 2012). Similarly, diffusivity studies report results from a range of sample sizes; from n= 13 (Ciccarelli et al., 2006) to n= 87 (Rajagopalan et al., 2013). In general, task (paradigm) based functional MRI studies are particularly small; from n= 6 (Schoenfeld et al., 2005) to n= 22 (Mohammadi et al., 2011). Resting state fMRI studies are somewhat larger; from n= 12 (Verstraete et al., 2010a) to n= 25 (Douaud et al., 2011). Spectroscopy studies range from n= 8 (Yin et al., 2004) to n= 70 (Pohl et al., 2001; Block et al., 2002). Studies of specific genotypes and phenotypes often draw conclusions from even smaller – frequently single digit – sample sizes (Table 2).

The majority of ALS imaging papers use age and gender matched study groups. Age is sometimes included as a covariate in the analyses, but gender, education and handedness are seldom considered. The effect of gender on MR variables is well established in healthy populations (Chen et al., 2007; Menzler et al., 2011) and can also be demonstrated in ALS cohorts (Bede et al., 2013b). Similarly, the link between handedness and corticospinal tract/motor cortex asymmetry has been confirmed in healthy individuals (Hervé et al., 2009). In ALS, there is evidence that handedness may be associated with side of onset in ALS (Turner et al., 2011), therefore correction for handedness in ALS imaging studies may be judicious. Moreover, neuroimaging data from healthy aging cohorts also demonstrate the effect of education on structural data, especially in older populations which are typically studied in ALS (Arenaza-Urquijo et al., 2013; Noble et al., 2012). The typically small sample sizes of ALS imaging studies are often further subdivided to characterise specific phenotypes, which is likely to accentuate the confounding effects of the above demographic factors even more.

Table 1.
Common shortcomings for ALS imaging studies.

Common methodological limitations of individual ALS imaging studies
• Technique-driven rather than clinical problem-driven studies
• Confirmatory as opposed to original study designs
• Small to moderate sample sizes, lack of power calculations
• Inadequate discussion or interpretation of unilateral findings
• Suboptimal clinical patient characterisation
• Lack of comprehensive genotyping i.e. *C9orf72* which may contribute to extra-motor changes
• Limited imaging methods i.e. white matter only, grey matter only studies, as opposed to multifaceted, multimodal structural/functional, cortical/subcortical characterisation
• Lack of disease controls and "ALS-mimic" controls
• Correlation of brain changes with clinical measures that also heavily depend on lower motor neuron function (ALSFRS-r, tapping rates)
• Lack of post-mortem validation of imaging findings
• Lenient statistical models, insufficient correction for demographic factors (education, handedness, age, gender)
• Reports of statistical "trends" uncorrected for multiple testing
Shortcomings of the current literature of ALS imaging
• Paucity of presymptomatic studies
• Paucity of classifier (diagnostic) studies
• Paucity of meta-analyses
• Paucity of high-field MRI studies
• Lack of large, cross-platform, multi-centre studies
• Lack of post-mortem imaging studies in ALS
• Relative paucity of spinal cord studies
• Lack of quantitative LMN/plexus/PNS imaging studies
• Paucity of muscle imaging studies

Table 2
A selection of sample size examples from imaging studies characterising specific ALS phenotypes or genotypes. The highlighted studies also included larger reference groups of controls or sporadic ALS patients.

ALS-dementia
n= 4 (Neary et al., 1990; Tanaka et al., 1993), *n*= 8 (Talbot et al., 1995), *n*= 17 (Rajagopalan et al., 2013)
ALS-PD-Guam complex
n= 4 (Snow et al., 1990)
ALS-FTD
n= 10 (Chang et al., 2005), *n*= 12 (Cistaro et al, 2014)
D90a-SOD1 genotype
n= 6 (Stanton et al., 2009b), *n*= 7 (Blain et al., 2011; Turner et al., 2007a), *n*= 10 (Turner et al., 2005)
C9orf72 hexanucleotide repeat expansion in ALS
n= 9 (Bede et al., 2013a; Bede et al., 2013d), *n*= 15 (Cistaro et al., 2014)
Progressive lateral sclerosis
n= 4 (Turner et al., 2007b), *n*= 6 (Ciccarelli et al., 2009; Mitsumoto et al., 2007), *n*= 12 (van der Graaff et al., 2011), *n*= 19 (Iwata et al., 2011)
Progressive muscular atrophy
n= 8 (Cosottini et al., 2005a), *n*= 9 (Mitsumoto et al., 2007), *n*= 12 (van der Graaff et al., 2011)
Presymptomatic studies of homozygous D90A-SOD1
n= 2 (Turner et al., 2005), *n*= 8 (Ng et al., 2008), *n*= 24 (Carew et al., 2011)
Bulbar onset ALS
n= 8 (Ellis et al., 2001; Ellis et al., 1998), *n*= 12 (van der Graaff et al., 2011), *n*= 13 (Cistaro et al., 2012), *n*= 13 (Bede et al., 2013c)
Spinal onset ALS
n= 8 (Ellis et al., 2001; Ellis et al., 1998), *n*= 12 (van der Graaff et al., 2011), *n*= 19 (Cistaro et al., 2012), *n*= 20 (Bede et al., 2013c)

