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Mapping and Modulating Spatial Attention Asymmetries in Young and Older Adults

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Abstract

Healthy young adults demonstrate a group-level, systematic preference for stimuli presented in the left side of space relative to the right ('pseudoneglect') (Bowers & Heilman, 1980). This results in an overestimation of features such as size, brightness, numerosity and spatial frequency in the left hemispace, probably as a result of right cerebral hemisphere dominance for visuospatial attention. This spatial attention asymmetry is reduced in the healthy older population, and can be shifted entirely into *right* hemispace under certain conditions. Although this rightward shift has been consistently documented in behavioural experiments, there is very little neuroimaging evidence to explain this effect at a neuroanatomical level. In this thesis, I used behavioural methodology and electroencephalography (EEG) to *map* spatial attention asymmetries in young and older adults. I then use transcranial direct current stimulation (tDCS) to *modulate* these spatial biases, with the aim of assessing age-related differences in response to tDCS.

In the first of three experiments presented in this thesis, I report in Chapter Two that five different spatial attention tasks provide consistent *intra*-task measures of spatial bias in young adults across two testing days. There were, however, no *inter*-task correlations between the five tasks, indicating that pseudoneglect is at least partially driven by task-dependent patterns of neural activity. In Chapter Three, anodal tDCS was applied separately to the left (P5) and right (P6) posterior parietal cortex (PPC) in young and older adults, with an aim to improve the detection of stimuli appearing in the contralateral visual field. There were no age differences in response to tDCS, but there were significant differences depending on baseline performance. Relative to a *sham* tDCS protocol, tDCS applied to the right PPC resulted in maintained visual detection across both visual fields in adults who were *good* at the task at baseline. In contrast, left PPC tDCS resulted in reduced detection sensitivity across both visual fields in *poor* performers. Finally, in Chapter Four, I report a right-hemisphere lateralisation of EEG activity in young adults that was present for long (but not short) landmark task lines. In contrast, older adults demonstrated no lateralised activity for either line length, thus providing novel evidence of an age-related reduction of hemispheric asymmetry in older adults.

The results of this thesis provide evidence of a highly complex set of factors that underlie spatial attention asymmetries in healthy young and older adults.

Declaration

I declare that this thesis represents my own work except unless indicated in the text and that it does not include work forming part of a thesis presented for another degree.

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Gemma Learmonth

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Published articles

<u>The findings in Chapter Two have been published</u>:

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<u>The findings in Chapter Three have been published</u>:

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<u>The findings in Chapter Four have been submitted for publication</u>:

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<u>Chapter Four has also been presented at the European Conference on Visual Perception, and has been published as an abstract</u>:

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Chapter One

Spatial Attention Asymmetries: A General Introduction

Spatial Attention

Whenever we interact with our environment, our senses are bombarded with a vast amount of competing information, all of which may be potentially important to achieving our current goals. However, due to limited processing resources within the human brain, not all of this information is, or can be, processed equally. Indeed, we may not even notice that a coffee cup is sitting on a messy desk when we are quickly searching for our mislaid car keys, but we can locate the coffee cup with ease the following morning whilst making breakfast. *Attention* is the mechanism which enables us to selectively filter out task-irrelevant information and to prioritise particular aspects of our environment (Posner, 1980). More specifically, *spatial attention* refers to the distribution of this resource across the environment, and this tends to be asymmetrically distributed to favour the left side of space in the general population (Bowers & Heilman, 1980).

