Prefrontal contributions to attention in ageing and stroke: implications for cognitive reserve.

by

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Declaration

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Summary

Global life expectancy is increasing dramatically with a corresponding rise in the prevalence of pathological ageing conditions such as dementia and stroke. Maintaining high levels of cognitive function in the face of dementia-related neuropathology or following acquired brain damage is of pressing societal importance. The ability to maintain endogenous levels of attentional engagement is a domain-general process underlying many higher-order cognitive capabilities. Deficits in this capacity are evident across a range of neurodegenerative diseases, interfere with functional recovery following right hemisphere stroke, and are associated with an increased likelihood of falling in older adults. In healthy ageing, superior levels of attentional engagement have been proposed to promote plasticity processes contributing to 'cognitive reserve': Older adults with more cognitively stimulating environments, achieved through education, complex professions, or social engagements, present with less clinical symptomatology in a range of conditions, such as dementia, given the degree of disease-related neuropathology.

Sustained attention is postulated to contribute to cognitive reserve such that high levels of attention, necessitated by cognitively demanding environments, lead to greater environmental enrichment. This encourages plasticity processes that, in turn, contribute to a neuroprotective effect against disease. The neural underpinnings of this effect have recently been proposed to result from the continuous engagement of the right lateralised fronto-parietal networks (FPN) and the repeated activation of the neurotransmitter noradrenaline (norepinephrine), which plays a pivotal role in arousal and plasticity. Throughout a lifetime, the repeated activation of this system strengthens the right-lateralised network creating a neuro-cognitive buffer.

Although the right-lateralised fronto-parietal networks play a well-established role in aspects of attention, it remains to be seen whether plasticity of the underlying networks can be harnessed directly in older adults to increase this cognitive function. The first aim of this thesis

therefore was to assess whether activity in the right prefrontal cortex (PFC), a flexible dynamic cortical region, could be upregulated in older adults in order to increase facets of attentional function that are crucial contributors to cognitive reserve.

Following damage to the right hemisphere, the capacity for sustained attention is reduced, and this interferes with functional recovery. Our understanding of these deficits and how best to ameliorate them is coarse. The second aim of the thesis therefore, was to explore how damage to the right hemisphere effects the temporal dynamics of sustained attention system, and whether plasticity of the right PFC could be targeted in chronic stroke to ameliorate deficits in engagement.

The first empirical chapter was designed to examine how behavioural and electrophysiological markers of sustained attention would change in older adults when activity in the right prefrontal cortex was directly upregulated using transcranial Direct Current Stimulation (tDCS), a non-invasive brain stimulation technique. Two separate experiments are presented where tDCS was employed to increase neuronal excitability of the right PFC while sustained attention was monitored. In Experiment 1 tDCS was administered during simultaneous electroencephalography (EEG) recordings in group of cognitively healthy older adults with suboptimal sustained attention performance. During tDCS, fewer lapses in attention occurred and electrophysiological markers of frontal engagement and early visual attention were enhanced, suggesting that attentional improvements were achieved through modulating processes involved in top-down endogenous control and early visual attention. In Experiment two, the extent to which the observed improvements in accuracy generalized to a very different sustained attention paradigm was examined. Consistent with Experiment 1, fewer attentional lapses occurred during tDCS. These findings suggest the right prefrontal cortex plays a critical role in supporting sustained attention in ageing, and that this region may be targeted in older adults to increase attentional engagement.

The speed at which visual information can be processed is an aspect of visual attention that is increasingly considered a biomarker of cognitive decline. The second experimental chapter explored the relationship between visual attention, hemisphere asymmetries, and cognitive reserve, and assessed whether visual processing speed could be enhanced in older adults by increasing activity in the right prefrontal cortex. For this purpose, computational modeling of visual attention was combined with tDCS. Using a highly specified formal framework, visual attention processes were quantified in older adults, unbiased by age-related motor slowing. During the performance of a lateralised whole-report task, older adults with higher levels of cognitive reserve showed a stronger processing speed asymmetry towards objects in the left hemifield. This was in contrast to younger adults who showed a rightward processing speed asymmetry, thus suggesting functional reorganization involving the right hemisphere in older adults with high levels of cognitive reserve. Correspondingly, when activity in the right PFC was increased in older adults using tDCS, processing speed improved. In older adults with lower levels of reserve, tDCS altered their processing speed within the left and not right hemifield, thus mimicking that of their high reserve peers. This chapter provides empirical support for the role of the RH in cognitive reserve and suggests that the right PFC is a promising target region to increase cognitive reserve in later years and provides further evidence in support of the first experimental chapter, that the PFC can be targeted in ageing to enhance top-down modulation over visual attention processes.

In the third empirical chapter, using a behavioural paradigm that elicits steep decrements in sustained attention performance, the temporal dynamics of attentional engagement were explored in stroke patients with unilateral damage to the right hemisphere. Relative to neurologically healthy older adults, right hemisphere damage was associated with sharp drops in sustained attention over a short temporal window (less than 3 1⁄2 minutes). This vigilance decrement is within a shorter temporal window than previously noted in the literature, which

provides valuable practical information for informing rehabilitation protocols for RH stroke patients.

In the final experimental chapter, the feasibility of upregulating activity in the right PFC to improve sustained attention deficits in patients with right hemisphere damage was assessed. The same tDCS protocol (from Chapter 1, Experiment 2) that improved sustained attention performance in neurologically healthy older adults was applied to a group of stroke patients with unilateral right hemisphere damage. It was hypothesized that right prefrontal tDCS would increase excitability in the perilesional and residual areas of the damaged right hemisphere to improve sustained attention. However, preliminary data suggests that tDCS disrupted sustained attention. Further work will be necessary to determine whether prefrontal tDCS to the damage hemisphere is disrupting a natural compensatory process of the contralesional network in stroke patients with persisting sustained attention deficits at the chronic stage.

The work presented in this thesis constitutes important information regarding the role of the right hemisphere in facets of attention, that can be employed to inform neurorehabilitation programs to enhance attentional function in healthy ageing and following stroke, and potentially increase cognitive reserve in older adults. The implications of this work and future directions are discussed.

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Publications arising from this thesis

Brosnan, M., Arvaneh, M., Harty, S., Maguire, T, O'Connell, R., Robertson, I., & Dockree, P. Right prefrontal tDCS Modulates Behavioural and Electrophysiological Signatures of Sustained Attention in Older Adults (under review)

Brosnan, M., Demaria, G., Petersen, A., Dockree, P., Robertson, I., & Wiegand, I. Plasticity of the Right-Lateralised Cognitive Reserve Network in Ageing. *Cerebral Cortex*.

Brosnan, M. & Wiegand, I. The Dorsolateral Prefrontal Cortex, a Dynamic Cortical Area to Enhance Top-Down Attentional Control. *Journal Club Article, Journal of Neuroscience*

Brosnan, M., Robertson, I., Dockree, P., O'Connell, R., Levenstein, J., Harty, S., Humphreys, G., & Demeyere, N. The Temporal Dynamics of Attentional Engagement following RH Stroke (submitted)

Related co-authored publications

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Subramanian L, Morris MB, **Brosnan** M, Turner DL, Morris HR, & Linden DEJ (2016). Functional Magnetic Resonance Imaging Neurofeedback-guided Motor Imagery Training and Motor Training for Parkinson's Disease: Randomized Trial. *Frontiers in Behavioral Neuroscience*.

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Published Abstracts

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Brosnan, **M.,** Arvaneh, M., Robertson, I., & Dockree, P. Plasticity of the sustained attention network in ageing: a simultaneous tDCS-EEG approach. *The Oxford Autumn School of Cognitive Neuroscienc*e, Oxford, UK, September, 2016.

King, R. L., **Brosnan, M**., Humphreys. G. W. & Demeyere, N. Post-stroke deficits in attention and working memory: prevalence and impact on subacute and long term functional status. *British Neuropsychological Society Autumn Meeting*, London, UK, October 2016.

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Brosnan, **M.,** Arvaneh, M., Robertson, I., & Dockree, P. Neuromodulation of the Sustained Attention Network in Ageing, a tDCS-EEG co-registration approach. *International Neuropsychological Society meeting*, London, UK, July 2016.

Brosnan, **M.,** Arvaneh, M., Dockree, P., & Robertson, I. The effect of facilitating the right prefrontal cortex on ERP and spectral markers of attention in ageing. *The 4th International Theory of Visual Attention (iTVA) meeting*, Copenhagen, Denmark, June 2016.

Demaria, G., **Brosnan**, **M.,** Dockree, P., Robertson, I., & Wiegand, I. Investigating the Effects of Brain Stimulation on Visual Attention in Older Adults. *Cognitive Neuroscience Society,* New York, USA, March 2016.

Brosnan, **M.,** Arvaneh, M., Robertson, I., & Dockree, P. Neurorehabilitation of Attention in Ageing using Transcranial Direct Current Stimulation (tDCS). *Society for Neuroscience*, Chicago, USA, October 2015.

Introduction

As life-expectancy increases across the globe there is a concomitant increase in age-related pathological conditions. By 2050, the prevalence of Alzheimer's Disease worldwide is expected to rise from 46 to 131.5 million people (International, 2015). Similarly, the negative impact of stroke is expected to double by 2030 across the globe (Feigin et al., 2014). Pathological cognitive impairment is not just a devastating experience for patients and families but also places a substantial economic burden on societies (International, 2015). Understanding how best to maintain high levels of cognitive function during the healthy ageing process and to buffer against cognitive decline during pathological ageing conditions, is therefore not only of importance for the well-being of individual patients but is of pivotal societal importance.

The aim of the current chapter is to introduce the research which has motivated this thesis. In the proceeding section the concept of cognitive reserve, a naturally occurring phenomenon which provides a neuroprotective effect against a wide range of age-related cognitive impairments, is discussed. High levels of attentional engagement have been proposed to cultivate cognitive reserve through strengthening of the right lateralised fronto-parietal networks (FPN). In Section I2 an overview of the behavioural relevance and neural underpinnings of two aspects of attention, sustained attention and processing speed is provided, along with an outlook as to how right FPN damage impacts on these processes. Section 3 offers insight into how these facets of attention are affected by the ageing process. The fourth section details promising approaches that are emerging to remediate attention deficits in older adults and stroke patients, and explores how these interventions may be supported by the brain. In Section I5, established characteristics of the dorsolateral prefrontal cortex are outlined that place this region in a particularly advantaged position to support rehabilitation of attention deficits in ageing and following stroke. The sixth section details an outline of the objectives of this thesis.

I.1 Cognitive Reserve

Older adults who partake in more cognitively stimulating activities are relatively protected against cognitive decline in the face of pathological ageing conditions such as Alzheimer's Disease (Stern, 2012). A major aim of this thesis is to investigate whether the networks underpinning this phenomenon maintain preserved levels of plasticity such that they can be targeted to improve cognitive function in older adults. This section outlines the phenomenon of cognitive reserve, and a recent cognitive neuroscientific proposal of its neural underpinnings.

I.1.1 Cognitive reserve and pathological ageing

Cognitive reserve, refers to the observation that older adults with higher levels of education, intelligence, and with more cognitively stimulating environments show less clinical symptomology in the face of neuropathology (Stern, 2012; Stern, Alexander, Prohovnik, & Mayeux, 1992). In their seminal paper, Stern and colleagues (1992) compared three groups of Alzheimer's Disease (AD) patients, matched for clinical severity but differing in levels of educational attainment. Regional cerebral blood flow over parietotemporal cortex was employed as a proxy neuromarker of disease progression. The authors observed lower levels of parietotemporal perfusion (denoting more advanced AD-related pathology) in the group with the highest levels of educational attainment (Fig. I.1), indicating that these maintained functioning for longer, given the disease progression. As such, high levels of education were posited to result in a neuroprotective effect against the clinical symptoms of the disease (Stern et al., 1992). Over the last two decades a considerable body of work has substantiated this initial observation regarding a neuroprotective effect of an enriched environment. Cognitively stimulating environments have been associated with reduced clinical impairments across a wide range of pathological ageing conditions including Alzheimer's Disease (Stern, 2012), stroke (Ojala-Oksala, Jokinen, Kopsi, & Lehtonen, 2012), traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003), and multiple

sclerosis (Sumowski, Chiaravalloti, & DeLuca, 2009). This neurocognitive buffer has been shown to result not only from higher levels of education but also through complex occupations, and engagement in cognitively stimulating leisure activities (Valenzuela & Sachdev, 2006; see Opdebeeck, Martyr, & Clare, 2015 for a recent meta-analysis)

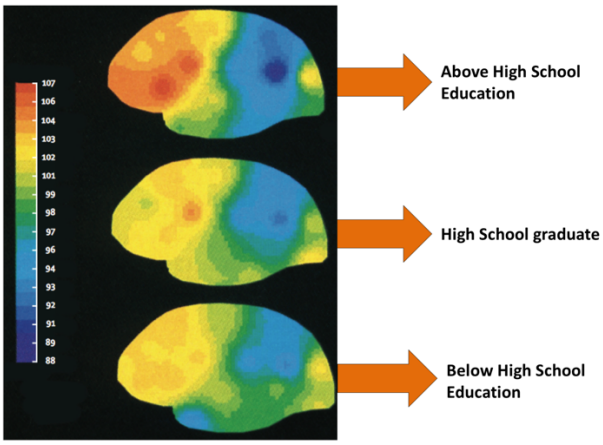

Figure I.1: Cerebral blood perfusion in Alzheimer's Disease according to education. Despite presenting with matched levels of clinical severity, the group with highest levels of education showed more severe reductions in perfusion over parietotemporal regions. *Note.* Darker blue denotes lower levels of perfusion. Figure adapted from Stern et al. (1992).

I.1.2 The neural underpinnings of cognitive reserve

Understanding how the brain supports the exciting phenomenon of cognitive reserve will inform approaches to nurture this phenomenon and mitigate cognitive loss in older adults. Likewise, the neural underpinnings behind the robust benefits associated with cognitively stimulating environments are of fundamental interest to cognitive neuroscience to shed light on the influence of environmental factors on brain function. In the first cognitive neuroscientific theory of cognitive reserve (Robertson, 2013; 2014), Robertson proposed that repeated norepinephrine (noradrenaline) activation over the course of a lifetime cultivates cognitive reserve.

Noradrenaline, which originates in the locus coeruleus (LC), is critical for arousal and alertness: The identification of the locus coeruleus–noradrenaline system involvement in cortical

arousal stemmed from initial observations that activation in LC neurons fluctuates in line with the sleep-wake cycle (Roussel, Buguet, & Bobillier, 1967). More recently, these data have been substantiated by optogenetic techniques demonstrating that LC firing is causally implicated in the transition from sleep to wake cycles, and in arousal within cortical regions (A. R. Carter et al., 2010a). A right hemisphere dominance has been demonstrated for noradrenaline (Debecker, Laget, & Raimbault, 1978; Grefkes, Wang, Eickhoff, & Fink, 2010b; Robinson, 1979b) with strong projections to fronto-parietal networks (Jodo & Aston-Jones, 1997; Jodoj, Chiang, & Aston-Jones, 1998; Singewald, 1998).

In human participants, the right-lateralised noradrenergic system has been proposed by several authors to substantially contribute to non-spatial aspects of attention such as alertness (Corbetta & Shulman, 2002; 2011; Posner & Petersen, 1990; Robertson, 2014). Alertness is considered a foundation attentional function on which more global aspects of attention are built (A. Raz & Buhle, 2006). Hence, the locus-coeruleus noradrenaline system has well-documented links with a wide breadth of functions including cognitive flexibility, aspects of attention, processing of sensory information across a range of modalities, vigilance, and working memory processes (Hurley, Devilbiss, & Waterhouse, 2004; Sara, 2009; 2015; Sara & Bouret, 2012).

Five core cognitive processes have been identified by Robertson (2014) to support and cultivate cognitive reserve. Sustained attention, arousal, working memory, response to novelty and performance monitoring (error awareness) rely, to varying degrees, on the right lateralised fronto-parietal networks which are subserved by noradrenaline (Robertson, 2014). Cognitively stimulating environments, such as those demanded by high levels of education, complex professional activities, and engaging social interactions, demand these core cognitive processes. Over the course of a lifetime, this leads to higher secretion of noradrenaline and strengthening of the right-lateralised FPN (Fig. I.2), thus a specific role for these networks has been proposed to underpin cognitive reserve (Robertson, 2013; 2014).

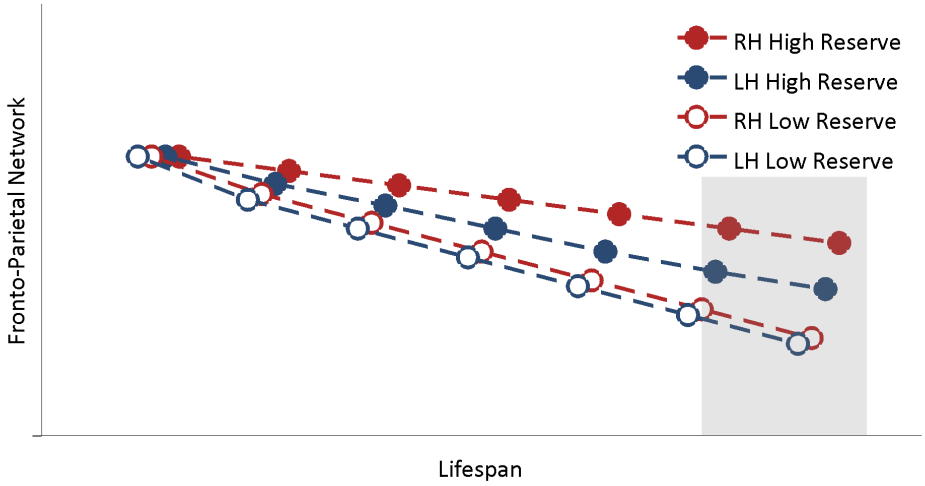

Figure I.2: Visualisation of Robertson's model of cognitive reserve In the first cognitive neuroscientific model of cognitive reserve, Robertson (2013) proposed that cognitive reserve develops through repeated noradrenaline activation over a lifetime. Given noradrenaline's privileged relationship with right FPN underpinning cognitive operations such as arousal, novelty, and sustained attention, a distinct role for this network in cognitive reserve is proposed (Robertson, 2014). Specifically, throughout a lifetime (X Axis) the continuous engagement of the core cognitive processes supported by the right FPN is assumed to strengthen these networks (Y axis), thereby cultivating greater levels of cognitive reserve. An aim of this thesis is to address whether this network maintains preserved levels of plasticity in later years (shaded in grey) through increasing excitability of the right prefrontal tDCS and assessing the effects on aspects of attention.

A major aim of this thesis is to better understand facets of attention that show right hemisphere dominance in ageing and following stroke. Over a lifetime, greater levels of attentional engagement may provide greater enrichment from intellectual activities, social connectivity, physical activity, and employment activities, all factors which are proposed to increase cognitive reserve during life (Valenzuela & Sachdev, 2006). Environment enrichment enables experience-dependent cortical plasticity (Polley, Steinberg, & Merzenich, 2006; Recanzone, Schreiner, & Merzenich, 1993) which in turn facilitates a neuro-protective effect against cognitive impairments in the presence of neuropathology occurring with clinical diseases such as Alzheimer's (Robertson, 2013; 2014; Stern, 2012; Valenzuela & Sachdev, 2006). Thus, efforts to enhance attention in older adults hold potential to preserve higher cognitive functioning in older adults (Robertson 2014).

This predominant focus of this thesis is on the right-lateralised network proposed by Robertson to underpin cognitive reserve (2013, 2014). The broad spectrum of cognitive functions that are underpinned by alertness (A. Raz and Buhle 2006) and this right-lateralised system (Corbetta and Shulman 2002; Robertson 2013; Robertson 2014) provide a solid theoretical basis for understanding mechanisms to strengthen this proposed network in both healthy and pathological ageing conditions. However, limitations of the theoretical framework on which this thesis is based must be acknowledged.

Firstly, it is unlikely that the preservation of cognitive function in older adults is uniquely contingent on this right-lateralised system. For example, Franzmeier and colleagues have recently demonstrated that prodromal Alzheimer's Disease patients with higher levels of education (a frequently used cognitive reserve proxy; Stern, 2012) show higher global connectivity with a seed region in the left frontal cortex. This finding suggests that cognitive reserve was associated with grater functional integrity of this left hemisphere region (though it must be noted that the authors did not examine global connectivity within the homologous right hemisphere region).

Franzmeier and colleagues (Franzmeier et al. 2017) also demonstrated that preservation of episodic memory (a cognitive function which shows left lateralization in young healthy adults (Cole et al. 2013)) in the face of prodromal Alzheimer's pathology, was associated with higher global connectivity with this left frontal cortex seed region. This points to a seemingly contradictory phenomenon to cognitive reserve - 'brain (neural) maintenance', which proposes that individuals who maintain youth-like brain structures exhibit relative preservation of cognition in older age (Nyberg et al. 2012). Cognitive reserve and brain maintenance can be considered orthogonal concepts concepts (Habeck et al. 2016) which interactively determine an aging individual's cognitive status over the lifespan. In order to thoroughly dissociate how mechanisms of brain maintenance and reserve contribute to the preservation of cognitive function in ageing, a wide range of measures including neuroimaging, cognitive assessment, and

post-mortem examinations will need to be assessed longitudinally in older individuals (N. Raz and Lindenberger 2011).

I.2 Attention and the Right Fronto-Parietal Network

As outlined in Section I.1, enhancing cognitive reserve in older adults may constitute a viable means for preventing or delaying cognitive decline in ageing. It has been proposed that the continuous engagement of the right lateralised FPN, given its close links with the LC-noradrenaline system, supports cognitive reserve in older adults. The following section outlines two aspects of attention that are dependent on the right lateralised alerting system that is posited to underpin cognitive reserve: sustained attention and visual attention capacity. Behavioural and neurophysiological descriptions of these two cognitive capacities in neurologically healthy individuals are first described, followed by a summary of how these cognitive capacities are impaired following damage to the right FPN.

I.2.1 Sustained attention

Sustained attention can be described as maintaining a goal-directed focus in repetitive nonarousing conditions (Robertson, 2003). In neurologically healthy individuals, lapses in sustained attention are associated with failure to engage with the task at hand (Smilek, Carriere, & Cheyne, 2010) leading to work-related errors (Schwebel, Lindsay, & Simpson, 2007; Taylor-Phillips et al., 2014) and locomotive accidents (Edkins & Pollock, 1997). Patient groups afflicted by impaired sustained attention abilities, such as children with attention deficit hyperactivity disorder (Bellgrove, Hawi, Gill, & Robertson, 2006), show difficulty in engaging attention, even when performing tasks such as watching television (Whirley, Lorch, Lemberger, & Milich, 2016).

An extensive cortico-subcortical network incorporating frontal, parietal, thalamic and brain-stem regions contributes to endogenously maintaining attentional focus (Clemens et al., 2011; Sturm & Willmes, 2001a). Within this network, the prefrontal regions are of particular value for supporting the capacity to sustain attention. Evidence for a robust right hemisphere dominance underlying the ability to maintain attention comes from lesion studies (Malhotra, Coulthard, & Husain, 2009; Manly et al., 2003; Rueckert & Grafman, 1996; 1998), psychophysical studies using lateralised stimuli (Warm, Richter, Sprague, Porter, & Schumsky, 1980), and neuroimaging studies (Johannsen et al., 1997; Langner & Eickhoff, 2013a; Sturm & Willmes, 2001b).

Genetic (Greene, Bellgrove, Gill, & Robertson, 2009) and pharmacological (O'Neill, Fitten, Siembieda, Ortiz, & Halgren, 2000) research points to noradrenergic involvement in sustained attention. For example, pharmacological upregulation of noradrenaline via *atomoxetine*, a selective noradrenaline reuptake inhibitor, has been shown to improve sustained attention in ADHD participants (Weiss et al., 2005), with preliminary evidence suggesting similar benefits may be achieved for right hemisphere stroke patients (Malhotra, Parton, Greenwood, & Husain, 2006; Singh-Curry, Malhotra, Farmer, & Husain, 2011). Conversely, downregulation of noradrenaline using noradrenergic α2 agonists (such as *clonidine* or *dexmedetomidine*) has been shown to impair performance on sustained attention tasks (Coull, Jones, Egan, Frith, & Maze, 2004; A. Smith & Nutt, 1996).

I.2.2 Visual attention

Goal directed attention is considered to be subserved by two interacting networks (Corbetta & Shulman, 2002). A myriad of work has demonstrated the involvement of a bilateral dorsal system (incorporating regions such as the frontal eye fields and intraparietal cortex), which is symmetrically organised and predominantly accounts to contralateral space (Corbetta & Shulman, 2002; Ungerleider, 2000).

However, modulation of sensory processing is not inherent to the bilaterally organized sensory cortices themselves but rather results from the top-down influences of higher-order control regions (Gazzaley & Nobre, 2012; Kerchner et al., 2012). Cumulative evidence supports a role for a right lateralised fronto-parietal network (so-called ventral attention network) in the top-down modulation of visual attention processes (Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015; de Schotten, 2005). For example, Shulman and colleagues used functional magnetic resonance imaging (fMRI) to explore hemispheric contributions to attentional processes using lateralised stimulus displays. Analysis of the blood-oxygen-level dependent (BOLD) data revealed the well-documented dorsal attention system, bilaterally activated for contralateral stimuli during selective attention processes. However, regions of the ventral attention network, including the DLPFC, showed a right lateralisation for target detection – regardless of what hemifield the target was presented in (Shulman et al., 2010). Similarly, it has been shown that while left parietal activity increases monotonically with memory load for contralateral targets, activity in the homologous right hemisphere region increases irrespective of hemifield (i.e., both for ipsi- and contralateral targets), suggesting that a right lateralised network supports visual attention processing within both hemifields (Sheremata, Bettencourt, & Somers, 2010).

The speed at which information in the environment can be processed (processing speed) is an aspect of visual attention that places a limiting factor on higher cognitive functioning (Salthouse, 1996). Several lines of indirect evidence in healthy individuals suggests the right prefrontal cortex may support this capacity. Firstly, processing speed capacity has been shown to be compromised when levels of alertness, a cognitive operation that relies greatly on the right PFC (cf Robertson, 2014) are reduced (Matthias et al., 2009). Secondly, younger adults who are faster at processing visual information have greater white matter integrity of the inferior fronto-occipital fasciculus (IFOF) in the right relative to left hemisphere (Fig. I.3, Chechlacz et al., 2015). The IFOF is a long association white matter pathway connecting the frontal lobes with posterior parietal and occipital regions, thus indirectly supporting the involvement of the right

prefrontal cortex in the top-down modulation of early visual attention processes (Chechlacz et al., 2015).

Several reports indicate noradrenergic involvement in visual attention processes. Task relevant attended-stimuli selectively activate LC neurons (Aston-Jones, Rajkowski, & Kubiak, 1994), and levels of phasic LC firing to targets and distractors are associated with corresponding behavioural patterns of better and worse performance, respectively (Rajkowski, Kubiak, Ivanova, & Aston-Jones, 1997).

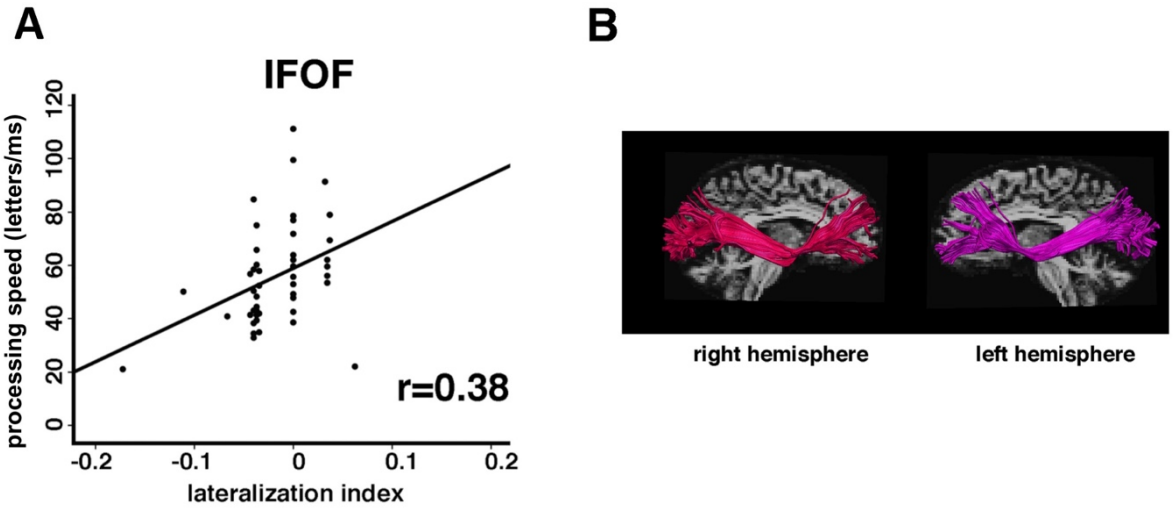

Figure I.3: Right lateralization of long association white matter tracts predicts processing speed capacity in healthy younger adults. A. Right lateralisation of the inferior fronto-occipital fasciculus (IFOF), a long-association white matter tract connecting the frontal lobes with parietal and occipital regions, predicts processing speed capacity in younger adults, suggesting a role for the right FPN underpinning this capacity **B.** Visualisation of the IFOF in a single participant. Both figures adapted from Chechlacz et al. (2015)

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I.2.3 Attention capacity following right FPN damage

The substantial contribution of the right FPN to both sustained and visual attention processes is well characterized following damage to the right lateralised fronto-parietal regions. Unilateral damage to the right fronto-parietal regions, is associated with both a reduced capacity to maintain attentional engagement (Rueckert & Grafman, 1996; 1998) as well as impaired

processing speed to both visual hemifields (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999a; Habekost & Rostrup, 2007), highlighting the importance of the right FPN for both of these capacities.

Visual neglect following stroke is associated with failure to attend to the contralesional side of space. Several features of this condition highlight the importance of the right lateralised alerting system for both sustained and visual attention processes (Corbetta & Shulman, 2002; Husain & Rorden, 2003). Firstly, although neglect can occur following damage to either hemisphere, persistent and severe deficits are more frequently observed following RH damage (Stone, Halligan, & Greenwood, 1993, Corbetta, & Shulman, 2011). Secondly, neglect commonly co-exists with deficits in both sustained attention (Malhotra et al., 2009; Robertson, Manly, Beschin, & Daini, 1997b) and processing speed (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999a), likely due to hypoactivation of the right hemisphere (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Heilman, Bowers, Coslett, Whelan, & Watson, 1985). Correspondingly, when alertness is increased in neglect patients (for example through behavioural interventions, alerting cues, or reward), attention is typically shifted leftward i.e. neglect symptoms are temporarily reduced (Finke, Matthias, Keller, Müller, & Schneider, 2012; Olgiati, Russell, Soto, & Malhotra, 2016; Robertson, Mattingley, Rorden, & Driver, 1998; Robertson, Tegnér, Tham, & Lo, 1995). This right-lateralised ventral attention network is therefore of importance for maintaining attentional engagement but also for supporting more basic aspects of visual attention.

I.3 Attention in Ageing and following Stroke

As demonstrated in section I.2, the right-lateralised alertness network crucially contributes to both the capacity to maintain attention, and the rate at which visual information in the environment can be processed. Support for this claim arises from neuroimaging paradigms,

psychophysical tasks, pharmacological manipulation of noradrenergic activity, and from patients with unilateral damage to the right FPN who show pronounced deficits in both capacities. The following section outlines how these capacities are affected by the ageing process.

I.1.1 Sustained attention deficits

Like many cognitive functions, attention is vulnerable to age-related decline. Sustained attention is considered a key constituent of healthy cognition in aging (Robertson, 2014), is susceptible to significant degradation with healthy aging (McAvinue et al., 2012), and is associated with an increased likelihood of falling in older adults (O'Halloran, Pénard, Galli, & Fan, 2011). Deficits in the capacity to maintain attentional engagement afflicts sufferers of several age-related neurodegenerative diseases including frontotemporal dementia and Alzheimer's Disease (Berardi, Parasuraman, & Haxby, 2005; O'Keeffe et al., 2007; Perry, Watson, & Hodges, 2000). The integrity of the sustained attention system is particularly compromised following damage to the right hemisphere (Malhotra et al., 2006; Rueckert & Grafman, 1996; 1998). Sustained attention deficits, in turn, interfere with rehabilitation outcomes (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997a) and functional recovery following stroke (King, Brosnan, Humphreys, & Demeyere, in prep, Appendix A).

I.1.2 Visual attention deficits

Visual attention processes are susceptible to age-related performance decrements (McAvinue et al., 2012; Wiegand et al., 2014) and are characteristic of cognitive ageing (Salthouse, 1996). Impairments in the speed at which visual information can be processed hinders many aspects of day-to-day functionality in older adults by for example reducing mobility, and increasing the risk of car accidents (Ball, Edwards, Ross, & McGwin, 2010; Wood & Owsley, 2014). A recent large (N=628) longitudinal study (Ritchie, Tucker-Drob, & Deary, 2014) following older adults from ages 70-76 reported a strong association between changes in processing speed and changes in fluid intelligence, supporting the proposal for processing speed as a useful biomarker of cognitive decline (Deary, Johnson, & Starr, 2010; Gregory, Nettelbeck,

Howard, & Wilson, 2008; Ritchie et al., 2014). In line with this, the neurodegenerative progression of Alzheimer's Disease from mild-cognitive impairment to full diagnosis of the disease is associated with staged declines in processing speed (Bublak et al., 2011). Processing speed can also be impaired following stroke, with unilateral damage to the right hemisphere resulting in bilateral impairments in the rate at which visual information can be processed (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999a; Habekost & Rostrup, 2007).

I.4 Approaches to Ameliorate Attention Deficits

Section I.3 outlined how sustained attention and processing speed are both vulnerable to age-related decline and are substantially impacted by right hemisphere stroke. The proceeding section will examine recent advances towards ameliorating attention deficits in ageing to address questions of pressing interest: can attentional functioning be improved, and what are the neural mechanisms underpinning promising remediation approches?

I.4.1 Attention and plasticity

Attention is of pivotal importance for brain plasticity and cortical remapping (Fritz, Elhilali, & Shamma, 2007a; Kamke et al., 2012; Polley et al., 2006; Recanzone et al., 1993). Brain plasticity processes, in turn, support learning new skills (Zatorre, Fields, & Johansen-Berg, 2012), optimal recovery following stroke (Di Lazzaro et al., 2010; Fu & Zuo, 2011; Hallett, 2001), and underpin the cognitive benefits of an environmental enrichment (Harley, 2004; Robertson, 2013; 2014; Van Praag, Kempermann, & Gage, 2000). Attention is therefore an attractive cognitive capacity to target in ageing as the potential for benefits to generalize beyond the trained attentional domain might be realised.

I.4.2 Sustained attention interventions

One promising approach for remediating sustained attention deficits is self-alert training, a behavioural technique where individuals learn to acquire control over their arousal levels (O'Connell, Bellgrove, Dockree, & Lau, 2008a; Robertson et al., 1995). A recent randomized control trial (Milewski-Lopez et al., 2014) assessed the effects of an alertness intervention that incorporated attention education, strategies for increasing endogenous levels of alertness (e.g. sit up straight, say 'focus'), and biofeedback training using skin conductance, a measure of autonomic arousal (Dawson, Schell, Filion, & Berntson, 2009) on cognitive performance in older adults. Improvements in both sustained attention and executive function measures were observed immediately post-training. Although further work will be necessary to optimize the self-alerting protocol such that benefits may be maintained at follow-up time periods, this study exemplifies the potential for self-alerting to improve attentional engagement in ageing. Similarly, this technique has been shown to temporarily ameliorate both sustained attention deficits and visual neglect symptoms in stroke patients with damage to the right hemisphere (Robertson et al., 1995).

Pharmacological upregulation of noradrenaline, with noradrenergic agonists such as guanfacine, has shown promise for alleviating sustained attention impairments in patients with unilateral damage to the right hemisphere (Malhotra et al., 2006; Singh-Curry et al., 2011). Preliminary animal work suggests that similar benefits of noradrenergic agonists may be observed for aspects of attentional function in older adults (O'Neill et al., 2000), however it remains to be seen whether these effects translate to human participants.

I.4.3 Visual attention interventions

The consideration of processing speed as a biomarker for cognitive decline (Deary et al., 2010; Gregory et al., 2008; Ritchie et al., 2014; Salthouse, 1996) has sparked considerable interest in speed-based training paradigms in older adults. Emerging data from a large-scale longitudinal study suggests processing speed training may result in substantial benefits for healthy older

adults, over and above those relating to the speed at which visual information can be processed. In the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) multi-center clinical trial, older adults (N = 2832) were randomly assigned to computerised interventions training processing speed, memory, or reasoning abilities (ten 60-75 minute sessions over 5-6 weeks). In the processing speed training group, participants were required to processes increasingly complex visual information presented in incrementally shorter durations. This training lead to processing speed improvements, evident at a 10-year follow-up period, that were associated with reduced functional decline (Fig. I.4, Rebok et al., 2014). While similar reductions of functional impairment were noted for the memory and reasoning training groups (relative to a no-contact control group), only the older adults who underwent speed-based training showed a reduced likelihood of developing depressive symptoms (Wolinsky et al., 2009) and a protective effect against declines in health-related quality of life (Wolinsky et al., 2006). These compelling results therefore suggest that strengthening the networks underpinning processing speed may not only delay functional decline in ageing, but may provide a neuroprotective effect against clinically relevant impairments.

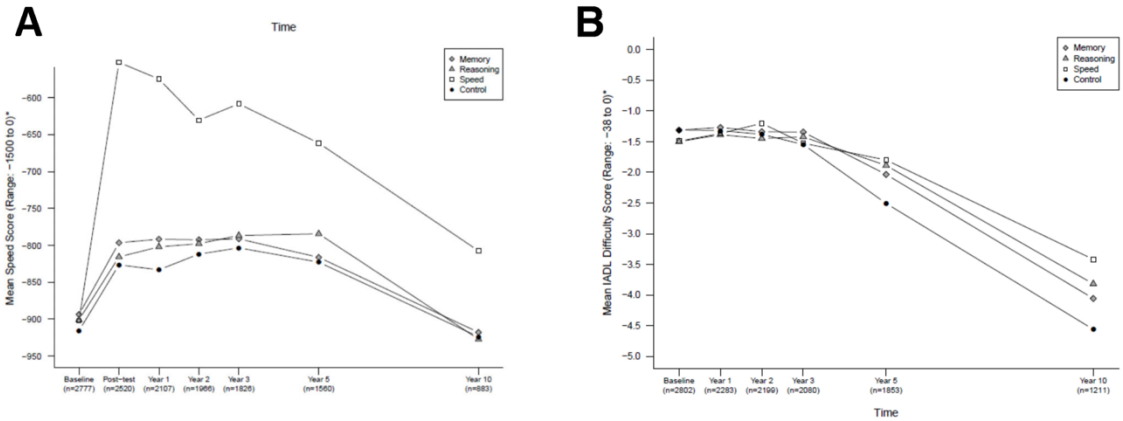


Figure I.4: Processing speed training in older adults. A. Processing speed training in older human individuals is associated with long-lasting benefits at a 10-year follow-up assessment. **B.** Processing speed training and reasoning training leads to a protective effect against functional decline (Rebok et al., 2014).

The Neural Effects of Processing Speed Training

The benefits of processing speed training for older adults (Rebok et al., 2014) suggests that plasticity, in at least some of the networks supporting this capacity, is preserved. But what are the plausible networks underpinning these benefits? Arguably the most persuasive observations regarding the role of attention in plasticity processes come from animal work in early sensory areas (e.g. Recanzone et al., 1993), where highly specific cortical remapping has been observed uniquely for attended stimulus dimensions following attention-based perceptual training (Polley et al., 2006).

Animal work from Michael Merzenich's group suggests that plasticity processes in primary sensory regions may be altered in the ageing brain: de Villers-Sidani and colleagues administered 20 hours of intensive auditory speed-based training to older rats (de Villers-Sidani et al., 2010). Following training, the authors observed substantial reversal of the majority of functional and structural markers of age-related impairments in the primary auditory cortex A1 (Fig. I.5). For example, in the young healthy rat, receptive fields in A1 respond selectively to a relatively narrow range of frequencies (Fig. 1.5A, 'Young'). With age, these neurons respond relatively unselectively to a wider range of frequencies resulting in larger, 'detuned' receptive fields (Fig. I.5A, 'Aged'). De Villers-Sidanu and colleagues showed that post intervention, this marker of neural precision was remediated in the older rat brain such that it more closely resembled the younger rat (Fig. 5A, 'Aged-Trained')

These animal findings that the potential for the ageing brain to show cortical remapping in early sensory regions have been indirectly corroborated by work in human participants showing altered electrophysiological markers of early visual processesing in older adults following visual perceptual discrimination training (Fig. I.5B, Berry, Zanto, Clapp, Hardy, & Delahunt, 2010; Mishra, Rolle, & Gazzaley, 2014).

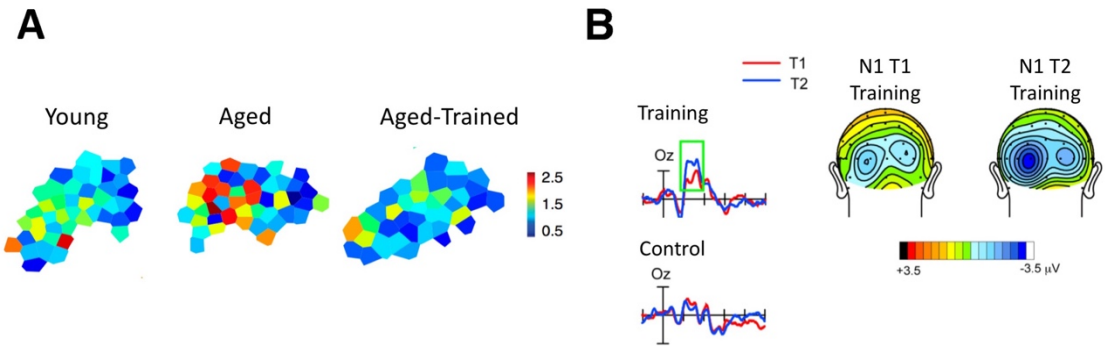


Figure I.5: The neural basis for processing speed training. A. Intensive processing speed training normalizes receptive field frequency maps in primary auditory cortex of older rats similar to the young healthy rat brain (de Villers-Sidani et al., 2010). **B.** Perceptual training modifies early sensory processing in human participants as evidenced by an enhanced N1 amplitude (adapted from Mishra et al., 2014). *Note.* The scale on the ERP maps is -/+ 2.5uV with higher values representing more negative amplitudes.

1.4.4 Fronto-parietal underpinnings of attention remediation

The preceding section suggests that interventions targeting visual attention processes impact early visual regions of the ageing brain. What is still not clear is whether the FPN may support the remediation of attention in older adults. Although never assessed directly, several converging reports suggest that this may be the case.