3.4. Disease controls

Neurological disease controls, patients with lower motor neuron syndromes (Sperfeld et al., 2005), Kennedy's disease patients (Sperfeld et al., 2005), Alzheimer's disease cohorts (Block et al., 2002) and poliomyelitis groups (Dalakas et al., 1987) have been previously included in ALS imaging studies. However, the large majority of ALS imaging studies utilise healthy controls as a reference group to highlight ALS-specific changes. For the development of diagnostic markers capable of discriminating ALS from other neurological conditions, the inclusion of disease controls, especially common mimics of ALS, is essential.

3.5. Laterality of findings

Unilateral or asymmetrical imaging findings are frequently reported in ALS, yet they are seldom discussed comprehensively. Similarly to other neurodegenerative conditions, at an individual level, asymmetrical symptoms and brain pathology are established features of early stage ALS (Turner et al., 2011b). However, few imaging studies have examined the relationship of sidedness of symptoms and brain changes. Metabolite ratio changes in the motor cortex have been shown to correspond to the lateralisation of clinical symptoms (Pohl et al., 2001; Block et al., 2002). Morphometric studies report unilateral pathological changes in the left cingulum (Abrahams et al., 2005), left middle frontal gyrus (Kassubek et al., 2005), left inferior frontal gyrus (Agosta et al., 2007), left thalamus (Chang et al., 2005), left medial frontal region (Kassubek et al., 2005), left insula (Thivard et al., 2007), left anterior temporal region (Grossman et al., 2008), left parahippocampal gyrus (Bede et al., 2013c), right parahippocampal gyrus (Mezzapesa et al., 2007), right precentral gyrus (Kassubek et al., 2005; Grossman et al., 2008; Agosta et al., 2007; Grosskreutz et al., 2006), right superior temporal gyrus (Bede et al., 2013c; Mezzapesa et al., 2007), right cerebellum (Thivard et al., 2007), and right premotor regions (Grossman et al., 2008). Diffusivity studies have reported unilateral pathology in the left inferior frontal lobe (Canu et al., 2011) and right uncinate fasciculus (Agosta et al., 2010b). However, sample size effects, handedness, disability profile, disease duration and physiological CNS asymmetry are rarely considered in the interpretation of these unilateral findings. This is despite the recognition of physiological brain asymmetry in right-handed healthy populations (Takao et al., 2011) and that asymmetry of the primary motor cortex and corticospinal tract architecture is particularly well established

(Westerhausen et al., 2007). Sample size limitations, disability profile and disease duration are likely to be the key factors contributing to asymmetrical findings. It is probable that asymmetry decreases on longitudinal follow-up. Until large meta-analyses and prospective studies with extensive data sharing are undertaken, reports on laterality should be interpreted with caution, and emphasis should be placed on the specific structure affected rather than the side of involvement.

3.6. Patient characterisation

Multifaceted characterisation of patients is of importance given the unique clinical, psychological and imaging profile of specific ALS genotypes, such as those with *SOD1* mutations (Stanton et al., 2009a; Blain et al., 2011; Turner et al., 2005) and those carrying the hexanucleotide expansion in *C9orf72* (Bede et al., 2013a). Imaging studies of ALS often provide in-depth characterisation in selected domains e.g. detailed psychological and limited genetic or post-mortem profiling, or vice versa. This is frequently a function of local expertise and is likely to improve with the shared infrastructure of international collaborations.

3.7. Multimodal studies

In studies using whole-brain, functional imaging modalities, such as PET, SPECT or fMRI, single-technique approaches may be sufficient. However, in studies using region-of-interest (ROI) or segmentation based MRI techniques such as VBM, DTI or cortical thickness measurements, multimodal approaches may be superior by providing comprehensive characterisation of disease-specific pathology. Studies combining multiple imaging techniques that evaluate multiple measures of both grey and white matter integrity are more likely to capture the full spectrum of network degeneration in ALS. Multimodal papers have highlighted increased functional and decreased structural connectivity in ALS, suggesting inhibitory dysfunction in ALS (Douaud et al., 2011). The benefit of using multiple imaging parameters can be further illustrated with the use of multiple diffusivity variables. Many DTI studies only use fractional anisotropy (FA) or mean diffusivity (MD), despite the fact that these are composite measures of eigenvalues and are not associated with the specific nature of white matter pathology. Conversely, axial diffusivity (AD) and radial diffusivity (RD) are independent variables; AD is broadly considered an axonal marker (Sun et al., 2006) and RD a myelin marker (Song et al., 2005). Multimodal biomarker studies are also ideal as a method to compare the sensitivity and specificity profiles of various techniques. For example, multimodal studies have suggested that MR spectroscopy may be more sensitive in detecting UMN degeneration than TMS (Kaufmann et al., 2004).