Hemispatial Neglect

Particularly before the advent of modern neuroimaging techniques, much of our insight into how spatial attention is represented within a typical brain has been gained by studying cases where there is disruption to the system. The most extreme cases of left vs right asymmetries of spatial attention are observed in patients with a condition called *hemispatial neglect;* a pathological inattention to one side of space or objects that develops as a result of stroke. This condition is characterised by an inability to ‘report, respond, or orient to novel or meaningful stimuli presented to the side opposite a brain lesion' (Heilman, Valenstein & Watson, 1985). Patients with neglect often experience a marked reduction in overall quality of life, with difficulty in eating, dressing and independently navigating within their environment (Nijboer, Kollen & Kwakkel, 2013) and unfortunately at present there is a lack of evidence to support any effective method of rehabilitation (Bowen & Lincoln, 2007; Bowen et al., 2013). Although the most common method of diagnosing and quantifying neglect-related deficits is by visual confrontation and bedside paper and pencil assessments (e.g. the Behavioural Inattention Test (BIT): Wilson, Cockburn & Halligan (1987)), it is important to emphasise that hemispatial neglect is a disorder of *attention* rather than vision *per se*. Patients may exhibit inattention within any one of the sensory domains, or indeed within a combination: they may fail to notice when they are touched on one side of their body (De Renzi, Faglioni & Scotti, 1970) or when an auditory tone is played into one ear (Heilman & Valenstein, 1972), and even neglect one side of imaginary scenes ('representational neglect', Bisiach & Luzzatti, 1978). Furthermore, hemispatial neglect is estimated to affect up to 80% of patients who present with a right hemisphere stroke (Stone et al., 1992; Stone, Halligan & Greenwood, 1993), at least to some extent, and tends to be more severe and persistent after right- relative to left-hemisphere damage (Mesulam, 1981). An estimated 17% of right-lesioned patients exhibit persistent neglect at 3 months post-stroke, compared to only 5% of left-hemisphere patients (Ringman et al., 2004).

Anatomical Basis of Hemispatial Neglect

The reason why damage to the right hemisphere exerts a comparatively stronger effect on neglect symptoms compared to left-sided damage is related to the dominant role of the *right* posterior parietal cortex (PPC) for the control of visuospatial attention. More than 30 years ago Heilman & Van Den Abell (1980) proposed the 'hemifield' model of spatial attention processing within the cerebral cortex to attempt to explain how attentional asymmetries develop after stroke. In this model, the right hemisphere directs attention to both the ipsilateral right and contralateral left visual fields, whereas the left hemisphere directs attention only to the contralateral right side of space. Hemispatial neglect is therefore less persistent after left hemisphere damage because the right hemisphere is able to compensate for this damage due to its ability to direct attention towards both visual hemifields, whereas the left hemisphere cannot (Szczepanski, Konen & Kastner, 2010).

In an alternative 'interhemispheric competition' model, Kinsbourne (1970, 1977, 1994) asserted that both hemispheres direct attention towards the contralateral visual fields, but that the right hemisphere exerts a comparatively stronger effect. Importantly, this model proposes that each cerebral hemisphere exerts a reciprocal inhibition on the other in order to maintain a balance of neural activity across both sides of the brain. When damage occurs within one hemisphere as a result of stroke, the undamaged hemisphere (usually the left side in cases of neglect) becomes hyperactive as a result and pathologically directs attention towards the right side of space. Evidence to support this hyperexcitability of the intact hemisphere has been supported by functional imaging studies, mostly for early visual processing (Corbetta et al., 2005; Fink et al., 2000a; Forss et al., 1999; Koch et al., 2008).

Although these models of visuospatial attention go some way to explain theoretically how hemispatial neglect symptoms may manifest, there is a remarkable degree of heterogeneity in the location of lesions in patients with this condition. Early neuroimaging and voxel-based lesion mapping studies of human patients with neglect identified the posterior parietal cortex (Mesulam, 1999; Azouvi et al., 2002) as a commonly damaged area across the patients studied, and in particular the right inferior parietal lobule (IPL) and temporoparietal junction (Heilman et al., 1983; Vallar & Perani, 1986; Leibovitch et al., 1998; Vallar, 2001). However, visual neglect has been reported in patients with spatially distributed cortical (and subcortical) areas (e.g. the superior temporal gyrus (Karnath, Ferber & Himmelbach, 2001), insula (Karnath et al., 2004), and basal ganglia (Vallar & Perani, 1986; Ferro, Kertesz & Black, 1987; Karnath et al., 2004) and a variety of theories have been proposed to account for these cases as a result (e.g. Mort et al., 2003; Karnath, Ferber & Himmelbach, 2001; Milner & Goodale, 1995, 2006).

Here I focus on perhaps the most influential of these recent models, proposed by Corbetta & Shulman (2002; 2011), who suggest that there are two partially segregated frontoparietal attention networks within the brain which dynamically interact with each other. The *dorsal* frontoparietal attention network is bilaterally represented in both hemispheres and connects the intraparietal sulcus with the frontal eye fields, with strong connections along the superior longitudinal fasciculus white matter tracts (Corbetta & Shulman, 2002;