Although well established that activity in early sensory regions is modulated by top-down processes from the FPN (Erez & Duncan, 2015; Gazzaley & Nobre, 2012; Habes et al., 2016; Kerchner et al., 2012; Nelissen, Stokes, Nobre, & Rushworth, 2013), the contribution of the FPN to training paradigms targeting visual attention processes in the ageing brain remains unclear. Nevertheless, indirect evidence suggests involvement of the FPN in training early perceptual capacities. Firstly, following perceptual discrimination training in older adults, changes in stimulus-evoked electrophysiological markers of visual attention are directly associated with post-training improvements in working memory (Berry et al., 2010; Mishra et al., 2014). Similarly, intensive perceptual training in the auditory domain in older life is associated with improved memory performance which is maintained at a 3 month follow-up period (Mahncke et al., 2006). Thus, stimulus-driven perceptual based training appears an effective mechanism to improve

working memory, a cognitive process that activates the right FPN in older adults (Robertson, 2014).

Firstly, in relation to sustained attention interventoons, self-alert training holds promise to improve this capacity (Milewski-Lopez et al., 2014) through increasing arousal levels (O'Connell, Bellgrove, Dockree, & Lau, 2008b) which rely on the right lateralised fronto-parietal networks (Corbetta & Shulman, 2002; Posner & Petersen, 1990; Robertson, 2014). Furthermore, successful pharmacological modulation of sustained attention has been observed with the administration of noradrenergic agonists (Malhotra et al., 2006; Singh-Curry et al., 2011) which stimulate post-synaptic adrenoceptors in prefrontal regions (Avery, 2000; Lapiz & Morilak, 2006).

In compliment to the experiments described above that demonstrate how training early perceptual processing in older adults may be accompanied with benefits in higher order cognitive processing, recent work suggests that the opposite may also hold true. Park and colleagues found that an intervention demanding high levels of engagement in older adults was associated with improvements in processing speed (D. C. Park et al., 2014a). Older adults who spent ~16.5 hours per week for three months learning multiple new skills requiring high levels of engagement showed significant improvements in processing speed and episodic memory (D. C. Park et al., 2014a). These benefits were not observed for individuals in two active control groups that participated in less engaging activities, nor were they observed for participants who learned a single skill in isolation. Acquiring cognitively demanding new skills likely necessitates higher order cognitive functions, such as sustained attention, response to novelty, performance monitoring, arousal, and working memory, which require engagement of the right FPN (Robertson, 2014). Therefore, the finding that learning new skills in older adults is associated with improvements in processing speed provides further indirect support for right FPN involvement underpinning attention remediation in ageing.

I.5 The Dorsolateral Prefrontal Cortex as a Target Area to Improve Attention in Ageing

Although the neural underpinning supporting the benefits of attention-based training protocols in human interventions remain speculative, the work reviewed in the previous section suggests the right lateralised FPN might be a key contributor. Understanding the neural underpinnings of these interventions is of relevance when developing rehabilitation protocols. Advances in neuroimaging techniques have lead to approaches, such as fMRI neurofeedback (deCharms et al., 2005) and non-invasive brain stimulation techniques (Kadosh, 2015; Nitsche & Paulus, 2000) that can directly manipulate neuronal activity within the brain. This gives rise to the exciting possibility of boosting interventions and rehabilitation outcomes by simultaneously manipulating brain activity within the relevant network (Allman, Amadi, & Winkler, 2016; Subramanian et al., 2016). Particular attributes of the right dorsolateral prefrontal cortex (DLPFC) render this an attractive target for upregulation to improve aspects of attention in ageing and following stroke (Brosnan & Wiegand, Appendix C). These features will be outlined in the following section.

I.5.1 Flexible neuronal coding of the prefrontal regions

Many areas of the brain demonstrate highly specialized functions For example, visual receptive fields exist in occipital regions which respond exclusively to motion (Newsome & Pare, 1988), and a subregion of the fusiform gyrus (the fusiform face area) is highly specialised for processing faces (Kanwisher, McDermott, & Chun, 1997). However, the DLPFC is the largest functional component of a domain-general 'multiple demands' system of frontal, parietal, and insular brain regions (Duncan, 2001; 2013), that is activated during a wide range of cognitive operations (Fedorenko & Duncan, 2013). This network is identified by temporal correlations of resting state fMRI data (Cole & Schneider, 2007; Vincent, Kahn, Snyder, Raichle, & Buckner,

2008), and is strongly correlated tests of fluid intelligence (Bishop, Fossella, Croucher, & Duncan, 2008; Duncan et al., 2000).

Animal electrophysiology and human neuroimaging suggests that within the DLPFC, flexible neuronal tuning takes place to support top-down modulation of task relevant processes (Erez & Duncan, 2015; Freedman, Riesenhuber, Poggio, & Miller, 2001). Freedman and colleagues (Freedman et al., 2001) trained macaque monkeys to categorise cats and dogs from morphed images of the animals and recorded electrophysiological single cell data from lateral prefrontal neurons. Following training, many prefrontal neurons (more than 20%) were tuned specifically to the relevant category of interest, suggesting that the neurons adapted their properties to code information that was directly relevant to the task demands (Duncan, 2001). In support of this interpretation, when one animal was retrained to differentially categorise the same stimuli, this cat/dog category tuning was lost from the prefrontal neurons and replaced by the new classification category.

The convincing demonstration of the capacity for flexible tuning of prefrontal neurons for task-relevant processing (Freedman et al., 2001) was recently corroborated in human participants using multi-voxel pattern analysis of functional Magnetic Resonance Imaging (fMRI). Erez and Duncan (2015) employed a cued-detection task where participants were asked whether a visually presented object belonged to one of two previously cued target categories. Importantly, the visual stimuli served as targets on some trials, and non-targets on other trials, depending on the previously presented cue. Across the MD system including the DLPFC, and within a region of the lateral occipital complex, categorical distinctions were successfully discriminated using MVPA. Crucially, these discriminations occurred only when the distinctions were behaviourally relevant (e.g., between target and non-target) and not when the distinction was behaviourally irrelevant (e.g., between target and target).

The flexible neuronal tuning of the prefrontal cortices may explain the contribution of these regions to the successful performance of many higher order cognitive operations including

components of attention (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015a; Habekost & Rostrup, 2006) and cognitive control (Egner & Hirsch, 2005; Gbadeyan, McMahon, Steinhauser, & Meinzer, 2016) but also its contribution to more 'basic' aspects of attention and perceptual processing (Helfrich & Knight, 2016; Voytek et al., 2010). This adaptive tuning supports the processing of related information in other systems such as the visual attention system (Desimone & Duncan, 1995; Duncan, 2001). Frontal and parieto-occipital regions are connected anatomically and functionally (Chechlacz et al., 2015; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Marshall, Bergmann, & Jensen, 2015). Correlational neuroimaging studies suggest that the DLPFC may exert top down attentional control over early visual attention processes in both younger (Nelissen et al., 2013; Rutman, Clapp, & Chadick, 2010; Zanto, Rubens, Thangavel, & Gazzaley, 2011) and older adults (Berry et al., 2010; Mishra et al., 2014), possibly via frontal theta band processes that may relay relevant information from prefrontal regions to spatially distal systems (Cavanagh & Frank, 2014; Fries, 2005; Liebe, Hoerzer, Logothetis, & Rainer, 2012).

The role of the DLPFC in a myriad of cognitive operations lends tangible advantages when considering training this structure, as the possibility of 'domain-general' cognitive improvements would be very advantageous for interventions remediating age-related cognitive decline. Moreover, the relative and not absolute specialisation of the DLPFC is extremely adaptable, a characteristic that places the DLPFC as an ideal brain area to support functional compensation in response to age-related structural brain changes (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008) and following damage occurring through brain injury or stroke (Rosen et al., 2000; Thulborn, Carpenter, & Just, 1999; Voytek et al., 2010). Thus, the flexible, adaptive nature of the DLPFC seats this cortical region in a strong position to support cognitive rehabilitation in healthy and pathological ageing.

I.5.2 Right prefrontal modulation over LC-noradrenaline projections

Several converging properties of the right prefrontal cortex support targeting this area to remediate attention in ageing. The first is regarding the relationship of this region with noradrenaline. Noradrenaline produced in the locus coeruleus, is projected to almost all brain areas, and a single locus coeruleus neuron is capable of innervating widespread regions (Foote & Morrison, 1987; Sara, 2009). Reciprocal connections exist between the locus coeruleus and prefrontal cortex (Jodo & Aston-Jones, 1997; Jodo & Kayama, 1992; Singewald, 1998). Recent animal electrophysiology work has shown that locus coeruleus projections to frontal regions hold specific physiological characteristics, and different phenotypes (such as increased spontaneous firing rate, and greater responsiveness to glutamate) relative to more caudally projecting neurons (Chandler, Gao, & Waterhouse, 2014). These properties enable noradrenaline to stimulate frontal regions independently and in advance of other cortical areas. Evidence suggests that the prefrontal cortex exerts a top-down modulatory role over noradrenergic activity in the LC (Jodoj et al., 1998; Robinson, 1979a; Robinson & Coyle, 1980a), which may be evaluated via the thalamic 'gates' in advance of stimulating relevant cortical regions (Sturm & Willmes, 2001b). For example, photoinhibition of LC neurons using optogenetic techniques results in a decrease in noradrenaline content in prefrontal regions (M. E. Carter et al., 2010b), whereas chemical stimulation of prefrontal areas activates LC cells (Jodoj et al., 1998). At the behavioural level, manipulations that facilitate or limit noradrenergic efflux within prefrontal regions in the rat respectively improve (Lapiz & Morilak, 2006) and hinder (McGaughy, Ross, & Eichenbaum, 2008) performance on attention tasks. Finally, methylphenidate (brand name Ritalin), a common pharmacological treatment for attention deficit hyperactivity disorder, has been shown to preferentially enhance noradrenergic (and dopamine) release within prefrontal regions but not other cortical areas of the rat (Berridge et al., 2006). In support of these physiological observations, noradrenaline action in the prefrontal cortex strengthens network connectivity and regulates performance across a range of conditions (see Arnsten, 2011 for a review)

Right hemisphere dominance of noradrenaline is evident from asymmetric organisation of the noradrenergic system in rats (Robinson, 1979a), higher noradrenergic concentrations in the right thalamus in post-mortem human neurochemical studies (Debecker et al., 1978), and increased BOLD activation exclusively within the right hemisphere during pharmacological upregulation of noradrenaline (Grefkes, Wang, Eickhoff, & Fink, 2010b). Surgical lesions in the right fronto-parietal regions in rats has been shown to cause widespread depletion of noradrenaline across injured and non-injured regions of the lesioned hemisphere, and bilaterally in the locus coeruleus (Robinson, 1979b; Robinson & Coyle, 1980a), indicating that damage to right frontal areas may disrupt top-down modulation of the noradrenergic projections from the LC (Robinson, 1979a; Robinson & Coyle, 1980b; Sturm & Willmes, 2001a). Human neuroimaging has demonstrated increased activity in the right PFC in concert with enhanced LC activation when attention resources were demanded (Raizada & Poldrack, 2008). Interestingly, while activity in the right PFC increased monotonically with augmenting levels of task difficulty, LC activity increased exclusively for the most difficult condition, suggesting the right PFC may signal an attention challenge to the LC under situations demanding high levels of attention (Raizada & Poldrack, 2008).

Further support for the utility of targeting the right PFC to improve attentional processes relates to the important contributions of this region to visual attention (Corbetta & Shulman, 2002). As outlined in Section I.2.2, the processing of visual information is subserved by a bilaterally organised dorsal attention networks and the right lateralised FPN (Corbetta & Shulman, 2002; 2011; Ungerleider, 2000). It has been proposed that the right prefrontal cortex may be a pivot point between these two interacting networks (Corbetta & Shulman, 2011). Several converging studies suggest that this indeed may be the case: Activity in the right prefrontal cortex positively correlates with temporal fluctuations within both the ventral and dorsal attention networks during resting state fMRI (He et al., 2007). The lateral prefrontal cortex shares task-evoked properties with both stimulus-driven activity in the dorsal attention network, and goal-directed activation within the ventral attention network (Asplund, Todd, Snyder, &

Marois, 2010). Finally, damage to ventral frontal regions has been associated with greater deficits in spatial attention than posterior parietal lesions (Rengachary, He, Shulman, & Corbetta, 2011).

Finally, as aforementioned, several lines of indirect evidence from behavioural pharmacological and interventions suggest that targeting the right prefrontal cortex may remediate sustained attention deficits (Malhotra et al., 2006; Milewski-Lopez et al., 2014; O'Neill et al., 2000; Robertson et al., 1995; Singh-Curry et al., 2011)

I.5.3 Adaptive prefrontal recruitment in ageing

Ageing is associated with progressive reductions in both grey and white matter in the frontal lobes. (P. M. Greenwood, 2000; N. Raz et al., 2005; West, 2000). Interindividual differences exist in atrophy rates, with preserved grey matter volume and white matter integrity typically associated with less decline in cognitive functioning (e.g. Kievit et al., 2014).

Accumulating evidence suggests that higher levels of prefrontal engagement in ageing are associated with better performance across a range of cognitive processes including visual perception, episodic retrieval, visual, and sustained attention (Davis et al., 2008; Staub, Doignon-Camus, Bacon, & Bonnefond, 2014; Staub, Doignon-Camus, Marques-Carneiro, Bacon, & Bonnefond, 2015; Wiegand, Finke, Müller, & Töllner, 2013). Enhanced recruitment of the DLPFC in older adults in concert with reduced activation in more posterior regions (Fig. I.6) is considered an adaptive response of prefrontal regions to age-related declines in the capacity of posterior regions to process information (Cabeza, 2004; Davis et al., 2008; J. R. Gilbert & Moran, 2016; Wiegand et al., 2014).

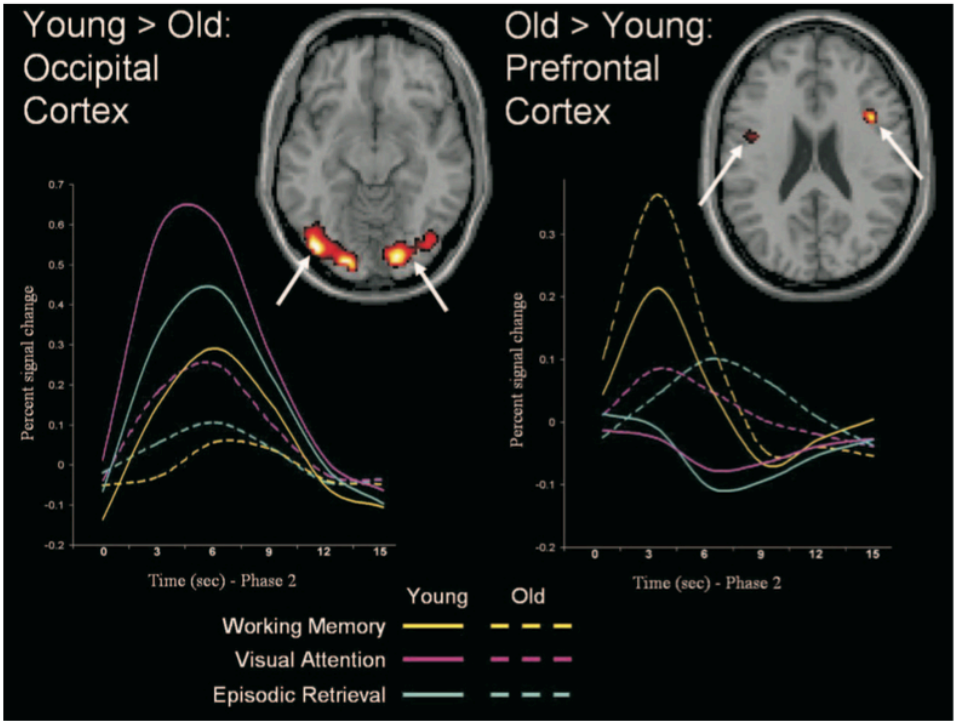


Figure I.6: Older adults show reduced occipital activity with concomitant increases in prefrontal recruitment (Cabeza, 2004).

Understanding the causal role of prefrontal activity as an adaptive mechanism to improve attentional capacity in ageing has been somewhat limited by correlational neuroimaging approaches. However, a recent computational modelling approach exploring feedforward and backward connections in older adults has shed some light on this issue. Gilbert and Moran (2016) employed dynamic causal modelling of EEG data and assessed network connectivity elicited by a visual stimulus. The authors observed that for younger adults bottom-up signals from early visual regions drove activity throughout the visual network via reciprocal connections with fronto-parietal and temporal regions, whereas for older adults a combination of both prefrontal and early visual inputs governed network activity (J. R. Gilbert & Moran, 2016). This suggests a causal, adaptive contribution of prefrontal regions for processing of early visual information.

A recent investigation of multitasking training in older adults (Anguera, Boccanfuso, Rintoul, & Al-Hashimi, 2013) showed training-related improvements that were associated with enhanced frontal theta amplitude, a putative electrophysiological signature of attention and

cognitive control (Cavanagh & Frank, 2014; Clayton, Yeung, & Cohen Kadosh, 2015). Of relevance, the degree of frontal engagement post-training predicted the training-induced improvements in sustained attention at a 6-month follow up period, thereby indirectly implicating frontal involvement underpinning lasting improvements in attention. Nevertheless, the direct manipulation of prefrontal activity in older adults would affirm a causal involvement of prefrontal areas to attention processes in older adults

I.5.4 tDCS as a method for upregulating the right prefrontal cortex

The prefrontal regions demonstrate flexible, adaptive neuronal properties and are correspondingly recruited to perform a wide range of cognitive operations (Duncan, 2001; Fedorenko & Duncan, 2013). The PFC exerts a top-down modulatory influence over the right-lateralised noradrenergic 'alerting' system (A. R. Carter et al., 2010a; Jodoj et al., 1998; Robinson & Coyle, 1980b), placing this area in a strong position to support alertness and related functions. Moreover, increased recruitment of the frontal lobes in ageing has been associated with superior cognitive outcomes (Davis et al., 2008; Harty, Robertson, Miniussi, Sheehy, Devine, McCreery, & O'Connell, 2014a). Thus, the prefrontal cortex is an ideal target region for interventions aiming to improve cognitive function in healthy and pathological ageing. The effects of directly upregulating the region to improve aspects of attentional function in ageing has not yet been assessed. The section below will describe a non-invasive brain stimulation technique that may be employed in older adults to increase activity in the right PFC.

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that can be used to manipulate cortical excitability (Nitsche & Paulus, 2000). There is growing interest and support for tDCS over prefrontal regions as a tool to enhance aspects of cognition in healthy ageing (Harty, Robertson, Miniussi, Sheehy, Devine, McCreery, & O'Connell, 2014a; S. H. Park, Seo, Kim, & Ko, 2014b) and in pathological ageing conditions such as Alzheimer's Disease (Hsu, Ku, Zanto, & Gazzaley, 2015), Parkinson's Disease (Boggio, Ferrucci, Rigonatti, & Covre, 2006), and stroke (Jo, Kim, Ko, Ohn, & Joen, 2009)

tDCS is proposed to impact brain plasticity by interacting with simultaneously active neuronal populations in an excitatory or inhibitory manner, through increasing neuronal excitability of the area under the anode and decreasing excitability under the cathode (Nitsche & Paulus, 2000). Animal work has shown that tDCS increases synaptic plasticity processes that are dependent on brain-derived neurotrophic factor (BDNF) secretion (Fritsch et al., 2010; Podda et al., 2016). How tDCS induces BDNF is still not clear but possibilities include circulation, microglia, or through adrenergic receptors (Monai & Hirase, 2016). A recent animal investigation of tDCS-induced synaptic plasticity in sensory regions suggests adrenergic receptors may account for tDCS-related BNDF processes (Monai et al., 2016). Monai and colleagues demonstrated that tDCS in mice activates noradrenergic release which in turn enhances astrocytic calcium (Ca^{2+}) signalling via alpha-1 adrenergic receptors leading to enhanced sensory evoked potentials (Monai et al., 2016). Astrocytic Ca^{2+} elevation is implicated in information processing (Agulhon et al., 2008), the integration of information (Volterra, Liaudet, & Savtchouk, 2014), and has been postulated to promote synaptic plasticity (Hirase, Iwai, Takata, Shinohara, & Mishima, 2014; Monai & Hirase, 2016). As outlined in Section I.5.2, a strong rationale for targeting the right PFC via tDCS in the current thesis is its proposed modulatory role over the right lateralised noradrenergic system (M. E. Carter et al., 2010b; Chandler et al., 2014; Jodoj et al., 1998; Robinson & Coyle, 1980b). It is hypothesized that tDCS over right PFC will increase noradrenergic drive in prefrontal regions, enhance activation in the right lateralised noradrenergic alerting system and improve aspects of attention.

It has recently been demonstrated that the application of anodal tDCS over right PFC leads to significant improvements in error awareness in healthy older adults (Harty, Robertson, Miniussi, Sheehy, Devine, McCreery, & O'Connell, 2014b). This effect was shown to be both polarity and hemisphere specific, with no improvements observed either for cathodal stimulation of right PFC or anodal stimulation of left PFC (Fig. I.7). Error awareness and sustained attention are closely linked (Harty, O'Connell, & Hester, 2013; McAvinue, O'Keeffe, McMackin, &

Robertson, 2005; O'Keeffe et al., 2007; Robertson, 2014), thus setting precedent to explore the effects of right prefrontal tDCS on the sustained attention system in aging.

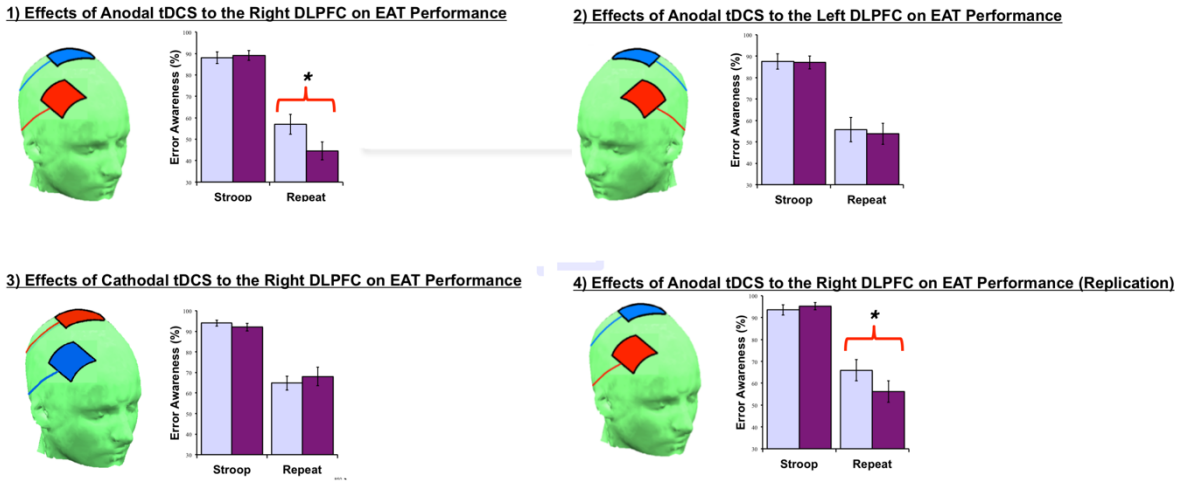


Figure I.7: tDCS over right PFC temporarily improves online performance monitoring in older adults. In a series of experiments Harty and colleagues (2014) demonstrated that tDCS over the right PFC improved online awareness of errors for repeated stimuli in no-go task. This effect was shown to be hemispheric and polarity specific (Experiment 1 and Replication Experiment 4), with no improvements observed during stimulation of the left PFC (Experiment 2), and no changes in performance during cathodal stimulation of the right PFC (Experiment 3). Figure adapted from Harty et al.

I.6 Overall summary and objectives of thesis

Understanding the neural underpinnings of cognitive reserve will aid our understanding of how to preserve high levels of cognition in healthy ageing, and remediate cognitive decline in the face of age-related neuropathology. Two aspects of attentional function that rely on the right lateralised FPN recently proposed to underpin cognitive reserve (Robertson, 2013; 2014) are sustained attention and visual processing speed. As outlined in Section I2 and I3, both the capacity to maintain attention and the rate at which visual information in the environment can be processed are susceptible to age-related degradation (McAvinue et al., 2005), and are impaired

following damage to the right FPN (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999a; Rueckert & Grafman, 1996).

Emerging work suggests that both of these capacities can be improved in ageing through various interventions (Milewski-Lopez et al., 2014; D. C. Park et al., 2014a; Rebok et al., 2014; Singh-Curry et al., 2011) supporting animal work suggesting the ageing brain holds preserved capacity for plasticity processes to remediate cognitive deficits (de Villers-Sidani et al., 2010). Although never assessed directly, several lines of indirect evidence suggest that the so-called ventral attention network, encompassing the right fronto-parietal networks, may support remediation of attention in ageing and following stroke (Berry et al., 2010; Malhotra et al., 2009; D. C. Park et al., 2014a). Within this network, the right DLPFC holds several unique characteristics that place it as an ideal target region for interventions aimed at improving attention. These include dynamic flexible neuronal coding, bidirectional connections with the locus-coeruleus, and its dramatic capacity for adaptive compensation following stroke (Duncan, 2001; Singewald, 1998; Thulborn et al., 1999; Voytek et al., 2010)

The main aim of this thesis is to explore the potential for the right prefrontal cortex as a target region for remediating attention deficits in ageing and stroke. The empirical work in this thesis is divided into two parts. The first part (Empirical Chapter 1 and 2) will combine electroencephalography (EEG) and computational modelling with tDCS to assess the effects of increasing neuronal excitability in the right PFC on aspects of attentional function in older adults. The second part (Empirical Chapter 3 and 4) will investigate the temporal dynamics of sustained attention deficits occurring with damage to the right hemisphere, and the effects of stimulating the right prefrontal cortex on sustained attention performance in these patients.

Sustained attention is vulnerable to age-related declines and deficits in this domain are observed in many age-related pathological conditions (O'Keeffe et al., 2007). The aim of Empirical Chapter 1 will be to determine to promise of targeting the right prefrontal cortex to improve sustained attention in ageing.

There has been no direct assessment of the proposed relationship between the right hemisphere and cognitive reserve in older adults (Robertson, 2013; 2014). In Empirical Chapter 2, this will be addressed by exploring the relationship between hemisphere asymmetries in visual attention and cognitive reserve. This chapter will also evaluate the causal contribution of the right prefrontal cortex to processing speed capacity in ageing.

Though sustained attention deficits are commonly reported following RH damage and have been shown to interfere with rehabilitation following stroke, the temporal dynamics are not well understood. Empirical Chapter 3 will assess the capacity to maintain attention in stroke patients with unilateral damage to the right hemisphere using a temporal attention task that is sensitive to decrements in attentional engagement (O'Connell, Dockree, Robertson, et al., 2009b).

Finally, despite the substantial sustained attention deficits experienced by patients with right hemisphere damage, approaches to remediate this capacity have been limited. Empirical Chapter 4 will assess whether increasing excitability of the right prefrontal cortex can temporarily ameliorate sustained attention deficits in chronic stroke patients with unilateral right hemisphere damage.

Empirical Chapter 1: Right Prefrontal tDCS Modulates Behavioural and Electrophysiological Signatures of Sustained Attention in Older Adults.

1.1 Introduction

As outlined in Section I.3 the integrity of the sustained attention system is a key constituent of healthy cognition in aging (Robertson 2014). Deficits in this domain are associated with negative functional outcomes in both healthy older adults (O'Halloran et al., 2011; O'Halloran, Finucane, Savva, Robertson, & Kenny, 2013), and patients who have experienced right hemisphere stroke (Robertson, Ridgeway, Greenfield, & Parr, 1997c).

Behavioural and pharmacological interventions targeting the right lateralised noradrenergic arousal system have shown promise at increasing sustained attention performance in healthy ageing (Milewski-Lopez et al., 2014) and stroke (Malhotra et al., 2006; Singh-Curry et al., 2011). Evidence suggests the right prefrontal cortex plays a top-down modulatory role over noradrenergic activity (A. R. Carter et al., 2010a; Robinson & Coyle, 1980a; Sturm & Willmes, 2001a). Moreover, within the right-lateralised network supporting the successful maintenance of endogenous attention (Langner & Eickhoff, 2013b; Rueckert & Grafman, 1996; Singh-Curry & Husain, 2009), the prefrontal cortex (PFC) has been identified as particularly critical (Lawrence, Ross, & Hoffmann, 2003; Manly et al., 2003; O'Connor, Robertson, & Levine, 2011; Sturm & Willmes, 2001a).

Preliminary evidence manipulating prefrontal regions using fMRI neurofeedback and tDCS has shown sustained attention improvements in young participants (deBettencourt, Cohen,

Lee, Norman, & Turk-Browne, 2015a; J. T. Nelson, McKinley, Golob, Warm, & Parasuraman, 2014). However, to our knowledge, activity in the prefrontal cortices has never been directly targeted in older adults to manipulate sustained attention. It therefore remains to be seen whether plasticity of this region can be harnessed in later life to ameliorate deficits in this capacity.

The current chapter investigates, in two separate experiments, whether the behavioural and electrophysiological markers of successful sustained attention could be modulated in older adults by increasing the excitability of the right PFC using tDCS. In the first experiment, a tDCS-EEG co-registration approach was employed to assess how behavioural task performance and ERP markers of sustained attention would change during tDCS in an older adult sample who are cognitively healthy but exhibit relatively low sustained attention capacity. The second experiment assessed whether the tDCS-related behavioural effects observed in experiment 1 generalize to an independent sample of healthy older adults, and to a second sustained attention task, free from response inhibition requirements.

1.2 Material and Methods

Study Outline

Two independent cohorts of older adults (*N*=56) were recruited for two separate experiments. All participants were right handed, had no history of neurological illness and no personal or family history of seizures, and scored 23 or higher on the cognitive screening tool, the Montreal Cognitive Assessment (Nasreddine et al., 2005). In experiment 1 tDCS-related changes were in sustained attention measured using the well-known Sustained Attention to Response Task (SART). This task correlates with attentional failures occurring in everyday life (Smilek et al., 2010), and has established electrophysiological markers of successful performance (Dockree, Kelly, Robertson, Reilly, & Foxe, 2005b; O'Connell, Dockree, Bellgrove, et al., 2009a; Staub et al., 2015). The second experiment assesses whether the tDCS-related behavioural effects observed in experiment 1, generalize to an independent sample of healthy older adults. For this

purpose, performance is assessed on a different sustained attention task, free from any response inhibition requirements, and known to be particularly sensitive to performance decrements over short time windows (~3 minutes; the Continuous Temporal Expectancy During both experiments participants received real and sham tDCS over two sessions in a single-blind crossover design. The two tDCS sessions were separated by at least a 6-day period to minimize carryover effects. The order of sham and real tDCS was counterbalanced and randomized across participants. For both experiments the right PFC was targeted using the F4-Cz tDCS montage employed by Harty et al. 2014 (see tDCS protocol below). tDCS was always applied during performance of the tasks and no stimulation was administered during any breaks.

Participants

For Experiment 1, the tDCS-EEG coregistration approach, cognitive healthy older adults whose sustained attention capacity was relatively low were recruited. For this purpose, 107 older adults were prescreened using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) to screen for cognitive impairment, and the fixed version of the Sustained Attention to Response Task ($SART_{fixed}$; Robertson, Manly, et al. 1997; O'Halloran et al. 2013, see task description below) to assay sustained attention capacity. A participants' performance on the task was classified with reference to normative data (from unpublished observations on 5470 older adults who participated in The Irish Longitudinal Study of Aging, TILDA), according to their age, gender, and level of education.

All prescreened participants were ranked based on their normative performance, and individuals were invited to participate in the tDCS-EEG co-registration study in ascending order based on these normative sustained attention percentile score (as measured by commission errors). During the initial testing session, participants who were subsequently included in Experiment 1 made an average of 5.99 (SD = 3.44) commission errors, with 88.5 % of participants classified (via the TILDA norms) as performing in the 50^{th} percentile or lower. The version of the SART used during the initial behavioural testing session was identical to that used

for developing the normative TILDA data see (O'Halloran et al. 2013) except that 225 (as opposed to 223) iterations of the 1-9 sequence were administered.

From the pool of 107 prescreened participants, a total of thirty-two participants were recruited for Experiment 1. Five of these participants did not return for the second stimulation session, and one participant was excluded due to difficulty with coordinating timely responses to stimuli (i.e., 19.25% omission errors, which was less than 3 SD from the mean). The final sample for Experiment 1 therefore, consisted of 26 participants (7 male; see Table 1.1 for demographic information).

Experiment 2 was designed to further verify the role of the right prefrontal cortex in sustained attention in aging by assessing the extent to which the tDCS-related behavioural effects generalized to an independent sample of older adults and a different sustained attention paradigm (described below). Twenty-four participants were recruited for this recapitulation experiment. This cohort was prescreened using the MoCA. This sample were not preselected based on sustained attention capacity, to assess whether the effects of stimulating the right PFC on sustained attention generalised older adults with 'typical' sustained attention levels. One participant did not return for the second tDCS session, therefore the final sample consisted of 23 older adults (11 male; see Table 1.1 for demographic information).

Transcranial Direct Current Stimulation (tDCS) Protocol

Stimulation was administered using a battery-driven DC Brain Stimulator Plus (NeuroConn) with two 5x7cm electrodes, using high-chloride EEG electrode gel (Abralyt HiCl, EasyCap) as a conducting paste. The anodal electrode was placed over the right frontal cortex and the reference electrode was placed over the vertex (i.e. areas F4 and Cz, respectively, according to the 10 –20 international system for EEG electrode placement; see Fig. 1.1B, Fig. 1.2B). The same electrode montage was used for both sham and real stimulation. During real stimulation, tDCS was administered at 1mA continuously during task performance with ramp-

up/ramp-down periods of 20s, resulting in a current density of 0.02857 mA/cm2 at the scalp. During Experiment 1, in order to minimize potential artifacts in the EEG signals at the beginning of stimulation, the current was administered and allowed to settle for 30 seconds after the ramp-up period before the task began. The ramp-down began after performance of the task had finished. There was no stimulation during the rest periods in between the blocks. During sham stimulation, tDCS was administered at 1mA for 15s at the beginning of each block with ramp-up/ramp-down periods of 20s. This is a frequently used sham protocol to ensure that the sensations often experienced with the onset of tDCS (such as a prickling sensation underneath the electrodes) are analogous across real and sham sessions (Gandiga, Hummel, & Cohen, 2006).

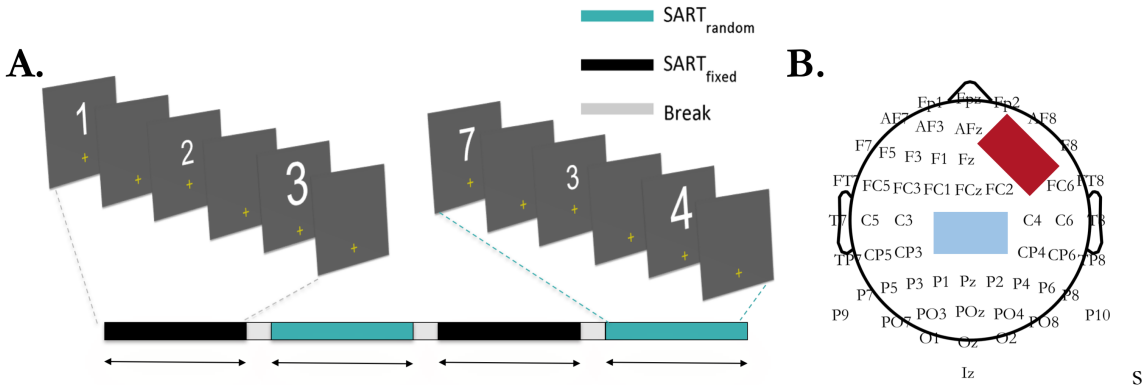


Figure 1.1: Outline of the task procedure for Experiment 1. A. During both sham and real tDCS sessions participants underwent interleaved blocks of the $SART_{fixed}$ and $SART_{random}$ and the order was counterbalanced across participants. tDCS was delivered for the duration of each task block (8 minutes, 25 seconds) and no tDCS was administered during the breaks between blocks. **B.** tDCS was administered during simultaneous EEG recordings with the anode (in red) placed over F4 and the cathode (blue) over Cz. Participants received sham and real stimulation separated by a minimum of 6 days. The same tDCS electrode montage was used for both stimulation sessions.

Table 1.1: Demographic and Cognitive Characteristics of the Sample.

	Age (yrs)	MoCA	Education (yrs)	PFS IQ
Experiment 1 (*N*=26)	72.42 (5.43)	26.80 (2.28)	13.61 (4.62)	112.83 (7.99)
Experiment 2 (*N*=23)	72.70 (5.93)	27.81 (1.63)	15.91 (3.66)	122.86 (3.86)

Note PFS IQ denotes predicted full scale IQ as estimated from the National Adult Reading test (NART; Nelson, 1982), a measure of premorbid intelligence. MoCA denotes Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), a validated cognitive screening tool. Values denote mean and standard deviations, M(SD).

Monitoring Sustained Attention Performance during tDCS

Experiment 1

The Sustained Attention to Response Task

During experiment 1 a modified version of the Sustained Attention to Response Task (SART) was used to monitor performance during tDCS. In this task, a series of single digits from 1 to 9 are presented, and participants were required to make a response to each number (go trials) with the exception of the number 3 (no-go trial). Longer blocks were administered to participants during the tDCS sessions with 450 digits presented per block, representing 50 iterations of each 1 to 9 sequence, such that each block lasted 8 min 25 sec in duration (Fig. 1.1A).

Two task blocks comprised of modified version of the fixed SART ($SART_{fixed}$), administered during the prescreening session to assay sustained attention capacity. In the $SART_{fixed}$ numbers were presented in a fixed, predictable order (1 through until 9; see task description below). Sustained attention is considered the predominant cognitive process underlying successful performance on the $SART_{fixed}$ as an individual is required to continuously maintain intrinsic levels of alertness throughout the repeating, monotonous 1-9 sequence (Dockree, Kelly, Robertson, & Reilly, 2005a; Manly et al., 2003; O'Connell, Dockree, Robertson, et al., 2009b). The task also necessitates that an individual successfully withholds their response

to the critical no-go trial. However, given the critical trial is embedded within the predictable, repeating sequence, the response inhibition requirements on the $SART_{fixed}$ are minimal.

Nevertheless, in order to confirm that any behavioural effects of tDCS could be attributed to changes in sustained attention, and not response inhibition, two blocks of the $SART_{random}$ were administered to participants. In the $SART_{random}$, stimulus characteristics and task requirements (withhold for digit '3') were identical but the numbers were presented in a random unpredictable order, thus requiring response inhibition to unpredicted, randomly presented targets. Although sustained attention is required for optimal performance of this task, inhibitory control processes are considered predominant processes required for successful task performance on this task (Fassbender et al., 2004; O'Connell, Dockree, Bellgrove, et al., 2009a), e.g., as evidenced by an N2/P3 complex on the critical no-go trial during the $SART_{random}$ which is enhanced for correct withholds relative to errors, and is completely absent during the $SART_{fixed}$ (O'Connell, Dockree, Bellgrove, et al., 2009a). Participants performed four blocks of the SART during each experimental session. Blocks of the $SART_{fixed}$ and $SART_{random}$ were interleaved and the order was pseudorandomized across participants.

Five randomly assigned digit sizes (as described in (O'Connell, Dockree, and Bellgrove 2009) were used in order to increase the processing demands of the presented number and to minimize the likelihood that participants would search for some perceptual feature of the target digit ("3"). Digits were presented above a central yellow fixation cross on a grey background (Fig. 1). The task was programmed and stimuli were delivered using Presentation® software (Neurobehavioural Systems, Albany, NY, USA). For each trial, the digit was presented for 300 msec followed by an interstimulus interval of 800 msec. Participants were instructed to respond with a left mouse button press using their right forefinger when each digit (go target) was presented, with the exception of digit '3' (no-go target). Participants were asked to respond as quickly and as accurately as possible but were cautioned to wait until the digit appeared on the screen before responding. The following error awareness component was added to the task:

Participants were asked to indicate their awareness of commission errors with a right mouse button press using their right middle finger immediately after committing an aware error. In order to ensure that all participants fully understood the task requirements, practice trials were undertaken at the beginning of each session. All participants performed the task until three successful iterations of the sequence were completed (i.e., the participant clicked for all go-trials and successfully withheld on each no-go trial). Participants also demonstrated the error awareness button press.

Three performance measures were calculated to measure the effects of stimulation on the SART: commission errors, omission errors, and error awareness of commission errors. Any response occurring 1s after the stimulus onset was excluded from the analysis in order to exclude anticipatory responses for upcoming stimuli. Given the very low prevalence of omission errors in both the $SART_{fixed}$ (M=0.3%, SD=0.29) and the $SART_{random}$ (M=0.59%, SD=0.82), omission errors were excluded from further analyses. Commission errors were normalized as the percentage of commission errors divided by the total number of no-go trials as can be seen in equation 1. Error awareness was calculated as the percentage of commission errors that were followed by an error awareness click up to 1500ms after the error took place. Evidently error awareness was not calculated during blocks where '0' commission errors were made.