A large longitudinal multimodal ALS study utilising DTI, MUNE, MRS and TMS has concluded that MUNE changes considerably over time in comparison with other markers (DTI, TMS) that showed less significant longitudinal changes (Mitsumoto et al., 2007). Multimodal studies are also optimal cross-validation platforms, establishing novel imaging approaches such as whole-brain MRS against more recognised techniques (Govind et al., 2012). Whole brain MR spectroscopy demonstrated that metabolic changes along the corticospinal tracts correlate with more established measures of CST integrity (Stagg et al., 2013). Multimodal approaches are also essential in diagnostic, classifier analyses. Discriminant analyses utilising multiple imaging variables have been consistently shown to improve the sensitivity and specificity of group classification (Filippini et al., 2010).

3.8. Presymptomatic studies

Very few studies have examined presymptomatic carriers of ALS causing mutations to date (Ng et al., 2008; Carew et al., 2011; Turner et al., 2005). In a large spectroscopy study of presymptomatic *SOD1* carriers, metabolic changes were detected in the spinal cord prior to development of symptoms (Carew et al., 2011). A landmark DTI study of asymptomatic *SOD1* carriers identified decreased fractional anisotropy and increased radial diffusivity in the posterior limb of the internal capsule compared to healthy *SOD1* negative controls (Ng et al., 2008). These pioneering studies should help to pave the way for future studies, so this relatively arcane, presymptomatic phase of ALS, representing a crucially important diagnostic and therapeutic window, can be explored.

3.9. Multicentre ALS imaging studies

The Neuroimaging Society in ALS (NISALS) had its founding meeting in 2010 attracting considerable technical, clinical, psychology, and imaging expertise from various centres around the world. The challenges, objectives and potential benefits of multicentre collaboration in ALS imaging have been candidly discussed (Turner et al., 2011a). Another example of a multicentre ALS imaging and biomarker initiative is the SOPHIA 99 Consortium of the European Union Neurodegenerative Disease Research Programme (JPND). The obvious advantage of such collaborations is generating large patient numbers of relatively rare ALS phenotypes. The challenges of such initiatives include harmonisation across different scanner field-strengths and manufacturers, funding and authorship issues, time contribution of participating individuals, data management, storage and protection, ethics approvals, etc. Despite these difficulties however, multicentre neuroimaging is routinely used in clinical trials of multiple sclerosis drugs with established cross-platform harmonisation and calibration protocols (Moraal et al., 2009). Multicentre MR studies have also been successfully conducted in Alzheimer's disease, as evidenced by the Alzheimer's Disease Neuroimaging Initiative (ADNI). The cross platform calibration of ADNI, utilising travelling MRI phantoms has been comprehensively described (Gunter et al., 2009). By contrast, few cross-platform ALS imaging studies have been published to date. A large two-centre imaging study of ALS and ALS-FTD has been conducted in Germany using identical scanners and imaging protocol (Schuster et al., 2013), and the First NISALS coordinated DTI project is currently underway with the participation of 12 European and North American centres.

3.10. Meta-analyses

While meta-analyses could potentially presage the sort of information large multicentre studies can offer, surprisingly few meta-analyses have been carried out in ALS. An individual patient data (IPD) meta-analysis of DTI data of 221 ALS patients and 187 healthy controls suggested that corticospinal tract DTI alone lacked diagnostic specificity (Foerster et al., 2013a). However, a voxel-based meta-analysis of DTI date from eight studies, comprising 143 ALS patients and 145 healthy controls highlighted bilateral corticospinal tract changes in the posterior limb of the internal capsule as well as bilateral frontal and cingulate diffusivity changes (Li et al., 2012). A meta-analysis of 5 VBM studies demonstrated that right precentral grey matter atrophy is an important feature of ALS (Chen and Ma 2010). The data repositories of multicentre MRI initiatives of ALS, such as NISALS and SOPHIA, will be ideal platforms for individual patient data meta-analyses.