Ptak, 2011; Thiebaut de Schotten et al., 2011). This dorsal network controls the top-down direction of attention towards salient stimuli (i.e. where an object is located). The second (*ventral*) network is asymmetrically represented, being more lateralised to the right hemisphere in the majority of the healthy adult population, and connects the temporoparietal junction with the ventral frontal cortex. This network supports general attentional arousal, vigilance and orientation towards unexpected stimuli. The two pathways are likely to interact along the superior longitudinal fissure (SLF II), where there are physically overlapping connections between the parietal region of the ventral network and the prefrontal region of the dorsal network (Thiebaut de Schotten et al., 2011). Hemispatial neglect is typically characterised by an inability to endogenously direct attention towards the contralesional hemispace (a function controlled by the *dorsal* pathway). However neglect is most commonly associated with damage to the *ventral* pathway, which exogenously orients attention towards unexpected stimuli occurring within the environment (Corbetta et al., 2005; Corbetta & Shulman, 2002, 2011; He et al., 2007; Rengachary et al., 2011). Importantly, Corbetta & Shulman argue that *both* of these attention networks are disrupted in cases of neglect, specifically that disruption to the ventral pathway exerts a knock-on effect on the right-lateralised dorsal network, indicating that ordered visuospatial attention involves a complex interaction between both of these cortical networks.

In summary, the three chosen models of spatial attention described here are an important starting point for this thesis because each of these models emphasises the dominant role of the right hemisphere in spatial attention processing (albeit via slightly different mechanisms). In turn these models provide important information regarding the neural mechanisms that give rise to spatial attention asymmetries that are present in the healthy adult population.

Pseudoneglect

In contrast to the left-sided inattention observed in hemispatial neglect, healthy young adults typically display an attentional *advantage* towards the left side of space relative to the right side. This non-pathological asymmetry of spatial attention is known as ‘pseudoneglect’, due to its apparent mechanistic similarity to hemispatial neglect (albeit in the opposite direction) observed on tests such as the line bisection task (Bowers & Heilman, 1980). This simple behavioural task involves presenting individuals with a horizontal line and asking them to place a vertical mark at the horizontal midpoint. This typically leads to a large right-of-centre placement of the mark in hemispatial neglect, and a left-of-centre error in pseudoneglect (Figure 1). Although the leftward bias in pseudoneglect tends to be markedly smaller than the rightward bias elicited in hemispatial neglect, it is nevertheless a consistently observed phenomenon within the general population (see Jewell & McCourt, 2000 for review).

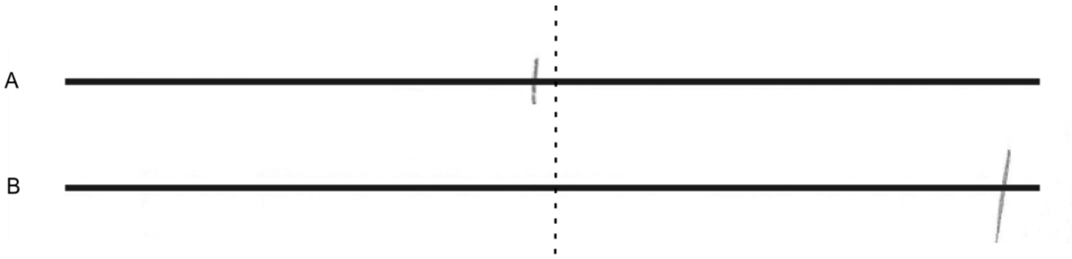

Figure 1. Line bisection task examples, demonstrating A) a small leftward bias typical of pseudoneglect in young adults and B) an extreme rightward bias in a patient with severe left hemispatial neglect. The dashed line indicates the veridical horizontal midpoint.

In the same way that hemispatial neglect can be conceptualised as a multi-component disorder that can manifest within multiple sensory domains (e.g. visual, auditory and tactile), pseudoneglect has also been quantified across a range of different tasks involving judgements of object size (McCourt & Jewell, 1999), brightness (Mattingley et al., 1994a), spatial frequency (Niemeier, Stojanoski & Greco, 2007), numerosity (Nicholls, Bradshaw & Mattingley, 1999) and even emotion perception in chimeric faces (Luh, Rueckert, & Levy, 1991; Luh, 1995). Young adults systematically over-estimate these features in the left relative to the right hemispace, strongly implying that pseudoneglect does not represent an isolated error of size judgement (as per the line bisection task), but instead represents a more widespread asymmetry of the allocation of spatial attention towards the left side of space. Interestingly, recent studies of animal cognition have demonstrated that pseudoneglect is also present in a number of other animal species, specifically in pigeons and chicks (*Gallus gallus*), suggesting that there may be a long evolutionary history for this cerebral asymmetry (Diekamp et al., 2005; Chiandetti et al., 2013, 2014; Regolin, 2006; Skiba, Diekamp & Güntürkün, 2002). In Chapter Two of this thesis I discuss the relationship between 5 spatial attention tasks and assess whether they all reflect asymmetries within a common underlying factor of the spatial attention networks. The principal aim of Chapter Two is to determine what is meant when we describe pseudoneglect and ultimately whether the experimental findings obtained in experiments using one of these tasks (e.g. line bisection) can be applied interchangeably to the study of pseudoneglect in other domains, such as numerosity and brightness.