Outliers were defined in SPSS using the interquartile range (IQR). The interquartile range is the 3rd quartile (75th percentile) minus the 1st quartile (25th percentile). A value was identified as an outlier if either of the following conditions were met: if the value was <25th percentile - 1.5*IQR or if the value was >75th percentile – 1.5*IQR. These participants were then excluded on the given performance measure from further analyses and the mean and SD were subsequently recalculated. Given the sensitivity of tDCS to timing parameters, particularly in older adults (Fertonani, Brambilla, Cotelli, & Miniussi, 2014), and given that elderly participants have been shown to improve their performance on the SART over longer durations (Staub et al. 2015), the effects of stimulation were investigated per block. Changes in performance during

stimulation were therefore assessed using repeated measures ANOVAs with "Intervention" (Real vs. Sham tDCS) and "Time" (Block 1 vs. Block 2) as within subject factors. Significant main and interaction effects were followed up with simple effects analyses. All statistical analyses were performed using SPSS Statistics v21.0.0.1 (IBM) and all figures were designed using customized scripts in MATLAB R2014a 8.3.0.532 (Mathworks, Natick, MA, USA). In all figures, the error bars indicate the standard error of the mean (s.e.m).

$$\frac{\#CommissionErrors \ 100}{(\#CommissionErrors + \#CorrectWithholds)}$$

Equation 1. Normalized Commission Errors

Simultaneous tDCS-Electroencephalogram (EEG) recordings

During experiment 1, continuous EEG data were acquired during both tDCS sessions, concurrently with stimulation. The data were acquired using the ActiveTwo system (BioSemi, The Netherlands) from 53 scalp electrodes, digitized at 512 Hz. EEG data were collected during all of the task blocks simultaneously with tDCS. Resting state data were also collected pre and post stimulation and will not be discussed in the current manuscript. A standard 64-channel system was used but EEG was not recorded from the EEG scalp electrodes that were positioned at the tDCS electrode locations, i.e., channels C1, Cz, C2, CP1, CPz, CP2 under the cathodal tDCS electrode, and channels F2, F4, F6, AF4, FC4 under the anodal tDCS electrode (Fig. 1B). EEG data were discarded for 3 participants on both tasks and for an additional 4 participants on the $SART_{random}$ due to issues during data collection and excessive movement artefacts, resulting in a total of N=23 and N=19 participants for the $SART_{fixed}$ and $SART_{random}$ EEG analyses, respectively. Data were analysed using custom scripts and EEGLAB functions (Delorme and Makeig 2004) in MATLAB. EEG data were re-referenced offline to the average reference using the average of all available electrodes except electrodes over left prefrontal regions (AF3, F1, F3, F5 and FC3) which were homologous to the missing right frontal EEG electrodes, and the corresponding parietal electrodes (CP3, P1, P3, P5, P03, CP4, P2, P4, P6, P04). The data were high-pass filtered above 0.03 Hz and low-pass filtered below 35 Hz offline using an optimum

Butterworth infinite impulse response filter. The 'filtfilthd' function in MATLAB was implemented to allow for a non-causal zero-phase filtering approach to eliminate any nonlinear phase distortion associated with using an infinite impulse response filter.

For the ERP analysis, EEG data were segmented into epochs centred on stimulus onset using windows of -100 to 1100 ms relative to the onset of each digit. The epochs were then baseline-corrected relative to the 100-ms interval prior to digit onset. Epochs were rejected if the changes in amplitude of any scalp channel exceeded an absolute value 100μV during the epoch.

A notable strength of using the Sustained Attention to Response Task (SART) to measure the effects of tDCS is that electrophysiological signatures of successful performance have been previously established in both younger and older adults (Dockree, Kelly, Robertson, Reilly, et al. 2005; O'Connell et al. 2009; Staub et al. 2015). Components were therefore selected based on these prior studies (visual evoked P1, visual evoked N1, frontal P2, and frontal P3). In order to ensure that the selection of electrodes and time windows for each of these components was identified orthogonal to the effect of interest (real relative to sham tDCS), grand average waveforms of the real and sham condition were combined, and collapsed across go and no-go trials.

The electrode with the greatest peak amplitude for each of the components of interest was identified from these grand average waveforms. For the visual evoked components (P1 and N1) the peak amplitudes over a right parieto-occipital scalp region, electrode P08, 6.52μV and -6.39μV, respectively. The P1 component peak amplitude was identified at 96 ms, which is within the time-window of previous literature investigating this ERP in ageing (De Sanctis et al. 2008; Zanto et al. 2011; Daffner et al. 2013). The N1 component peak was identified at 150ms, also in line with previous work on the N1 in ageing (De Sanctis et al. 2008; Daffner et al. 2013; Wiegand et al. 2014). Mean amplitude values for the P1 and N1 components were calculated over a 50ms window, centered on the peak amplitude of interest (i.e., from 71-121ms for P1 and 125-175ms for the N1). The frontal P2 peak amplitude was identified at 158ms (4.14μV), which is within the

time-window previously reported for this component in older adults performing the SART (Staub et al. 2015). Mean amplitude values for the fP2 were calculated over a 50ms window, centred on this peak (i.1., 133-183ms). For the P1, N1 and fP2, electrode selection was performed using the $SART_{fixed}$, the task of predominant interest for this study. The fP3, however, was identified using the $SART_{random}$, as previous work has shown that this common marker of response inhibition (Bekker et al. 2005) is crucial to performance in the $SART_{random}$ and of minimal relevance to the $SART_{fixed}$ (Dockree, Kelly, Robertson, Reilly, et al. 2005; O'Connell et al. 2009). Again, this component was selected using the grand average waveforms of real and sham combined, collapsed over go and no-go trials. The fP3 component peak was at 488 ms (5.14μV), and the component was measured over a 100ms window (438-538ms), centred on this peak.

ERPs were computed separately for Go-trials (digits 1, 2, 4, 5, 6, 7, 8, 9) and for the No-Go trials (digit '3'). Only No-Go trials for which responses were correctly withheld by the elderly were included in the analysis. Outliers were defined as described for the al performance measures above. Separate repeated measures ANOVAs were calculated for the $SART_{fixed}$ and the $SART_{random}$ with Intervention (Real vs Sham tDCS) and Trial Type (Go Trials vs No-go Trials) as within subject factors. To identify sources of significant main and interaction effects, follow-up ANOVAs were calculated where appropriate. In the text the reported mean values are followed by standard error (i.e., $M \pm SE$).

Experiment 2

The Continuous Temporal Expectancy Task

During experiment 2, the Continuous Temporal Expectancy Task (O'Connell, Dockree, Robertson, et al. 2009) was employed to measure sustained attention. This is a temporal judgment task designed to elicit frequent lapses in attention. For example, O' Connell et al. reported average accuracy levels of 64% (*SD*=15, range 37-85). In this task, a patterned stimulus was presented centrally and was constantly rotated at 90° angles (see Fig. 1.2). In the 'standard' trials (~90% of trials) the stimuli were presented for a temporal duration of 690 ms. The

participant's task was to identify the infrequent 'target' trials by a button press using their right index finger, where the stimulus was presented for a longer temporal duration (1020 ms) as compared to the standard trials. In contrast to the SART here target detection was indicated by a button press, thus eliminating any response inhibition requirement. The CTET was designed such that these temporal judgments were perceptually undemanding for participants but challenging when asked to continuously perform the judgments over longer periods of time; thus all participants were required to demonstrate 100% accuracy during an initial practice trial before advancing to the experimental blocks. For the practice block, three targets were randomly interspersed among 25 standard stimuli. Target stimuli were presented at the target duration of 1020 ms, i.e., 330 ms /47.83% longer than standard trials. If participants missed one or more target stimuli, the practice was performed again. All participants demonstrated 100% accuracy on two consecutive trials before commencing the experimental blocks. The pattern stimulus consisted of a single 8 cm^2 large square divided into a 10 x 10 grid of identical square tiles (0.8 mm^2), each one diagonally split into black and white halves. The tile orientation shifted by 90° in a random direction (clockwise or counter- clockwise) on each frame change yielding four distinct patterns. All stimuli were presented on a grey background. Stimuli were pseudo-randomly presented such that there were between 7 and 15 (average of 11) standard trials between each target presentation. A target response was accepted if the participant responded up to 2070ms (the length of three standard trials) post target onset. Participants completed 5 blocks of the task and were given a rest break in between each block. Each block consisted of 225 stimulus rotations with a total duration of approximately 3 min and 5 s. The number of targets varied between 18 and 22 per block. Following tDCS, participants performed three blocks of the error awareness task which won't be discussed in the current thesis. Pupil diameter was recorded during all tasks and was not analysed for the current thesis.

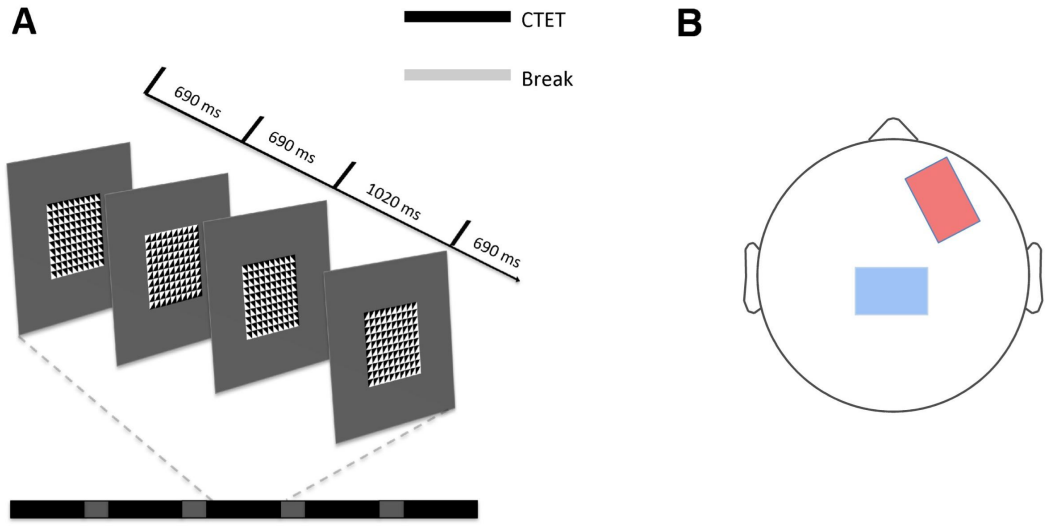


Figure 1.2: Outline of the continuous temporal expectancy task and the tDCS procedure for Experiment 2. A. During both sham and real tDCS sessions participants underwent 5 blocks of CTET. **B.** tDCS was delivered for the duration of each task block (approximately 3 minutes, 5 seconds) and no tDCS was administered during the break periods between blocks. The anodal electrode (in red) was placed over F4 and the cathode (blue) over Cz. There were no simultaneous tDCS-EEG recordings during Experiment 2. Participants received sham and real stimulation separated by a minimum of 6 days. The same tDCS electrode montage was used for both stimulation sessions.

Sustained attention changes occurring during tDCS were assessed via accuracy (% correctly identified targets) on the CTET. For three participants there were technical difficulties recording data for one of the task blocks. For these participants, performance was calculated on the average of the remaining four blocks and to facilitate the analysis within and across blocks, the value for the missing block was filled in with the average of the other four blocks for that participant, for the session in question. Outliers were defined on a per-block basis, as described above. Changes in performance during stimulation were assessed using repeated measures ANOVAs with "Stimulation" (Active vs. Sham tDCS) "Block" (across the five task blocks), and "Quartile" (each block sub-divided into four quarters) as within subject factors. Significant main and interaction effects were followed up with simple effects analyses. Greenhouse-geisser corrected degrees of freedom are reported in cases where the assumption of sphericity was violated. All statistical analyses were performed using SPSS Statistics v21.0.0.1 (IBM) and all

figures were designed using customized scripts in MATLAB R2014a 8.3.0.532 (Mathworks, Natick, MA, USA). In all figures, the error bars indicate the standard error of the mean (s.e.m).

1.3 Results

Experiment 1: Behavioural Performance changes during tDCS (SART)

Commission Errors ($SART_{fixed}$)

Consistent with our hypothesis that right PFC would constitute a viable target for modulating sustained attention in aging there was a main effect of Intervention ($F_{1,21}$=5.1, p=.035, η_p^2= 0.2, Fig. 1.3A) on commission errors. Specifically, significantly fewer commission errors were made during the $SART_{fixed}$ during real (M=4.06% SD = 3.36), compared to, sham stimulation (M=6.20% SD= 4.24). There was a trend towards a main effect of Time on the $SART_{fixed}$ ($F_{1,21}$=4.00, p=.06, η_p^2= .16), such that regardless of stimulation less errors were made during block 2 (M=4.47%, SD = 2.56) as compared with block 1 (M=5.79%, SD = 4.19). There was no interaction between Intervention and Time for commission errors during either the $SART_{fixed}$ ($F_{1,21}$= .82, p=.38).

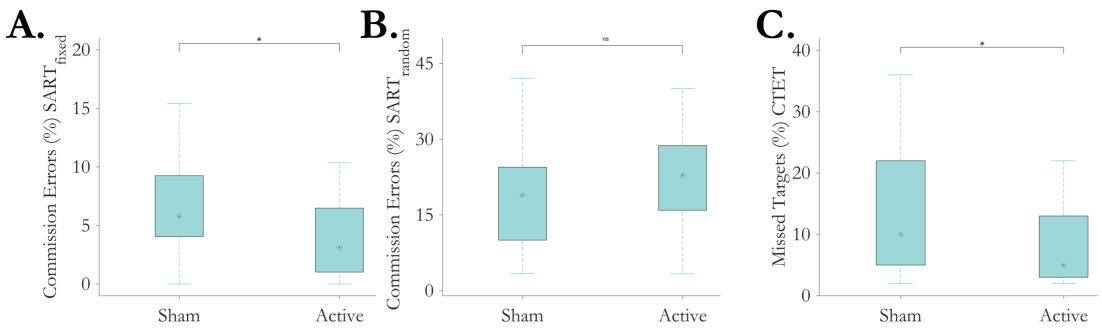


Figure 1.3: The effect of right PFC tDCS during the $SART_{fixed}$, $SART_{random}$, and CTET. For clarity, the CTET Accuracy results were visualized here as the % missed targets (100-% accuracy); thus for all tasks higher values on the y-axis denote worse performance (i.e., less accurate). Stimulation over the right prefrontal cortex reduces commission errors during the $SART_{fixed}$ **(A)**, reduces the amount of missed targets on the CTET **(C)** , and does not alter accuracy during the $SART_{random}$ **(B)**. *Note.* * denotes p≤0.05, 'ns' denotes no significant difference between real and sham stimulation. Circular markers in the boxplots represent the median values.

Error Awareness ($SART_{fixed}$)

There was no main effect of Intervention (sham M=51.25, SD=36.59; real M=46.92, SD=30.1), Time, or any interaction effect on Error Awareness during the $SART_{fixed}$ (all $F_{1,11}$< .5, p>.5). Note that the high accuracy levels of the $SART_{fixed}$ resulted in only 12 participants having sufficient error trials for inclusion in this error awareness calculation.

Commission Errors ($SART_{random}$)

In contrast to the $SART_{fixed}$, tDCS did not reduce the percentage of commission errors during the $SART_{random}$ ($F_{1,25}$=.02, p=.88, Fig 1.3B; sham M= 20.27%, SD= 9.89; real M= 20.50%, SD= 10.35). There was a main effect of Time on the $SART_{random}$, whereby the percentage of commission errors made during block 2 (M=18.91% SD = 10.25) was less than during block 1 (M=21.86% SD= 9.71; $F_{1,25}$=4.43, p< .05, η_p^2= 0.15). There was no interaction between Intervention and Time for commission errors during the $SART_{random}$ ($F_{1,25}$=.07, p=0.8).

Error Awareness ($SART_{random}$)

There was no main effect of Intervention (sham M=41.69, SD=3.65; real M=41.86, SD=3.34), Time, or any interaction effect on Error Awareness during the $SART_{random}$ (all $F_{1,20}$< 2.9, p > .1).

Experiment 1: Modulation of ERP components during tDCS

The visual-evoked occipital P1 component

The P1 component is an early visual-evoked positivity, sensitive to manipulations of attention (Hillyard and Anllo-Vento 1998; O'Connell et al. 2011). There was no effect of Intervention ($F_{1,21}$ = 1.7, p = .21), or Trial Type ($F_{1,21}$ = 1.27, p = 0.27) on the P1 amplitude during the $SART_{fixed}$ (Fig. 1.4 A and B; see Table 1.2 for ERP summary). There was, however, an interaction between Intervention and Trial Type ($F_{1,21}$=8.48 , p =.008, η_p^2=.29). During sham stimulation, there was no difference in P1 amplitude between no-go (3.68 μV ± .49) and go trials (3.9 μV ± .51; $F_{1,21}$= 1.06, p =.32). During real stimulation, the P1 showed a significantly lower

amplitude for no-go (3.04μV ± .65) reative to go trials (3.66 μV ± .54; $F_{1,21}$=6.32, p=.02, η_p^2= .23).

During the $SART_{random}$ there was no effect of Intervention ($F_{1,16}$=2.3, p > .14), Trial Type ($F_{1,16}$ = 0, p = .99), or any interaction effect ($F_{1,16}$< .83, p > .37) on the P1 amplitude (Fig. 1.4 C and D; see Table 1.2 for ERP summary).

The visual-evoked occipital N1 component

The N1 component is an early visual-evoked negativity involved in discrimination of object features (Vogel and Luck 2000). TDCS was associated with a notably enhanced N1 amplitude during the $SART_{fixed}$ as evidenced by the main effect of Intervention ($F_{1,20}$=8.07, p =.01, η_p^2=0.29), such that the average N1 amplitude was -4.82μV (± .60) during real stimulation as compared with -3.6μV (± .6) during sham stimulation (Fig. 1.4 A and B). There was a main effect of Trial Type ($F_{1,20}$=9.94, p=.005, η_p^2=.33), with stronger N1 amplitudes for no-go (-4.71 μV ± .61) relative to go trials (-3.71 μV± .61). There was no interactions term for the N1 component during the $SART_{fixed}$ ($F_{1,20}$ < 2.5, p>.12).

During the $SART_{random}$ there was no difference in N1 amplitude during tDCS as signified by no main effect of Intervention ($F_{1,14}$ = .64, p = .44; Fig. 1.4C). Stronger mean N1 amplitude was noted for no-go (-5.67μV ± .64) compared to go trials (-4.05μV ± .78) during the random version of the task, as illustrated by a main effect of Trial Type ($F_{1,14}$= 33.26, p < .0005, η_p^2= .7). There was interaction term for the amplitude of N1 during the $SART_{random}$ ($F_{1,14}$ < .07, p>.78).

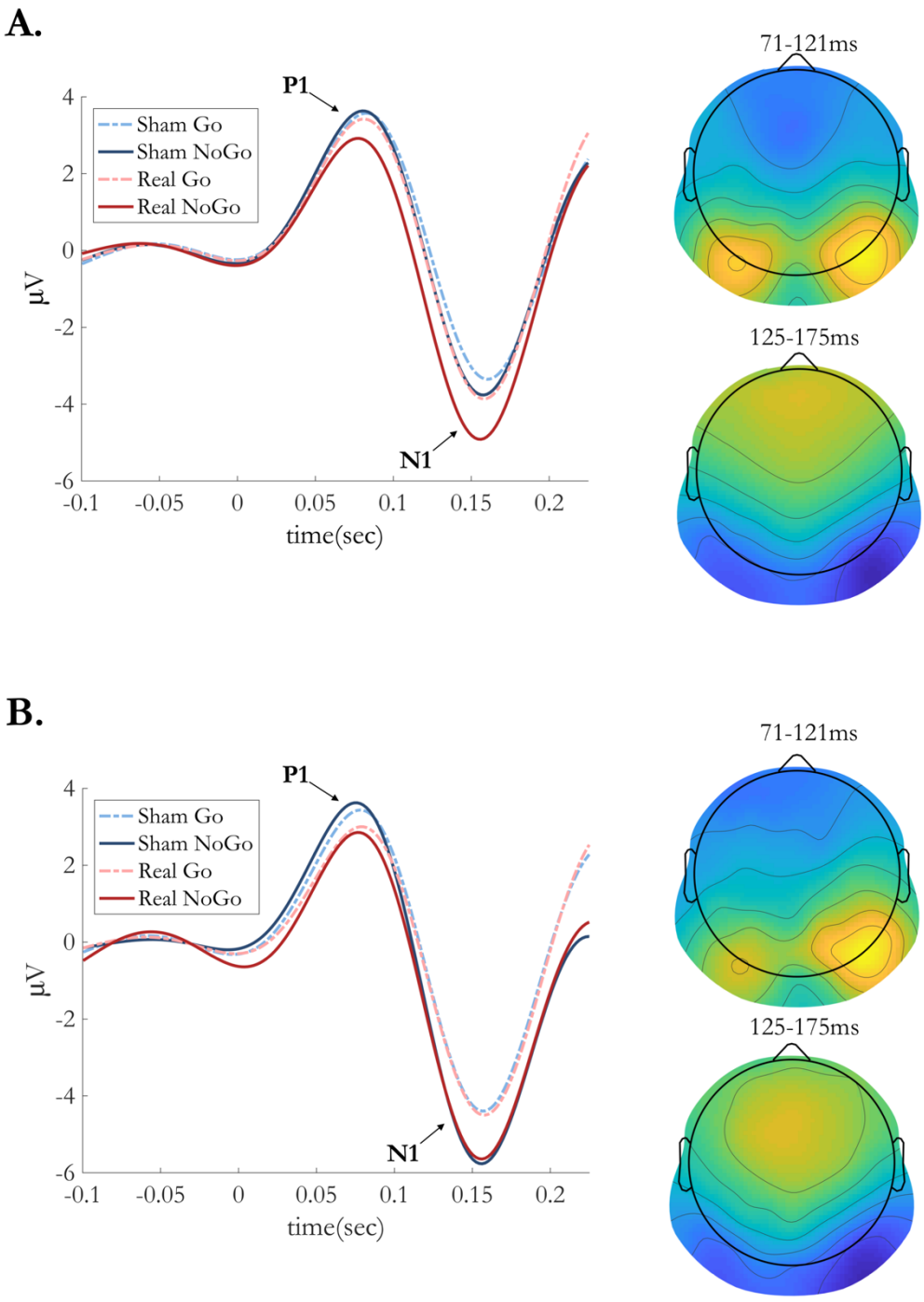


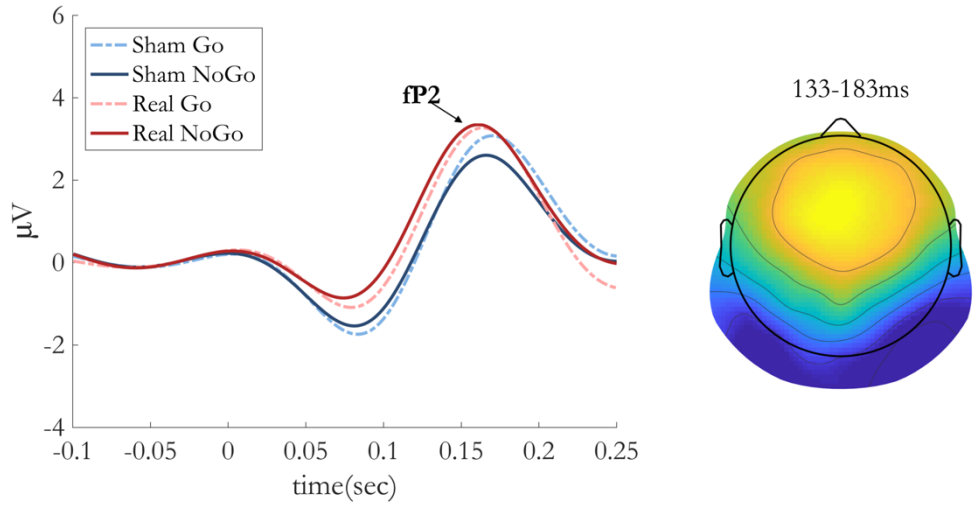
Figure 1.4: The effect of tDCS on the visual evoked P1 and N1 components during the $SART_{fixed}$ (A) and the $SART_{random}$ (B). ERP plots (left) illustrating the effect of stimulation at electrode P08, and scalp plots (right) showing the topography of the components of interest (P1, 71-121ms; N1 125-175ms) during sham stimulation (collapsed across go and no-go trials).

The frontal P2 (P2f) component

The frontal P2 (fP2) component is a frontal positivity, proposed to contribute to greater allocation of attentional resources during performance of the SART in older adults (Staub et al. 2014; Staub et al. 2015). During performance of the $SART_{fixed}$, an enhanced P2f amplitude was observed during real (3.85μV ± .40) versus sham tDCS (2.9μV ± .45; Fig. 1.5 A and B) as evidenced by the main effect of Intervention ($F_{1,21}$ = 5.1, p=.035, η_p^2=.2). There was no main effect of Trial Type ($F_{1,21}$ = .09, p=.77) or any interaction between Trial Type and Intervention on the $SART_{fixed}$ (all $F_{1,21}$< .58, p>.45.

There was no main effect of Intervention during the $SART_{random}$ ($F_{1,16}$ = 3.72, p = .07; Fig. 1.5 C and D). There was no main effect of Trial Type ($F_{1,16}$ = 3.14, p = 0.1), or any interaction term during the $SART_{random}$ ($F_{1,16}$ < .04, p > .8).

A.



B.

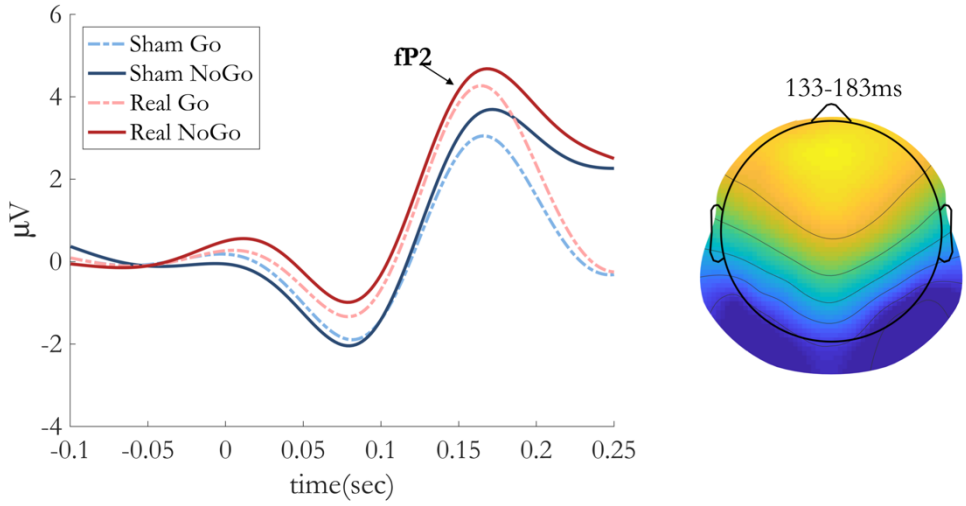


Figure 1.5: The effect of tDCS on the frontal P2 component during the SART$_{fixed}$ (A) and the SART$_{random}$ (B). ERP plots (left) illustrating the effect of stimulation on the P2 component at electrode Fz, and scalp plots (right) showing the topography of the frontal P2 (fP2; 133-183ms) during sham stimulation (collapsed across go and no-go trials

The frontal P3 (P3f) component

The frontal P3 (fP3) component is a frontal positivity with established links to response inhibition processes (Bekker et al. 2005; Dockree, Kelly, Robertson, and Reilly 2005; O'Connell et al. 2009). There was no effect of Intervention ($F_{1,21}$= 1.66, p = .21) on the fP3 during the SART$_{fixed}$ (Fig. 1.6 A and B). There was a main effect of Trial Type ($F_{1,21}$= 9.66, p =.005, η_p^2=.32), with greater fP3 amplitudes for go (2.44μV ± .73) relative to no-go (.73μV ±.58) trials. There was no interaction term ($F_{1,21}$ < .44, p > .51) on the mean amplitude between 438 ms to 538 (Fig. 1.6 A).

The frontal P3 (P3f) component during the SART$_{random}$

The fP3 was not modulated by tDCS during the SART$_{random}$ as evidenced by a main effect of Intervention ($F_{1,16}$ = 2.38, p = .14, η_p^2= .13; Fig. 1.6 B and C). In direct contrast to the SART$_{fixed}$, a main effect of Trial Type ($F_{1,16}$ = 10.61, p = .005, η_p^2= .4) demonstrated that

enhanced fP3 amplitudes were elicited for no-go (6.62μV ± 1.08) versus go trials (3.36μV ± .67) during performance of the $SART_{random}$. There was no interaction effect ($F_{1,176} < .02, p > .88$).

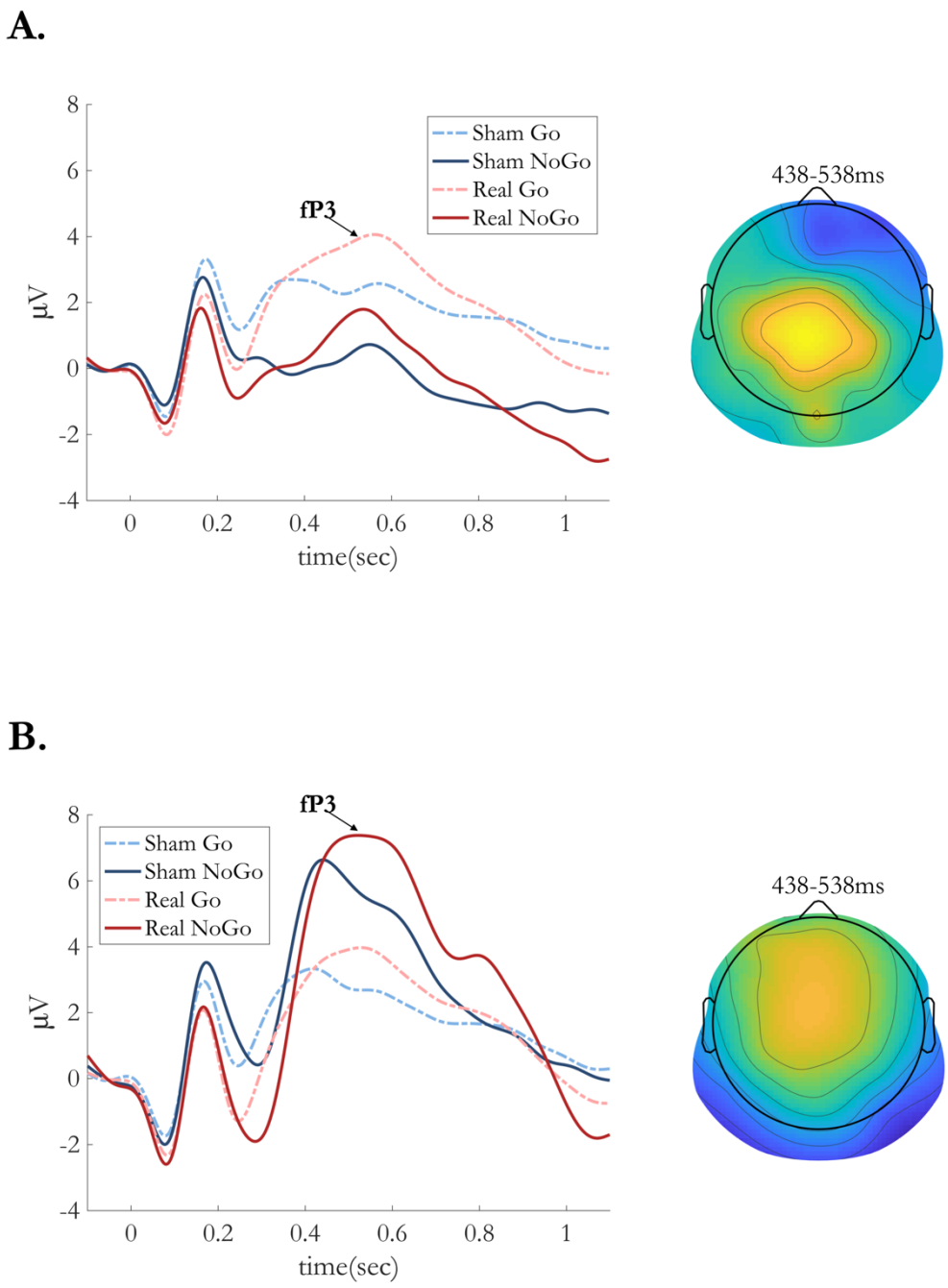


Figure 1.6: The effect of tDCS on the frontal P3 component during the $SART_{fixed}$ (A) and the $SART_{random}$ (B). ERP plots (left) illustrating the effect of stimulation on the frontal P3 (fP3) component at electrode FCz, and scalp plots (right) showing the topography of the P2 (133-183ms) during sham stimulation (collapsed across go and no-go trials).

Table 1.2: Summary of ERPs.

ERP component	Selected Region (electrode)	Time Window (ms)	Effect of Intervention (*p* value)	
			$SART_{fixed}$	$SART_{random}$
P1	Occipo-parietal (P08)	571 - 121	***[a]	×
N1	Occipito-parietal (P08)	125 – 175	**	×
P2f	Frontal (Fz)	1133 – 183	*	×
P3f	Fronto-central (FCz)	438 - 538	×	×

Note ** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$, × $p > 0.055$. a. Modulation of the visual-evoked P1 component during the $SART_{fixed}$ is specific to the No-Go trial (i.e., a significant interaction exists between Trial Type and Stimulation).

Experiment 2: Behavioural Performance changes during tDCS (CTET)

The rate of false alarms was low during the CTET (*M*= 2.64 %, *SD* = 1.99, range = 1-9%) indicating that all participants were performing above chance level. A main effect of Stimulation ($F_{1,20}$=4.67., p=.043., η_p^2=.19; Fig. 1.3C), indicated that accuracy was significantly higher during active (*M*=91.4 %, *SD*=7.36), compared with sham, stimulation (*M* = 86.45%, *SD*= 10.43). A main effect of Quartile demonstrated that regardless of stimulation, accuracy levels decreased within each block ($F_{3,60}$=6.51, p=.001, η_p^2= .25) as evidenced by the significant linear contrast ($F_{1,20}$=10.76, p=.004, η_p^2=.350). More specifically the older adults showed a significant drop in accuracy between the first and second ($F_{1,20}$=6.49, p=.01, η_p^2=.25), second and third ($F_{1,20}$=7.22, p=.014, η_p^2=.27), third and fourth ($F_{1,20}$=,11.12, p=.003, η_p^2=.36) quarters of the task blocks. A main effect of Block indicated that accuracy levels also changed significantly across the five task blocks ($F_{4,80}$=5.61, p=.005, η_p^2= .22). This effect was best fit to a cubic contrast ($F_{1,20}$=9.86, p=.005, η_p^2=.33); a significant decrease in accuracy was noted between the first task block and blocks 2 ($F_{1,20}$=9.53, p=.006, η_p^2=.32), 3 ($F_{1,20}$=10.34, p=.004, η_p^2=.34), 5 ($F_{1,20}$=,7.63,

p=.01, η_p^2=.28) but not block 4 ($F_{1,20}$=1.88, p=.19, η_p^2=.09). There were no significant interaction terms (all p>.07).

1.4 Discussion

This study showed in two independent cohorts using two very different task paradigms that increasing activity in the right PFC improves sustained attention performance in older adults. Of particular interest, simultaneous tDCS-EEG recordings revealed showed that these behavioural improvements were supported by an increased visual evoked N1 component over parieto-occipital scalp regions, as well as an enhanced frontally distributed P2f. These findings suggest that tDCS induced an adaptive increase in attention and stimulus processing resources, and may reflect early frontal engagement in concert with greater deployment of visual attention.

The visual evoked N1 is important for early visual attention processes and has been associated with the discrimination of high level visual object features (Vogel & Luck, 2000). Greater visual evoked neural responses are typically considered an adaptive compensatory strategy of cognitively healthy older adults (Daffner et al., 2006; De Sanctis et al., 2008; Wiegand et al., 2014) with emerging evidence to suggest that these signals may be driven by prefrontal inputs in the aging brain (J. R. Gilbert & Moran, 2016). It has previously been shown that early visual evoked responses in older adults are malleable in nature using al training, for example using visual discrimination paradigms (Berry et al., 2010; Mishra et al., 2014). The results presented in this chapter complement these earlier findings and show that early markers of visual attention can also be potentiated via top-down control from the prefrontal cortex.

tDCS was associated with a reduced amplitude of the temporally earlier visual-evoked P1 component, exclusively during the predictable no-go trials on the $SART_{fixed}$. The P1 is particularly sensitive to color, motion and manipulations of spatial attention (Hillyard & Anllo-Vento, 1998; C. E. Miller, Shapiro, & Luck, 2015; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011; Zanto et al., 2011; Zhang & Luck, 2009). Some evidence suggests that a decrease in the amplitude

of early visual attention components may represent the sharpening of tuning curves, reflected by a decrease in EEG signals (e.g., Ding et al. 2003). Why tDCS exerts differential effects of the visual P1 and N1 components is not clear. Further work will be necessary to understand the unique effects of top down modulation from prefrontal regions on the distinct stages of early visual processing.

The efficiency of the visual attention system is compromised with age (Salthouse 1996) and certain aspects of visual attention, such as the speed at which older adults can process visual information, are increasingly considered biomarkers of cognitive decline (Ritchie et al. 2014). Whether increasing activity in the right PFC is associated with improvements in visual attention capacity in older adults warrants investigation, as this would provide important information to inform neurorehabilitation protocols.

A frontally distributed P2f was observed in the current study during tDCS. Stronger P2f amplitudes during performance of the SART have been previously seen in older adults and have been interpreted as greater mobilization of top-down attentional resources (Staub et al., 2014; 2015). Frontal regions are connected to visual occipital regions through long association white matter pathways in the frontoparietal attentional networks (Chechlacz et al., 2015; Marshall et al., 2015). Recent modelling work suggests that ageing is associated with an increase in prefrontal inputs which in turn drive stimulus-evoked EEG signals emanating from visual regions (J. R. Gilbert & Moran, 2016). Here, during tDCS over the prefrontal cortex, an adaptive increase in early frontal activity in conjunction with enhanced early visual evoked responses was observed, thus supporting Gilbert and Moran's proposal that a functional pathway exists to support this top-down modulatory effect from prefrontal regions.

The current chapter supports previous behavioural and neurophysiological evidence regarding a distinct role of response inhibition for successful performance of the $SART_{random}$ and not the $SART_{fixed}$ (Dockree et al., 2005a; O'Connell, Dockree, Bellgrove, et al., 2009a). Previous work has shown that during response inhibition tasks with repeated stimulus-response mappings

(as in a go/no-go paradigm like the SART), a shift towards bottom-up automated inhibition processes is progressively observed while top down modulation from frontal control regions is gradually decreased (Shiffrin & Schneider, 1977; Verbruggen & Logan, 2008). Consistent with the automatic-inhibition hypothesis (Shiffrin & Schneider, 1977; Verbruggen & Logan, 2008) whereby automatic processes develop over practice, in the current cohort of older adults' performance on the $SART_{random}$ was significantly better during the second block relative to the first block, regardless of stimulation. Further evidence that response inhibition processes are predominating during performance of the $SART_{random}$ is the highly prevalent frontally distributed P3 component that has been conceptualized by many as a marker of effective response inhibition (e.g., Bekker, Kenemans, Hoeksma, Talsma, & Verbaten, 2005). In line with previous ERP investigations of the SART, this was more pronounced during no-go relative to go trials. (O'Connell, Dockree, and Bellgrove 2009). In support of different mechanisms performing the two version of the SART, during performance of the $SART_{fixed}$, a more pronounced fP3 was observed for go relative to no-go trials. Older adults have been previously noted to exhibit stronger P3 amplitudes to non-targets on the SART (Staub et al. 2015), relative to younger controls, which the authors interpret as the implementation of controlled, effortful processing by older adults, irrespective of stimulus type.

In the current study, tDCS targeting the right DLPFC reduced the number of attentional lapses on the two tasks ($SART_{fixed}$ and CTET), which heavily rely on the capacity for sustained attention. In contrast, lapses on the $SART_{random}$ was not altered by tDCS, and tDCS did not enhance any of the electrophysiological signals of interest. Manuel and colleagues (2010) have shown that training related improvements in response inhibition during a go/no-go task are marked by early electrophysiological changes in sensory processing, specific to the no-go trial, suggesting a bottom up enhancement of response inhibition processes with training (Manuel, Grivel, Bernasconi, Murray, & Spierer, 2010). Neuromodulation of regions of the so-called cognitive control network (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Chambers, Garavan,

& Bellgrove, 2009) involved in stopping a motor response (e.g., inferior frontal cortex or the pre-SMA) might be employed to enhance processes of response inhibition at play during $SART_{random}$.

Conclusions & Future Directions

This chapter demonstrated that tDCS targeting the right dorsolateral prefrontal cortex in older adults enhanced neural markers of frontal control and early sensory processing and improved to sustained attention. These findings suggest the right DLPFC is a viable target area to mitigate age-related decrements in sustained attention. Improvements in sustained attention were observed in older adults who presented with suboptimal attention performance, relative to normative data based on over 5000 individuals. The current findings therefore place the right prefrontal cortex as a promising target region to improve sustained attention in clinical populations whose capacity for sustained attention is compromised (e.g., following right hemisphere stroke (Robertson et al. 1997).

Empirical Chapter 2: Plasticity of the Right-Lateralised Cognitive Reserve Network in Ageing.

2.1 Introduction

Empirical Chapter 1 demonstrated that tDCS targeting the right dorsolateral prefrontal cortex in older adults temporarily improved sustained attention. Of particular interest, strong amplitude modulation of EEG markers of top-down frontal control and early visual attention processes over occipito-parietal scalp regions was observed, elucidating a potential mechanisms for improvements via long-range frontoparietal pathways that connect fronto-parietal and occipital regions (Chechlacz et al., 2015; Marshall et al., 2015). Empirical Chapter 2 will assess whether this tDCS protocol can be employed to enhance behavioural aspects of visual attention.

It is well-established that hemisphere asymmetries observed in younger adults during many cognitive operations, including visual attention, become more balanced with age, particularly within the prefrontal cortex (PFC; Cabeza, 2002a; 2004; Reuter-Lorenz, Jonides, & Smith, 2000). However, it is still unclear whether this pattern is due to a more bilateralised activation of the two hemispheres (Cabeza, 2002b), or a more pronounced unilateral decline of the right hemisphere (J. W. Brown & Jaffe, 1975). The functional implications of hemisphere asymmetries may be better understood by taking inter-individual differences in cognitive reserve into account. Specifically, changes in hemispheric asymmetries reported in previous studies may, at least partly, result from stronger activation of the right FPN in older adults with higher levels of cognitive reserve (Fig. I.2).

A hallmark of ageing, closely related to functional and structural changes of the FPN, is a decline in visual attention capacity (Kerchner et al., 2012; Madden et al., 2007). Of interest is the speed at which visual information is processed. This is associated with functional impairments experienced by older adults in everyday life (Wood & Owsley, 2014), and is increasingly considered a promising biomarker for cognitive decline (Ritchie et al., 2014). Furthermore, visual short-term storage capacity, the amount of information that can be perceived at one moment in time and will be available for conscious processing, decreases with age (Espeseth, Vangkilde, Petersen, Dyrholm, & Westlye, 2014; McAvinue et al., 2005).

As with many cognitive processes, visual attention capacity does not decline at the same rate, even in healthy aging (e.g. McAvinue et al., 2012; Wiegand et al., 2014). Accumulating evidence suggests that individuals brains' differ in their potential to compensate for a reduced capacity of early sensory regions to process visual information by increasing recruitment of prefrontal areas (Cabeza, 2004; Davis et al., 2008).

The Theory of Visual Attention (TVA, Bundesen, 1990) is a formal model that provides a method to measure these two core components of visual attention as two mathematically independent parameters processing speed *C* and storage capacity *K*. In line with the "biased competition" view of visual attention (Desimone & Duncan, 1995), TVA assumes that presented items are processed in parallel and compete for selection, which in this case equals conscious representation. Visual objects are processed in a "race", with those items processed most quickly entering the capacity-limited short-term memory. The two parameters can be quantified for an individual based on performance in a simple psychophysical task. Specifically, using a lateralised whole-report paradigm (Duncan et al., 1999), processing speed *C* and storage capacity *K* can be computed separately for the left and right visual hemifields.