3.11. Correlative studies

A number of ALS imaging studies have sought to correlate common clinical variables with various MRI measures. Decreased corticospinal tract FA (Thivard et al., 2007; Cosottini et al., 2005a) has been associated with decreased ALSFRS-r (Cedarbaum et al., 1999), composite upper motor neuron scores (Stanton et al., 2009a; Filippini et al., 2010; Blain et al., 2011) and disease progression rates (Ciccarelli

et al., 2006, 2009; Agosta et al., 2010b). Grey matter density measures (Grosskreutz et al., 2006; Bede et al., 2013c) and NAA/Cr ratios (Sivák et al., 2010) have been correlated with disability scores. In addition to motor variables, cognitive (Grossman et al., 2008; Sarro et al., 2011) and behavioural (Tsujimoto et al., 2011) deficits have also been correlated to structural changes in ALS.

Despite the abundance of clinically-correlated neuroimaging studies in ALS, important conceptual factors must be considered. The ALSFRS-r is heavily influenced by lower motor neuron degeneration which is not captured by current imaging technology. Correlation of disease duration with structural changes is relatively difficult to interpret, as progression rates vary considerably at an individual level. Contrary to the conclusions of some studies, imaging should not be proposed as an alternative clinical assessment tool. Clinical disability scales and neuropsychological tests can be easily and routinely applied in a clinic room, home or bedside setting. They reflect on key functional aspects of the disability and with minimal training, excellent inter-rater and test–retest reliability can be achieved. The role of imaging in ALS on the other hand points beyond simplified clinico-structural correlations and could be regarded as a sensitive and objective descriptive tool, able to capture subtle, phenotype-defining pathology in cross-sectional and longitudinal, group-level and individual-level analyses.

3.12. Diagnostic applications

There is considerable interest in developing imaging technology that can discriminate ALS from non-ALS and mimic syndromes at individual level. Discriminant analyses of diffusivity measures (Ben Bashat et al., 2011), machine-learning and support vector machine classifier-analyses (Wang and Summers, 2012), are increasingly used in other neurodegenerative conditions (Orrù et al., 2012) and show considerable promise in the interpretation of individual imaging data. In ALS, a discriminant analysis, combining radial diffusivity, fractional anisotropy and voxel-based morphometry, achieved study group classification with 92% sensitivity, 88% specificity, and 90% accuracy (Filippini et al., 2010). The use of the disease state classifier machine learning approach (support-vector machine) on resting-state fMRI data achieved over 71% accuracy for disease state classification (Welsh et al., 2013).

3.13. Future directions

The purpose of ALS imaging is twofold. The first is to further progress our understanding of disease pathology and pathophysiology, in which group analysis is appropriate; and the second is to develop an imaging based technology that enhances individualised diagnostic accuracy beyond best clinical practice. Based on the critical appraisal of the shortcomings and achievements of recent ALS imaging studies, optimised study recommendations can be outlined. ALS imaging studies should ideally encompass genetically, neuropsychologically, electrophysiologically, and pathologically characterised patient cohorts, a healthy reference group and disease controls. Multiple complementary imaging techniques should be ideally utilised in the same study to provide multifaceted grey and white matter assessments. The effect of demographic variables, such as age, gender, education and handedness, should be strictly accounted for, and comparisons of ALS sub-cohorts should be corrected for disease duration and disability. Correlative studies should take the network degeneration aspect of ALS into account and assess network integrity as opposed to selected grey or white matter measures. Individual patient data meta-analyses are required prior to initiating harmonised multicentre studies, which in turn are eagerly awaited and are likely to generate sufficiently large sample sizes for meaningful data interpretation.

From a technological standpoint, high-field MRI scanners i.e. 7 T systems are increasingly available, promising unprecedented resolution and detailed spectroscopic evaluation. Nonetheless, only a few ALS studies have been carried out on these systems to date (Verstraete et al., 2010; Kwan et al., 2012). Similarly, no post-mortem MRI studies have been conducted in ALS, a method increasingly used in other neurodegenerative conditions. Quantitative muscle MRI is another relatively overlooked field of ALS biomarker research (Bryan et al., 1998). Whole-brain MRS is a particularly promising technique and its potential in ALS is far from being fully explored (Stagg et al., 2013). Despite a number of very successful spinal cord MRI studies (Valsasina et al., 2007), quantitative spinal imaging methods seem surprisingly underutilised in ALS11. Finally, the emergence of combined PET/MRI scanners and access to magnetoencephalography (MEG) are other exciting developments which are likely to contribute to our understanding of ALS pathophysiology.

4. Conclusions

A critical review of ALS imaging has identified stereotypical shortcomings, the lessons of which should be considered in the design of future prospective MRI studies. At a time when large multicentre studies are underway a candid discussion of these factors is particularly timely.

Author contributions

Peter Bede and Orla Hardiman have drafted and reviewed the manuscript for intellectual content.

Conflict of interest statement

We have no conflicts of interests to disclose.

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Appendix A. Supplementary Material

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