Neuroanatomical Correlates of Pseudoneglect

There is now a very convincing body of neuroimaging evidence to assert that the right-hemispheric lateralisation of spatial attention networks is indeed responsible for the generation of leftward behavioural biases in the non-clinical population. Here I present a short summary of the early work in this area, but this subject is discussed in greater depth in Chapter Four of this thesis, with additional discussion of the evidence gained from electroencephalography research. The first of these functional neuroimaging studies by Marshall and colleagues (1997), involved participants undergoing positron emission tomography (PET) to localise cerebral blood flow whilst performing a non-manual variant of the line bisection task. Alternatively termed the *landmark* task (Harvey, Milner & Roberts, 1995; Milner, Brechmann & Pagliarini, 1992; Milner et al., 1993), this task required a forced-choice decision regarding whether or not a pre-transected horizontal line was correctly bisected at its veridical centre.

An additional control task that did not require a spatial judgement (participants instead indicated when a horizontal line stopped flickering) was presented to compare the cerebral response to both spatial and non-spatial tasks. Compared to the control task, the landmark task elicited increased blood flow within the right hemisphere, specifically the insula, superior temporal lobe and dorsolateral prefrontal cortex. Refining this work, Fink et al., (2000b) assessed the landmark task compared to a control ('is the line transected or not?') during functional magnetic resonance imaging (fMRI) and found activation of the right superior posterior and inferior parietal lobe. In their summary discussion, the authors explain that the more localised parietal activity in the latter experiment was due to a more appropriate control task that more purely subtracted the spatial judgement element of the landmark task. Finally, Çiçek, Deouell & Knight (2009) used fMRI to compare activity when completing the landmark task compared to the standard manual line bisection task. Both tasks involved activation of the right dorsal frontoparietal attention network (intra-parietal sulcus and lateral peristriate cortex), with the frontal eye fields being additionally activated in the manual bisection variant.

What then is the evidence that these cerebral activation asymmetries might be directly responsible for generating the visuospatial bias of pseudoneglect? It seems logical that individuals with a larger behavioural bias towards the left side of space should also exhibit a larger degree of right hemispheric lateralisation. Thiebaut de Schotten et al., (2011) performed diffusion tractography imaging in a group of twenty right-handed individuals to assess the volume of three dorsolateral white matter tracts that extend longitudinally within both cerebral hemispheres. They found a strong correlation between the lateralisation of the middle of the three superior longitudinal fissures (SLF II) (i.e. the size of the SLF II in the right *vs* the left hemisphere) and behavioural bias as indexed by the line bisection task. That is, participants who exhibited a more extreme leftward line bisection bias had a disproportionately larger right vs left hemisphere SLF II. There was no correlation between behavioural pseudoneglect and lateralisation of the SLF I (which is located dorsal to SLF II) nor with SLF III (located ventral to SLF II), suggesting that specific neuroanatomical asymmetries in SLF II lateralisation may be the neural source of spatial attention asymmetries.

Finally, but importantly, although the majority of the population are biased towards the left side of space, a small subset of individuals instead display an advantage for the *right* side. McCourt (2001) estimates this subgroup to comprise approximately 5% of the population, however larger estimates of 30-50% have been reported (Benwell et al., 2013a, Cowie & Hamil, 1998; Braun & Kirk, 1999; Dellatolas, Coutin & De Agostini, 1996; Manning, Halligan & Marshall, 1990). Similar to the consistent leftward bias in the majority of young adults, these individuals also exhibit a strong test-retest reliability of this rightward bias, suggesting that this might represent a cognitive trait which reflects neuroanatomical differences in hemispheric lateralisation for spatial attention (Benwell et al., 2013a; Thiebaut de Schotten et al., 2011). It is important to consider these individual differences in spatial attention asymmetries, and there are a multitude of factors that have been reported to influence bias, including gender (Hausmann et al., 2002; Roig & Cicero, 1994), handedness (Luh, 1995; Sampaio & Chokron, 1992; Scarisbrick, Tweedy & Kuslansky, 1987) and native language (Chokron & Imbert, 1993; Nicholls & Roberts, 2002). In Chapters Three and Four of this thesis I will explore in detail one of these relatively unexplored variables: the effect of age on spatial attention asymmetries.