Recent work combining electrophysiological recordings with the parametric assessment of visual attention based on the TVA (Bundesen, 1990) in ageing has shown differential involvement of the FPN in older adults with high visual processing speed and high storage

capacity, relative to their lower performing peers (Wiegand et al., 2014). Whether the right FPN can be targeted to increase parameters of visual attention capacity in ageing, and whether the visual attention system is mediated by cognitive reserve remains unexplored.

TVA has been used to quantify visual attention decline in healthy aging (Espeseth et al., 2014; McAvinue et al., 2012) as well as under pathological conditions (Bublak et al., 2011; Bublak, Redel, & Finke, 2006). The TVA framework provides several distinct advantages when assessing visual attention capacity in ageing. Firstly, processing speed and storage capacity are quantified within a highly specified framework (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999b) with a tractable biological basis (Bundesen, Habekost, & Kyllingsbæk, 2005; 2011). Secondly, the TVA assessment is based purely on the accuracy of a verbal report, thus unbiased by age-related motor slowing. Finally, the use of short, individualised, exposure durations of the visual stimuli presented to participants during testing, minimises the likelihood of task difficulty (due to individual differences in perceptual thresholds) or task strategy affecting the measurements of visual attention capacity.

The current chapter utilises TVA to investigate the relationship between distinct functions of visual attention capacity, hemisphere asymmetries, and cognitive reserve in ageing. The mathematically independent parameters processing speed *C*, and storage capacity *K* were measured for each individual based on performance in a lateralised whole-report paradigm (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999b), which permits *C* and *K* to be computed separately for the left and right visual hemifields. Given that visual input elicits strongest activity in the contralateral cortical hemisphere (Heinze et al., 1994; Mangun, Buonocore, Girelli, & Jha, 1998; Schiffer et al., 2004), this approach provides a psychophysical measure of hemisphere asymmetries in visual attention in ageing.

A question of pressing interest is whether the networks underpinning cognitive reserve show plasticity in older adults, so that reserve may be cultivated later in life. To test this, transcranial Direct Current Stimulation (tDCS) was employed during the whole report task, to

increase neuronal excitability in a causal manner. The right lateralised FPN was targeted to explore (a) whether plasticity of the right FPN can be harnessed in ageing to enhance visual attention and (b) whether this plasticity is related to individuals' levels of cognitive reserve. This was explored separately for processing speed *C* and storage capacity *K*, to test whether the mechanisms in the FPN underlying these two functions could be targeted, separately, supporting the distinctiveness of these two aspects of visual attention in ageing.

2.2 Materials and Methods

Participants

A total of 31 older adults aged between 65 and 85 (M = 71.55, SD=5.43) completed the current study. All participants were right handed, had no history of neurological illness and no personal or family history of seizures. This study was approved by the Trinity College Dublin School of Psychology Ethics Committee, and written consent was obtained prior to the study.

Study Procedure

Participants in the study attended four testing sessions. During the initial test session participants were screened for cognitive impairment using the Montreal Cognitive Assessment (MoCA), and a neuropsychological battery and cognitive reserve assessment were administered (described below). All participants were familiarized with the TVA task during this first session, and individual exposure durations were identified by a calibration procedure (described below). This was to ensure that each individual's exposure duration spanned from close to their perceptual thresholds to a duration that allowed the participant enough time to reach their full storage capacity, thereby allowing for accurate modelling of the TVA parameters. Following this session, all cognitive healthy older adults (scoring ≥ 23 on the MoCA) were invited to attend three TVA-tDCS sessions, where they received right prefrontal, right parietal, and sham stimulation in a pseudo-random, counter-balanced order.

The Theory of Visual Attention (TVA)

TVA whole report task

In each of the three TVA-tDCS sessions, participants completed a TVA whole report experiment divided into 10 blocks, each lasting approximately 3 min (Fig. 2.1). The task was to verbally report as many letters as possible from a briefly presented letter array. In masked trials, the display was terminated by pattern masks presented for 900 ms on all possible stimulus positions. In unmasked trials, a blank screen with the fixation dot was presented instead. A question mark then appeared on the screen, which indicated to the participants to verbally report the letters seen. The letters could be reported in any order and without any emphasis on speed, and were entered by the experimenter.

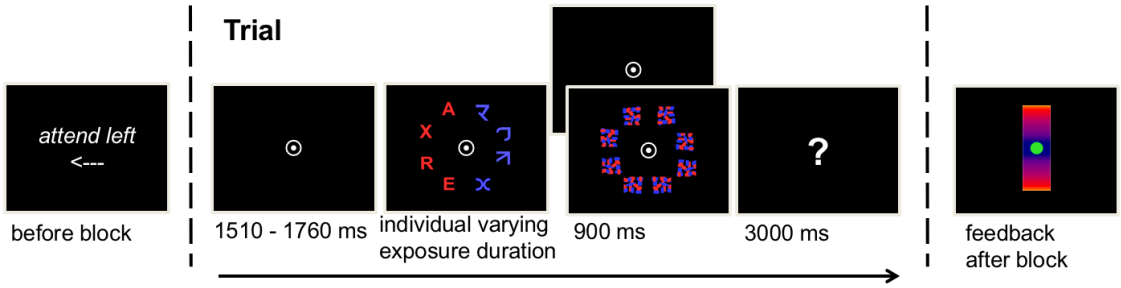


Figure 2.1: TVA whole report task. Experimental procedures used for TVA parameter assessment. Four equidistant letters arranged in a half circle were presented in red, on the left or right side of the display and 5 isoluminant scrambled filler blue letters were always presented in the opposite hemifield. Participants were informed before the beginning of the blocks whether the letters would appear to the right or left. Letters were presented at 5 different individually adapted exposure durations. Feedback was presented visually after each block, and participants were advised to maintain accuracy levels between 80 and 90%, which was visualized as a central green ball in a coloured bar; performance below and above this range was visualized as a yellow ball below and above the centre of the bar, respectively.

Participants were sitting in a comfortable chair with a distance of 47cm to the screen. The experiment was run on a HP Compaq dc5750 Microtower computer with a 100Hz refresh rate. The stimuli were arranged in a circle around a fixation dot. Participants were instructed to fixate the dot throughout the whole trial. On each trial, four red letters (Arial font bold) were presented briefly either on the left or right side of a fixation dot. The letters of a given trial were randomly chosen, without replacement, from a pre-specified set (ABDEFGHJKLMNOPRSTVXZ). Four

isoluminant scrambled filler blue letters were always presented in the opposite hemifield in order to balance sensory stimulation in the two hemifields.

At the beginning of each block, participants were informed about whether letters would be presented in the left or right hemifield. The side on which the letters were presented was constant within one block and systematically alternated between blocks (see (Cooreman, Wiegand, Petersen, Vangkilde, & Bundesen, 2015)). Participants were instructed to report letters they were "fairly certain" to have seen and refrain from pure guessing. To control for the level of guessing, feedback was displayed after each block showing the accuracy of the reported letters (i.e. the percentage of correct answers out of all given answers) and participants were advised to adhere to a level of 80-90% correctly reported letters.

Both masked and unmasked letter displays were presented, resulting in seven different effective exposure durations, which were individually determined in a pre-test (see below). Owing to visual persistence, exposure durations are effectively prolonged in unmasked- compared to masked-array conditions (Sperling, 1960). The variation in exposure durations was intended to generate a broad range of performance, specifying the whole probability distribution of the number of correctly reported elements as a function of the effective exposure duration. The whole report experiment contained 15 trials of each condition (5 masked and 2 unmasked display conditions for both left and right hemifields), resulting in a total amount of 210 trials. Conditions were balanced across blocks and each subject was presented with the same displays in random order, balanced across blocks.

During the initial testing session, participants performed a pre-test to familiarize them with the task and determine the individual distribution of exposure durations. Four practice blocks consisting of 12 trials each were run. As in the experiment, blocks with letters presented in the left and right hemifield alternated. In the practice blocks, three trial types were randomly intermixed: Two "easy" practice trial types with relatively long exposure durations (one 250 ms masked display, and one 200 ms unmasked display) and a calibration trial type to determine the

individual lowest exposure duration. Calibration trials always had masked displays and constituted 2/3 of the trials (32 trials) in the practice session. The initial exposure duration of the calibration trials was set to 100 ms. When the participant reported one or more letter correctly in a pair of calibration trials, the exposure duration was lowered 10 ms. If no letter was reported correctly in a pair of calibration trials and an adjustment of exposure duration was just made on the basis of the previous pair of calibration trials, the exposure duration remained. If no letter was reported correctly in a pair of calibration trials and no adjustment of exposure duration was just made on the basis of the previous pair of calibration trials, the exposure duration was increased for 10 ms. The final lowest exposure duration for both masked and unmasked displays was chosen 10 ms lower than the lowest exposure durations determined in the calibration procedure. The final lowest exposure duration could not be less than 10 ms or higher than 200 ms. The long exposure duration for the unmasked displays was always 200 ms. The remaining four exposure durations for the masked displays were chosen such that they were equally spaced on a logarithmic scale starting from the final lowest exposure duration to a maximal exposure duration of 190 ms + the final lowest exposure duration. (e.g., if the final lowest exposure duration was found to be 10 ms then 10, 20, 40, 90 and 200 ms were used as exposure duration for the masked displays, whereas 10 and 200 ms were used for the unmasked displays).

TVA parameter estimation

Individual parameter estimates for the left and right hemifield were derived separately by using a maximum likelihood procedure described in detail by (Dyrholm, Kyllingsbæk, Espeseth, & Bundesen, 2011). Based on the basic equations of TVA (see (Bundesen, 1990; Bundesen et al., 2005; Kyllingsbæk, 2006) a participant's accuracy of letter report was modeled by an exponential growth function as function of the effective exposure duration (Fig. 2.2). The function is defined by four parameters: (1) parameter *C*, the visual processing speed (elements processed per second); (2) parameter *K*, the storage capacity (maximum number of elements in vSTM); (3)

parameter t_0, the minimal effective exposure duration (in ms), below which information uptake from the display is assumed to be zero; and (4) parameter μ, the persistence of the iconic memory trace (in ms) in unmasked conditions. The model fitted to the data from each hemifield had 6 degrees of freedom (df): *K*, 3 df (the *K* value reported is the expected *K* given a particular distribution of the probability that on a given trial *K* = 1, 2, 3, or 4); t_0, 1 df; *C*, 1 df; μ, 1 df. Items were presented at a variety of exposure durations, controlled with a mask (Fig. 2.1) For those participants whose t0 was fit below 0, the data were re-fitted again fixing t0 to 0. In the present study, parameters t_0 and μ were estimated to obtain valid estimates of the two parameters of main interest, *C* and *K*, and will not be discussed.

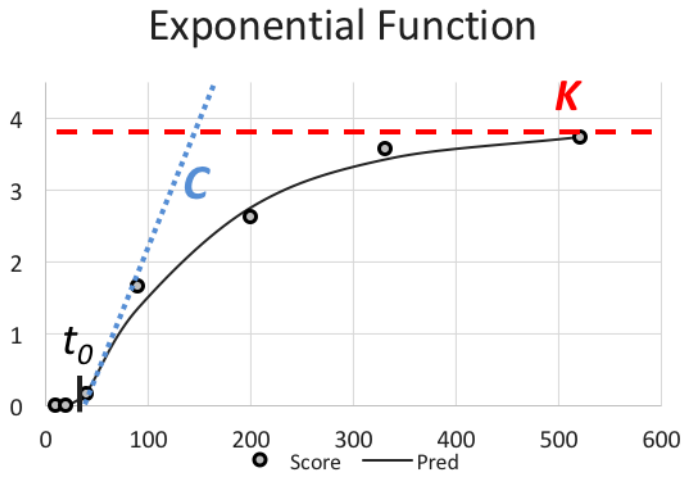


Figure 2.2: Schematic of the exponential distribution resulting from the TVA modelling procedure. Here parameter t_0 represents the minimal effective exposure duration (in ms), below which information uptake from the display is assumed to be zero. Parameter *C* represents the speed at which items can be processed and is illustrated as the slope of the curve at t_0. Parameter *K* represents storage capacity of vSTM and is illustrated as the asymptotic level of the curve.

Assessment of hemifield asymmetries in visual attention capacities

To measure the differences in visual attention capacity between hemifields, the data were modelled separately for trials with letters presented in the left and right hemifield (Duncan et al., 1999). The difference in parameters for right and left hemifields was compared for each parameter separately using paired-samples *t*-tests. In order to explore the hemifield asymmetries in visual attention capacity, laterality indices were computed for both *C* (C_λ) and *K* (K_λ) as the

ratio $C_{left}/(C_{left} - C_{right})$ and $K_{left}/(K_{left} - K_{right})$, respectively. Accordingly, an index of .5 would indicate balanced processing, an index > .5 would denote a leftward processing asymmetry, and an index <.5 would denote a rightward processing asymmetry. Overall visual attention capacity for the *C* and *K* parameters were calculated as the average of $C_{left} - C_{right}$ and $K_{left} - K_{right}$, respectively.

Cognitive Reserve and Neuropsychological Assessment

During the initial testing session, the following neuropsychological test battery was administered to all participants. The Montreal Cognitive Assessment (MoCA, (Nasreddine et al., 2005) was included as a standardized cognitive screening for age-related cognitive decline. The Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982) a self-report measure of everyday absent-mindedness and attentional failures was administered to participants. This was complemented by an informant-report of the CFQ, completed by a partner or relative of the participant in order to create a discrepancy score (CFQ-D) to assess the participants' awareness of absent-mindedness and attentional failures (as used by (Harty et al., 2013)). Levels of premorbid intelligence were assessed via the National Adult Reading Test (NART (H. E. Nelson, 1982)). Finally, cognitive reserve was measured using the Cognitive Reserve Index questionnaire (CRIq (Nucci, Mapelli, & Mondini, 2012)). This is a validated measure of day-to-day engagements which may contribute to an increased cognitive reserve with age. The index is comprised of the three subscales measuring educational attainment, professional complexity, and leisure activities.

tDCS targeting the right hemisphere

TDCS was employed to increase excitability of prefrontal and parietal regions of the right hemisphere in a single-blind sham controlled, within-subject crossover design. Each participant attended three stimulation sessions. Stimulation was administered using a battery-driven DC Brain Stimulator Plus (NeuroConn) with two 5x7cm electrodes used with high-chloride electroencephalography (EEG) gel (Abralyt HiCl, EasyCap). Electrodes were placed according to

the 10-20 international EEG system (NA, 1991) and kept in place using an EEG cap (Bio-Semi). Stimulation targeting the right prefrontal and right parietal cortical regions was delivered with the center of the anodal electrodes placed over F4 and P4, respectively. The position of the anode was alternated between F4 and P4 across participants during sham stimulation. In all conditions, the cathodal electrode was placed over Cz (vertex).

During active stimulation, 1mA of tDCS was delivered continuously during the performance of each block, with a ramp-up/ramp-down period of 20s, resulting in a current density of 0.02857 mA/cm2 at the scalp. During sham stimulation, tDCS was administered at 1mA for 15s at the beginning of each block with ramp-up/ramp-down periods of 20s. This is a commonly used sham procedure to ensure that the sensations regularly experienced during the onset of tDCS are kept constant during real and sham sessions (Gandiga et al., 2006). At the end of both testing sessions, participants were asked to rate the sensations experienced during stimulation using a five-point likert scale questionnaire for 8 separate sensations (e.g., itchiness, pain, pinching see (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010)). Please note this questionnaire was added to the study design half way through testing, therefore only N=18 participants completed this questionnaire. The results of the sensations questionnaire were assessed with repeated measures ANOVAS with "Stimulation" (Prefrontal, Parietal, Sham) as a within subject factor and revealed no differences in the sensations experienced between sham, prefrontal, and parietal tDCS (all p>.05).

Statistical Analysis

(a) Cognitive Reserve Analysis

In order to rule out the confound of age on levels of cognitive reserve (see (Nucci et al., 2012)), participants were classified to their corresponding age class using the computational approach described by Nucci and colleagues. Three linear models were used where the raw scores of the three subscores (CRI-*Education*, CRI- *WorkingActivity*, CRI-*LeisureTime*) were set as dependent variables, with age as the independent (or predictor) variable. The three CRIq

subscores were the residuals of the relative linear models. This allowed all participants to be systematically classified according to their corresponding age class. Lastly, the total CRI score (CRIq) was the average of the three subscores. The higher the CRIq score, the higher the estimated cognitive reserve.

To examine the baseline relationship between cognitive reserve and the parameters of visual attention capacity and asymmetry was investigated using data from the sham stimulation session. In order to test relationship between cognitive reserve and the distinct visual attention indices described above, an across-participant linear regression analysis was conducted (two-tailed Pearson's product–moment correlations) between the CRIq and TVA parameters of interest (*C,* $C_{\lambda,}$ *K* and K_{λ}), Bonferroni corrected for multiple comparisons. In order to verify the specificity of any associations between TVA parameters and cognitive reserve, significant correlations were followed up with a partial correlation analysis, controlling for the parameter of disinterest (i.e., relationship between C_{λ} and cognitive reserve was assessed controlling for K_{λ}). In the text all reported mean values are followed by standard error (i.e., $M \pm$ SE).

(b) TVA-FPN Stimulation Analysis

The effects of right prefrontal and right parietal stimulation on the TVA parameters were assessed using repeated measures ANOVAs with "Stimulation" (Prefrontal, Parietal, Sham) and "Hemifield" (Right, Left) as within subject factors. Significant main effects and interaction effects were followed up with simple effects analyses. All statistical analyses were performed using SPSS Statistics v21.0.0.1 (IBM) and all figures were designed using customised scripts in MATLAB R2014a 8.3.0.532 (Mathworks, Natick, MA, USA). In all figures, the error bars indicate the standard error of the mean. In the text all reported mean values are followed by standard error (i.e., $M \pm$ SE).

To further elucidate the relationship between stimulating the right prefrontal cortex and improvements in processing speed in ageing, the following follow-up analyses were employed; an across-participant linear regression analysis (two-tailed Pearson's product–moment correlations)

was conducted between the changes in *C* parameter during tDCS and (a) levels of cognitive reserve (CRIq) and (b) baseline hemifield processing asymmetries (C_λ). Indices of the tDCS-related change of the *C* parameter were calculated as the difference between real and sham tDCS for each hemifield separately (e.g.., $\Delta C_{\text{prefrontal right hemifield}} = [C_{\text{prefrontal right hemifield}} - C_{\text{sham right hemifield}}]$). As there was no significant main effect of stimulation for the *K* parameter, no follow-up analyses were performed.

2.3 Results

Demographic and Neuropsychological Profile

A total of 31 cognitively healthy (≥ 23 of the MoCA) older adults completed the four testing sessions (see Table 2.1 for neuropsychological profiling and demographic information). As expected, the cognitive reserve index questionnaire (CRIq) was strongly associated with the number formal years in education (r=.70, p<.0005), and premorbid intelligence as estimated from the NART (r=.38, p=.04). Interestingly, the CRIq was correlated with the CFQ-D (r=.47, p=.01) such that lower levels of reserve were associated with less awareness of everyday lapses in attentional control (relative to informant reports). The CRIq was not significantly correlated with scores on the MoCA in this healthy older sample (r=.28, p=.13).

Table 2.1: Demographic and Cognitive Characteristics of the Sample.

Participants (*N*=31)					
Age (yrs)	MoCA	Education (yrs)	PFS IQ*	CFQ-D*	CRIq
71.55	26.97	16.00	121.45	10.94	128.19
(5.43)	(1.62)	(3.58)	(3.84)	(17.36)	(15.68)

*N*ote MoCA denotes Montreal Cognitive Assessment (MoCA; (Nasreddine et al., 2005)), a validated cognitive screening tool. PFS IQ denotes predicted full scale IQ as estimated from the National Adult Reading test (NART; (H. E. Nelson, 1982)), a measure of premorbid intelligence. CFQ-D denotes Cognitive Failures Questionnaire Discrepancy Score, the difference between the self (CFQ) and informant (CFQ-other) report of everyday lapses in attention (Broadbent et al.,

1982). *Note calculation based on N=29 as two informant reports and two NART questionnaires were not returned/completed. CRIq denotes the total score of the Cognitive Reserve Index questionnaire (Nucci et al., 2012). Values denote mean and standard deviations, M (SD).

Table 2.2: TVA parameters (*C* and *K*) and laterality indices at baseline

TVA parameters				
	C	C_λ	*K*	K_λ
Mean	18.65	.48	2.42	.49
SD	9.43	.09	.57	.04
Range	6.82-54.41	.29-.70	1.26-3.53	.42-.56

Note λ denotes laterality indices as described in text. SD denotes standard deviation.

Cognitive Reserve and Visual Attention

Relationship between Processing Speed and Cognitive Reserve

The mean processing speed for the older adults in the current sample was 18.65 (± 1.69) items per second (see Table 2.2). There was no significant difference between processing speed for items in the right (*M*= 19.08 ± 1.74) versus left hemifield (*M*=18.21 ± 1.87; *t*(30) = 0.7, *p*= .49). Cognitive Reserve (CRIq) was not related to overall processing speed capacity (*C*; *r*=.04, *p*=.83). However, a leftward processing asymmetry was predicted by higher levels of cognitive reserve, as indicated by a positive relationship between the C_λ and CRIq (*r*=.52, *p*= .003; Fig. 2.3). This relationship remained significant when controlling for K_λ via a partial correlation (*r*=.49, *p*=.024).

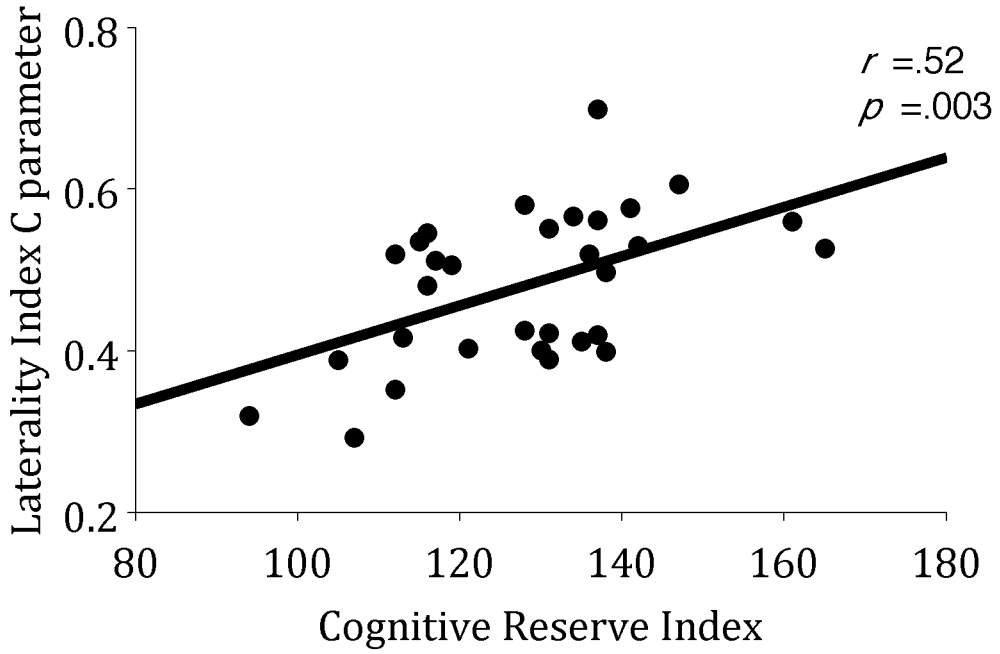


Figure 2.3:: The relationship between processing speed hemifield asymmetry and cognitive reserve. Y Axis denotes the Laterality index (C_i), whereby values greater than 0.5 indicate a leftward asymmetry. X axis denotes the Cognitive Reserve Index questionnaire (CRIq) where greater values indicate higher levels of cognitive reserve.

Relationship between Storage Capacity and Cognitive Reserve

The mean storage capacity for the current ageing sample was 2.42 (± .57), as estimated from the *K* parameter (see Table 2.2). There was a trend for higher storage capacity for items in the right (*M*= 2.48 ± .11) versus left hemifield (*M*= 2.35 ± .11). However this failed to reach conventional levels of significance ($t(30) = 1.93$, $p = .06$). There was no relationship between the CRIq and overall storage capacity (*K*; $r = .28$, $p = .19$), or the degree of hemifield asymmetry in storage capacity (K_i; $r = -.2$, $p = .29$).

The effects of tDCS to the right FPN for each TVA parameter

Processing Speed *C*

There was a significant main effect of Stimulation on processing speed ($F_{2,60} = 4.02$, $p = .02$, $\eta_p^2 = .21$, Fig. 2.4). Participants were significantly faster at processing visual information during right prefrontal stimulation (*M*= 20.60 ± 1.76), in comparison to right parietal (*M*= 17.47 ± 1.41, $p = .01$) and sham stimulation (*M*= 18.65 ± 1.69, $p = .05$ Fig. 2.3). There was no difference

between processing speed during right parietal stimulation relative to sham (p=.33). Regardless of stimulation, there was no difference in processing speed for items in the right (M= 19.75 ± 1.78) versus left hemifield (M= 18.06 ± 1.37), as evidenced by a non-significant main effect of Hemifield ($F_{1,30}$=2.47, p=.13, η_p^2=.08). There was no interaction between Stimulation and Hemifield ($F_{2,60}$= .78, p=.46, η_p^2=.03).

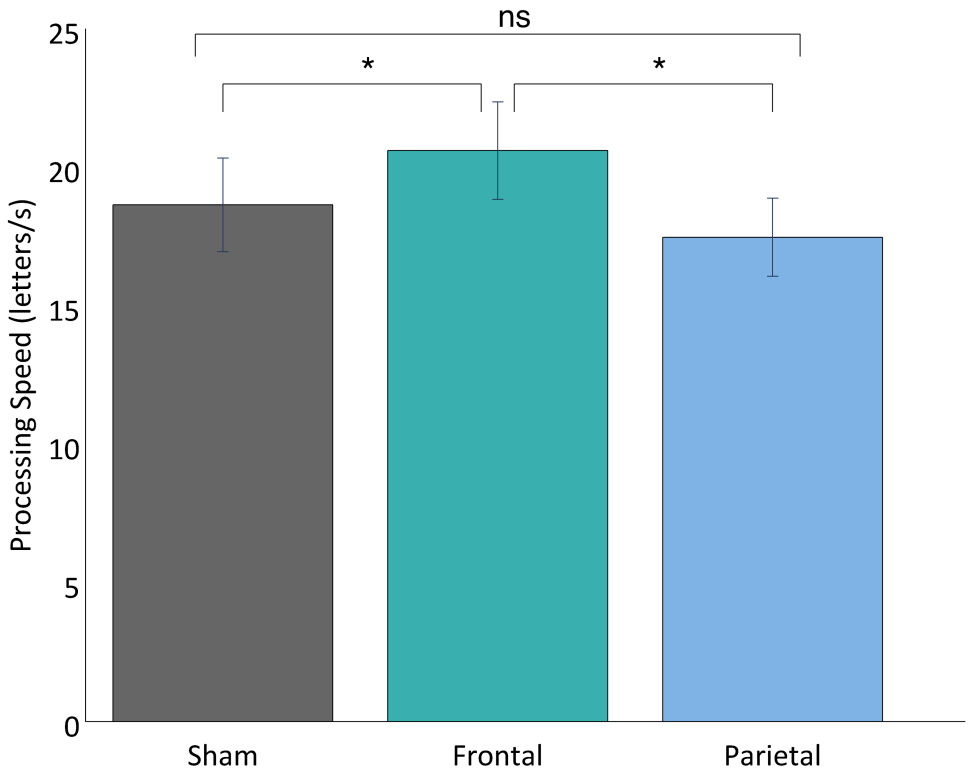


Figure 2.4: The effect of right prefrontal and right parietal stimulation on processing speed. Processing speed was significantly faster during stimulation of the right prefrontal cortex as compared with during right parietal and sham stimulation. *Note* ns denotes not significantly different.

Storage Capacity *K*

There was no difference in Storage Capacity during right prefrontal (M= 2.38 ± .11), right parietal (M= 2.37 ± .10), and sham stimulation (M= 2.42 ± .10) as evidenced by a non-significant main effect of Stimulation ($F_{2,60}$= .34, p=.71, η_p^2=.01; Fig. 5). Storage Capacity was higher for items presented to the right (M= 2.51 ± .10) versus left hemifield (M=2.27 ± .10) as

demonstrated by a main effect of Hemifield ($F_{1,30}$=49.95, p<.0005., η_p^2=.61). There was further a significant interaction between Stimulation and Hemifield ($F_{2,60}$=3.91, p=.025., η_p^2=.12; Fig. 2.5). During sham stimulation there was no significant difference between storage capacity for items in the right (M= 2.48 ± .11) versus left hemifield (M= 2.35 ± .10, p= .06). In contrast, during both right prefrontal and right parietal stimulation storage capacity was significantly higher for items in the right than in the left hemifield (prefrontal stimulation: right hemifield M= 2.55 ± .12, left hemifield M= 2.21 ± .10, p<.0005, parietal stimulation: right hemifield M= 2.51 ± .10, left hemifield M=2.24 ± .11, p<.0005). Planned comparisons testing effects of tDCS in each hemifield revealed that within the right hemifield there was no significant difference for storage capacity during right prefrontal relative to sham tDCS or during right parietal stimulation relative to sham stimulation (both p<.3). Within the left hemifield, storage capacity during right prefrontal stimulation was reduced relative to sham (p=.02). There was no significant difference in storage capacity during parietal relative to sham stimulation, for items in the left hemifield (p=.11).

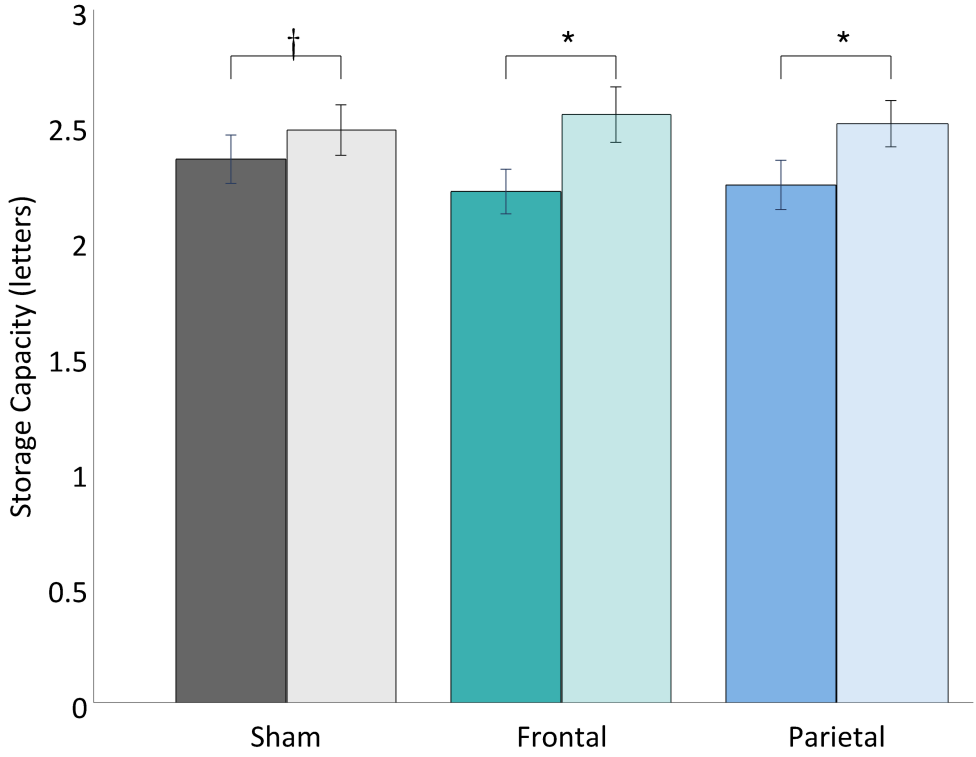


Figure 2.5: The effect of right prefrontal and right parietal stimulation on storage capacity. During sham stimulation, the difference in storage capacity for items in the right (lighter shades) relative to left hemifields was just short of significance. During both right prefrontal and right parietal stimulation, there was a significant difference in storage capacity for the right relative to left hemifield. *Note* † denotes $p \leq .06$, * denotes, $p < .05$.

The relationship between cognitive reserve and responsiveness to right prefrontal tDCS

Lower levels of cognitive reserve were associated with greater tDCS-related improvements in processing speed to items in the left ($r = -.36$ $p < .05$) hemifield (Fig. 2.7). Similarly, a stronger rightward processing speed asymmetry was associated with greater tDCS-related improvements in processing speed for items in the left ($r = -.64$, $p < .0005$) hemifield (Fig. 2.6). Importantly, these associations were not observed for items in the right hemifield either for cognitive reserve ($r = .04$, $p = .83$) or processing asymmetries ($r = .11$, $p = .56$, Fig. 2.7 & Fig. 2.6).

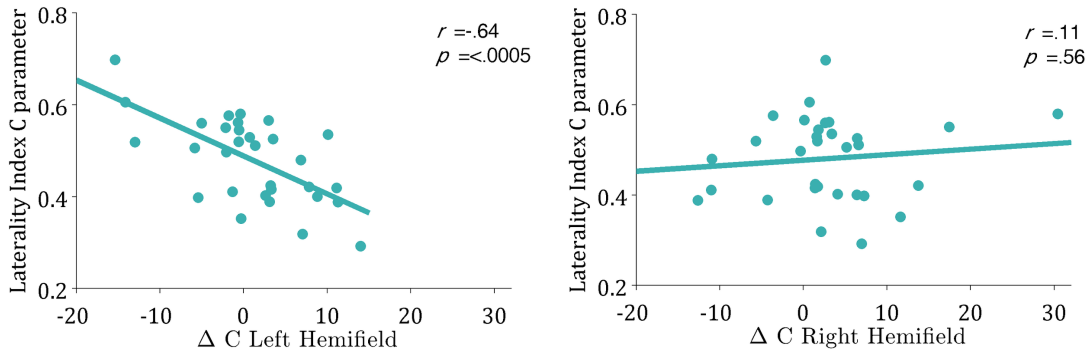


Figure 2.6: The relationship between baseline processing speed asymmetry and tDCS related improvements per hemifield. Δ=prefrontal-sham tDCS

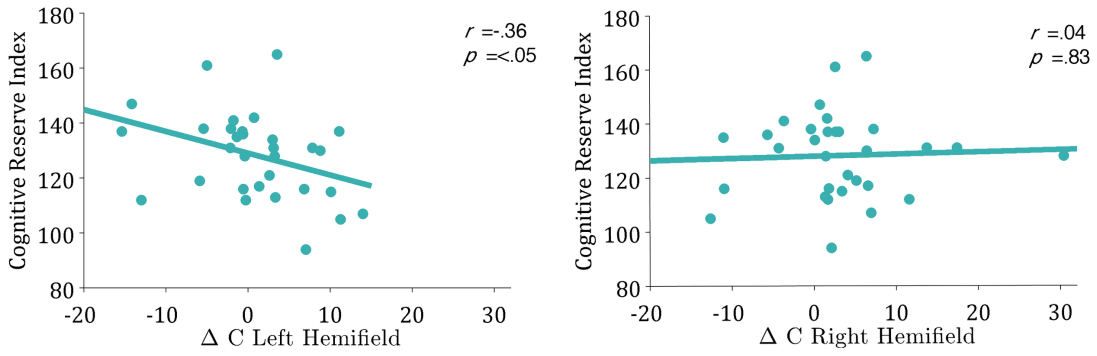


Figure 2.7: The relationship between cognitive reserve and tDCS related improvements per hemifield. Δ=prefrontal-sham tDCS

2.4 Discussion

This chapter provides evidence that high levels of cognitive reserve are associated with stronger involvement of the right hemisphere during the processing of visual information, as evidenced by a leftward processing speed asymmetry in these individuals. Correspondingly, when cortical activity in the right PFC was increased using tDCS, processing speed capacity improved. Older adults with lower levels of cognitive reserve showed tDCS-related benefits to items in the left but not right hemifield such that tDCS temporarily altered their processing speed asymmetry to mimic that of their high reserve peers.

A role of the right hemisphere in cognitive reserve

The current findings support the recently proposed hypothesis (Robertson, 2014) that the right hemisphere plays a particularly strong role in cognitive reserve in ageing. Firstly, older adults with higher levels of cognitive reserve showed a processing speed asymmetry towards the left side of space. Recent, unpublished data from the Centre for Visual Cognition, University of Copenhagen using a similar lateralised TVA whole-report task has shown that younger adults display significantly more asymmetries in their processing speed capacity to items in the right versus left hemifield (see supplementary Fig. 2.8, Appendix B).

The current data thereby suggests that, while elderly individuals with lower levels of cognitive reserve continue to show the same rightward asymmetry as younger adults, older adults with higher levels of cognitive reserve demonstrate functional reorganization involving the right hemisphere. This is in line with previous functional neuroimaging findings that mild cognitive impairment and Alzheimer's Disease patients with higher levels of cognitive reserve show reorganization of several brain areas, even within preserved cognitive domains that are unaffected by the disease (Bosch et al., 2010). Secondly, lower levels of cognitive reserve were associated with less awareness of day-to-day lapses in attentional control (relative to an informant report).

Previous work has demonstrated strong associations between awareness of cognitive functioning and the right prefrontal cortex in healthy ageing (Harty, Robertson, Miniussi, Sheehy, Devine, McCreery, & O'Connell, 2014a), Alzheimer's Disease (Harwood, 2005; Starkstein et al., 1995), and frontotemporal dementia (Mendez & Shapira, 2005) and there is strong evidence to suggest that error awareness is a core cognitive process related to cognitive reserve (Robertson, 2014). These findings therefore support the recent proposal that particularly the right hemisphere plays a prominent role in cognitive reserve (Robertson, 2014).

A causal role of the right prefrontal cortex in processing speed capacity in ageing

This chapter demonstrated that increasing excitability of the right prefrontal enhanced processing speed *C* in older adults. This improvement was location specific and not observed during stimulation of the right parietal cortex. This finding augments previous indirect evidence implicating a role of the right prefrontal cortex in the processing speed parameter of the TVA from several lines of previous research including: the assessment of patients with right prefrontal lesions (Habekost & Rostrup, 2006), neuroimaging work examining the hemispheric lateralization of white matter tracts connecting frontal and occipital lobes (Chechlacz et al., 2015), and experimental manipulations of alertness (Matthias et al., 2009).

With age, increased recruitment of the frontal cortices coupled with pervasive under-activation in more posterior sites in the occipital lobes during the processing of visual information is considered an adaptive compensatory mechanism of frontal regions in response to a reduced capacity for sensory processing (Davis et al., 2008). In line with this, recent work combining TVA-based assessment with EEG provided more direct evidence for the prefrontal cortex being particularly important for processing speed in older age. Specifically, older adults with higher processing speed levels showed a preserved amplitude of an early electrophysiological marker over frontal scalp regions (i.e., of similar magnitude as younger adults), whereas this marker was markedly reduced in those older individuals whose speed of information processing was considerably slower compared to younger individuals (Wiegand et al., 2014). The results

from the current chapter demonstrate that increasing the availability of the right prefrontal cortex with tDCS in older adults supports faster information uptake. This adaptive mechanism presumably helps to engage control processes governed by the right prefrontal cortex that contribute to the speed of visual information processing specifically in ageing (Cabeza, 2004; Davis et al., 2008).

Of note, while the contralateral organisation of the visual processing stream is established (Corbetta & Shulman, 2002; Ungerleider, 2000), there is also evidence for an involvement of the right PFC for processing stimuli both contra (left hemifield)- and ipsilaterally (right hemifield) (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999a; Sheremata et al., 2010; Shulman et al., 2010), in accordance with a right-hemispheric dominance for visual attention (Corbetta and Shulman, 2011). The current results support the bilateral influence of the right PFC for visual attention, as increasing activity in the right PFC by tDCS was associated with improvements in processing speed in both the left and the right hemifield.

Preserved plasticity of the right prefrontal cortex in ageing

Although preliminary evidence suggests it may be possible to increase cognitive reserve in later years (Lenehan et al., 2016), whether the right-lateralised fronto-parietal network postulated to underlie cognitive reserve (Robertson, 2014) can be strengthened in older adults is unclear. Here evidence is provided that the right PFC demonstrates preserved levels of plasticity in ageing. Firstly, increasing activity in this brain area in older adults improved visual processing speed, a fundamental cognitive process that is strongly correlated with age-related decline (Deary et al., 2010; Gregory et al., 2008; Ritchie et al., 2014). This finding is of relevance as the basic speed of perceptual processing constitutes a limiting factor on higher level cognitive abilities (Salthouse, 1996) and ameliorating deficits in early perceptual processing in ageing may show advantages that cascade throughout the cognitive hierarchy (see (Mishra et al., 2014)) and improve performance on day-to-day tasks (Ball et al., 2010; Rebok et al., 2014). Secondly, while the overall effect of processing speed enhancement by tDCS was not dependent on the

individuals' level of cognitive reserve, those older adults with lower levels of cognitive reserve showed tDCS-related speeding of information processing for visual items in the left and not right hemifield. Increasing activity in the right prefrontal cortex, therefore temporarily shifts the processing asymmetry leftward in older adults with lower levels of reserve, to resemble that of their high reserve peers. These results therefore provide support that plasticity of the right PFC may be harnessed in later life, and most importantly, that lower levels of cognitive reserve do not limit plasticity of the right prefrontal cortex. This supports the right PFC as a viable target brain region for mitigating processing speed deficits in ageing using neuromodulatory techniques such as fMRI neurofeedback (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015a; Habes et al., 2016), methods of non-invasive brain stimulation, or by combing neuromodulatory approaches with computerised speed training paradigms (e.g., (Rebok et al., 2014)) or pharmacological approaches (e.g., Newhouse, 2004). Moreover, these findings suggest the right PFC may, in fact, play a causal role in cultivating levels of cognitive reserve thus providing support for the first cognitive neuroscientific theory of cognitive reserve to have been proposed in the literature (Robertson, 2013; 2014).

Separate neural underpinnings for visual processing speed and storage capacity

A major strength of the TVA-based approach is that effects on distinct parameters of visual attention capacity, processing speed and storage capacity, can be independently assessed within one test. In the current sample, the association between visual attention and cognitive reserve was selective to the hemifield asymmetry in processing speed; neither the absolute individual limit nor hemifield asymmetries of visual storage capacity were associated with levels of cognitive reserve. Furthermore, tDCS targeting the right dorsolateral prefrontal cortex was associated with improved processing speed across both hemifields, while a concurrent reduction in storage capacity was observed during stimulation for items in the left hemifield. Our findings therefore are further evidence for a critical assumption of NTVA that at least partially distinct brain networks underlie the two TVA parameters of visual attention capacity (see (Habekost & STARRFELT, 2009), and that they are differently affected by aging (Wiegand et al., 2014).

Several studies utilizing behavioural or pharmacological approaches to target the efficiency of the visual attention system have successfully modulated processing speed *C* while storage capacity *K* remained unaffected by experimental manipulations (Bublak et al., 2011; Matthias et al., 2009; Vangkilde, Bundesen, & Coull, 2011), suggesting that processing speed may be a relatively more malleable capacity measure within individuals. Furthermore, although most studies report age-related declines in both processing speed and storage capacity (see Habekost, 2015 for a review) there is evidence to suggest that processing speed declines at a more dramatic rate with age (Habekost et al., 2013; Nielsen, 2015) and may be more richly associated with general cognitive decline. For example, in a cohort of patients with mild cognitive impairment and AD both storage capacity *K*, and processing speed *C* were related to standardised neuropsychological tests involving visual material, whereas only *C* was additionally correlated with measures of verbal memory (Bublak et al., 2011). The current results demonstrate another neural dissociation of the functions, specifically, that they are selectively sensitive to plasticity in the attention network induced by tDCS.

One possible explanation for the disruptive effect of tDCS on storage capacity in the left hemifield could be that neuronal activity in the contralateral frontal eye field regions, located posterior to the DLPFC and close to the cathodal electrode, was disrupted by the stimulation. Previous work has demonstrated topographic organisation within the frontal eye fields with a strong bias towards the contralateral hemifield during short-term memory tasks such as memory-guided saccades (Kastner et al., 2007) and face working-memory tasks (Hagler & Sereno, 2006). However, this can only be a speculation based on the present results. To shed further light on this, testing with a more focal and spatially specific neuromodulatory technique, such as TMS, would be needed.

Future Avenues

Of note, the asymmetries of visual attention capacity described in the present study assess overall levels of visual capacity are not akin to spatial bias measures that measure the relative

distribution of processing resources. The task paradigm employed in the current chapter requires participants to report visually presented letters, and has been shown to produce a rightward asymmetry in both processing speed and storage capacity in younger individuals (Kraft et al., 2015 and supplementary material, Appendix B), which likely reflects the left-hemisphere dominance for processing verbal stimuli (Gross, 1972).

In contrast, spatial bias measures assess the relative allocation of attentional weights across both hemifields. Parameter estimates of spatial bias have been shown to mark slight leftward bias (pseudo-neglect, Bowers and Heilman 1980; Dronkers et al., 2007) in healthy younger adults (Bowers & Heilman, 1980; Nicholls, Bradshaw, & Mattingley, 1999; D. Voyer, Voyer, & Tramonte, 2012), and account for visual neglect following right hemisphere damage (Finke et al., 2012), likely resulting from the right hemisphere dominance underpinning spatial attention processes (Corbetta and Shulman, 2011). Interestingly, changes in spatial bias (w_{index} in the TVA framework) have been shown to occur in early as well as severe stages of Alzheimer's Disease (AD; Redel et al., 2012; Sorg et al., 2012), independent of asymmetries in processing speed resources. In light of the present findings, it would be an interesting question for future studies to further explore and distinguish the relationship between spatial bias and asymmetries in processing speed capacity with regard to cognitive reserve and the development of AD.

Empirical Chapter 3: The Temporal Dynamics of Attentional Engagement following RH Stroke.

3.1 Introduction

The work presented in Empirical Chapters 1 and 2 extends previous reports that the right hemisphere in a particularly important contributor to attentional function (Corbetta & Shulman, 2002; Posner & Petersen, 1990; Robertson, 2014) by showing how increasing activity in this network via stimulation of the PFC improves facets of attention in older adults. Although it is well documented that the right hemisphere (RH) plays a privileged role in supporting sustained attention (cf (Langner & Eickhoff, 2013a; Robertson, 2014), the temporal dynamics of this relationship, i.e. how the right hemisphere contributes to the maintenance of attention over time, are less well understood. The current chapter addresses how the capacity to maintain attentional engagement over short time-scales is affected by damage to the right hemisphere.

Aspects of attentional function, particularly the capacity to sustain attention are predictive of rehabilitation outcomes following stroke (Bennett et al., 2002; Blanc-garin, 1994; Robertson, Ridgeway, Greenfield, & Parr, 1997c; van Zandvoort, Kessels, Nys, de Haan, & Kappelle, 2005). In a recent study, we assessed domain-general cognitive deficits in a large sample of sub-acute stroke patients (*N*=682) and observed that 36% of the patients presented with deficits in sustaining attention over time (King, Brosnan, Humphreys, & Demeyere, Appendix A). In a sub-sample of 230 patients, who were re-assessed at 9-months post-stroke, impaired sustained attention at the sub-acute stage significantly predicted functional status at follow up, even when accounting for stroke severity and age. Importantly, this prognostic prediction was specific to the performance decrement in sustained attention over the course of the task, and was not observed

for overall levels of accuracy on the task, or for working memory. These findings thus point to the relevance of taking the temporal dynamics of sustained attention deficits into account post-stroke.

An intact sustained attention system impacts post-stroke cognitive recovery in at least two ways. Firstly, lapses in sustained attention compromise the ability to engage with the task at hand (Smilek et al., 2010), (Whirley et al., 2016). Therefore, sustained attention deficits in stroke patients limit the extent to which they can engage with, and accordingly benefit from rehabilitation programmes. Secondly, the deployment of attention is known to be critical for gating plasticity processes (Polley et al., 2006; Recanzone et al., 1993) which underlie cortical remapping and functional reorganisation of the brain that are characteristic of good post-stroke recovery (Di Lazzaro et al., 2010; Fu & Zuo, 2011; Hallett, 2001). Thus, sustained attention deficits may also hinder the extent to which functional restoration can occur at the neural level.

Several studies in neurologically healthy participants have suggested that the sustained attention network is supported by a predominantly right-lateralised neural network (Johannsen et al., 1997; Langner & Eickhoff, 2013a; Singh-Curry & Husain, 2009; Warm et al., 1980; Whitehead, 1991). Consistent with this, pronounced sustained attention deficits have been reported in patients with damage to the RH (Malhotra et al., 2009; Robertson, Ridgeway, Greenfield, & Parr, 1997c; Rueckert & Grafman, 1996; 1998; Wilkins, Shallice, & McCarthy, 1987). Despite this, little is known about how the precise temporal dynamics of sustained attention are affected following insult to the RH (Malhotra et al., 2009; Rueckert & Grafman, 1996; 1998). It has been shown that when RH stroke patients are asked to respond to just one target stimulus (e.g., letter X), presented at irregular intervals over periods of 8-10 minutes, a performance decrement is not observed (Malhotra et al., 2009; Rueckert & Grafman, 1996; 1998). However, when such a target is interspersed between non-targets, such as other letters in the classic continuous performance test (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), a decrement in performance accuracy is observed (Rueckert & Grafman, 1996; 1998). One

limitation of these traditional Continuous Performance Tasks is that the distinct perceptual features of the target and non-target stimuli may exogenously engage attention such that successful performance on the task is not uniquely contingent on endogenous deployment of attentional control, thus this task may fail to identify decrements in attentional engagement occurring over shorter time scales. In the current study, this limitation is circumvented by employing a paradigm (Continuous Temporal Expectancy Task, CTET (O'Connell, Dockree, Robertson, et al., 2009b) in which targets and non-targets differ only in temporal duration and are otherwise perceptually homogeneous. This eliminates the attentional capture due to target onset and participants are required to deploy attention to the time domain. In the CTET, participants monitor a continuous stream of patterned stimuli that are presented centrally and make a button press when they detect a longer-duration stimulus. The CTET is sensitive to within block performance decrements (over approximately 3 minute windows) in neurologically healthy individuals and using electroencephalography signatures of attentional engagement lapses of attention have been shown to evolve over a period of 20 seconds (O'Connell, Dockree, Robertson, et al., 2009b)

In the current study, aspects of sustained attention that are susceptible to damage after RH stroke are investigated. By using a task in which target detection is not influenced by exogenous perceptual features, a more precise measure of the endogenous processes hypothesized to underpin deficits of sustained attention following RH stroke is expected.

3.2 Methods

Participants

Fourteen chronic stroke patients with unilateral damage to the RH were recruited through the Cognitive Neuropsychology Centre, Department of Experimental Psychology, Oxford University. All patients were >1 year post stroke (M=2.15, SD=1.07; *note* this data was not available for one self-referred patient). Twenty three healthy older adults were recruited as control subjects at Trinity College Institute of Neuroscience, The University of Dublin, Trinity

College, as part of the sham stimulation condition for the non-invasive brain stimulation study (Empirical Chapter 1, Experiment 2).

Demographics

All participants provided their age, gender, level of education, and were assessed using the Cognitive Reserve Index Questionnaire, CRIq (Nucci et al., 2012), as described in Empirical Chapter 2 (see Table 3.1).. The CRIq was not collected for 2 of the healthy older adults, and for 3 of the stroke patients, due to time-constraints. Differences in demographical factors between healthy older adults and the stroke patients were assessed using one way between subject ANOVAs with 'Group' as the between subject factor. The stroke patients and healthy older adults did not differ in age ($F_{1,36}$=.81; p=.37). Binomial tests conducted separately for the healthy older controls and the stroke patients indicated that the proportion of male to female participants did not differ significantly from the expected .50 (p>.4 for both groups). The RH stroke patients had spent fewer years in formal education ($F_{1,31}$=4.93, p=.03, η_p^2=.12). The stroke patients had significantly lower cognitive reserve scores, as measured via the CRIq total score ($F_{1,31}$=11.12, p=.002, η_p^2=.27). Follow-up analyses on the three sub-sections of the CRIq (Education, Working Activity, and Leisure), revealed that the stroke patients showed lower cognitive reserve in relation to education ($F_{1,31}$=9.74, p=.004) and leisure ($F_{1,31}$=8.59, p=.006), but not working activity ($F_{1,31}$=1.3, p=.26).

Table 3.1: Demographic information for the healthy older adults and RH stroke patients

	Controls (N=23)	Patients (N=14)
Age (yrs)	72.70 (5.93) 60-82	70.71 (7.32) 58-84
Gender	11 male (47.83%)	9 male (64.29%)

*Education (yrs)	15.91 (3.66)	13.23 (3.54)
	10-25	8-21
*CRIq	136.52 (20.70)	113.18 (14.29)
	95-169	88-145

Note Years in education was not available for one stroke participant, CRIq was not available for 5 participants (*N*=2 healthy, *N*=3 stroke patients). * indicates a significant difference between patients and controls

Lesions

Lesions were manually delineated by a highly trained research technician from the best available scan from either chronic MRI (N= 6), or clinical acute CT (N=6), depending on availability. For two patients, lesions were not yet visible on the Acute CT scan (which is taken upon admission and infarctions do not show up until 6-8 hours post stroke onset) but in both cases the medical presentation and diagnosis indicated RH stroke. An overlay for the 12 patients' lesions is given in Fig 3.1.

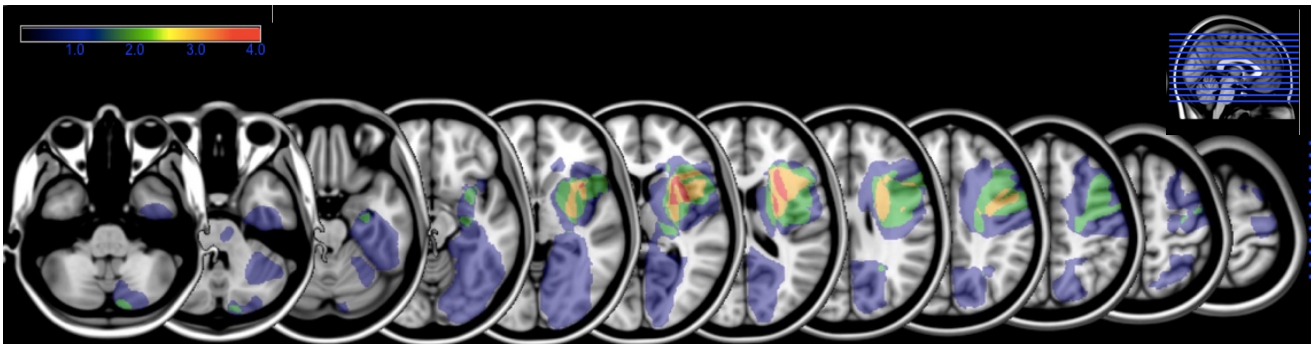


Figure 3.1: Lesion overlay for the right hemisphere stroke patients. Conjunction maps were created from each patients' delineated lesion mask (*N*=12) registered to a template space (MNI152 T1 1mm). Intensity values represent the number of subjects with overlapping lesion affected anatomy.

Task Battery

The Continuous Temporal Expectancy Task (CTET)

The Continuous Temporal Expectancy Task (O'Connell, Dockree, Robertson, et al. 2009) employed in Experiment 2, Empirical Chapter 1 (Fig. 1.2A) was adapted for some of the stroke patients such that all participants demonstrated 100% accuracy during an initial practice trial before advancing to the experimental blocks. As mentioned in Experiment 2, Empirical Chapter 1, the healthy older adults, all participants identified the target stimuli at 100% accuracy during the practice trials at the target duration of 1020 ms, i.e., 330 ms /47.83% longer than standard trials. For the stroke patients, *N*=7 identified the target stimulus at a duration of 1020 ms at 100% accuracy. For the other 7 patients, the duration of the target stimulus was adapted as follows such that all participants demonstrated 100% accuracy on two consecutive practice trials: If the patient did not achieve 100% accuracy during the first three practice trials, the duration of the target stimulus was increased to 1140ms. Participants were then given two practice trials with this target duration. If 100% accuracy was achieved during these trials, then this target duration was set for the rest of the experiment. If the patient did not exhibit 100% accuracy at this duration, the target duration was subsequently increased again to 1500ms, and following this to 1800ms. In order to ensure the stroke patients fully understood the task requirements all patients were required to complete two consecutive practice trials at 100% accuracy before proceeding to the experimental trials. For the experimental trials, the target durations for the stroke patients were either 1020ms (*N*=7), 1140ms (*N*=2), 1500ms (*N*=4), or 1800ms (*N*=1). This ensured that baseline performance was matched for all participants such that differences investigated during the experiment could be attributed to attention. Participants completed 5 blocks of the task and were given a break (~ 1 minute) in between all blocks. Each block consisted of 225 stimulus rotations with a total duration of between 3 min and 5 s and 3 min and 30 s.

Sustained attention changes were assessed via accuracy (% correctly identified targets) on the CTET. A target was considered correctly identified if a participant responded within 2.07 seconds (i.e. three standard trials) of a target trial. One stroke patient presented with working memory problems, identified by a previous study in the centre using the Oxford Cognitive Screen

(Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015) . In an effort to exclude the possibility that these deficits were contributing to performance on the task, this patient was required to recall the task instructions at the end of each block. Outliers were described as in Empirical Chapter 1, Experiment 1.

Given that the purpose of the current study was to assess the temporal evolution of the vigilance decrement following RH stroke, accuracy decrements were assessed both across blocks and across four epochs within each block. Differences in accuracy between the stroke patients and healthy elderly were evaluated using a repeated measures mixed ANOVA with 'Vigilance Decrement Across Blocks' (five blocks) and 'Vigilance Decrement Within Blocks' (within four quartiles of each block) as within subject factors. 'Group' (RH stroke, healthy ageing) was included as a between subject factor. In order to assess the effect of task break on performance, the average of the 4th quartile computed across blocks 1, 2, 3, and 4 was compared against the average of the 1st quartile across blocks 2, 3, 4, and 5 using a repeated measures ANOVA with group as a between-subjects factor.

In order to rule out the possibility that the extent of damage or the differences in formal education between the two groups could be associated with any observed effects, all significant ANOVAs were repeated with lesion size (total number of voxels affected) and years in formal education included as covariates. Note two stroke patients were excluded for these ANCOVAs because their lesion size could not be determined (see above).

3.3 Results

Overall Target Detection (Accuracy)

The rate of false alarms was low on the CTET (*M*=3.85, *SD*=2.36, range = 0-9.4%) indicating that all participants were performing well above chance level and had correctly understood the instructions. In line with previous reports, a main effect of Group ($F_{1,33}$=19.20,

p<.0005, η_p^2=.37, see Fig. 3.2) indicated that the RH stroke patients were significantly less accurate at identifying target stimuli, compared with the healthy older controls.

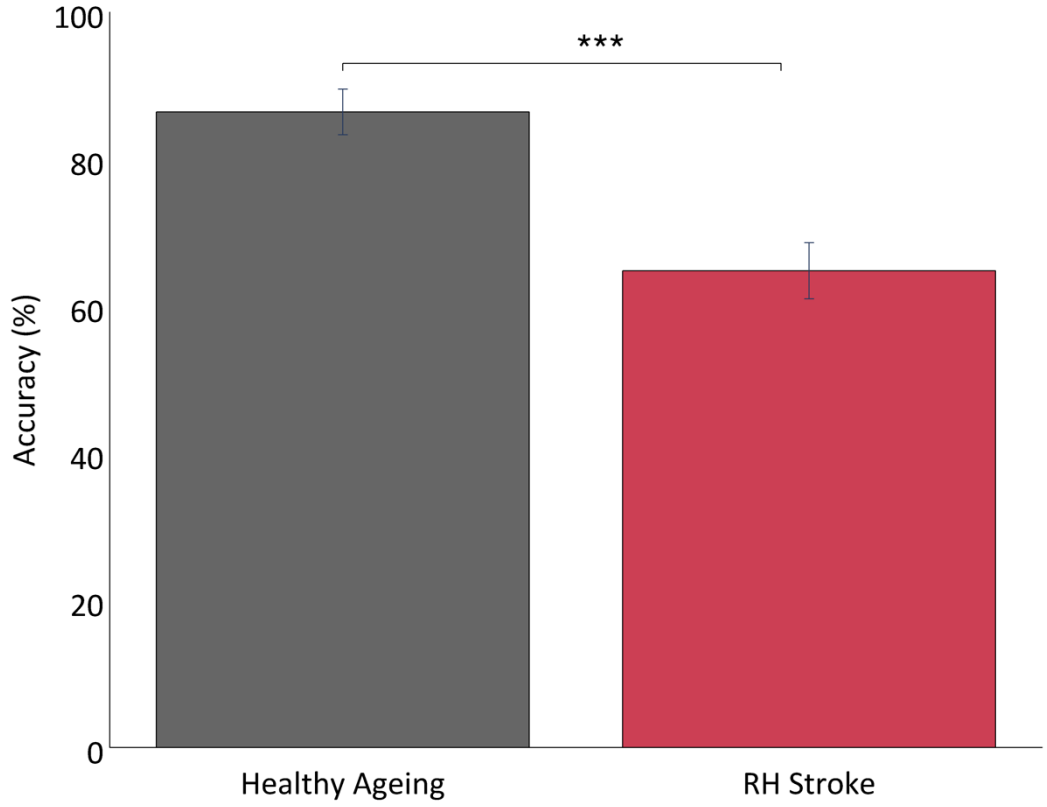


Figure 3.2: Overall accuracy levels for stroke patients and neurological healthy older adults. Stroke patients with unilateral RH damage show less accuracy on the CTET as compared with healthy older adults. *Note* *** denotes p<.0005

Time on Task Decrements: Within Block Effects

A main effect of Quartile ($F_{3,99}$=14.87, p<.0005, η_p^2=.31) demonstrated that regardless of group, accuracy on the task decreased within each block (see Fig. 3.3), as confirmed by the significant linear contrast ($F_{1,33}$=32.84, p<.0005, η_p^2= .5). Critically, this was qualified by a Group X Quartile interaction ($F_{3,99}$=3.62, p=.016). Follow up one-way ANOVAs conducted separately for the neurologically healthy older group and the RH stroke patients. For the healthy group the effect of Quartile was significant ($F_{3,60}$=3.16, p=.03) but planned difference contrasts revealed no significant differences between quartiles (all p>.05). For the RH stroke patients, there was a

highly significant main effect of Quartile ($F_{3,39}$=11.19, p<.0005, η_p^2=.46). In contrast to the healthy older controls, a significant drop in performance was noted between Quartile 2 and 1 ($F_{1,13}$=5.81, p=.03), Quartile 3 and the previous two quartiles ($F_{1,13}$=12.293, p<.004), and Quartile 4 and the previous three quartiles ($F_{1,13}$=16.29, p=.001)). Thus the significant Group X Quartile interaction was driven by a stronger within-block decrement in the stroke patients.

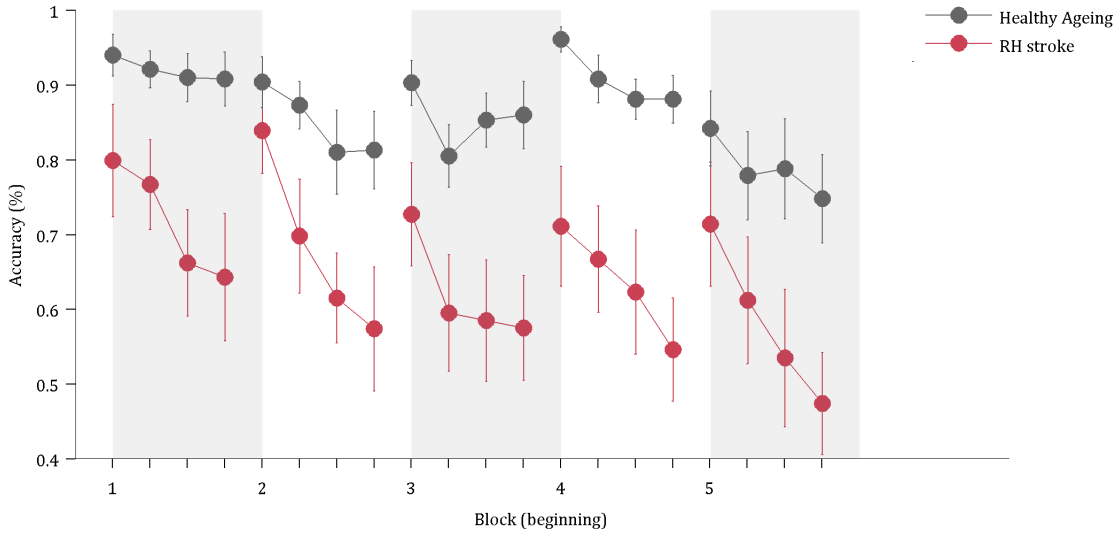


Figure 3.3: Performance decrements over time on the CTET.

RH stroke patients showed a significantly steeper performance decrement within the duration of the task blocks, relative to neurologically healthy older adults.

A main effect of Break was observed ($F_{1,57}$=20.78, p<.0005, η_p^2=.27), which crucially was qualified with a significant Break x Group interaction effect ($F_{1,57}$=9.02, p=.004, η_p^2=.14). For the healthy older adults, the main effect of Break was not significant ($F_{1,20}$=1.59, p=.22), demonstrating no difference in performance between the fourth (M=86.57%, SD=13.12) and first (M=90.26%, SD=8.32) quartiles. In contrast, for the RH stroke patients, accuracy during the fourth quartile (M=58.45%, SD=23.78) was significantly lower than during the first quartile

(*M*=74.79, *SD*=21.23; $F_{1,13}$=24.9, p<.0005, η_p^2=.66), thus demonstrating the capacity for the stroke patients to revive their performance decrement during the rest period between blocks.

Time on Task Decrements: Across Block Effects

There was a main effect of Block reflecting a decline in accuracy over time ($F_{4,92}$=5.76, p=.002, η_p^2=.15). Planned comparisons revealed that accuracy performance during Block 2 was lower than during Block 1 ($F_{1,33}$=4.37, p=.04), performance during Block 3 was lower than Block 1 ($F_{1,33}$=7.26, p=.01), performance during Block 4 was not significantly lower than Block 1 ($F_{1,33}$=3.54, p=.07) and performance during Block 5 was significantly lower than Block 1 ($F_{1,33}$=11.97, p=.002). There was no Group x Block interaction ($F_{4,92}$=.9, p=.44), or any other interaction terms (both p>.63). Thus, despite RH stroke patients showing a significantly greater vigilance decrement within each block compared to neurologically intact older adults, the decrements exhibited at the coarser time scale (i.e. across blocks) did not differ between the groups.

When years of education and lesion size were controlled for, the main effects of Quartile ($F_{3,87}$=.09, p=.97, η_p^2=.003), Break ($F_{1,48}$=.001, p=.98, η_p^2=.00, and Block ($F_{4,116}$=.87, p=.49, η_p^2=.03) were no longer significant. Crucially, however the main effect of Group ($F_{1,29}$=14.84, p=.001, η_p^2=.34), Group x Break ($F_{1,48}$=6.3, p=.02, η_p^2=.12). and Group x Quartile interaction ($F_{3,87}$=3.97, p=.01, η_p^2=.12) remained significant.

3.4 Discussion

The current chapter provides novel evidence that deficits in maintaining attention following damage to the RH are within much shorter time periods than previously noted in the literature. Despite the stroke patients demonstrating steep within-block performance declines, they also exhibited the capacity to temporarily revive their sustained attention following the brief within-block rest periods. This observation is supported by significantly higher performance

during the first quartiles of blocks 2,3,4, and 5 as compared with the last quartiles of blocks 1,2,3 and 4.

In line with previous research, RH damage was associated with an overall deficit in accuracy relative to age-matched controls (Robertson, Ridgeway, Greenfield, & Parr, 1997c; Rueckert & Grafman, 1996; 1998). RH stroke patients did not differ from the neurologically healthy controls in their performance decrement over the course of the five task blocks. In contrast, differences in performance between the RH stroke patients and healthy older adults were driven by sharp drops in attentional engagement occurring within a shorter time window (a linear decline in performance within ~ 3 ½ minutes). The sharp within block performance decrement observed in the current study is much shorter than has previously been reported in the literature (Rueckert & Grafman, 1996; 1998), suggesting that the CTET (O'Connell, Dockree, Robertson, et al., 2009b) is a sensitive tool to detect vigilance decrements in sustained attention occurring within a very short temporal window.

There are several aspects of the task that make it appealing for assessing attentional deficits, particularly in patient populations: Firstly, the task is not perceptually demanding – the target stimulus is adapted such that 100% accuracy is exhibited during the practice trials preceding the experimental blocks, thus the task is not confounded by an overall deficit at detecting targets. Secondly, unlike many sustained attention tasks, accuracy on the CTET does not depend on the identification of a visual 'target' stimulus (Malhotra et al., 2009; Manly et al., 2003; Rueckert & Grafman, 1996; 1998). This is potentially very advantageous in facilitating a vigilance decrement as visual-search processes, such as stimulus-driven attentional capture, which may help with the identification of target stimuli are eliminated on the CTET, thus placing greater demands on the sustained attention system.

In the current study, the within-block performance decrement observed in the RH stroke patients did not get worse with time (i.e., there was no interaction between this effect and the overall performance decrement over the course of the experiment). This suggests that the

sustained attention system of RH stroke patients can be revived within intervals as short as the between block breaks of approximately one minute. This is in line with literature suggesting the sustained attention system can be manipulated by increasing levels of alertness through the volitional control over biophysiological markers of arousal (O'Connell, Bellgrove, Dockree, & Lau, 2008a; Robertson et al., 1995), or by presenting salient sensory stimuli which act as external alerting cues (Robertson et al., 1998).

One likely explanation for these sharp decreases in arousal following RH damage is dysfunction of the noradrenergic system. Noradrenaline (norepinephrine), a neurotransmitter emanating from the Locus Coeruleus with widespread projections throughout the cortex plays a well established role in maintaining arousal (for a recent review see Sara, 2009). Pharmacological upregulation of noradrenaline is associated with increased BOLD activation, exclusively within the RH (Grefkes, Wang, Eickhoff, & Fink, 2010b), and preliminary evidence suggests noradrenergic agonists may be utilised to improve sustained attention deficits associated with damage to the RH (Malhotra et al., 2006; Singh-Curry et al., 2011). Future work should directly explore whether noradrenergic dysfunction underlies the pronounced decrements in sustained attention observed in the current study, and whether pharmacological manipulation of the system may ameliorate these performance decrements.

Although specific functional impairments resulting from a stroke have often been considered in the context of modular damage (e.g., (Broca, 1865), there is a growing consensus that is not only damage to specific regions but rather disruptions to inter-connected neural networks which are associated with functional impairments (e.g., (Forkel et al., 2014), cf (Baldassarre, Ramsey, Siegel, Shulman, & Corbetta, 2016; Corbetta & Shulman, 2011). With regards to the sustained attention system, recent multivariate analyses of fMRI data have identified a widespread network of cortical, sub-cortical and cerebellar regions underlying the capacity to maintain attentional engagement (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015b; Rosenberg et al., 2016). Rosenberg and colleagues recently showed that only

27% of an MVPA-derived network which successfully predicted the 'high' attention state both in healthy younger adults, and children and adults with attentional deficits (ADHD symptoms) included prefrontal and parietal nodes. These findings do not discount the fronto-parietal networks contributions to maintaining sustained attention (Rueckert & Grafman, 1996; 1998; Wilkins et al., 1987) but rather demonstrate the role of these regions within a widespread network. The heterogeneity of the lesions in the current cohort support these findings and suggest damage to widespread cortical regions within the right-lateralised noradrenergic-network results in deficits maintaining arousal over time (Corbetta & Shulman, 2011). The current findings hold important practical information for informing inform cognitive assessment and rehabilitation strategies for individuals who have experienced RH stroke

Empirical Chapter 4: Right Prefrontal tDCS Disrupts Sustained Attention Performance in Chronic Right Hemisphere Stroke Patients with Persisting Sustained Attention Deficits: A Pilot Study

4.1 Introduction

The prevalence of sustained attention deficits during the subacute stages of stroke (<3 months) has been estimated at 36% (King, Brosnan, Humphreys, & Demeyere, in prep; Appendix A). These impairments are particularly evident following unilateral damage to the right hemisphere (Malhotra et al., 2009; Rueckert & Grafman, 1996; 1998; Wilkins et al., 1987) and, as demonstrated in Empirical Chapter 3, are driven by decrements in attentional engagement over very short time periods. Impaired capacity for attentional engagement during the first few months following stroke is predictive of future motor and functional recovery (Robertson, Ridgeway, Greenfield, & Parr, 1997c); King, Brosnan ,Humphreys, & Demeyere, Appendix A), likely due to both a reduced ability for patients to maintain attentional engagement during rehabilitation along with impaired attention-gated plasticity processes which are necessary to promote functional reorganization post-stroke (Polley et al., 2006; Recanzone et al., 1993). Despite this, interventions to ameliorate sustained attention deficits post-stroke have remained relatively unexplored.

Following stroke, changes in brain activity can be coarsely categorised into two patterns; restoration of the original networks (for example, through functional remapping in adjacent perilesional tissue) and reorganization (via the recruitment of alternative compensatory networks).

Although still a contentious issue, considerable evidence from the last two decades suggests that optimal recovery post-stroke is associated with restoration of original functional pathways (Baldassarre et al., 2016; Fu & Zuo, 2011; Ramsey et al., 2016; Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012; Ward, Brown, Thompson, & Frackowiak, 2003), which may present the best trade-off between metabolic costs and network efficiency (Bullmore & Sporns, 2012). The restoration of functional networks supporting post-stroke recovery depends largely on processes of plasticity (Fu & Zuo, 2011), therefore techniques that can promote brain plasticity hold promise for rehabilitation.

tDCS has been shown to increase cortical excitability (Nitsche & Paulus, 2000) and reduce local inhibition (Stagg et al., 2009). Following stroke, ipsilesional anodal tDCS produces significant improvements in behaviour that are associated with increased activity within the damaged region and functionally connected networks (Meinzer, Lindenberg, Antonenko, Flaisch, & Floel, 2013; Stagg, Bachtiar, O'Shea, Allman, & Bosnell, 2012). Consequently, recent evidence suggests that anodal tDCS over the damaged hemisphere over multiple sessions enhances the stroke recovery process through modulation of the underlying neural networks, for example by restoring dysfunctional interhemispheric connectivity (Marangolo et al., 2016), and increasing cortical grey matter in the ipsilesional cortex (Allman et al., 2016), particularly when combined with rehabilitation protocols such as physiotherapy and language training (Allman et al., 2016; Marangolo et al., 2016).

To our knowledge, tDCS has never been employed to potentiate sustained attention recovery post stroke. The prefrontal cortices play a prominent role in maintaining attentional engagement (Sturm & Willmes, 2001a). Previous pharmacological interventions have pointed to the potential for guanfacine, a noradrenergic agonist that modulates cognitive function, most likely via receptors in the prefrontal cortex (Avery, 2000; Jäkälä et al., 1999) to ameliorate sustained attention deficits in selected stroke patients with right hemisphere damage (Malhotra et al., 2006; Singh-Curry et al., 2011), thus suggesting the prefrontal regions as a viable target for

rehabilitation of sustained attention post-stroke. It has been shown in three separate cohorts of neurologically healthy older adults (Empirical Chapter 1, Empirical Chapter 2) that tDCS can be employed to increase excitability of the right prefrontal cortex and enhance aspects of top-down attentional control and improve attention. This gives rise to the tantalising possibility for tDCS over right PFC to ameliorate sustained attention deficits that occur following stroke.

In this chapter, the same tDCS protocol that was associated with enhanced sustained attention performance in neurologically healthy adults was employed to assess whether sustained attention deficits could be improved in a small sample of right hemisphere stroke patients. It was hypothesized that increasing excitability in the right PFC would activate perilesional and residual areas of the damaged hemisphere to improve sustained attention performance.

4.2 Material and Methods

Study Outline

Stroke patients (*N*=6) who had experienced unilateral damage to the RH, at least one year before testing, were recruited to test the effects of tDCS over the right PFC on sustained attention performance. The experimental set-up was identical to that employed in Empirical Chapter 1, Experiment 2 except for the following alterations: Firstly, the target stimulus was adapted such that detection was 100% during the practice trials (see procedure described in Empirical Chapter 3). Secondly, in order to minimize Time of Day effects which can be more pronounced following stroke the patients were always tested at the same time of the day. Third, the stroke patients were recruited and tested in the Cognitive Neuropsychology Centre (CNC), at the University of Oxford, whereas the neurologically healthy participants in Empirical Chapter 2, Experiment 2) were recruited and tested at Trinity College Institute of Neuroscience, The University of Dublin, Trinity College. Finally, except for one patient (patient 1) whose data was collected as an initial pilot participant, the tDCS administration was double blinded for the stroke patients: a research assistant at the CNC, who was not presented for testing or otherwise involved in the study, selected the real/sham conditions as outlined from a randomization

procedure which was carried out by a member of the research team (ND) who was also not involved in the testing.

Participants

All stroke patients with unilateral RH damage who participated in Empirical Chapter 3 that had no personal or family history of seizures, and no pacemakers or brain stents, were invited to partake in this tDCS study (see Table 4.1 for overview of participants' demographics and clinical characteristics). In order to assay sustained attention capacity all participants were administered the fixed version of the Sustained Attention to Response Task ($SART_{fixed}$; Robertson, Manly, et al. 1997; O'Halloran et al. 2013; Fig. 1.1.A), as described in Chapter 1, Experiment 1. A participants' performance on the task was classified with reference to normative data as measured by commission errors (from unpublished observations on 5470 older adults who participated in The Irish Longitudinal Study of Aging, TILDA), according to their age, gender, and level of education. 'Please note, this normative data from TILDA was available as quantiles (more specifically into the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentiles), and as a result sustained attention capacity in Experiment 1 was classified based on these quantiles.'

Demographic Information

The stroke patients and healthy older adults (N=23) did not differ in the number of formal years in education ($F_{1,28}$=2.42, p=.13; stroke M = 13.17, SD=4.63; healthy older M=15.91, SD=3.65). Stroke patients were slightly younger than the healthy older adults, as evidenced by a marginally significant main effect of group ($F_{1,28}$=4.16, p=.051, stroke M=67.17, SD=5.85; healthy older M=72.70, SD=5.93). The stroke patients had lower levels of cognitive reserve ($F_{1,26}$=5.32, p=.03, as measured via the Cognitive Reserve Index questionnaire (Nucci et al., 2012) stroke M=114.83, SD=18.69; healthy older M=136.52, SD = 20.70). Binomial tests conducted separately for the healthy older controls and the stroke patients indicated that the

proportion of male to female participants did not differ significantly from the expected .50 (p>.68 for both groups). The right hemisphere lesions can be visualised in Fig. 4.1 and Fig. 4.2.

Table 4.1: Demographic and Cognitive Characteristics of the RH stroke patients.

Patient	Age (yrs)	Gender	Education (yrs)	CRIq	Sustained Attention %ile	Time Since Stroke (years)
1	69	M	10	110	50	2
2	62	M	15	123	25	missing
3	73	M	21	145	50	2
4	70	F	11	113	50	3
5	58	M	14	110	50	5
6	71	F	8	88	90	3

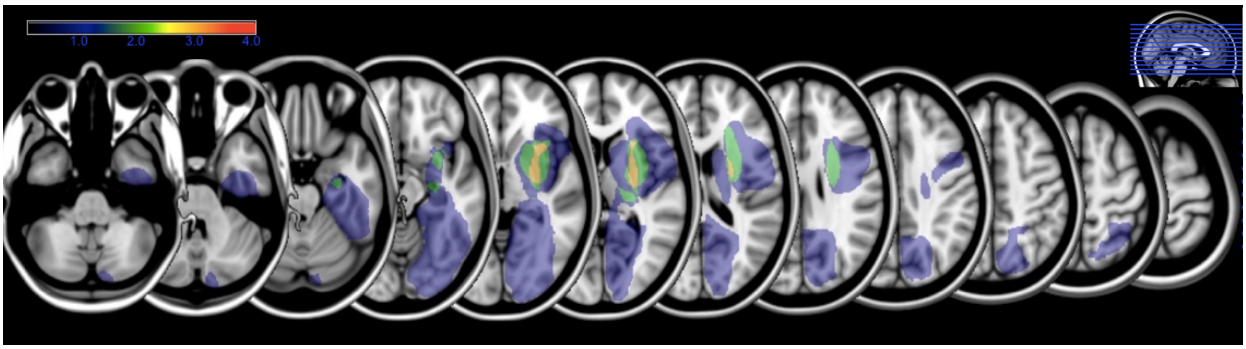


Figure 4.1: Lesion overlay for stroke patients. Conjunction maps were created from each patients' delineated lesion mask (N=5) registered to a template space (MNI152 T1 1mm). Intensity values represent the number of subjects with overlapping lesion affected anatomy.

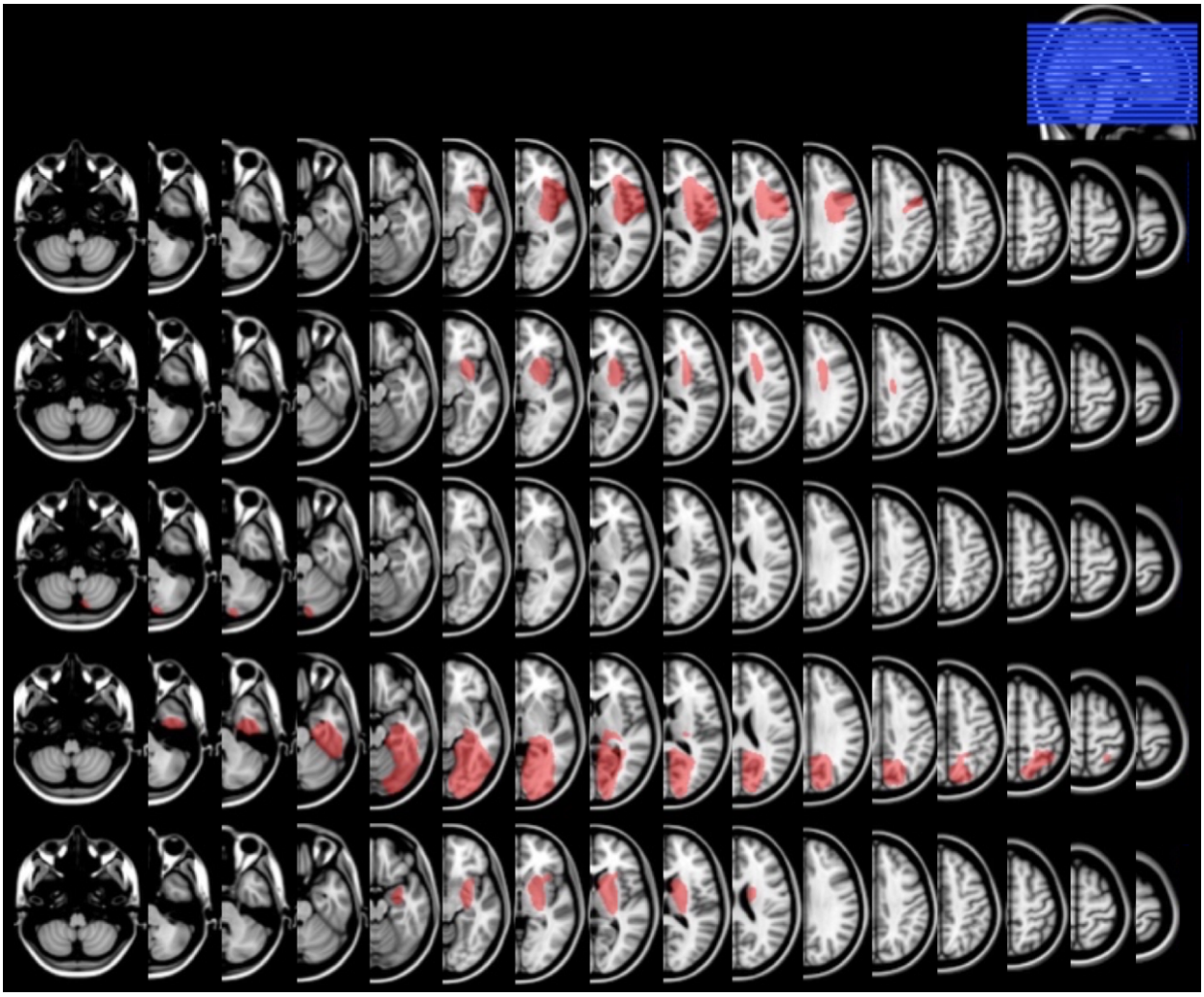


Figure 4.2: Individual lesion masks for the stroke patients. *Note.* lines represent patients 1, 2, 3, 4, and 6. No scan was available for patient 5.