Pseudoneglect in Older Adults

The majority of studies that investigate spatial attention asymmetries focus either on the clinical implications of hemispatial neglect or pseudoneglect in the healthy young adult population. However, there are now multiple convincing reports indicating a general rightward shift of spatial attention that accompanies healthy aging. In contrast to the leftward bias that is characteristic of pseudoneglect in young adults (studies typically classify 'young' as around 18-30 years old), older adults (aged approximately 60-90) do not display a strong leftward bias as a group. Instead, spatial bias has been variously observed to be either eliminated (i.e. there is no strong bias to either side of space) or there are reports of a small, consistent bias towards the *right.* This shift has been reported for a range of different spatial attention tasks: line bisection (Barrett & Craver-Lemley, 2008; Failla, Sheppard & Bradshaw, 2003; Fujii et al., 1995; Fukatsu et al., 1990; Stam & Bakker, 1990), the landmark task (Benwell et al., 2014a; Schmitz & Peigneux, 2011) and lateralised visual detection (Nagamatsu et al., 2009; 2011; 2013). However, it must be noted that a recent assessment of the visual and tactile versions of the line bisection task, together with a 'mental number line' bisection task (where individuals are asked to identify the middle number between a pair, e.g. ‘113_137’ (Gobel et al., 2006)), found that this group-level leftward bias was indeed preserved in the sample of older adults who were tested (Brooks et al., 2016).

In light of these behavioural observations, there are two fundamental questions that, in my opinion, remain unanswered: 1) Does the aging brain undergo specific neuroanatomical changes that might cause this rightward shift in spatial attention? and 2) Do these changes affect how older people cope at a functional level when interacting with their environment? Surprisingly, given the volume of studies that have shown a similar shift in behaviour, there have been comparatively few research studies that attempt to answer either of these outstanding questions within the spatial attention domain. In Chapters Three and Four of this thesis I specifically aim to address the first of these questions by using two techniques (transcranial direct current stimulation and electroencephalography) to investigate changes in the neural representation of spatial attention within the aging brain.

Changes in the Healthy Older Brain

Evidence for age-related changes in the functional organisation of the brain have been well documented since the early days of functional neuroimaging, but the research has been largely in the domain of memory. Here I will briefly review some of this evidence and the main issues, yet the models of cognitive aging that were developed from this evidence and their potential application to visuospatial attention are discussed in greater depth in Chapter Four of this thesis.

One of the first neuroimaging studies to identify changes in functional activation across the lifespan, Cabeza et al., (1997) asked young (mean age of 26 years) and older adults (mean age of 70) to remember word pairs whilst undergoing PET scanning. During recall of the word pairs, young adults showed lateralised activity within the right prefrontal cortex whereas older adults exhibited activation bilaterally across both frontal hemispheres. Corroborated by a number of subsequent PET and fMRI studies showing similar shifts towards bilateral activity in senior adults (e.g. Bäckman et al., 1997; Grady et al., 1994; Madden et al., 1999; Reuter-Lorenz et al., 2000), these findings were developed into a framework of cognitive aging termed the *hemispheric asymmetry reduction in older adults (HAROLD)* model. This asserts that functions that are lateralised to one hemisphere in young adults become generally more bilaterally represented in older adults (Cabeza, 2002).

Interestingly, Cabeza et al., (2002) subsequently found that the extent of bilateral activity correlated with the performance level of the older adults. Similar to their previous experiment, the episodic memory of young and older adults was tested during PET scanning and young adults once again exhibited right prefrontal activation during the recall phase. Older adults exhibited a more bilateral pattern of activity, but this time the bilateral activation was only present in the older adults who performed as well as the young on a battery of memory tests (i.e. those who were high functioning). The lower-functioning adults showed the same right prefrontal cortex lateralisation as the young adults. Thus, the reduction of lateralisation in older adults perhaps represents a beneficial compensatory mechanism, whereby cognitive performance is maintained into older age via the recruitment of neural resources across both cerebral hemispheres. However, this may be an overly simplistic explanation for the bilateral activation pattern, given that Duverne, Motamedinia & Rugg (2009) have reported the opposite effect: bilateral activity was observed for older adults in the *encoding* (rather than recall) phase and this was more pronounced for *low*- rather than *high*-performing seniors. A second, more recent model of cognitive neuroplasticity in aging, the *compensatory-related utilisation of neural circuits hypothesis* (CRUNCH) model agrees that older adults recruit additional neural resources to support cognitive processing. However it differs from the HAROLD model in that it does not confine this recruitment to the opposite hemisphere; resources may be co-opted anywhere within the brain (Reuter-Lorenz & Cappell, 2008).