The Continuous Temporal Expectancy Task

As in Empirical Chapter 1, Experiment 2, sustained attention changes occurring during tDCS were assessed via accuracy (% correctly identified targets) on the CTET. As an additional sustained attention measure, sensitivity to targets was also explored using D-Prime, a signal-detection measure (Macmillan & Creelman, 2004). Given the small number of patients, stimulation-induced changes in within-block and across-block accuracy were not explored, and parametric inferential statistics were not implemented for the patient group. In order to assess whether damage to the right hemisphere was associated with a differential response to stimulation as compared with neurologically healthy older adults, the healthy older adults sample

from Empirical Chapter 1, Experiment 2 was employed as a control group. The effect of stimulation on accuracy and D-Prime for the healthy older adults was assessed using a one way within subject ANOVA with 'Stimulation' as a factor. Outliers were defined on a per-block basis, as described in Chapter 1. Changes in performance during stimulation for the 6 patients included in this pilot study were described and visualised. All figures were designed using customized scripts in MATLAB R2014a 8.3.0.532 (Mathworks, Natick, MA, USA). In all figures, the error bars indicate the standard error of the mean (s.e.m).

4.3 Results

Behavioural Performance changes during tDCS

Accuracy

As noted in Empirical Chapter 2, Experiment 1, there was a main effect of Stimulation ($F_{1,20}$=4.67., p=.043., η_p^2=.19) for the older adults, demonstrating that accuracy was significantly higher during active (M=91.4 %, SD=7.36), compared with sham stimulation (M = 86.45%, SD= 10.43). For the stroke patients, five out of the six patients were descriptively worse during real relative to sham stimulation (Fig. 4.3).

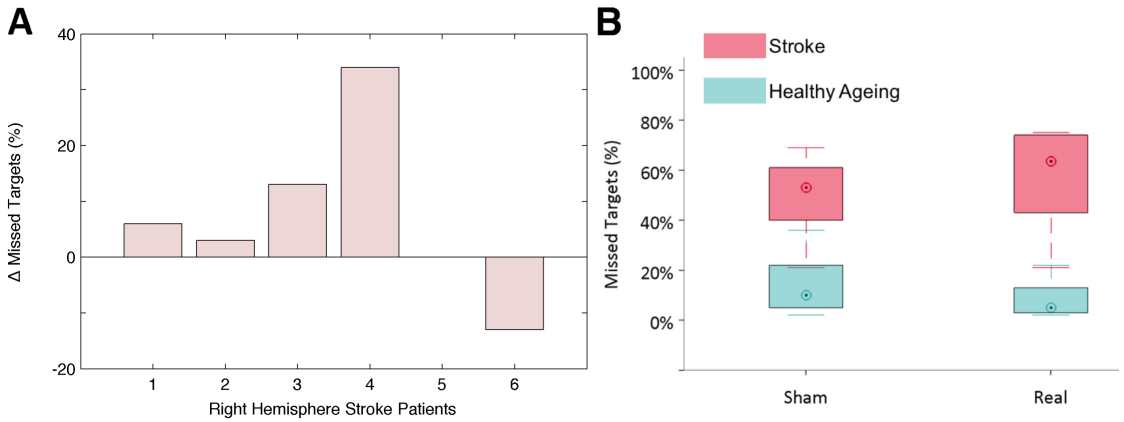


Figure 4.3: The effects of tDCS on accuracy during performance of the CTET. A. The tDCS-induced change in accuracy for each of the individual patients with damage to the RH. *Note.* Δ denotes change in performance (real-sham). **B.** The effects of tDCS on Accuracy visualized for the healthy older adults (improved performance) and right

hemisphere stroke patients (impaired performance). *Note* There was no change in accuracy for patient 5.

D-prime

For the neurologically healthy older adults, sensitivity to targets was increased during real (M=3.7, SD = .43) relative to sham stimulation (M=3.3, SD=.44; $F_{1,20}$=8.8, p=.008, η_p^2= .31). Five out of the six stroke patients exhibited lower sensitivity to targets during real relative to sham stimulation.

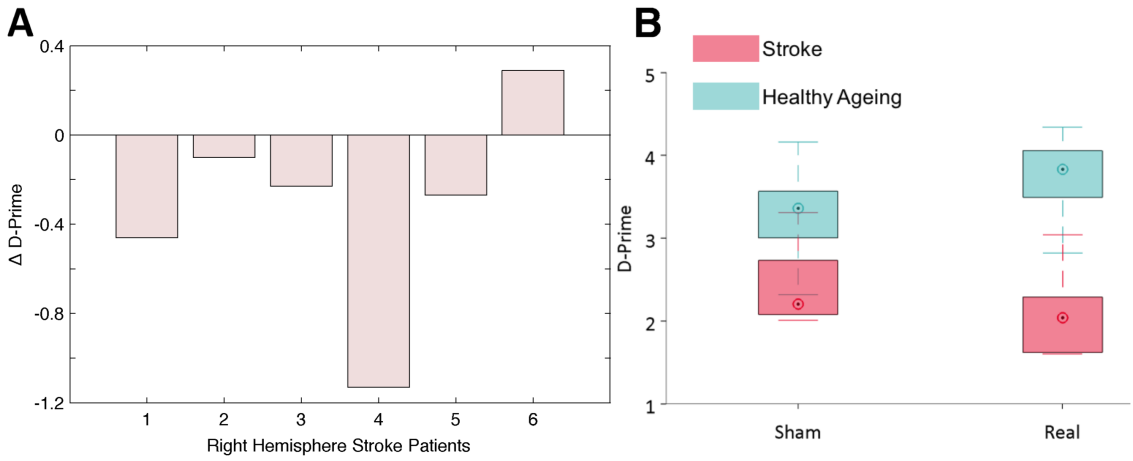


Figure 4.4: The effects of tDCS on sensitivity to targets (d-prime) during performance of the CTET. A. The tDCS-induced change in D-Prime for each of the individual patients with damage to the RH. *Note.* Δ denotes change in performance (real-sham). **B.** The effects of tDCS on D-Prime visualized for the healthy older adults (improved performance) and right hemisphere stroke patients (impaired performance).

4.4 Discussion

The current pilot study assessed the feasibility of increasing excitability of the right prefrontal cortex (PFC) to ameliorate sustained attention deficits following right hemisphere stroke.

Increased perilesional activity typically parallels improvement

An abundance of evidence suggests that following stroke, optimal recovery of motor functioning, language capacities, and hemispatial neglect, is associated with the restoration of networks within the damaged hemisphere (Baldassarre et al., 2016; Bullmore & Sporns, 2012; Fu & Zuo, 2011; Ramsey et al., 2016; Rehme et al., 2012; Ward et al., 2003). This is believed to occur through the recruitment of perilesional tissue where available, or the remapping of functions onto adjacent regions (Ramsey et al., 2016). Capitalising on these findings, non-invasive brain stimulation techniques targeting plasticity processes of the damaged networks, for example through anodal tDCS over perilesional areas, have been shown to normalize network activity normalize network activity and improve rehabilitation outcomes in many domains (Allman et al., 2016; Làdavas et al., 2015; Marangolo et al., 2016). However, contrary to our hypothesis that right prefrontal tDCS over the damaged hemisphere would temporarily ameliorate sustained attention deficits there was no evidence of improved sustained attention, and descriptively five out of six stroke patients were more severely impaired during stimulation.

One explanation for why tDCS could have disrupted performance is if the homologous contralateral left hemisphere network was recruited to perform the task, and there are at least two indications that the stroke patients in the current study may have been recruiting the left, contralesional prefrontal cortex during performance of the CTET. Firstly, recruitment of the contralesional hemisphere following stroke has been noted in severely impaired patients typically shifts back to the ipsilesional hemisphere in parallel with recovery (Anglade, Thiel, & Ansaldo, 2014; Johansen-Berg et al., 2002; Rehme et al., 2012; Ward et al., 2003; Xerri, Zennou-Azogui, Sadlaoud, & Sauvajon, 2014). However, persisting deficits are often accompanied with increased activity in the contralesional networks (Johansen-Berg et al., 2002; Ward et al., 2003), which in turn exerts inhibitory influences on the damaged hemisphere (Grefkes, Nowak, Wang, Dafotakis, Eickhoff, et al., 2010a; Murase, Duque, Mazzocchio, & Cohen, 2004; Nowak et al., 2008).

In the current study, sustained attention was assessed in the stroke patients using the fixed version of the Sustained Attention to Response Task (O'Halloran et al., 2011; Robertson,

Manly, Andrade, Baddeley, & Yiend, 1997a), an established sustained attention measure which correlates with day-to-day lapses in attention (Smilek et al., 2010). Five out of the six patients tested scored in the 50th percentile or lower on this test, relative to their age, gender, and education-matched peers, suggesting persisting impairments of sustained attention in this cohort. It is quite possible these patients, presenting with sustained attention impairments in the chronic stages of stroke, recruited the contralesional left hemisphere network to perform the task. In support of this it is worth noting that the only patient (patient 6) whose performance improved during right prefrontal tDCS, in the same direction as the neurologically healthy older adults, was the patient whose normative sustained attention performance was in the 90th percentile.

Secondly, the flexible, adaptive neural coding within prefrontal cortex (Duncan, 2001; 2013) places this cortical region in an ideal position to compensate for unilateral damage. For example, in healthy individuals, low frequency repetitive trains of TMS, employed to create a 'virtual lesion' over the PFC has been shown to disrupt working memory performance (T. G. Lee & D'Esposito, 2012). Importantly, Lee and D'Esposito noted that the degree of increased activity in this homologous (non-stimulated) PFC region was directly associated with resilience against the virtual lesion, i.e., less performance disruption as measured on a working memory task, thus suggesting beneficial involvement of the contra-'lesional' hemisphere to functionally compensate. Similarly in patients with acquired brain injury, compensatory activity of the homologous prefrontal cortex is observed and positively associated with working memory performance (Rosen et al., 2000; Turner, McIntosh, & Levine, 2011). Finally, Voytek et al. (2010) showed that following unilateral prefrontal damage, chronic stroke patients exhibit dynamic compensation within the intact prefrontal cortex during an attention task.

Of relevance, it is not the increased involvement of the intact prefrontal regions in isolation that has been associated with performance restoration following lesions (either artificially induced through rTMS or stroke), but rather the degree of activation in the prefrontal regions in concert with ipsilesional activity within the task-relevant network such as higher visual

areas (T. G. Lee & D'Esposito, 2012; Voytek et al., 2010). This suggests that it may be the capacity of the intact prefrontal region to recruit the relevant ipsilesional network that supports the adaptability of these prefrontal regions following damage.

Although a clear right lateralised network subserves the capacity to sustain attention, many studies also note activation, albeit weaker in left hemisphere regions during sustained attention tasks (Langner & Eickhoff, 2013a; Rosenberg et al., 2016), suggesting a less active functional left hemisphere network. It is possible that stroke patients with damage to right hemisphere nodes within the widespread sustained attention network may recruit the intact contralesional network, via the PFC, in situations demanding sustained engagement. As observed in Empirical Chapter 3, the CTET places high demands on the sustained attention system, as evidenced by pronounced vigilance decrements in patients with RH damage. Thus, it is plausible to suggest that chronic stroke patients with persisting sustained attention deficits following unilateral right hemisphere damage may take advantage of the dynamic nature of the DLPFC regions and recruit left hemisphere networks.

If indeed the stroke patients with persisting impairments in the current study were engaging the left hemisphere to perform the CTET, increasing activation in the right prefrontal cortex is likely to have disrupted performance by exerting interhemispheric inhibitory processes over the homologous contralateral network (Grefkes, Nowak, Wang, Dafotakis, Eickhoff, et al., 2010a; Murase et al., 2004; Nowak et al., 2008), thus interrupting dynamic compensatory functions of the intact left hemisphere. In complement to this hypothesis, Bradnam and colleagues (Bradnam, Stinear, Barber, & Byblow, 2012) showed that cathodal tDCS over the contralesional motor cortex, employed to facilitate activity in the ipsilesional network, worsened upper limb control for moderately to severely impaired chronic stroke patients, but improved performance for mildly affected patients. In light of Bradman et al.'s findings, the preliminary data presented in this chapter suggests that facilitating ipsilesional networks post-stroke (either through ipsilesional anodal stimulation, or contralesional cathodal stimulation) may only be

beneficial for mildly impaired patients who hold preserved capacity to recruit ipsilesional networks.

Limitations and Future Directions

Evidently, a substantial limitation of this report is the small sample size, as the availability of suitable chronic patients was limited during the period of testing. Nevertheless, the current data provides preliminary pilot data to suggest that stimulating the right prefrontal cortex in patients with persisting sustained attention deficits following unilateral right hemisphere damage does not aid, and potentially disrupts performance. This preliminary data suggests that right prefrontal tDCS may not be a viable technique to ameliorate sustained attention deficits in these patients. This hypothesis warrants further investigation not just from a cognitive neuroscience perspective to further our understanding of natural compensatory processes following stroke, but also from a rehabilitation perspective. Future work will benefit from a larger sample, combining tDCS with neuroimaging to directly address the compensatory function of the contralesional prefrontal cortex, and, most importantly, from a more extensive examination of tDCS protocols by exploring whether anodal tDCS over the contralesional prefrontal cortex or cathodal stimulation over the ipsilesional (right) hemisphere would preferentially improve performance.

Discussion

D.1 Contributions

A major aim of this thesis was to investigate the contribution of right hemisphere networks to attentional function in healthy ageing and stroke. This was mainly motivated by the proposal that repeated activation of the right FPN underpinning facets of attention may be a key contributor to cognitive reserve, the neuroprotective buffer that older adults with more cognitively stimulating environments hold against cognitive decline in the face of neuropathology. The experiments in this thesis were designed with the following specific purposes:

- to assess the contribution of the right hemisphere to cognitive reserve in healthy ageing
- to understand whether the right prefrontal node of this right-lateralised network can be upregulated in older adults to improve aspects of attentional function
- to explore how the capacity to maintain attentional engagement over time is impaired in right hemisphere stroke patients
- to probe the feasibility of increasing excitability of the right PFC in patients with unilateral damage to the right hemisphere.

The conclusions of these investigations along with suggestions for future research are discussed below.

D.1.1 Right prefrontal contributions to sustained attention in ageing

The ability to sustain attention is integral to healthy cognition in ageing (O'Halloran et al., 2011; O'Halloran et al., 2013; Robertson, 2014). This capacity is fundamental to maintaining engagement with the task at hand (Smilek et al., 2010), and optimising the impact of brain

plasticity processes that likely support cognitive reserve (Fritz, Elhilali, David, & Shamma, 2007b; Polley et al., 2006; Recanzone et al., 1993; Robertson, 2014). The two experiments presented in Empirical Chapter 1 were designed to investigate the contributions of the right PFC to sustained attention in older adults. The results presented in Empirical Chapter 1 demonstrated in two independent cohorts of older adults, using two very different task paradigms, that increasing activity in the right PFC temporarily improves sustained attention performance. In Experiment 1, simultaneous tDCS-EEG recordings revealed that stimulation was associated with enhanced electrophysiological signals of frontal engagement and early visual attention, suggesting that attentional improvements were achieved via the modulation of long-association frontoparietal pathways.

These findings present a novel contribution to the literature signifying a causal role for this region in sustained attention processes in ageing. The results demonstrate that upregulation of the right PFC is feasible in the ageing brain. It has recently been shown that increasing excitability of the right prefrontal cortex enhances error awareness in older adults (Harty et al. 2014). Empirical Chapter 1 therefore corroborates previous evidence that the right PFC can be directly targeted in older adults (Harty et al. 2014), and suggests that the well-documented links between sustained attention and error awareness in both healthy and pathological ageing (McAvinue et al. 2005; O'Keeffe et al. 2007; Harty et al. 2013) may be subserved, at least in part, by the right prefrontal cortex. Moreover the results in Empirical Chapter 1 suggest that upregulating the right PFC is a promising approach to enhance aspects of cognition in older adults that have been proposed to cultivate cognitive reserve (Robertson, 2014).

D.1.2 The right hemisphere role in cognitive reserve

The recent proposal that the right lateralised noradrenergic system underpins cognitive reserve (Robertson, 2013; 2014) was addressed in Empirical Chapter 2. It is well established that

visually presented stimuli produce strongest activation in the contralateral hemisphere (Heinze et al., 1994; Mangun et al., 1998; Schiffer et al., 2004). Capitalising on this, a TVA whole report task with lateralised stimulus displays (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999a) was used as a psychophysical assessment of hemisphere asymmetries.

In line with previous experiments showing a reduction in hemisphere asymmetries with age (Cabeza, 2002b; 2004; Reuter-Lorenz et al., 2000), older adults did not show an asymmetry in processing speed capacity, at the group level. However, older adults with higher levels of cognitive reserve showed greater leftward asymmetry in the speed at which they process visual information, suggesting dominant right hemisphere activation in these individuals. Interestingly, younger healthy adults, tested in The University of Copenhagen using a similar lateralised paradigm exhibited a rightward processing speed asymmetry on this task. Therefore, the results in Empirical Chapter 2 suggest functional reorganisation involving the right hemisphere occurs in high reserve individuals.

Error awareness is another core cognitive process proposed to contribute to cognitive reserve, given the links between awareness, noradrenaline, and the right FPN networks (Robertson, 2013; 2014). In Empirical Chapter 2 it was observed that older adults with higher levels of reserve exhibited higher awareness of their everyday lapses of attention, which was assessed via the discrepancy between an individual's subjective report, and the report of a close relative (Broadbent et al., 1982). This link between cognitive reserve and awareness provides further indirect support for a right hemisphere contribution to cognitive reserve.

A recent study assessed older adults annually for several years (5.8 on average) on an extensive cognitive battery (R. S. Wilson et al., 2013) and examined the integrity of the brainstem aminergic nuclei post-mortem. Brain autopsies revealed that higher neuronal density within the locus coeruleus was associated with less cognitive decline, a phenomenon that was not the case

for any of the other brainstem aminergic nuclei. The locus coeruleus is the only source of noradrenaline in the brain (Foote & Morrison, 1987; Sara, 2009). The results from Wilson et al. therefore demonstrate that greater availability of noradrenaline in the ageing brain is associated with less cognitive decline, an association that may be mediated by strengthened activation within the right FPN (Robertson, 2013). In Empirical Chapter 2, the right hemisphere dominance of older adults with higher levels of cognitive reserve extend these findings by exemplifying how cognitive reserve, presumably accompanied with increased noradrenergic activity, is represented in the forebrain.

Right prefrontal contributions to processing speed in ageing

Processing speed capacity shows linear decrements with age (McAvinue et al., 2012), with recent work demonstrating a robust association between the decline of processing speed and higher order cognitive abilities in ageing (Ritchie et al., 2014). Large-scale interventions, where older adults are trained to increase processing speed, have shown favourable results, including lasting benefits (Rebok et al., 2014) and generalisation of training to real life domains such as reduced motor-collision accidents (Ball et al., 2010), and improved health-related qualify of life (Wolinsky et al., 2006). However, the neural basis for such benefits has not been shown. Empirical Chapter 2 demonstrated that tDCS over right PFC temporarily increases processing speed in older adults. These results substantiate previous reports providing indirect evidence for the right PFC in processing speed capacity (Chechlacz et al., 2015; Matthias et al., 2009). Furthermore, these findings suggest the right PFC is a viable target region to improve the speed of information processing in older adults and indicate that this area may contribute to the promising benefits of processing speed training in older adults (Rebok et al., 2014).

The stimulation results in Empirical Chapter 2 demonstrated that for older adults with lower levels of cognitive reserve, increasing excitability of the right PFC temporarily shifted this

asymmetry leftward such that it resembled the high reserve older adults. This finding, that older adults with lower levels of cognitive reserve show preserved capacity for plasticity in the right PFC holds enthusing societal implications as it suggests that the potential to increase cognitive reserve in older adults may not be restricted to those who have engaged in cognitively stimulating activities throughout their lifetime. This is in line with recent approaches aimed at increasing cognitive reserve in middle-aged adults ('Sending your Grandparents to University Increases Cognitive Reserve'; Lenehan et al., 2016)

D.1.3 Preserved plasticity of the right prefrontal cortex in ageing

The findings from Empirical Chapter 1 and 2 indicate that right prefrontal tDCS temporarily improves aspects of attention in ageing. It would be interesting to understand how tDCS is affecting the brain at the cellular level. Emerging animal studies suggest that tDCS exerts its effects, at least on stimulus processing, through an increase in noradrenergic drive (Monai et al., 2016). The work presented in this thesis suggests that tDCS in humans can also enhance stimulus processing: right PFC tDCS was associated with a markedly enhanced amplitude of the visual-evoked N1 component (Empirical Chapter 1) and with improvements in the speed at which perceptual information in the environment can be processed (Empirical Chapter 2). One mechanism by which noradrenaline is proposed to enhance stimulus processing is through an increasing stimulus-evoked neural activity while correspondingly decreasing spontaneous firing, i.e. by increasing the signal to noise ratio (cf Hurley et al., 2004; Waterhouse, Ausim Azizi, Burne, & Woodward, 1990). Whether tDCS is increasing noradrenaline and enhancing the naturally adaptive nature of the prefrontal cortices to selectively increase relevant inputs while decreasing irrelevant inputs (Duncan, 2001) will be an avenue for future work. Pupil diameter has been identified as a noninvasive proxy of noradrenergic activity (Murphy, O'Connell, & O'Sullivan, 2014; Sara, 2009), and could be used as a marker of noradrenaline in future work with human

participants, to assess whether the effects of tDCS over right PFC are mediated by noradrenergic activity (Murphy et al., 2014; Sara, 2009).

D.1.4 The temporal dynamics of sustained attention deficits following right hemisphere stroke

Aspects of attention, particularly the capacity to sustain attention are predictive of rehabilitation outcomes following stroke (Bennett et al., 2002; Blanc-garin, 1994; Robertson, Ridgeway, Greenfield, & Parr, 1997c; van Zandvoort et al., 2005). Empirical Chapter 3 provides novel evidence that sustained attention deficits experienced by patients with damage to the right hemisphere represent an impaired capacity to maintain engagement over short temporal durations (3-3.5 minutes), shorter than those previously reported (Malhotra et al., 2009; Rueckert & Grafman, 1996; 1998). This holds important practical information regarding the cognitive benefits of frequent rest periods for right hemisphere stroke patients. These findings also contribute to the methods by which sustained attention deficits are assessed. Previous task paradigms have demonstrated a deficit in overall sustained attention performance in right hemisphere stroke patients (Malhotra et al., 2009; Rueckert & Grafman, 1996; 1998), and a decline in performance over an 8-10 minute window under certain task conditions (Rueckert & Grafman, 1996; 1998). However, decrements in attentional engagement over shorter time scales have not previously been identified.

Traditional sustained attention tasks using visual target stimuli hold one critical limitation such that perceptual features of the target stimulus may exogenously capture attention, thus aiding task performance and potentially masking decrements in the capacity to endogenously maintain attentional engagement. The continuous temporal expectancy task (O'Connell, Dockree, Robertson, et al., 2009b) employed to assess sustained attention in the right hemisphere stroke patients in Empirical Chapter 3 provides distinct advantages for the assessment of performance

decrements, such that target detection is independent from the visual components of the task and rather relies on the temporal domain. These characteristics reduce the ease at which automated bottom-up processes can govern task performance, thereby providing a 'purer' measure of sustained attention decrements. This task is also sensitive to performance decrements over short time windows in healthy younger individuals, with sufficient error rates such that electrophysiological signatures of sustained attention can be examined (O'Connell, Dockree, Robertson, et al., 2009b). A direct comparison of the deployment of attention to the time, as opposed the visual domain is necessary to confirm a superiority of the former approach for detecting fluctuations in attention over short time windows. However, in light of previous work literature assessing vigilance decrements (Malhotra et al., 2009; Rueckert & Grafman, 1996; 1998), the work presented in Empirical Chapter 3 suggests this is the case.

D.1.5 The feasibility of right prefrontal tDCS in stroke patients

Heeding the results from the two experiments presented in Empirical Chapter 1, Empirical Chapter 4 was designed to assess whether the tDCS protocol that temporarily improved sustained attention performance in both cognitive healthy older adults, and older adults with suboptimal sustained attention performance, could be employed to temporarily remediate sustained attention deficits in chronic stroke patients with unilateral RH damage. Contrary to the hypothesis that tDCS would increase excitability of the right PFC and improve sustained attention, no significant difference was observed between real and sham, and descriptively tDCS temporarily impaired performance in five out of the six right hemisphere patients. The small sample size for these preliminary results hinders any conclusive interpretations from this data. Notwithstanding these limitations, these findings hold important information for the design of future interventions aiming to ameliorate sustained attention deficits in right hemisphere stroke patients. Of interest, the only patient who responded to tDCS in the same direction as the healthy older adults, was the only patient who did not present with persisting, chronic sustained attention deficits (as compared with age, gender, and education-matched normative data). Hence,

all five patients whose sustained attention performance did not improve, or was potentially disrupted via right PFC tDCS, showed persisting deficits at maintaining attention in the chronic stages of stroke.

One explanation for why tDCS may have impaired performance in Empricial Chapter 4 is if the contralesional left prefrontal cortex exerted inhibitory influences over the right hemisphere in a manner which aided sustained attention capacity (Grefkes, Nowak, Wang, Dafotakis, Eickhoff, et al., 2010a; Murase et al., 2004; Nowak et al., 2008). This poses the interesting question of whether chronic stroke patients with unilateral damage to the right hemisphere presenting with severe and persistent sustained attention deficits show an adaptive increase in left hemisphere network activity. This would suggested by neuroimaging studies assessing compensatory involvement in chronic stroke patients within the motor domain (Bradnam et al., 2012; Johansen-Berg et al., 2002; Ward et al., 2003). Adaptive left hemisphere compensatory involvement in RH stroke patients may have been overlooked by previous studies because, as demonstrated in Empirical Chapter 3, these patients still show impaired performance relative to healthy older adults at baseline (during the sham condition). However, the preliminary tDCS results presented in Empirical Chapter 4 suggest that without the left hemisphere involvement this impairment might be even more severe. An intriguing approach to shed light on this hypothesis would be to combine tDCS with functional neuroimaging (Meinzer et al., 2013). Firstly, this would clarify how the activation of right hemisphere pathways versus the compensatory involvement of left hemisphere networks contributes to sustained attention performance in chronic stroke. Secondly, the use of multiple tDCS protocols to exogenously increase and decrease excitability of both the right and left prefrontal regions during concurrent fMRI recordings, would enable a more thorough understanding of how baseline functional network activation contributes to the effects of tDCS. Specifically it would be interesting to see whether the benefits of anodal right PFC tDCS are dependent on right lateralisation of the sustained attention networks recruited at baseline.

D.2 Limitations and Future Directions

D.2.1 Limitations of tDCS

A promising application for tDCS is its potential to enhance learning in healthy individuals (Nitsche & Paulus, 2000) and to augment the benefits of interventions for pathological conditions such as stroke (Allman et al., 2016; Marangolo et al., 2016), through its facilitation of brain plasticity (Fritsch et al., 2010; Nitsche et al., 2006; Podda et al., 2016). It has been demonstrated in Empirical Chapter 1 and 2 that when cortical excitability of the right PFC is increased in older adults using tDCS, attentional engagement is increased. There is some evidence to suggest that tDCS may improve cognition when combined with relevant behavioural interventions (Ditye, Jacobson, Walsh, & Lavidor, 2012; Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010). Thus, an inviting avenue for future work may be to decipher whether right PFC tDCS over multiple sessions could be combined with emerging behavioural interventions (Milewski-Lopez et al., 2014; Rebok et al., 2014). This might be hypothesised to enhance cognitive outcomes in ageing and strengthen activation within the right lateralised cognitive reserve network to help cultivate the neurocognitive buffer against diseases such as Alzheimer's. However, tDCS holds several limitations that should be addressed in advance of research ventures aiming to apply this technique to improve current interventions, and even more importantly before advocating this technique as a commercially available tool for cognitive remediation (Steenbergen et al., 2015).

Arguably, the most substantial limitation of tDCS is the large variability observed in inter-individual responsiveness to stimulation (Li, Uehara, & Hanakawa, 2015; Wiethoff, Hamada, & Rothwell, 2014). For tDCS to be realised and optimised as an applicable tool to ameliorate cognitive deficits, it is essential that advances are made towards understanding these sources of variability. The distribution of current flow under the tDCS electrodes is affected by neuro-

anatomical factors such as skull thickness, gyral depth, cerebrospinal fluid, and the integrity of white matter structures within the relevant network (Bradnam et al., 2012; Laakso, Tanaka, Koyama, De Santis, & Hirata, 2015; Opitz, Paulus, Will, Antunes, & Thielscher, 2015). Moreover, unlike stimulation methods such as transcranial magnetic stimulation, where direct modulation of action potentials takes place (Terao & Ugawa, 2002), tDCS modulates the underlying neuronal activity by interacting with simultaneously active neuronal populations in either an excitatory or inhibitory manner (Nitsche et al., 2008; Stagg & Nitsche, 2011). Thus the underlying neural network is also of importance to the effects of stimulation (Benwell, Learmonth, Miniussi, Harvey, & Thut, 9999; Berryhill & Jones, 2012; Learmonth, Thut, Benwell, & Harvey, 2015). Computational modelling of current flow will facilitate a richer understanding of both the inter-individual variability in response to tDCS and the mechanistic effects of the technique (Berker, Bikson, & Bestmann, 2013; Bestmann, de Berker, & Bonaiuto, 2015). Moreover, the identification of biomarkers to predict responsiveness will optimise the application of this technique to cognitive rehabilitation in the future.

In addition to understanding sources of variability, identifying stimulation protocols that show replicable effects at the group level is relevant to studies aiming to ascribe a causal role of specific brain areas to particular cognitive functions. This thesis describes three separate experiments (Empirical Chapter 1, Empirical Chapter 2), using a tDCS montage designed to upregulate the right DLPFC, where aspects of attentional function were enhanced during active relative to sham stimulation.

Using an identical electrode montage (current strength, electrode size, adhesion, and placement), Harty et al (2014) showed that, in two separate cohorts of older adults, right anodal PFC tDCS improved error awareness, a cognitive process reliant on the same right lateralised network (Robertson, 2014). Collectively, these five experiments suggest that the right PFC stimulation protocol used throughout this thesis is a promising electrode montage to increase

activity in the right PFC in healthy older adults. Importantly, similar performance benefits were not observed for anodal left PFC (Harty, Robertson, Miniussi, Sheehy, Devine, McCreery, & O'Connell, 2014a), anodal right parietal (Empirical Chapter 2), or cathodal right PFC tDCS (Harty, Robertson, Miniussi, Sheehy, Devine, McCreery, & O'Connell, 2014a). Nonetheless, future work should address the replicability of these findings and affirm the right-lateralisation of the effects presented in this thesis by also assessing the effects of left prefrontal tDCS.

D.2.2 Future directions for upregulation of PFC

In light of these limitations it is imperative that future work exploring the efficacy of tDCS over right PFC to improve facets of attention is compared with other techniques used to directly manipulate brain activity.

Firstly, there are several other transcranial electrical stimulation (TES) techniques available. For example, transcranial random noise stimulation (tRNS) is an oscillatory form of brain stimulation where the frequency of the current varies in a rapid, randomized manner (Kadosh, 2015). The impact of tRNS is therefore polarity independent, which can give rise to facilitatory effects at both electrode sites (Kadosh, 2015). tRNS over right prefrontal and parietal regions may thereby constitute a means for creating a distributed impact of stimulation throughout the FPN. Transcranial alternating current stimulation is another TES approach that can be used to entrain specific cortical oscillations (Helfrich et al., 2014). This presents the potential of targeting specific frequency bands, that are known to fluctuate with attentional engagement (O'Connell, Dockree, Robertson, et al., 2009b).

Finally, a technique for modulating brain activity that is particularly compelling for it's spatial specificity is fMRI neurofeedback (deCharms et al., 2005). This technique enables individuals to gain volitional control over highly specific brain areas (Habes et al., 2016; Linden, 2016; Linden et al., 2012, Christopher deCharms, 2008), by learning to modulate the BOLD

response in real-time. Clinically relevant improvements have been observed following fMRI neurofeedback training for patients with Parkinson's Disease, suggesting that this technique is feasible for age-related neurodegenerative conditions (Subramanian et al., 2016; 2011). Moreover, it has recently been demonstrated that during fMRI neurofeedback from a distributed network, identified using multivariate pattern analysis, sustained attention lapses in healthy younger adults can be reduced (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015b). Superior improvements in attention were observed when feedback contained information from the FPN, thereby suggesting that fMRI neurofeedback could be a viable tool for targeting the right FPN in older adults.

D.2.3 The bigger picture

The focus of this thesis has been to enhance the understanding of attention networks in healthy ageing and stroke in an effort to inform future approaches towards mitigating cognitive loss. However, techniques to successfully enhance attention may also be associated with benefits beyond the cognitive domains in aspects of affect and emotional well-being. For example, in the influential 'flow' model, Csikszentmihalyi reports how peoples' most enjoyable and positive experiences are frequently accompanied by high degrees of attentional engagement, task absorption, or 'flow' (Abuhamdeh & Csikszentmihalyi, 2011; Csikszentmihalyi, Abuhamdeh, & Nakamura, 2005; Csikszentmilhalyi et al., 1982). A recent large study (*N*=2250) probed healthy younger individuals at random intervals throughout the day using a smartphone application and assessed self-reported mind-wandering, and subjective affect (happiness). The results demonstrated that low levels of attentional engagement with the task at hand (mind wandering) across a wide range of daily activities were associated with lower subjective happiness ratings (Killingsworth & Gilbert, 2010). The identification of a target area to enhance attentional engagement in older adults (Empirical Chapter 1 and 2) may thereby be of relevance, not solely for cognitive function in ageing, but may also have implications for improving affect. In line with

this, stimulation of the prefrontal regions is emerging as a promising intervention for depression (Kalu, Sexton, Loo, & Ebmeier, 2012; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). In older adults, compromised emotional wellbeing (e.g., depression) increases the risk of Alzheimer's Disease (R. S. Wilson et al., 2002; 2007), and predicts worse functional outcomes following stroke (Ayerbe, Ayis, Wolfe, & Rudd, 2013). Thus, it would be noteworthy for interventions targeting attention in ageing to explore associations with emotional wellbeing.

It is important to acknowledge that the work presented in this thesis has focused exclusively on enhancing aspects of attentional function through training the underlying networks, with a specific interest on the right-lateralised 'alerting' system given its proposed relation with cultivating cognitive reserve (Corbetta & Shulman, 2002; Posner & Petersen, 1990; Robertson, 2014). Tang and Posner describe the training of specific networks that underpin executive functions as a 'western' approach to improving attention (Tang & Posner, 2009). However, 'eastern' methods provide an alternative school of thought. For example, with mindfulness meditation, the focus is based on self-regulation of the attentional state rather than training the networks identified during attention-tasks (Tang & Posner, 2009). Longterm meditators show superior performance on attention tasks (Prakash et al., 2012; van Leeuwen, Müller, & Melloni, 2009) and preliminary evidence suggests that expert meditators may hold a protective effect against age-related cognitive decline (see Gard, Hölzel, & Lazar, 2014 for a review; Sperduti, Makowski, & Piolino, 2016). Such studies are limited by potential confounding variables between expert- and non-meditators. However, intensive meditation interventions in younger adults have been shown to improve aspects of attention (Tang et al., 2007), including sustained attention and perceptual discrimination abilities (MacLean et al., 2010). Meditation-based interventions have also been shown to improve emotional responses in younger adults (Tang et al., 2007; cf Tang & Posner, 2009), thus warranting the investigation of these techniques to ameliorate attention deficits in both healthy and pathological ageing.

Appendix A

Post-stroke deficits in attention and working memory: prevalence and impact on subacute and long term functional status.

King, R. L., Brosnan, M., Humphreys. G. W. & Demeyere, N.

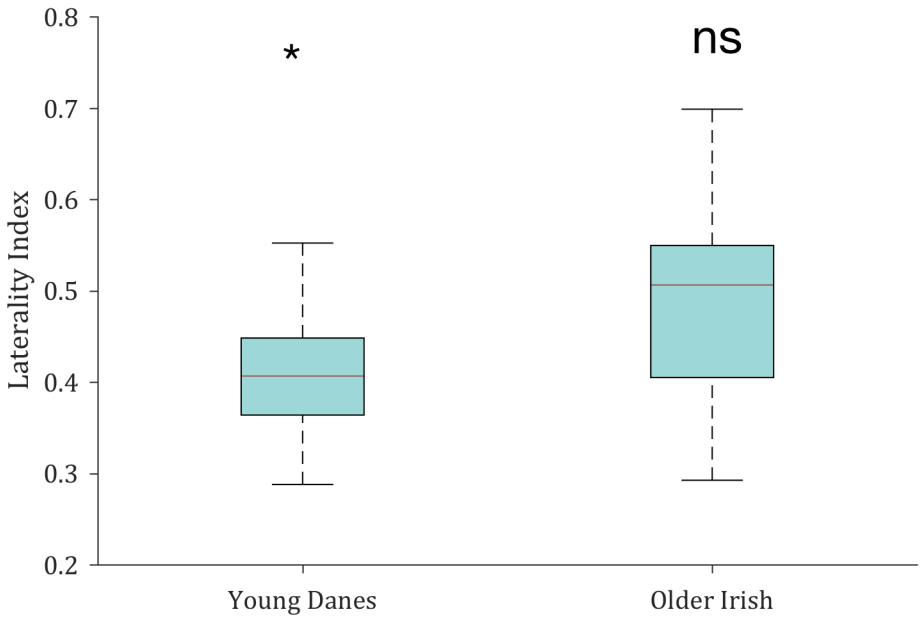
Abstract: *British Neuropsychological Society Autumn Meeting*, London, UK, October 2016.

In the UK there are approximately 1.2 million stroke survivors. Of that population over half will experience disability and over a third will be dependent on others in their daily lives (State of the Nation, 2016). It is important to understand what types of disability are experienced and how deficits can influence functional recovery. For example, domain general cognitive impairments have been linked with wider spread cognitive deficits (Massa, Wang, Bickerton, & Demeyere, 2015) and poorer functional recovery (Robertson, Ridgeway, Greenfield, & Parr, 1997c; Schoenmakers, 2016). This study aims to explore the prevalence of domain general deficits in attention and working memory, the relationship between these impairments and other cognitive problems (< 100 days) and finally the impact of deficits on long term (>9 months) functional recovery. In a large sample of 682 stroke patients, 53% had impaired selective attention, 36% had impaired sustained attention and between 25% and 33% had impaired working memory. These impairments were significantly correlated with poorer performance on multiple cognitive domains and functional status at the subacute phase of recovery. Furthermore, in a sample of 230 patients assessed at follow-up, impaired sustained attention during the sub-acute stage significantly predicted functional status at 9 months post stroke, even when taking stroke severity and age into consideration. The results highlight not only the prevalence of these deficits,

but also the short and long term influence they may play on cognitive and functional recovery. These findings indicate the importance of successful integration of cognitive assessment and rehabilitation into the stroke pathway.

Appendix B

Supplementary information for Empirical Chapter 2.



Supplementary Figure 2.8: The difference in Processing Speed Hemifield Asymmetry between right and left hemifields in younger and older adults.

Y Axis denotes the Laterality index (C_{λ}), whereby values greater than 0.5 indicate a leftward asymmetry. Younger adults (mean age 24.8 years, SD=3.1, range = 20-36), show a significant rightward asymmetry in Processing Speed *C* towards items in the right hemifield. There is no significant difference in processing speed capacity for right vs left hemifields for the older Irish participants who participated in the current study. *Note* * denotes $p<.05$, *ns* denotes no significant difference between right and left hemifields. Data for the younger adults was collected by Bart Cooreman and colleagues at the Centre for Visual Cognition, Copenhagen University.

Appendix C

The Dorsolateral Prefrontal Cortex, a Dynamic Cortical Area to Enhance Top-Down Attentional Control

Brosnan, M. & Wiegand, I. Journal Club article (Journal of Neuroscience).

Original Article Citation

Gbadeyan O, McMahon K, Steinhauser M, Meinzer M. 2016. Stimulation of Dorsolateral Prefrontal Cortex Enhances Adaptive Cognitive Control: A High-Definition Transcranial Direct Current Stimulation Study. J. Neurosci. 36:12530–12536.

Article

The dorsolateral prefrontal cortex (DLPFC) is part of a domain-general network of frontal, parietal, and insular brain regions activated in response to a wide range of de- manding task conditions (Duncan, 2013). Both animal electrophysiology and human neuroimaging suggest that, within the DLPFC, flexible neuronal tuning supports top-down modulation of task-relevant pro- cesses (Freedman et al., 2001; Duncan, 2013; Erez and Duncan, 2015). Neuroimaging work has demonstrated that the DLPFC implements cognitive control adjustments, contingent on the detection of conflict (Egner and Hirsch, 2005). In complement with these correlational findings, Gbadeyan et al. (2016) assessed whether exogenously increasing the neuronal excitability of the DLPFC using tDCS was associated with an increase in cognitive control.

The authors used a double-blind, sham- controlled approach to investigate the ef- fects of high-definition (HD) transcranial direct current stimulation (tDCS). A total of 120 healthy young participants received HD tDCS over right DLPFC, left DLPFC, or right or left primary motor cortex (M1). The aims were to ascribe a causal role of the DLPFC to cognitive control and to assess hemispheric differences in this function. Participants performed a visual flanker task, in which they had to respond to a centrally

presented target (arrow) surrounded by dis- tractor stimuli that were associated with ei- ther the same (congruent, arrow pointing in the same direction) or a different (incon- gruent, arrow pointing in the opposite di- rection) response to the target stimulus. In this task, slower response times (RTs) are observed for incongruent compared with congruent trials (Eriksen and Eriksen, 1974). A measure of cognitive control in this task is the magnitude of the "conflict adap- tation effect" (Botvinick et al., 2001), ac- cording to which the flanker effect is markedly reduced after incongruent trials and increased after congruent trials.

Gbadeyan et al., 2016 found both a ro- bust flanker effect (faster RTs for congruent trials than for incongruent trials) and a con- flict adaptation effect (a larger flanker effect after congruent trials than after incongruent trials). Crucially, the conflict adaptation ef- fect was enhanced when activity in the DLPFC was exogenously increased using tDCS. There were no differences in the effect of right and left DLPFC stimulation on the conflict adaptation effect, and stimulation of M1 over either hemisphere did not alter this measure of cognitive control.

These findings corroborate previous fMRI work, which has shown increased DLPFC activity during cognitive control (MacDonald et al., 2000; Egner and Hirsch, 2005), and they provide novel evidence sug- gesting that the prefrontal cortex plays a causal role in enhancing conflict adaptation. One caveat to the study, however, is that participants who received tDCS over right DLPFC had significantly slower RTs than those who received tDCS over left DLPFC. tDCS is known to interact with already ac- tive neuronal populations (Fertonani and Miniussi, 2016). Baseline differences in task performance are therefore of potential im- portance, calling into question the interpre- tation that lateralization of the DLPFC did not play a role in cognitive control processes in the present study. This is of particular rel- evance given discrepancies in the neuroim- aging literature regarding lateralization of the DLPFC in cognitive control (MacDon- ald et al., 2000). One aspect contributing to the diversity of findings might be differences in the type of stimulus material and tasks used in the studies. Paradigms that are sen- sitive to lateralization of cognitive functions, such as tasks with laterally presented stimuli often used in the assessment of visual pro- cesses (Habekost and Rostrup, 2007), might be better suited to detect potential hemi- spheric asymmetries in cognitive control.

An important question arising from the causal role that the DLPFC plays in cognitive control

adjustments, as demonstrated in the present study, regards the neural mechanisms behind this effect. Previous neuroimaging work (Egner and Hirsch, 2005) has suggested that cognitive control adjustments are associated with an increase in DLPFC activity in concert with enhanced activation in target-specific processing re- gions in higher-order visual areas. We sug- gest that the enhanced conflict adaptation effect during stimulation of the DLPFC ob- served in the present visual flanker task is likely achieved via increased top-down at- tentional modulation over early visual pro- cesses, thus facilitating the deployment of attentional resources to the relevant change in the presented stimulus (i.e., to the target following incongruent trials and the distrac- tor following congruent trials). Anatomical and functional connections among fron- tal, parietal, and occipital regions exist (Chechlacz et al., 2015; Marshall et al., 2015), and increased activity in visual occip- ital areas are often observed concurrently with enhanced prefrontal activity (Erez and Duncan, 2015). Furthermore, evidence from correlational neuroimaging studies suggests that the DLPFC exerts top-down modulatory control over early visual atten- tion processes (Zanto et al., 2011). Specifi- cally regarding conflict adaptation, previous imaging work (Egner and Hirsch, 2005) has identified increased functional coupling be- tween a subregion of the DLPFC and extra- striate visual regions during processing of the target stimulus (i.e., activity in the fusi- form face area during the processing of target face stimuli). However, whether stim- ulation of the DLPFC indeed increases the conflict adaptation effect via the modula- tion of visual attention processes remains to be explored. Future work combing HD tDCS with neurophysiological techniques such as simultaneous tDCS-EEG recordings will shed light on this issue, for example by assessing whether stimulation of the DLPFC is associated with enhanced visual evoked potentials to the task-relevant stimuli.

Gbadeyan et al. (2016) have demon- strated the feasibility of HD tDCS to effec- tively upregulate the DLPFC in cognitively healthy younger adults. Whether this tech- nique could be used to enhance the excit- ability of prefrontal regions in individuals with suboptimal cognitive capacities to re- mediate performance is an exciting avenue for future research. The DLPFC is a flexible cortical region, which makes it an attractive target region for neurorehabilitation of cog- nitive function. The cortical region has a ca- pacity for adaptive compensation following unilateral stroke (Voytek et al., 2010). Simi- larly, enhanced recruitment of the DLPFC in older adults is considered an adaptive re- sponse to age-related declines in early sen- sory regions to process visual information (Davis et al., 2008). Of significance, the DLPFC plays a crucial role in the speed at which visual information is processed (Ha- bekost and Rostrup,

2007; Chechlacz et al., 2015). Visual processing speed is impaired in many clinical populations (Habekost, 2015) and is increasingly considered a bio- marker of cognitive aging (Ritchie et al., 2014). Future studies should extend the work presented by Gbadeyan et al. (2016) and assess whether prefrontal tDCS can ameliorate cognitive deficits occurring in both healthy and pathological aging.

Journal Club References

Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. Psychol Rev 108:624 – 652. CrossRef Medline

Chechlacz M, Gillebert CR, Vangkilde SA, Petersen A,HumphreysGW (2015) Structuralvariabil- ity within frontoparietal networks and individ- ual differences in attentional functions: an approach using the theory of visual attention. J Neurosci 35:10647–10658. CrossRef Medline

Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R (2008) Que´ PASA? The posterior– anterior shift in aging. Cereb Cortex 18:1201– 1209. CrossRef Medline

Duncan J (2013) The structure of cognition: at- tentional episodes in mind and brain. Neuron 80:35–50. CrossRef Medline

Egner T, Hirsch J (2005) Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nat Neurosci 8:1784 –1790. CrossRef Medline

ErezY,DuncanJ (2015) Discriminationofvisualcat- egories based on behavioral relevance in wide- spread regions of frontoparietal cortex. J Neurosci 35:12383–12393. CrossRef Medline

Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys 16: 143–149. CrossRef

Fertonani A, Miniussi C (2016) Transcranial electri- cal stimulation: what we know and do not know about mechanisms. Neuroscientist. Advance on- line publication. Retrieved March 5, 2017. doi: 10.1177/1073858416631966. CrossRef Medline

Freedman DJ, Riesenhuber M, Poggio T, Miller EK (2001) Categorical representation of vi- sual stimuli in the primate prefrontal cortex. Science 291:312–316. CrossRef Medline

Gbadeyan O, McMahon K, Steinhauser M, Meinzer M (2016) Stimulation of dorsolateral prefron- tal cortex enhances adaptive cognitive control: a high-definition transcranial direct current stimulation study. J Neurosci 36:12530 –12536. CrossRef Medline

Habekost T (2015) Clinical TVA-based studies: a general review. Front Psychol 6:290. CrossRef Medline

Habekost T, Rostrup E (2007) Visual attention ca- pacity after right hemisphere lesions. Neuropsy- chologia 45:1474 –1488. CrossRef Medline

MacDonald AW 3rd, Cohen JD, Stenger VA, CarterCS (2000) Dissociatingtheroleofthe dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288:1835– 1838. CrossRef Medline

Marshall TR, Bergmann TO, Jensen O (2015) Fron- toparietal structural connectivity mediates the top- down control of neuronal synchronization as- sociated with selective attention. PLoS Biol 13: e1002272. CrossRef Medline

Ritchie SJ, Tucker-Drob EM, Deary IJ (2014) A strong link between speed of visual discrimi- nation and cognitive ageing. Curr Biol 24: R681–R683. CrossRef

Voytek B, Davis M, Yago E, Barcelo´ F, Vogel EK, Knight RT (2010) Dynamic neuroplasticity after human prefrontal cortex damage. Neu- ron 68:401– 408. CrossRef Medline

Zanto TP, Rubens MT, Thangavel A, Gazzaley A (2011) Causalroleoftheprefrontalcortexin top-down modulation of visual processing and working memory. Nat Neurosci 14:656 – 661. CrossRef Medline

References

Abuhamdeh, S., & Csikszentmihalyi, M. (2011). Attentional involvement and intrinsic motivation. *Motivation and Emotion*, *36*(3), 257–267. http://doi.org/10.1007/s11031-011-9252-7

Agulhon, C., Petravicz, J., McMullen, A. B., Sweger, E. J., Minton, S. K., Taves, S. R., et al. (2008). What Is the Role of Astrocyte Calcium in Neurophysiology? *Neuron*, *59*(6), 932–946. http://doi.org/10.1016/j.neuron.2008.09.004

Allman, C., Amadi, U., & Winkler, A. M. (2016). Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke. *Science Translational* ….

Anglade, C., Thiel, A., & Ansaldo, A. I. (2014). The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: A critical review of literature. *Brain Injury*, *28*(2), 138–145. http://doi.org/10.3109/02699052.2013.859734

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., & Al-Hashimi, O. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*(7465), 97–101. http://doi.org/10.1038/nature12486

Arnsten, A. F. T. (2011). Catecholamine Influences on Dorsolateral Prefrontal Cortical Networks. *Biological Psychiatry*, *69*(12), e89–e99. http://doi.org/10.1016/j.biopsych.2011.01.027

Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a Cognitive Control Network Using Diffusion-Weighted Magnetic Resonance Imaging (MRI) and Functional MRI. *The Journal of Neuroscience*, *27*(14), 3743–3752. http://doi.org/10.1523/JNEUROSCI.0519-07.2007

Asplund, C. L., Todd, J. J., Snyder, A. P., & Marois, R. (2010). A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. *Nature Neuroscience*, *13*(4), 507–512. http://doi.org/10.1038/nn.2509

Aston-Jones, G., Rajkowski, J., & Kubiak, P. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *The Journal of* ….

Avery, R. (2000). The Alpha-2A-Adrenoceptor Agonist, Guanfacine, Increases Regional Cerebral Blood Flow in Dorsolateral Prefrontal Cortex of Monkeys Performing a Spatial Working Memory Task. *Neuropsychopharmacology*, *23*(3), 240–249. http://doi.org/10.1016/S0893-133X(00)00111-1

Ayerbe, L., Ayis, S., Wolfe, C. D. A., & Rudd, A. G. (2013). Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *The British Journal of Psychiatry*, *202*(1), 14–21. http://doi.org/10.1192/bjp.bp.111.107664

Baldassarre, A., Ramsey, L. E., Siegel, J. S., Shulman, G. L., & Corbetta, M. (2016). Brain connectivity and neurological disorders after stroke. *Current Opinion in Neurology*, *29*(6), 706–713. http://doi.org/10.1097/WCO.0000000000000396

Ball, K., Edwards, J. D., Ross, L. A., & McGwin, G., Jr. (2010). Cognitive Training Decreases Motor Vehicle Collision Involvement of Older Drivers. *Journal of the American Geriatrics Society*, *58*(11), 2107–2113. http://doi.org/10.1111/j.1532-5415.2010.03138.x

Bekker, E. M., Kenemans, J. L., Hoeksma, M. R., Talsma, D., & Verbaten, M. N. (2005). The pure electrophysiology of stopping. *International Journal of Psychophysiology*, *55*(2), 191–198. http://doi.org/10.1016/j.ijpsycho.2004.07.005

Bellgrove, M. A., Hawi, Z., Gill, M., & Robertson, I. H. (2006). The Cognitive Genetics of Attention Deficit Hyperactivity Disorder (ADHD): Sustained attention as a Candidate Phenotype. *Cortex*, *42*(6), 838–845. http://doi.org/10.1016/S0010-9452(08)70426-X

Bennett, H. P., Corbett, A. J., Gaden, S., Grayson, D. A., Kril, J. J., & Broe, G. A. (2002). Subcortical Vascular Disease and Functional Decline: A 6-Year Predictor Study. *Journal of the American Geriatrics Society*, *50*(12), 1969–1977. http://doi.org/10.1046/j.1532-5415.2002.50608.x

Benwell, C. S. Y., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (9999). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex*, *69*(C), 152–165. http://doi.org/10.1016/j.cortex.2015.05.007

Berardi, A. M., Parasuraman, R., & Haxby, J. V. (2005). Sustained Attention in Mild Alzheimer's Disease. *Developmental Neuropsychology*, *28*(1), 507–537. http://doi.org/10.1207/s15326942dn2801_4

Berker, A. O. de, Bikson, M., & Bestmann, S. (2013). Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. *Front Hum Neurosci*, *7*. http://doi.org/10.3389/fnhum.2013.00613

Berridge, C. W., Devilbiss, D. M., Andrzejewski, M. E., Arnsten, A. F. T., Kelley, A. E., Schmeichel, B., et al. (2006). Methylphenidate Preferentially Increases Catecholamine Neurotransmission within the Prefrontal Cortex at Low Doses that Enhance Cognitive Function. *Biological Psychiatry*, *60*(10), 1111–1120. http://doi.org/10.1016/j.biopsych.2006.04.022

Berry, A. S., Zanto, T. P., Clapp, W. C., Hardy, J. L., & Delahunt, P. B. (2010). The influence of perceptual training on working memory in older adults. *PloS One*, *5*(7), e11537. http://doi.org/10.1371/journal.pone.0011537

Berryhill, M. E., & Jones, K. T. (2012). tDCS selectively improves working memory in older adults with more education. *Neuroscience Letters*, 1–4. http://doi.org/10.1016/j.neulet.2012.05.074

Bestmann, S., de Berker, A. O., & Bonaiuto, J. (2015). Understanding the behavioural consequences of noninvasive brain stimulation. *Trends in Cognitive Sciences*, *19*(1), 13–20. http://doi.org/10.1016/j.tics.2014.10.003

Bishop, S. J., Fossella, J., Croucher, C. J., & Duncan, J. (2008). COMT val158met Genotype Affects Recruitment of Neural Mechanisms Supporting Fluid Intelligence. *Cerebral Cortex*, *18*(9), 2132–2140. http://doi.org/10.1093/cercor/bhm240

Blanc-garin, J. (1994). Patterns of recovery from hemiplegia following stroke. *Neuropsychological Rehabilitation*, *4*(4), 359–385. http://doi.org/10.1080/09602019408401606

Boggio, P. S., Ferrucci, R., Rigonatti, S. P., & Covre, P. (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *Journal of the …*, *249*(1), 31–38. http://doi.org/10.1016/j.jns.2006.05.062

Bosch, B., Bartrés-Faz, D., Rami, L., Arenaza-Urquijo, E. M., Fernández-Espejo, D., Junqué, C., et al. (2010). Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. *Cortex*, *46*(4), 451–461. http://doi.org/10.1016/j.cortex.2009.05.006

Bowers, D., & Heilman, K. M. (1980). Pseudoneglect: Effects of hemispace on a tactile line bisection task. *Neuropsychologia*, *18*(4-5), 491–498. http://doi.org/10.1016/0028-3932(80)90151-7

Bradnam, L. V., Stinear, C. M., Barber, P. A., & Byblow, W. D. (2012). Contralesional Hemisphere Control of the Proximal Paretic Upper Limb following Stroke. *Cerebral Cortex*, *22*(11), 2662–2671. http://doi.org/10.1093/cercor/bhr344

Broadbent, D. E., Cooper, P. F., FitzGerald, P., & Parkes, K. R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of …*, *21*(1), 1–16. http://doi.org/10.1111/j.2044-8260.1982.tb01421.x

Broca, P. (1865). Sur le siège de la faculté du langage articulé.

Brown, J. W., & Jaffe, J. (1975). Hypothesis on cerebral dominance. *Neuropsychologia*, *13*(1), 107–110. http://doi.org/10.1016/0028-3932(75)90054-8

Bublak, P., Redel, P., & Finke, K. (2006). Spatial and non-spatial attention deficits in neurodegenerative diseases: Assessment based on Bundesen's theory of visual attention (TVA). *Restorative Neurology and* ….

Bublak, P., Redel, P., Sorg, C., Kurz, A., Förstl, H., Müller, H. J., et al. (2011). Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *32*(7), 1219–1230. http://doi.org/10.1016/j.neurobiolaging.2009.07.012

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*. http://doi.org/10.1038/nrn3214

Bundesen, C. (1990). A theory of visual attention. *Psychological Review*, *97*(4), 523–547. http://doi.org/10.1037/0033-295X.97.4.523

Bundesen, C., Habekost, T., & Kyllingsbæk, S. (2005). A Neural Theory of Visual Attention: Bridging Cognition and Neurophysiology. *Psychological Review*, *112*(2), 291–328. http://doi.org/10.1037/0033-295X.112.2.291

Bundesen, C., Habekost, T., & Kyllingsbæk, S. (2011). A neural theory of visual attention and short-term memory (NTVA). *Neuropsychologia*, *49*(6), 1446–1457. http://doi.org/10.1016/j.neuropsychologia.2010.12.006

Cabeza, R. (2002a). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. http://doi.org/10.1037/0882-7974.17.1.85

Cabeza, R. (2002b). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. http://doi.org/10.1037/0882-7974.17.1.85

Cabeza, R. (2004). Task-independent and Task-specific Age Effects on Brain Activity during Working Memory, Visual Attention and Episodic Retrieval. *Cerebral Cortex*, *14*(4), 364–375. http://doi.org/10.1093/cercor/bhg133

Carter, A. R., Astafiev, S. V., Lang, C. E., Connor, L. T., Rengachary, J., Strube, M. J., et al. (2010a). Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. *Annals of Neurology*, *67*(3), 365–375. http://doi.org/10.1002/ana.21905

Carter, M. E., Yizhar, O., Chikahisa, S., Nguyen, H., Adamantidis, A., Nishino, S., et al. (2010b). Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nature Neuroscience*, *13*(12), 1526–1533. http://doi.org/10.1038/nn.2682

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences*, *18*(8), 414–421. http://doi.org/10.1016/j.tics.2014.04.012

Chambers, C. D., Garavan, H. P., & Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neuroscience & Biobehavioral Reviews*, *33*(5), 631–646. http://doi.org/10.1016/j.neubiorev.2008.08.016

Chandler, D. J., Gao, W. J., & Waterhouse, B. D. (2014). Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. *Proceedings of the National Academy of Sciences*, *111*(18), 6816–6821. http://doi.org/10.1073/pnas.1320827111

Chechlacz, M., Gillebert, C. R., Vangkilde, S. A., Petersen, A., & Humphreys, G. W. (2015). Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention. *The Journal of Neuroscience*, *35*(30), 10647–10658. http://doi.org/10.1523/JNEUROSCI.0210-15.2015

Christopher deCharms, R. (2008). Applications of real-time fMRI. *Nature Reviews Neuroscience*, *9*(9), 720–729. http://doi.org/10.1038/nrn2414

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2015). The roles of cortical oscillations in sustained attention. *Trends in Cognitive Sciences*, *19*(4), 188–195. http://doi.org/10.1016/j.tics.2015.02.004

Clemens, B., Zvyagintsev, M., Sack, A., Heinecke, A., Willmes, K., & Sturm, W. (2011). Revealing the Functional Neuroanatomy of Intrinsic Alertness Using fMRI: Methodological Peculiarities. *PloS One*, *6*(9), e25453. http://doi.org/10.1371/journal.pone.0025453

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, *16*(9), 1348–1355. http://doi.org/10.1038/nn.3470

Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, *37*(1), 343–360. http://doi.org/10.1016/j.neuroimage.2007.03.071

Cooreman, B., Wiegand, I., Petersen, A., Vangkilde, S., & Bundesen, C. (2015). Cue-it? We say: Block-it! *Journal of Vision*, *15*(12), 1335. http://doi.org/10.1167/15.12.1335

Corbetta, M., & Shulman, G. L. (2002). CONTROL OF GOAL-DIRECTED AND STIMULUS-DRIVEN ATTENTION IN THE BRAIN. *Nature Reviews Neuroscience*, *3*(3), 215–229. http://doi.org/10.1038/nrn755

Corbetta, M., & Shulman, G. L. (2011). Spatial Neglect and Attention Networks. *Annu Rev Neurosci*, *34*(1), 569–599. http://doi.org/10.1146/annurev-neuro-061010-113731

Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., & Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature Neuroscience*, *8*(11), 1603–1610. http://doi.org/10.1038/nn1574

Coull, J. T., Jones, M. E. P., Egan, T. D., Frith, C. D., & Maze, M. (2004). Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. *NeuroImage*, *22*(1), 315–322.

Csikszentmihalyi, M., Abuhamdeh, S., & Nakamura, J. (2005). Handbook of competence and motivation. A. Elliot & C. Dweck (Eds.).

Csikszentmilhalyi, M., Csikszentmilhalyi, I., Graef, R., Holcomb, J. H., Hendin, J., & John, M. (1982). Beyond Boredom and Anxiety.

Daffner, K. R., Ryan, K. K., Williams, D. M., Budson, A. E., Rentz, D. M., Wolk, D. A., & Holcomb, P. J. (2006). Age-related differences in attention to novelty among cognitively high performing adults. *Biological Psychology*, *72*(1), 67–77. http://doi.org/10.1016/j.biopsycho.2005.07.006

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Qué PASA? The Posterior–Anterior Shift in Aging. *Cerebral Cortex*, *18*(5), 1201–1209. http://doi.org/10.1093/cercor/bhm155

Dawson, M. E., Schell, A. M., Filion, D. L., & Berntson, G. G. (2009). The Electrodermal System. (J. T. Cacioppo, L. G. Tassinary, & G. Berntson, Eds.)*Handbook of Psychophysiology* (3rd ed., pp. 157–181). Cambridge: Cambridge University Press. http://doi.org/10.1017/cbo9780511546396.007

De Sanctis, P., Katz, R., Wylie, G. R., Sehatpour, P., Alexopoulos, G. S., & Foxe, J. J. (2008). Enhanced and bilateralized visual sensory processing in the ventral stream may be a feature of normal aging. *Neurobiology of Aging*, *29*(10), 1576–1586. http://doi.org/10.1016/j.neurobiolaging.2007.03.021

de Schotten, M. T. (2005). Direct Evidence for a Parietal-Frontal Pathway Subserving Spatial Awareness in Humans. *Science*, *309*(5744), 2226–2228. http://doi.org/10.1126/science.1116251

de Villers-Sidani, E., Alzghoul, L., Zhou, X., Simpson, K. L., Lin, R. C. S., & Merzenich, M. M. (2010). Recovery of functional and structural age-related changes in the rat primary auditory cortex with operant training. *Proceedings of the National Academy of Sciences*, *107*(31), 13900–13905. http://doi.org/10.1073/pnas.1007885107

Deary, I. J., Johnson, W., & Starr, J. M. (2010). Are processing speed tasks biomarkers of cognitive aging? *Psychology and Aging*, *25*(1), 219–228. http://doi.org/10.1037/a0017750

Debecker, E., Laget, P., & Raimbault, J. (1978). Lateralization of norepinephrine in human thalamus. *Science*.

deBettencourt, M. T., Cohen, J. D., Lee, R. F., Norman, K. A., & Turk-Browne, N. B. (2015a). Closed-loop training of attention with real-time brain imaging. *Nature Neuroscience*, *18*(3), 470–475. http://doi.org/10.1038/nn.3940

deBettencourt, M. T., Cohen, J. D., Lee, R. F., Norman, K. A., & Turk-Browne, N. B. (2015b). Closed-loop training of attention with real-time brain imaging. *Nature Neuroscience*, *18*(3), 470–475. http://doi.org/10.1038/nn.3940

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences*, *102*(51), 18626–18631. http://doi.org/10.1073/pnas.0505210102

Demeyere, N., Riddoch, M. J., Slavkova, E. D., Bickerton, W.-L., & Humphreys, G. W. (2015). The Oxford Cognitive Screen (OCS): Validation of a stroke-specific short cognitive screening tool. *Psychological Assessment*, *27*(3), 883–894. http://doi.org/10.1037/pas0000082

Desimone, R., & Duncan, J. (1995). Neural Mechanisms of Selective Visual Attention. *Dx.Doi.org*, *18*(1), 193–222. http://doi.org/10.1146/annurev.ne.18.030195.001205

Di Lazzaro, V., Profice, P., Pilato, F., Capone, F., Ranieri, F., Pasqualetti, P., et al. (2010). Motor Cortex Plasticity Predicts Recovery in Acute Stroke. *Cerebral Cortex*, *20*(7), 1523–1528. http://doi.org/10.1093/cercor/bhp216

Ding, Y., Song, Y., Fan, S., Qu, Z., & Chen, L. (2003). Specificity and generalization of visual perceptual learning in humans: an event-related potential study. *Neuroreport*, *14*(4), 587.

Ditye, T., Jacobson, L., Walsh, V., & Lavidor, M. (2012). Modulating behavioral inhibition by tDCS combined with cognitive training, *219*(3), 363–368. http://doi.org/10.1007/s00221-012-3098-4

Dockree, P. M., Kelly, S. P., Robertson, I. H., & Reilly, R. B. (2005a). Neurophysiological markers of alert responding during goal-directed behavior: a high-density electrical mapping study. *NeuroImage*, *27*(3), 587–601. http://doi.org/10.1016/j.neuroimage.2005.05.044

Dockree, P. M., Kelly, S. P., Robertson, I. H., Reilly, R. B., & Foxe, J. J. (2005b). Neurophysiological markers of alert responding during goal-directed behavior: A high-density electrical mapping study. *NeuroImage*, *27*(3), 587–601. http://doi.org/10.1016/j.neuroimage.2005.05.044

Doricchi, F., Thiebaut de Schotten, M., Tomaiuolo, F., & Bartolomeo, P. (2008). White matter (dis)connections and gray matter (dys)functions in visual neglect: Gaining insights into the brain networks of spatial awareness. *Cortex*, *44*(8), 983–995. http://doi.org/10.1016/j.cortex.2008.03.006

Duncan, J. (2001). An adaptive coding model of neural function in prefrontal cortex. *Nature Reviews Neuroscience*. http://doi.org/10.1016/s1053-8119(01)92614-x

Duncan, J. (2013). The Structure of Cognition: Attentional Episodes in Mind and Brain. *Neuron*, *80*(1), 35–50. http://doi.org/10.1016/j.neuron.2013.09.015

Duncan, J., Bundesen, C., Olson, A., Humphreys, G., Chavda, S., & Shibuya, H. (1999a). Systematic analysis of deficits in visual attention. *Journal of Experimental Psychology: General*, *128*(4), 450–478. http://doi.org/10.1037//0096-3445.128.4.450

Duncan, J., Bundesen, C., Olson, A., Humphreys, G., Chavda, S., & Shibuya, H. (1999b). Systematic analysis of deficits in visual attention. *Journal of Experimental Psychology: General*, *128*(4), 450–478. http://doi.org/10.1037/0096-3445.128.4.450

Duncan, J., Seitz, R. J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., et al. (2000). A Neural Basis for

General Intelligence. *Science*, *289*(5478), 457–460. http://doi.org/10.1126/science.289.5478.457

Dyrholm, M., Kyllingsbæk, S., Espeseth, T., & Bundesen, C. (2011). Generalizing parametric models by introducing trial-by-trial parameter variability: The case of TVA. *Journal of Mathematical Psychology*, *55*(6), 416–429. http://doi.org/10.1016/j.jmp.2011.08.005

Edkins, G. D., & Pollock, C. M. (1997). The influence of sustained attention on Railway accidents. *Accident Analysis & Prevention*, *29*(4), 533–539. http://doi.org/10.1016/S0001-4575(97)00033-X

Egner, T., & Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature Neuroscience*, *8*(12), 1784–1790. http://doi.org/10.1038/nn1594

Erez, Y., & Duncan, J. (2015). Discrimination of Visual Categories Based on Behavioral Relevance in Widespread Regions of Frontoparietal Cortex. *The Journal of Neuroscience*, *35*(36), 12383–12393. http://doi.org/10.1523/JNEUROSCI.1134-15.2015

Espeseth, T., Vangkilde, S. A., Petersen, A., Dyrholm, M., & Westlye, L. T. (2014). TVA-based assessment of attentional capacities-associations with age and indices of brain white matter microstructure. *Frontiers in Psychology*, *5*, 71. http://doi.org/10.3389/fpsyg.2014.01177

Fassbender, C., Murphy, K., Foxe, J. J., Wylie, G. R., Javitt, D. C., Robertson, I. H., & Garavan, H. (2004). A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. *Cognitive Brain Research*, *20*(2), 132–143. http://doi.org/10.1016/j.cogbrainres.2004.02.007

Fedorenko, E., & Duncan, J. (2013). Broad domain generality in focal regions of frontal and parietal cortex. Presented at the Proceedings of the …. http://doi.org/10.1073/pnas.1315235110/-/DCSupplemental

Feigin, V. L., Forouzanfar, M. H., Krishnamurthi, R., Mensah, G. A., Connor, M., Bennett, D. A., et al. (2014). Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet*, *383*(9913), 245–255. http://doi.org/10.1016/S0140-6736(13)61953-4

Fertonani, A., & Miniussi, C. (2016). Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. *The Neuroscientist*, 1–15. http://doi.org/10.1177/1073858416631966

Fertonani, A., Brambilla, M., Cotelli, M., & Miniussi, C. (2014). The timing of cognitive plasticity in physiological aging: a tDCS study of naming. *Frontiers in Aging Neuroscience*, *6*.

Fertonani, A., Rosini, S., Cotelli, M., Rossini, P. M., & Miniussi, C. (2010). Naming facilitation induced by transcranial direct current stimulation. *Behavioural Brain Research*, *208*(2), 311–318. http://doi.org/10.1016/j.bbr.2009.10.030

Finke, K., Matthias, E., Keller, I., Müller, H. J., & Schneider, W. X. (2012). How does phasic alerting improve performance in patients with unilateral neglect? A systematic analysis of attentional processing capacity and spatial weighting …. *Neuropsychologia*, *50*(6), 1178–1189. http://doi.org/10.1016/j.neuropsychologia.2012.02.008

Foote, S. L., & Morrison, J. H. (1987). Extrathalamic Modulation of Cortical Function. *Annu Rev Neurosci*, *10*(1), 67–95. http://doi.org/10.1146/annurev.ne.10.030187.000435

Forkel, S. J., Thiebaut de Schotten, M., Dell'Acqua, F., Kalra, L., Murphy, D. G. M., Williams, S. C. R., & Catani, M. (2014). Anatomical predictors of aphasia recovery: a tractography study of bilateral perisylvian language networks. *Brain*, *137*(7), 2027–2039. http://doi.org/10.1093/brain/awu113

Franzmeier, N., Duering, M., Weiner, M., Dichgans, M., Ewers, M., For the Alzheimer's Disease Neuroimaging Initiative (ADNI). (2017). Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. *Neurology*, *88*(11), 1054–1061. http://doi.org/10.1212/WNL.0000000000003711

Freedman, D. J., Riesenhuber, M., Poggio, T., & Miller, E. K. (2001). Categorical Representation of Visual

Stimuli in the Primate Prefrontal Cortex. *Science*, *291*(5502), 312–316. http://doi.org/10.1126/science.291.5502.312

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, *9*(10), 474–480. http://doi.org/10.1016/j.tics.2005.08.011

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. *Neuron*, *66*(2), 198–204. http://doi.org/10.1016/j.neuron.2010.03.035

Fritz, J. B., Elhilali, M., & Shamma, S. A. (2007a). Adaptive Changes in Cortical Receptive Fields Induced by Attention to Complex Sounds. *Journal of Neurophysiology*, *98*(4), 2337–2346. http://doi.org/10.1152/jn.00552.2007

Fritz, J. B., Elhilali, M., David, S. V., & Shamma, S. A. (2007b). Does attention play a role in dynamic receptive field adaptation to changing acoustic salience in A1? *Hearing Research*, *229*(1-2), 186–203. http://doi.org/10.1016/j.heares.2007.01.009

Fu, M., & Zuo, Y. (2011). Experience-dependent structural plasticity in the cortex. *Trends in Neurosciences*, *34*(4), 177–187. http://doi.org/10.1016/j.tins.2011.02.001

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology*, *117*(4), 845–850.

Gard, T., Hölzel, B. K., & Lazar, S. W. (2014). The potential effects of meditation on age-related cognitive decline: a systematic review. *Annals of the New York Academy of Sciences*, *1307*(1), 89–103. http://doi.org/10.1111/nyas.12348

Gazzaley, A., & Nobre, A. C. (2012). Top-down modulation: bridging selective attention and working memory. *Trends in Cognitive Sciences*, *16*(2), 129–135. http://doi.org/10.1016/j.tics.2011.11.014

Gbadeyan, O., McMahon, K., Steinhauser, M., & Meinzer, M. (2016). Stimulation of Dorsolateral Prefrontal Cortex Enhances Adaptive Cognitive Control: A High-Definition Transcranial Direct Current Stimulation Study. *The Journal of Neuroscience*, *36*(50), 12530–12536. http://doi.org/10.1523/JNEUROSCI.2450-16.2016

Gilbert, J. R., & Moran, R. J. (2016). Inputs to prefrontal cortex support visual recognition in the aging brain. *Nature Publishing Group*, 1–9. http://doi.org/10.1038/srep31943

Greene, C. M., Bellgrove, M. A., Gill, M., & Robertson, I. H. (2009). Noradrenergic genotype predicts lapses in sustained attention. *Neuropsychologia*, *47*(2), 591–594. http://doi.org/10.1016/j.neuropsychologia.2008.10.003

Greenwood, P. M. (2000). The frontal aging hypothesis evaluated. *Journal of the International Neuropsychological Society*, *6*(6), 705–726. http://doi.org/10.1017/S1355617700666092

Grefkes, C., Nowak, D. A., Wang, L. E., Dafotakis, M., Eickhoff, S. B., & Fink, G. R. (2010a). Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. *NeuroImage*, *50*(1), 233–242. http://doi.org/10.1016/j.neuroimage.2009.12.029

Grefkes, C., Wang, L. E., Eickhoff, S. B., & Fink, G. R. (2010b). Noradrenergic Modulation of Cortical Networks Engaged in Visuomotor Processing. *Cerebral Cortex*, *20*(4), 783–797. http://doi.org/10.1093/cercor/bhp144

Gregory, T., Nettelbeck, T., Howard, S., & Wilson, C. (2008). Inspection Time: A biomarker for cognitive decline. *Intelligence*, *36*(6), 664–671. http://doi.org/10.1016/j.intell.2008.03.005

Habekost, T. (2015). Clinical TVA-based studies: a general review. *Frontiers in Psychology*, *6*(1177), 71–18. http://doi.org/10.3389/fpsyg.2015.00290

Habekost, T., & Rostrup, E. (2006). Persisting asymmetries of vision after right side lesions.

Neuropsychologia, *44*(6), 876–895. http://doi.org/10.1016/j.neuropsychologia.2005.09.002

Habekost, T., & Rostrup, E. (2007). Visual attention capacity after right hemisphere lesions. *Neuropsychologia*, *45*(7), 1474–1488. http://doi.org/10.1016/j.neuropsychologia.2006.11.006

Habekost, T., & STARRFELT, R. (2009). Visual attention capacity: A review of TVA-based patient studies. *Scandinavian Journal of Psychology*, *50*(1), 23–32. http://doi.org/10.1111/j.1467-9450.2008.00681.x

Habekost, T., VOGEL, A., Rostrup, E., Bundesen, C., Kyllingsbæk, S., GARDE, E., et al. (2013). Visual processing speed in old age. *Scandinavian Journal of Psychology*, *54*(2), 89–94. http://doi.org/10.1111/sjop.12008

Habes, I., Rushton, S., Johnston, S. J., Sokunbi, M. O., Barawi, K., Brosnan, M., et al. (2016). fMRI neurofeedback of higher visual areas and perceptual biases. *Neuropsychologia*, *85*(C), 208–215. http://doi.org/10.1016/j.neuropsychologia.2016.03.031

Hagler, D. J., Jr., & Sereno, M. I. (2006). Spatial maps in frontal and prefrontal cortex. *NeuroImage*, *29*(2), 567–577. http://doi.org/10.1016/j.neuroimage.2005.08.058

Hallett, M. (2001). Plasticity of the human motor cortex and recovery from stroke. *Brain Research Reviews*, *36*(2-3), 169–174. http://doi.org/10.1016/S0165-0173(01)00092-3

Harley, C. W. (2004). Norepinephrine and Dopamine as Learning Signals. *Neural Plasticity*, *11*(3-4), 191–204. http://doi.org/10.1155/NP.2004.191

Harty, S., O'Connell, R. G., & Hester, R. (2013). Older adults have diminished awareness of errors in the laboratory and daily life. *Psychology and Aging*, *28*(4), 1032–1041. http://doi.org/10.1037/a0033567

Harty, S., Robertson, I. H., Miniussi, C., Sheehy, O. C., Devine, C. A., McCreery, S., & O'Connell, R. G. (2014a). Transcranial Direct Current Stimulation over Right Dorsolateral Prefrontal Cortex Enhances Error Awareness in Older Age. *The Journal of Neuroscience*, *34*(10), 3646–3652. http://doi.org/10.1523/JNEUROSCI.5308-13.2014

Harty, S., Robertson, I. H., Miniussi, C., Sheehy, O. C., Devine, C. A., McCreery, S., & O'Connell, R. G. (2014b). Transcranial Direct Current Stimulation over Right Dorsolateral Prefrontal Cortex Enhances Error Awareness in Older Age. *The Journal of Neuroscience*, *34*(10), 3646–3652. http://doi.org/10.1523/JNEUROSCI.5308-13.2014

Harwood, D. G. (2005). Frontal Lobe Hypometabolism and Impaired Insight in Alzheimer Disease. *American Journal of Geriatric Psychiatry*, *13*(11), 934–941. http://doi.org/10.1176/appi.ajgp.13.11.934

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of Functional Connectivity in Frontoparietal Networks Underlies Behavioral Deficits in Spatial Neglect. *Neuron*, *53*(6), 905–918. http://doi.org/10.1016/j.neuron.2007.02.013

Heilman, K. M., Bowers, D., Coslett, H. B., Whelan, H., & Watson, R. T. (1985). Directional hypokinesia Prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect. *Neurology*, *35*(6), 855–855. http://doi.org/10.1212/WNL.35.6.855

Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., Münte, T. F., et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *, Published Online: 08 December 1994; | Doi:10.1038/372543a0*, *372*(6506), 543–546. http://doi.org/10.1038/372543a0

Helfrich, R. F., & Knight, R. T. (2016). Oscillatory Dynamics of Prefrontal Cognitive Control. *Trends in Cognitive Sciences*, *20*(12), 916–930. http://doi.org/10.1016/j.tics.2016.09.007

Helfrich, R. F., Knepper, H., Nolte, G., Strüber, D., Rach, S., Herrmann, C. S., et al. (2014). Selective Modulation of Interhemispheric Functional Connectivity by HD-tACS Shapes Perception. *PLOS Biology*, *12*(12), e1002031. http://doi.org/10.1371/journal.pbio.1002031

Hillyard, S. A., & Anllo-Vento, L. (1998). Event-related brain potentials in the study of visual selective attention. *Proceedings of the National Academy of Sciences*, *95*(3), 781–787. http://doi.org/10.1073/pnas.95.3.781

Hirase, H., Iwai, Y., Takata, N., Shinohara, Y., & Mishima, T. (2014). Volume transmission signalling via astrocytes. *Phil. Trans. R. Soc. B*, *369*(1654), 20130604–20130604. http://doi.org/10.1098/rstb.2013.0604

Hsu, W.-Y., Ku, Y., Zanto, T. P., & Gazzaley, A. (2015). Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. *Neurobiology of Aging*, *36*(8), 2348–2359. http://doi.org/10.1016/j.neurobiolaging.2015.04.016

Hurley, L., Devilbiss, D., & Waterhouse, B. (2004). A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks. *Current Opinion in Neurobiology*, *14*(4), 488–495. http://doi.org/10.1016/j.conb.2004.06.007

Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, *4*(1), 26–36. http://doi.org/10.1038/nrn1005

International, A. D. (2015). World Alzheimer Report 2015, The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends, 1–87.

Jäkälä, P., Riekkinen, M., Sirviö, J., Koivisto, E., Kejonen, K., Matti, & Riekkinen, P. (1999). Guanfacine, But Not Clonidine, Improves Planning and Working Memory Performance in Humans. *Neuropsychopharmacology*, *20*(5), 460–470. http://doi.org/10.1016/S0893-133X(98)00127-4

Jo, J. M., Kim, Y. H., Ko, M. H., Ohn, S. H., & Joen, B. (2009). Enhancing the working memory of stroke patients using tDCS. *American Journal of …*, *88*(5), 404–409. http://doi.org/10.1097/phm.0b013e3181a0e4cb

Jodo, E., & Aston-Jones, G. (1997). Activation of locus coeruleus by prefrontal cortex is mediated by excitatory amino acid inputs. *Brain Research*, *768*(1-2), 327–332. http://doi.org/10.1016/S0006-8993(97)00703-8

Jodo, E., & Kayama, Y. (1992). Relation of a negative ERP component to response inhibition in a Go/No-go task. *Electroencephalography and Clinical Neurophysiology*, *82*(6), 477–482. http://doi.org/http://dx.doi.org/10.1016/0013-4694(92)90054-L

Jodoj, E., Chiang, C., & Aston-Jones, G. (1998). Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience*, *83*(1), 63–79. http://doi.org/10.1016/S0306-4522(97)00372-2

Johannsen, P., Jakobsen, J., Bruhn, P., Hansen, S. B., Gee, A., Stødkilde-Jørgensen, H., & Gjedde, A. (1997). Cortical Sites of Sustained and Divided Attention in Normal Elderly Humans. *NeuroImage*, *6*(3), 145–155. http://doi.org/10.1006/nimg.1997.0292

Johansen-Berg, H., Dawes, H., Guy, C., Smith, S. M., Wade, D. T., & Matthews, P. M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*, *125*(12), 2731–2742. http://doi.org/10.1093/brain/awf282

Kadosh, R. C. (2015). Modulating and enhancing cognition using brain stimulation: Science and fiction. *Journal of Cognitive Psychology*, *27*(2), 141–163. http://doi.org/10.1080/20445911.2014.996569

Kadosh, R. C., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating Neuronal Activity Produces Specific and Long-Lasting Changes in Numerical Competence. *Current Biology*, *20*(22), 2016–2020. http://doi.org/10.1016/j.cub.2010.10.007

Kalu, U. G., Sexton, C. E., Loo, C. K., & Ebmeier, K. P. (2012). Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychological Medicine*, *42*(9), 1791–1800. http://doi.org/10.1017/S0033291711003059

Kamke, M. R., Hall, M. G., Lye, H. F., Sale, M. V., Fenlon, L. R., Carroll, T. J., et al. (2012). Visual Attentional Load Influences Plasticity in the Human Motor Cortex. *The Journal of Neuroscience*, *32*(20), 7001–7008. http://doi.org/10.1523/JNEUROSCI.1028-12.2012

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The Fusiform Face Area: A Module in Human Extrastriate Cortex Specialized for Face Perception. *The Journal of Neuroscience*, *17*(11), 4302–4311. http://doi.org/10.1523/JNEUROSCI.1706-16.2016

Kastner, S., DeSimone, K., Konen, C. S., Szczepanski, S. M., Weiner, K. S., & Schneider, K. A. (2007). Topographic Maps in Human Frontal Cortex Revealed in Memory-Guided Saccade and Spatial Working-Memory Tasks. *Journal of Neurophysiology*, *97*(5), 3494–3507. http://doi.org/10.1152/jn.00010.2007

Kerchner, G. A., Racine, C. A., Hale, S., Wilheim, R., Laluz, V., Miller, B. L., & Kramer, J. H. (2012). Cognitive Processing Speed in Older Adults: Relationship with White Matter Integrity. *PloS One*, *7*(11), e50425. http://doi.org/10.1371/journal.pone.0050425

Kesler, S. R., Adams, H. F., Blasey, C. M., & Bigler, E. D. (2003). Premorbid Intellectual Functioning, Education, and Brain Size in Traumatic Brain Injury: An Investigation of the Cognitive Reserve Hypothesis. *Applied Neuropsychology*, *10*(3), 153–162. http://doi.org/10.1207/S15324826AN1003_04

Kievit, R. A., Davis, S. W., Mitchell, D. J., Taylor, J. R., Duncan, J., Tyler, L. K., et al. (2014). Distinct aspects of frontal lobe structure mediate age-related differences in fluid intelligence and multitasking. *Nature Communications*, *5*, 5658. http://doi.org/10.1038/ncomms6658

Killingsworth, M. A., & Gilbert, D. T. (2010). A Wandering Mind Is an Unhappy Mind. *Science*, *330*(6006), 932–932. http://doi.org/10.1126/science.1192439

Kyllingsbæk, S. (2006). Modeling visual attention. *Behavior Research Methods*, *38*(1), 123–133. http://doi.org/10.3758/BF03192757

Laakso, I., Tanaka, S., Koyama, S., De Santis, V., & Hirata, A. (2015). Inter-subject Variability in Electric Fields of Motor Cortical tDCS. *Brain Stimulation*, 1–8. http://doi.org/10.1016/j.brs.2015.05.002

Langner, R., & Eickhoff, S. B. (2013a). Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*. http://doi.org/10.1037/a0030694.supp

Langner, R., & Eickhoff, S. B. (2013b). Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*, *139*(4), 870–900. http://doi.org/10.1037/a0030694

Lapiz, M. D. S., & Morilak, D. A. (2006). Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. *Neuroscience*, *137*(3), 1039–1049. http://doi.org/10.1016/j.neuroscience.2005.09.031

Lawrence, N. S., Ross, T. J., & Hoffmann, R. (2003). Multiple neuronal networks mediate sustained attention. *Journal of Cognitive Neuroscience*, *15*(7), 1028–1038. http://doi.org/10.1162/089892903770007416

Làdavas, E., Giulietti, S., Avenanti, A., Bertini, C., Lorenzini, E., Quinquinio, C., & Serino, A. (2015). a-tDCS on the ipsilesional parietal cortex boosts the effects of prism adaptation treatment in neglect. *Restorative Neurology and Neuroscience*, *33*(5), 647–662. http://doi.org/10.3233/RNN-140464

Learmonth, G., Thut, G., Benwell, C. S. Y., & Harvey, M. (2015). The implications of state-dependent tDCS effects in aging_ Behavioural response is determined by baseline performance. *Neuropsychologia*, 1–12. http://doi.org/10.1016/j.neuropsychologia.2015.01.037

Lee, T. G., & D'Esposito, M. (2012). The Dynamic Nature of Top-Down Signals Originating from Prefrontal Cortex: A Combined fMRI-TMS Study. *The Journal of Neuroscience*, *32*(44), 15458–15466. http://doi.org/10.1523/JNEUROSCI.0627-12.2012

Lenehan, M. E., Summers, M. J., Saunders, N. L., Summers, J. J., Ward, D. D., Ritchie, K., & Vickers, J. C. (2016). Sending your grandparents to university increases cognitive reserve: The Tasmanian Healthy Brain Project. *Neuropsychology*, *30*(5), 525–531. http://doi.org/10.1037/neu0000249

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in Cellular Neuroscience*, *9*(180), 898. http://doi.org/10.3389/fncel.2015.00181

Liebe, S., Hoerzer, G. M., Logothetis, N. K., & Rainer, G. (2012). Theta coupling between V4 and prefrontal cortex predicts visual short-term memory performance. *Nature Neuroscience*, *15*(3), 456–462. http://doi.org/10.1038/nn.3038

Linden, D. E. J. (2016). Functional Magnetic Resonance Imaging Neurofeedback-guided Motor Imagery Training and Motor Training for Parkinson's Disease: Randomized Trial. *Frontiers in Behavioral Neuroscience*, *10*, 1–13. http://doi.org/10.3389/fnbeh.2016.00111

Linden, D. E. J., Habes, I., Johnston, S. J., Linden, S., Tatineni, R., Subramanian, L., et al. (2012). Real-Time Self-Regulation of Emotion Networks in Patients with Depression. *PloS One*, *7*(6), e38115. http://doi.org/10.1371/journal.pone.0038115

MacLean, K. A., Ferrer, E., Aichele, S. R., Bridwell, D. A., Zanesco, A. P., Jacobs, T. L., et al. (2010). Intensive Meditation Training Improves Perceptual Discrimination and Sustained Attention. *Psychological Science*, *21*(6), 829–839. http://doi.org/10.1177/0956797610371339

Macmillan, N. A., & Creelman, C. D. (2004). Detection Theory. Psychology Press.

Madden, D. J., Spaniol, J., Whiting, W. L., Bucur, B., Provenzale, J. M., Cabeza, R., et al. (2007). Adult age differences in the functional neuroanatomy of visual attention: A combined fMRI and DTI study. *Neurobiology of Aging*, *28*(3), 459–476. http://doi.org/10.1016/j.neurobiolaging.2006.01.005

Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., Wood, R. A., et al. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: A randomized, controlled study. *Proceedings of the National Academy of Sciences*, *103*(33), 12523–12528. http://doi.org/10.1073/pnas.0605194103

Malhotra, P. A., Parton, A. D., Greenwood, R., & Husain, M. (2006). Noradrenergic modulation of space exploration in visual neglect. *Annals of Neurology*, *59*(1), 186–190. http://doi.org/10.1002/ana.20701

Malhotra, P., Coulthard, E. J., & Husain, M. (2009). Role of right posterior parietal cortex in maintaining attention to spatial locations over time. *Brain*, *132*(3), awn350–660. http://doi.org/10.1093/brain/awn350

Mangun, G. R., Buonocore, M. H., Girelli, M., & Jha, A. P. (1998). ERP and fMRI measures of visual spatial selective attention. *Human Brain Mapping*, *6*(5-6), 383–389. http://doi.org/10.1002/(SICI)1097-0193(1998)6:5/6<383::AID-HBM10>3.0.CO;2-Z

Manly, T., Owen, A. M., McAvinue, L., Datta, A., Lewis, G. H., Scott, S. K., et al. (2003). Enhancing the Sensitivity of a Sustained Attention Task to Frontal Damage: Convergent Clinical and Functional Imaging Evidence. *Neurocase*, *9*(4), 340–349. http://doi.org/10.1076/neur.9.4.340.15553

Manuel, A. L., Grivel, J., Bernasconi, F., Murray, M. M., & Spierer, L. (2010). Brain Dynamics Underlying Training-Induced Improvement in Suppressing Inappropriate Action. *The Journal of Neuroscience*, *30*(41), 13670–13678. http://doi.org/10.1523/JNEUROSCI.2064-10.2010

Marangolo, P., Fiori, V., Sabatini, U., De Pasquale, G., Razzano, C., Caltagirone, C., & Gili, T. (2016). Bilateral Transcranial Direct Current Stimulation Language Treatment Enhances Functional Connectivity in the Left Hemisphere: Preliminary Data from Aphasia. *Journal of Cognitive Neuroscience*, *28*(5), 724–738. http://doi.org/10.1162/jocn_a_00927

Marshall, T. R., Bergmann, T. O., & Jensen, O. (2015). Frontoparietal Structural Connectivity Mediates the Top-Down Control of Neuronal Synchronization Associated with Selective Attention. *PLOS*

Biology, *13*(10), e1002272. http://doi.org/10.1371/journal.pbio.1002272

Massa, M. S., Wang, N., Bickerton, W. L., & Demeyere, N. (2015). On the importance of cognitive profiling: A graphical modelling analysis of domain-specific and domain-general deficits after stroke. *Cortex*, *71*, 190–204. http://doi.org/10.1016/j.cortex.2015.06.006

Matthias, E., Bublak, P., Costa, A., Müller, H. J., Schneider, W. X., & Finke, K. (2009). Attentional and sensory effects of lowered levels of intrinsic alertness. *Neuropsychologia*, *47*(14), 3255–3264. http://doi.org/10.1016/j.neuropsychologia.2009.08.004

McAvinue, L. P., Habekost, T., Johnson, K. A., Kyllingsbæk, S., Vangkilde, S., Bundesen, C., & Robertson, I. H. (2012). Sustained attention, attentional selectivity, and attentional capacity across the lifespan. *Attention, Perception, & Psychophysics*, *74*(8), 1570–1582. http://doi.org/10.3758/s13414-012-0352-6

McAvinue, L., O'Keeffe, F., McMackin, D., & Robertson, I. (2005). Impaired sustained attention and error awareness in traumatic brain injury: Implications for insight. *Neuropsychological Rehabilitation*, *15*(5), 569–587. http://doi.org/10.1080/09602010443000119

McGaughy, J., Ross, R. S., & Eichenbaum, H. (2008). Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. *Neuroscience*, *153*(1), 63–71. http://doi.org/10.1016/j.neuroscience.2008.01.064

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Floel, A. (2013). Anodal Transcranial Direct Current Stimulation Temporarily Reverses Age-Associated Cognitive Decline and Functional Brain Activity Changes. *The Journal of Neuroscience*, *33*(30), 12470–12478. http://doi.org/10.1523/JNEUROSCI.5743-12.2013

Mendez, M. F., & Shapira, J. S. (2005). Loss of Insight and Functional Neuroimaging in Frontotemporal Dementia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(3), 413–416. http://doi.org/10.1176/appi.neuropsych.17.3.413

Milewski-Lopez, A., Greco, E., van den Berg, F., McAvinue, L. P., McGuire, S., & Robertson, I. H. (2014). An evaluation of alertness training for older adults. *Frontiers in Aging Neuroscience*, *6*(60), 843. http://doi.org/10.3389/fnagi.2014.00067

Miller, C. E., Shapiro, K. L., & Luck, S. J. (2015). Electrophysiological measurement of the effect of inter-stimulus competition on early cortical stages of human vision. *NeuroImage*, *105*, 229–237. http://doi.org/10.1016/j.neuroimage.2014.10.033

Mishra, J., Rolle, C., & Gazzaley, A. (2014). Neural plasticity underlying visual perceptual learning in aging. *Brain Research*, 1–12. http://doi.org/10.1016/j.brainres.2014.09.009

Monai, H., & Hirase, H. (2016). Astrocytic calcium activation in a mouse model of tDCS—Extended discussion. *Neurogenesis*, *3*(1), e1240055. http://doi.org/10.1080/23262133.2016.1240055

Monai, H., Ohkura, M., Tanaka, M., Oe, Y., Konno, A., Hirai, H., et al. (2016). Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. *Nature Communications*, *7*, 1–10. http://doi.org/10.1038/ncomms11100

Murase, N., Duque, J., Mazzocchio, R., & Cohen, L. G. (2004). Influence of interhemispheric interactions on motor function in chronic stroke. *Annals of Neurology*, *55*(3), 400–409. http://doi.org/10.1002/ana.10848

Murphy, P. R., O'Connell, R. G., & O'Sullivan, M. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Human Brain …*. http://doi.org/10.1002/hbm.22466/full

NA. (1991). American Electroencephalographic Society Guidelines for Standard Electrode Position Nomenclature. *Journal of Clinical Neurophysiology*, *8*(2), 200–202. http://doi.org/10.1097/00004691-199104000-00007

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. http://doi.org/10.1111/j.1532-5415.2005.53221.x

Nelissen, N., Stokes, M., Nobre, A. C., & Rushworth, M. F. S. (2013). Frontal and Parietal Cortical Interactions with Distributed Visual Representations during Selective Attention and Action Selection. *The Journal of Neuroscience*, *33*(42), 16443–16458. http://doi.org/10.1523/JNEUROSCI.2625-13.2013

Nelson, H. E. (1982). National Adult Reading Test (NART): For the assessment of premorbid intelligence in patients with dementia: Test manual.

Nelson, J. T., McKinley, R. A., Golob, E. J., Warm, J. S., & Parasuraman, R. (2014). Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *NeuroImage*, *85*(P3), 909–917. http://doi.org/10.1016/j.neuroimage.2012.11.061

Newhouse, P. (2004). Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology*, *4*(1), 36–46. http://doi.org/10.1016/j.coph.2003.11.001

Newsome, W. T., & Pare, E. B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *Journal of Neuroscience*.

Nicholls, M. E. R., Bradshaw, J. L., & Mattingley, J. B. (1999). Free-viewing perceptual asymmetries for the judgement of brightness, numerosity and size. *Neuropsychologia*, *37*(3), 307–314. http://doi.org/10.1016/S0028-3932(98)00074-8

Nielsen, S. (2015). Cognitive aging on latent constructs for visual processing capacity: a novel structural equation modeling framework with causal assumptions based on a theory of visual attention, 1–13. http://doi.org/10.3389/fpsyg.2014.01596/abstract

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(3), 633–639.

Nitsche, M. A., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2009). Treatment of depression with transcranial direct current stimulation (tDCS): A Review. *Experimental Neurology*, *219*(1), 14–19.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., et al. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. http://doi.org/10.1016/j.brs.2008.06.004

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2006). Facilitation of Implicit Motor Learning by Weak Transcranial Direct Current Stimulation of the Primary Motor Cortex in the Human. *Dx.Doi.org*, *15*(4), 619–626. http://doi.org/10.1162/089892903321662994

Nowak, D. A., Grefkes, C., Dafotakis, M., Eickhoff, S., Küst, J., Karbe, H., & Fink, G. R. (2008). Effects of Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Contralesional Primary Motor Cortex on Movement Kinematics and Neural Activity in Subcortical Stroke. *Archives of Neurology*, *65*(6), 741–747. http://doi.org/10.1001/archneur.65.6.741

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research*. http://doi.org/10.3275/7800

O'Connell, R. G., Bellgrove, M. A., Dockree, P. M., & Lau, A. (2008a). Self-alert training: Volitional modulation of autonomic arousal improves sustained attention. *Neuropsychologia*, *46*(5), 1379–1390. http://doi.org/10.1016/j.neuropsychologia.2007.12.018

O'Connell, R. G., Bellgrove, M. A., Dockree, P. M., & Lau, A. (2008b). Self-alert training: Volitional modulation of autonomic arousal improves sustained attention. *Neuropsychologia*, *46*(5), 1379–1390. http://doi.org/10.1016/j.neuropsychologia.2007.12.018

O'Connell, R. G., Dockree, P. M., Bellgrove, M. A., Turin, A., Ward, S., Foxe, J. J., & Robertson, I. H. (2009a). Two types of action error: electrophysiological evidence for separable inhibitory and sustained attention neural mechanisms producing error on go/no-go tasks. *Journal of Cognitive Neuroscience*, *21*(1), 93–104. http://doi.org/10.1162/jocn.2009.21008

O'Connell, R. G., Dockree, P. M., Robertson, I. H., Bellgrove, M. A., Foxe, J. J., & Kelly, S. P. (2009b). Uncovering the Neural Signature of Lapsing Attention: Electrophysiological Signals Predict Errors up to 20 s before They Occur. *Journal of Neuroscience*, *29*(26), 8604–8611. http://doi.org/10.1523/jneurosci.5967-08.2009

O'Connell, R. G., Schneider, D., Hester, R., Mattingley, J. B., & Bellgrove, M. A. (2011). Attentional Load Asymmetrically Affects Early Electrophysiological Indices of Visual Orienting. *Cerebral Cortex*, *21*(5), 1056–1065. http://doi.org/10.1093/cercor/bhq178

O'Connor, C., Robertson, I. H., & Levine, B. (2011). The prosthetics of vigilant attention: Random cuing cuts processing demands. *Neuropsychology*, *25*(4), 535–543. http://doi.org/10.1037/a0022767

O'Halloran, A. M., Pénard, N., Galli, A., & Fan, C. W. (2011). Falls and falls efficacy: the role of sustained attention in older adults. *BMC Geriatrics*, *11*(1), 85. http://doi.org/10.1186/1471-2318-11-85

O'Keeffe, F. M., Murray, B., Coen, R. F., Dockree, P. M., Bellgrove, M. A., Garavan, H., et al. (2007). Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. *Brain*, *130*(3), 753–764. http://doi.org/10.1093/brain/awl367

O'Neill, J., Fitten, L. J., Siembieda, D. W., Ortiz, F., & Halgren, E. (2000). Effects of guanfacine on three forms of distraction in the aging macaque. *Life Sciences*, *67*(8), 877–885. http://doi.org/10.1016/S0024-3205(00)00681-0

Ojala-Oksala, J., Jokinen, H., Kopsi, V., & Lehtonen, K. (2012). Educational history is an independent predictor of cognitive deficits and long-term survival in postacute patients with mild to moderate ischemic stroke. *Stroke*, *43*(11), 2931–2935. http://doi.org/10.1161/strokeaha.112.667618

Olgiati, E., Russell, C., Soto, D., & Malhotra, P. (2016). Motivation and attention following hemispheric stroke. *Progress in Brain Research* (Vol. 229, pp. 343–366). Elsevier. http://doi.org/10.1016/bs.pbr.2016.06.011

Opdebeeck, C., Martyr, A., & Clare, L. (2015). Cognitive reserve and cognitive function in healthy older people: a meta-analysis. *Aging, Neuropsychology, and Cognition*, *23*(1), 40–60. http://doi.org/10.1080/13825585.2015.1041450

Opitz, A., Paulus, W., Will, S., Antunes, A., & Thielscher, A. (2015). Determinants of the electric field during transcranial direct current stimulation. *NeuroImage*, *109*(C), 140–150. http://doi.org/10.1016/j.neuroimage.2015.01.033

O'Halloran, A. M., Finucane, C., Savva, G. M., Robertson, I. H., & Kenny, R. A. (2013). Sustained attention and frailty in the older adult population. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*.

Park, D. C., Lodi-Smith, J., Drew, L., Haber, S., Hebrank, A., Bischof, G. N., & Aamodt, W. (2014a). The Impact of Sustained Engagement on Cognitive Function in Older Adults: The Synapse Project. *Psychological Science*, *25*(1), 103–112. http://doi.org/10.1177/0956797613499592

Park, S. H., Seo, J. H., Kim, Y. H., & Ko, M. H. (2014b). Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. *Neuroreport*, *25*(2), 122–126. http://doi.org/10.1097/wnr.0000000000000080

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia*, *38*(3), 252–271. http://doi.org/10.1016/S0028-3932(99)00079-2

Podda, M. V., Cocco, S., Mastrodonato, A., Fusco, S., Leone, L., Barbati, S. A., et al. (2016). Anodal

transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. *Scientific Reports*, *6*, 22180. http://doi.org/10.1038/srep22180

Polley, D. B., Steinberg, E. E., & Merzenich, M. M. (2006). Perceptual Learning Directs Auditory Cortical Map Reorganization through Top-Down Influences. *The Journal of Neuroscience*, *26*(18), 4970–4982. http://doi.org/10.1523/JNEUROSCI.3771-05.2006

Posner, M. I., & Petersen, S. E. (1990). The Attention System of the Human Brain. *Annu Rev Neurosci*, *13*(1), 25–42. http://doi.org/10.1146/annurev.ne.13.030190.000325

Prakash, R., Rastogi, P., Dubey, I., Abhishek, P., Chaudhury, S., & Small, B. J. (2012). Long-term concentrative meditation and cognitive performance among older adults. *Aging, Neuropsychology, and Cognition*, *19*(4), 479–494. http://doi.org/10.1080/13825585.2011.630932

Raizada, R. D. S., & Poldrack, R. A. (2008). Challenge-driven attention: interacting frontal and brainstem systems. *Front Hum Neurosci*, *2*. http://doi.org/10.3389/neuro.09.003.2007

Rajkowski, J., Kubiak, P., Ivanova, S., & Aston-Jones, G. (1997). State-Related Activity, Reactivity of Locus Ceruleus Neurons in Behaving Monkeys (Vol. 42, pp. 740–744). Elsevier.

Ramsey, L. E., Siegel, J. S., Baldassarre, A., Metcalf, N. V., Zinn, K., Shulman, G. L., & Corbetta, M. (2016). Normalization of network connectivity in hemispatial neglect recovery. *Annals of Neurology*, *80*(1), 127–141. http://doi.org/10.1002/ana.24690

Raz, A., & Buhle, J. (2006). Typologies of attentional networks. *Nature Reviews Neuroscience*, *7*(5), 367–379. http://doi.org/10.1038/nrn1903

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cerebral Cortex*, *15*(11), 1676–1689. http://doi.org/10.1093/cercor/bhi044

Rebok, G. W., Ball, K., Guey, L. T., Jones, R. N., Kim, H.-Y., King, J. W., et al. (2014). Ten-Year Effects of the Advanced Cognitive Training for Independent and Vital Elderly Cognitive Training Trial on Cognition and Everyday Functioning in Older Adults. *Journal of the American Geriatrics Society*, *62*(1), 16–24. http://doi.org/10.1111/jgs.12607

Recanzone, G. H., Schreiner, C. E., & Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *The Journal of Neuroscience*, *13*(1), 87–103.

Redel, P., Bublak, P., Sorg, C., Kurz, A., Förstl, H., Müller, H. J., et al. (2012). Deficits of spatial and task-related attentional selection in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *33*(1), 195.e27–195.e42. http://doi.org/10.1016/j.neurobiolaging.2010.05.014

Rehme, A. K., Eickhoff, S. B., Rottschy, C., Fink, G. R., & Grefkes, C. (2012). Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. *NeuroImage*, *59*(3), 2771–2782. http://doi.org/10.1016/j.neuroimage.2011.10.023

Rengachary, J., He, B. J., Shulman, G. L., & Corbetta, M. (2011). A Behavioral Analysis of Spatial Neglect and its Recovery After Stroke. *Front Hum Neurosci*, *5*. http://doi.org/10.3389/fnhum.2011.00029

Reuter-Lorenz, P. A., Jonides, J., & Smith, E. E. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience*, *12*(1), 174–187. http://doi.org/10.1162/089892900561814

Ritchie, S. J., Tucker-Drob, E. M., & Deary, I. J. (2014). A strong link between speed of visual discrimination and cognitive ageing. *Current Biology*.

Robertson, I. H. (2003). The absent mind: attention and error. *The Psychologist*, *16*, 476–479.

Robertson, I. H. (2013). A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. *Neurobiology of Aging*, *34*(1), 298–308. http://doi.org/10.1016/j.neurobiolaging.2012.05.019

Robertson, I. H. (2014). A right hemisphere role in cognitive reserve. *Neurobiology of Aging*, *35*(6), 1375–1385. http://doi.org/10.1016/j.neurobiolaging.2013.11.028

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997a). `Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*, *35*(6), 747–758. http://doi.org/10.1016/S0028-3932(97)00015-8

Robertson, I. H., Manly, T., Beschin, N., & Daini, R. (1997b). Auditory sustained attention is a marker of unilateral spatial neglect. *Neuropsychologia*, *35*(12), 1527–1532. http://doi.org/10.1016/s0028-3932(97)00084-5

Robertson, I. H., Mattingley, J. B., Rorden, C., & Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature*, *395*(6698), 169–172. http://doi.org/10.1038/25993

Robertson, I. H., Ridgeway, V., Greenfield, E., & Parr, A. (1997c). Motor recovery after stroke depends on intact sustained attention: a 2-year follow-up study. *Neuropsychology*, *11*(2), 290.

Robertson, I. H., Tegnér, R., Tham, K., & Lo, A. (1995). Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. *Journal of Clinical …*, *17*(3), 416–430. http://doi.org/10.1080/01688639508405133

Robinson, R. (1979a). Differential behavioral and biochemical effects of right and left hemispheric cerebral infarction in the rat. *Science*, *205*(4407), 707–710. http://doi.org/10.1126/science.462179

Robinson, R. G. (1979b). Differential behavioral and biochemical effects of right and left hemispheric cerebral infarction in the rat. *Science*, *205*(4407), 707–710. http://doi.org/10.1126/science.462179

Robinson, R. G., & Coyle, J. T. (1980a). The differential effect of right versus left hemispheric cerebral infarction on catecholamines and behavior in the rat. *Brain Research*, *188*(1), 63–78. http://doi.org/10.1016/0006-8993(80)90557-0

Robinson, R. G., & Coyle, J. T. (1980b). The differential effect of right versus left hemispheric cerebral infarction on catecholamines and behavior in the rat. *Brain Research*, *188*(1), 63–78. http://doi.org/10.1016/0006-8993(80)90557-0

Rosen, H. J., Petersen, S. E., Linenweber, M. R., Snyder, A. Z., White, D. A., Chapman, L., et al. (2000). Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. *Neurology*, *55*(12), 1883–1894. http://doi.org/10.1212/WNL.55.12.1883

Rosenberg, M. D., Finn, E. S., Scheinost, D., Papademetris, X., Shen, X., Constable, R. T., & Chun, M. M. (2016). A neuromarker of sustained attention from whole-brain functional connectivity. *Nature Neuroscience*, *19*(1), 165–171. http://doi.org/10.1038/nn.4179

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D. J., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology*, *20*(5), 343–350. http://doi.org/10.1037/h0043220

Roussel, B., Buguet, A., & Bobillier, P. (1967). Locus ceruleus, paradoxal sleep, and cerebral noradrenaline. Comptes rendus des ….

Rueckert, L., & Grafman, J. (1996). Sustained attention deficits in pat ients with right frontal lesions. *Neuropsychologia*, *34*(10), 953–963.

Rueckert, L., & Grafman, J. (1998). Sustained attention deficits in patients with lesions of posterior cortex. *Neuropsychologia*, *36*(7), 653–660.

Rutman, A. M., Clapp, W. C., & Chadick, J. Z. (2010). Early top–down control of visual processing predicts working memory performance. *Journal of Cognitive Neuroscience*, *22*(6), 1224–1234. http://doi.org/10.1162/jocn.2009.21257

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological*

Review, *103*(3), 403–428. http://doi.org/10.1037/0033-295X.103.3.403

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience*, *10*(3), 211–223. http://doi.org/10.1038/nrn2573

Sara, S. J. (2015). Locus Coeruleus in time with the making of memories. *Current Opinion in Neurobiology*, *35*, 87–94.

Sara, S. J., & Bouret, S. (2012). Orienting and Reorienting: The Locus Coeruleus Mediates Cognition through Arousal. *Neuron*, *76*(1), 130–141. http://doi.org/10.1016/j.neuron.2012.09.011

Schiffer, F., Mottaghy, F. M., Vimal, R. L. P., Renshaw, P. F., Cowan, R., Pascual-Leone, A., et al. (2004). Lateral visual field stimulation reveals extrastriate cortical activation in the contralateral hemisphere: an fMRI study. *Psychiatry Research: Neuroimaging*, *131*(1), 1–9. http://doi.org/10.1016/j.pscychresns.2004.01.002

Schoenmakers, M. H. (2016). Cognition in relation to independency in older, comorbid stroke patients in a stroke unit. … *Journal of Geriatric* …. http://doi.org/10.1002/gps.4518/full

Schwebel, D. C., Lindsay, S., & Simpson, J. (2007). Brief Report: A Brief Intervention to Improve Lifeguard Surveillance at a Public Swimming Pool. *Journal of Pediatric Psychology*, *32*(7), 862–868. http://doi.org/10.1093/jpepsy/jsm019

Sheremata, S. L., Bettencourt, K. C., & Somers, D. C. (2010). Hemispheric Asymmetry in Visuotopic Posterior Parietal Cortex Emerges with Visual Short-Term Memory Load. *The Journal of Neuroscience*, *30*(38), 12581–12588. http://doi.org/10.1523/JNEUROSCI.2689-10.2010

Shiffrin, R. M., & Schneider, W. (1977). Controlled and automatic human information processing: II. Perceptual learning, automatic attending and a general theory. *Psychological Review*, *84*(2), 127–190. http://doi.org/10.1037/0033-295x.84.2.127

Shulman, G. L., Pope, D. L. W., Astafiev, S. V., McAvoy, M. P., Snyder, A. Z., & Corbetta, M. (2010). Right Hemisphere Dominance during Spatial Selective Attention and Target Detection Occurs Outside the Dorsal Frontoparietal Network. *The Journal of Neuroscience*, *30*(10), 3640–3651. http://doi.org/10.1523/JNEUROSCI.4085-09.2010

Singewald, N. (1998). Release of neurotransmitters in the locus coeruleus. *Progress in* …, *56*(2), 237–267.

Singh-Curry, V., & Husain, M. (2009). The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. *Neuropsychologia*, *47*(6), 1434–1448. http://doi.org/10.1016/j.neuropsychologia.2008.11.033

Singh-Curry, V., Malhotra, P., Farmer, S. F., & Husain, M. (2011). Attention deficits following ADEM ameliorated by guanfacine. *Journal of Neurology, Neurosurgery & Psychiatry*, *82*(6), 688–690. http://doi.org/10.1136/jnnp.2009.195792

Smilek, D., Carriere, J. S. A., & Cheyne, J. A. (2010). Failures of sustained attention in life, lab, and brain: Ecological validity of the SART. *Neuropsychologia*, *48*(9), 2564–2570. http://doi.org/10.1016/j.neuropsychologia.2010.05.002

Smith, A., & Nutt, D. (1996). Noradrenaline and attention lapses. *Nature*, *380*(6572), 291–291. http://doi.org/10.1038/380291a0

Sorg, C., Myers, N., Redel, P., Bublak, P., Riedl, V., Manoliu, A., et al. (2012). Asymmetric Loss of Parietal Activity Causes Spatial Bias in Prodromal and Mild Alzheimer's Disease. *Bps*, *71*(9), 798–804. http://doi.org/10.1016/j.biopsych.2011.09.027

Sperduti, M., Makowski, D., & Piolino, P. (2016). The protective role of long-term meditation on the decline of the executive component of attention in aging: a preliminary cross-sectional study. *Aging, Neuropsychology, and Cognition*, *23*(6), 691–702. http://doi.org/10.1080/13825585.2016.1159652

Sperling, G. (1960). The information available in brief visual presentations. *Psychological Monographs: General*

and Applied, *74*(11), 1–29. http://doi.org/10.1037/h0093759

Stagg, C. J., & Nitsche, M. A. (2011). Physiological Basis of Transcranial Direct Current Stimulation. *The Neuroscientist*, *17*(1), 37–53. http://doi.org/10.1177/1073858410386614

Stagg, C. J., Bachtiar, V., O'Shea, J., Allman, C., & Bosnell, R. A. (2012). Cortical activation changes underlying stimulation-induced behavioural gains in chronic stroke. *Brain*, *135*(1), 276–284. http://doi.org/10.1093/brain/awr313

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-Sensitive Modulation of Cortical Neurotransmitters by Transcranial Stimulation. *The Journal of Neuroscience*, *29*(16), 5202–5206. http://doi.org/10.1523/JNEUROSCI.4432-08.2009

Starkstein, S. E., Vázquez, S., Migliorelli, R., Tesón, A., Sabe, L., & Leiguarda, R. (1995). A Single-Photon Emission Computed Tomographic Study of Anosognosia in Alzheimer's Disease. *Archives of Neurology*, *52*(4), 415–420. http://doi.org/10.1001/archneur.1995.00540280105024

Staub, B., Doignon-Camus, N., Bacon, É., & Bonnefond, A. (2014). The effects of aging on sustained attention ability: An ERP study. *Psychology and Aging*, *29*(3), 684–695. http://doi.org/10.1037/a0037067

Staub, B., Doignon-Camus, N., Marques-Carneiro, J. E., Bacon, É., & Bonnefond, A. (2015). Age-related differences in the use of automatic and controlled processes in a situation of sustained attention. *Neuropsychologia*, *75*, 607–616. http://doi.org/10.1016/j.neuropsychologia.2015.07.021

Steenbergen, L., Sellaro, R., Hommel, B., Lindenberger, U., Kühn, S., & Colzato, L. S. (2015). "Unfocus" on foc.us: commercial tDCS headset impairs working memory. *Experimental Brain Research*, *234*(3), 637–643. http://doi.org/10.1007/s00221-015-4391-9

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006–1012. http://doi.org/10.1016/S1474-4422(12)70191-6

Stern, Y., Alexander, G. E., Prohovnik, I., & Mayeux, R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Annals of Neurology*, *32*(3), 371–375. http://doi.org/10.1002/ana.410320311

Stone, S. P., Halligan, P. W., & Greenwood, R. J. (1993). The Incidence of Neglect Phenomena and Related Disorders in Patients with an Acute Right or Left Hemisphere Stroke. *Age and Ageing*, *22*(1), 46–52. http://doi.org/10.1093/ageing/22.1.46

Sturm, W., & Willmes, K. (2001a). On the Functional Neuroanatomy of Intrinsic and Phasic Alertness. *NeuroImage*, *14*(1), S76–S84. http://doi.org/10.1006/nimg.2001.0839

Sturm, W., & Willmes, K. (2001b). On the functional neuroanatomy of intrinsic and phasic alertness. *NeuroImage*, *14*(1), S76–S84. http://doi.org/10.1006/nimg.2001.0839

Subramanian, L., Hindle, J. V., Johnston, S., Roberts, M. V., Husain, M., Goebel, R., & Linden, D. (2011). Real-Time Functional Magnetic Resonance Imaging Neurofeedback for Treatment of Parkinson's Disease. *The Journal of Neuroscience*, *31*(45), 16309–16317. http://doi.org/10.1523/JNEUROSCI.3498-11.2011

Subramanian, L., Morris, M. B., Brosnan, M., Turner, D. L., Morris, H. R., & Linden, D. E. J. (2016). Functional Magnetic Resonance Imaging Neurofeedback-guided Motor Imagery Training and Motor Training for Parkinson's Disease: Randomized Trial. *Frontiers in Behavioral Neuroscience*, *10*, 105–13. http://doi.org/10.3389/fnbeh.2016.00111

Sumowski, J. F., Chiaravalloti, N., & DeLuca, J. (2009). Cognitive reserve protects against cognitive dysfunction in multiple sclerosis. *Journal of Clinical …*, *31*(8), 913–926. http://doi.org/10.1080/13803390902740643

Tang, Y.-Y., & Posner, M. I. (2009). Attention training and attention state training. *Trends in Cognitive*

Sciences, *13*(5), 222–227. http://doi.org/10.1016/j.tics.2009.01.009

Tang, Y.-Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q., et al. (2007). Short-term meditation training improves attention and self-regulation. *Proceedings of the National Academy of Sciences*, *104*(43), 17152–17156. http://doi.org/10.1073/pnas.0707678104

Taylor-Phillips, S., Elze, M. C., Krupinski, E. A., Dennick, K., Gale, A. G., Clarke, A., & Mello-Thoms, C. (2014). Retrospective Review of the Drop in Observer Detection Performance Over Time in Lesion-enriched Experimental Studies. *Journal of Digital Imaging*, *28*(1), 32–40. http://doi.org/10.1007/s10278-014-9717-9

Terao, Y., & Ugawa, Y. (2002). Basic Mechanisms of TMS. *Journal of Clinical Neurophysiology*, *19*(4), 322.

Thulborn, K. R., Carpenter, P. A., & Just, M. A. (1999). Plasticity of Language-Related Brain Function During Recovery From Stroke. *Stroke*, *30*(4), 749–754. http://doi.org/10.1161/01.STR.30.4.749

Turner, G. R., McIntosh, A. R., & Levine, B. (2011). Prefrontal Compensatory Engagement in TBI is due to Altered Functional Engagement Of Existing Networks and not Functional Reorganization. *Frontiers in Systems …*, *5*. http://doi.org/10.3389/fnsys.2011.00009

Ungerleider, S. K. A. L. G. (2000). Mechanisms of Visual Attention in the Human Cortex. *Annu Rev Neurosci*, *23*(1), 315–341. http://doi.org/10.1146/annurev.neuro.23.1.315

Valenzuela, M. J., & Sachdev, P. (2006). Brain reserve and cognitive decline: a non-parametric systematic review. *Psychological Medicine*, *36*(08), 1065–9. http://doi.org/10.1017/S0033291706007744

Vallesi, A. (2011). Targets and non-targets in the aging brain: A go/nogo event-related potential study. *Neuroscience Letters*, *487*(3), 313–317.

Vallesi, A., & Stuss, D. T. (2010). Excessive sub-threshold motor preparation for non-target stimuli in normal aging. *NeuroImage*, *50*(3), 1251–1257. http://doi.org/10.1016/j.neuroimage.2010.01.022

Vallesi, A., Stuss, D. T., McIntosh, A. R., & Picton, T. W. (2009). Age-related differences in processing irrelevant information: evidence from event-related potentials. *Neuropsychologia*, *47*(2), 577–586. http://doi.org/10.1016/j.neuropsychologia.2008.10.018

van Leeuwen, S., Müller, N. G., & Melloni, L. (2009). Age effects on attentional blink performance in meditation. *Consciousness and Cognition*, *18*(3), 593–599. http://doi.org/10.1016/j.concog.2009.05.001

Van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of enviromental enrichment. *Nature Reviews …*, *1*(3), 191–198. http://doi.org/10.1038/35044558

van Zandvoort, M. J. E., Kessels, R. P. C., Nys, G. M. S., de Haan, E. H. F., & Kappelle, L. J. (2005). Early neuropsychological evaluation in patients with ischaemic stroke provides valid information. *Clinical Neurology and Neurosurgery*, *107*(5), 385–392. http://doi.org/10.1016/j.clineuro.2004.10.012

Vangkilde, S., Bundesen, C., & Coull, J. T. (2011). Prompt but inefficient: nicotine differentially modulates discrete components of attention. *Psychopharmacology*, *218*(4), 667–680. http://doi.org/10.1007/s00213-011-2361-x

Verbruggen, F., & Logan, G. D. (2008). Automatic and controlled response inhibition: Associative learning in the go/no-go and stop-signal paradigms. *Journal of Experimental Psychology: General*, *137*(4), 649–672. http://doi.org/10.1037/a0013170

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a Frontoparietal Control System Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology*, *100*(6), 3328–3342. http://doi.org/10.1152/jn.90355.2008

Vogel, E. K., & Luck, S. J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology*, *37*(2), 190–203. http://doi.org/10.1111/1469-8986.3720190

Volterra, A., Liaudet, N., & Savtchouk, I. (2014). Astrocyte Ca2+ signalling: an unexpected complexity.

Nature Reviews Neuroscience, *15*(5), 327–335. http://doi.org/10.1038/nrn3725

Voyer, D., Voyer, S. D., & Tramonte, L. (2012). Free-viewing laterality tasks: A multilevel meta-analysis. *Neuropsychology*, *26*(5), 551–567. http://doi.org/10.1037/a0028631

Voytek, B., Davis, M., Yago, E., Barceló, F., Vogel, E. K., & Knight, R. T. (2010). Dynamic Neuroplasticity after Human Prefrontal Cortex Damage. *Neuron*, *68*(3), 401–408. http://doi.org/10.1016/j.neuron.2010.09.018

Ward, N. S., Brown, M. M., Thompson, A. J., & Frackowiak, R. S. J. (2003). Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*, *126*(11), 2476–2496. http://doi.org/10.1093/brain/awg245

Warm, J. S., Richter, D. O., Sprague, R. L., Porter, P. K., & Schumsky, D. A. (1980). Listening with a dual brain: Hemispheric asymmetry in sustained attention. *Bulletin of the Psychonomic Society*, *15*(4), 229–232. http://doi.org/10.3758/BF03334516

Waterhouse, B. D., Ausim Azizi, S., Burne, R. A., & Woodward, D. J. (1990). Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin microiontophoresis. *Brain Research*, *514*(2), 276–292. http://doi.org/10.1016/0006-8993(90)91422-D

Weiss, M., Tannock, R., Kratochvil, C., Dunn, D., Velez-Borras, J., Thomason, C., et al. (2005). A Randomized, Placebo-Controlled Study of Once-Daily Atomoxetine in the School Setting in Children With ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(7), 647–655. http://doi.org/10.1097/01.chi.0000163280.47221.c9

West, R. (2000). In defense of the frontal lobe hypothesis of cognitive aging. *Journal of the International Neuropsychological Society*, *6*(6), 727–729. http://doi.org/10.1017/S1355617700666109

Whirley, K. S., Lorch, E. P., Lemberger, C. C., & Milich, R. (2016). Online cognitive engagement of boys with ADHD. *Journal of Attention Disorders*, *7*(2), 71–81. http://doi.org/10.1177/108705470300700201

Whitehead, R. (1991). Right Hemisphere Processing Superiority During Sustained Visual Attention. *Journal of Cognitive Neuroscience*, *3*(4), 329–334. http://doi.org/10.1162/jocn.1991.3.4.329

Wiegand, I., Finke, K., Müller, H. J., & Töllner, T. (2013). Event-related potentials dissociate perceptual from response-related age effects in visual search. *Neurobiology of Aging*, *34*(3), 973–985. http://doi.org/10.1016/j.neurobiolaging.2012.08.002

Wiegand, I., Töllner, T., Dyrholm, M., Müller, H. J., Bundesen, C., & Finke, K. (2014). Neural correlates of age-related decline and compensation in visual attention capacity. *Neurobiology of Aging*, *35*(9), 2161–2173. http://doi.org/10.1016/j.neurobiolaging.2014.02.023

Wiethoff, S., Hamada, M., & Rothwell, J. C. (2014). Variability in Response to Transcranial Direct Current Stimulation of the Motor Cortex. *Brain Stimulation*, *7*(3), 468–475. http://doi.org/10.1016/j.brs.2014.02.003

Wilkins, A. J., Shallice, T., & McCarthy, R. (1987). Frontal lesions and sustained attention. *Neuropsychologia*, *25*(2), 359–365.

Wilson, R. S., Barnes, L. L., de Leon, C. F. M., Aggarwal, N. T., Schneider, J. S., Bach, J., et al. (2002). Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*, *59*(3), 364–370. http://doi.org/10.1212/WNL.59.3.364

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., et al. (2007). Loneliness and Risk of Alzheimer Disease. *Archives of General Psychiatry*, *64*(2), 234–240. http://doi.org/10.1001/archpsyc.64.2.234

Wilson, R. S., Nag, S., Boyle, P. A., Hizel, L. P., Yu, L., Buchman, A. S., et al. (2013). Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology*, *80*(13), 1202–1208. http://doi.org/10.1212/WNL.0b013e3182897103

Wolinsky, F. D., Unverzagt, F. W., Smith, D. M., Jones, R., Wright, E., & Tennstedt, S. L. (2006). The Effects of the ACTIVE Cognitive Training Trial on Clinically Relevant Declines in Health-Related Quality of Life. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *61*(5), S281–S287. http://doi.org/10.1093/geronb/61.5.S281

Wolinsky, F. D., Vander Weg, M. W., Martin, R., Unverzagt, F. W., Ball, K. K., Jones, R. N., & Tennstedt, S. L. (2009). The Effect of Speed-of-Processing Training on Depressive Symptoms in ACTIVE. *The Journals of Gerontology: Series A*, *64A*(4), 468–472. http://doi.org/10.1093/gerona/gln044

Wood, J. M., & Owsley, C. (2014). Useful Field of View Test. *Gerontology*, *60*(4), 315–318. http://doi.org/10.1159/000356753

Xerri, C., Zennou-Azogui, Y., Sadlaoud, K., & Sauvajon, D. (2014). Interplay between intra- and interhemispheric remodeling of neural networks as a substrate of functional recovery after stroke: Adaptive versus maladaptive reorganization. *Neuroscience*, *283*, 178–201. http://doi.org/10.1016/j.neuroscience.2014.06.066

Zanto, T. P., Rubens, M. T., Thangavel, A., & Gazzaley, A. (2011). Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. *Nature Neuroscience*, *14*(5), 656–661. http://doi.org/10.1038/nn.2773

Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nature Neuroscience*, *15*(4), 528–536. http://doi.org/10.1038/nn.3045

Zhang, W., & Luck, S. J. (2009). Feature-based attention modulates feedforward visual processing. *Nature Neuroscience*, *12*(1), 24–25. http://doi.org/10.1038/nn.2223