Why are these models of neurocognitive aging relevant to the study of spatial attention asymmetries in healthy older adults? Firstly, as a theoretical tool, the HAROLD model might predict the behavioural evidence of eliminated pseudoneglect in this group; specifically that a reduced hemispheric asymmetry for spatial attention directly leads to this reduced behavioural bias. However it cannot adequately account for observations of a behavioural shift fully into the right hemispace (Benwell et al., 2014a), and hence this issue is considered fully in Chapter Four of this thesis. Secondly, these models provide an initial framework in with which to identify neural circuits that may be functioning less optimally or can be deemed susceptible to the effects of cognitive aging. For instance, Nagamatsu et al., (2009, 2011) found that older adults who have a specifically reduced ability to direct attention to the left side of space were at a higher risk of falls than seniors who had a preserved ERP response to targets in the left hemifield. Finally, by precisely identifying how spatial attention is represented within the older brain, and particularly what patterns are associated with preserved cognitive abilities, methods of improving cognitive function and quality of life in older age can be developed, for example by targeting these networks using non-invasive brain stimulation techniques. In Chapter Three I describe the results of an experiment that uses transcranial direct current stimulation (tDCS) with the aim of improving spatial attention in both young and older adults.

Transcranial Direct Current Stimulation

Within the past 15 years, there has been a burgeoning interest in the use of non-invasive brain stimulation methods as a way of both quantifying and modulating neural activity within the brain. A PubMed search for journal articles utilising one of these methods, transcranial direct current stimulation (tDCS), finds that in excess of 2100 academic publications have been generated since the first reported use of the technique in humans in the late 1990s. TDCS involves the application of a small, constant electric current (typically 1-2 milliamps for 10-30 minutes) through the scalp and underlying brain tissue via carbon rubber electrodes (usually sized between 4 x 4 and 5 x 7cm^2). The standard tDCS system involves the application of an anode and a cathode to the scalp in a configuration (*montage*) aimed at increasing neural activity underneath the anode and decreasing activity underneath the cathode. Recently developed systems, such as high definition tDCS (HD-tDCS), enable the application of an array of multiple small, circular (~4mm radius) anodes and cathodes in customisable configurations to improve the focality of the stimulation to a more targeted area of the cortex (Datta et al., 2009).

Mechanism of Action in tDCS

Unlike transcranial magnetic stimulation (TMS), which directly generates action potentials within the underlying neural populations, tDCS instead modulates the underlying neurons to render them more (anode) or less (cathode) likely to fire. The precise mechanism of this tDCS action is still quite poorly understood, but MR spectroscopy studies have linked these modulatory effects to changes in neurotransmitter concentrations around the electrode site. Stagg et al., (2009) observed that the area of cortex located underneath the anode had a reduced concentration of the inhibitory neurotransmitter gamma aminobutyric acid (GABA), whereas the concentration of both GABA and the excitatory neurotransmitter glutamate were reduced around the site of the cathode. As a direct result of this neurochemical action, the anode has the effect of lowering the firing threshold of the neurons and making them more likely to fire, whereas the cathode increases the firing threshold making the neurons less likely to activate (Kim et al., 2014; Stagg et al., 2009; Stagg & Nitsche, 2011).

The action of GABA and glutamate have mainly been linked to short-term *online* (i.e. during tDCS) stimulation effects, but many studies have reported more long-term effects of a few hours (Nitsche & Paulus, 2001), and even up to 6-months post-stimulation after multiple consecutive tDCS sessions (Cohen Kadosh et al., 2010). Indeed, non-invasive brain stimulation *must* be shown to elicit lasting effects over and above the duration of stimulation if the technique is to be formally adopted as a rehabilitation technique in patient populations. Rather than neurotransmitter fluctuations, these lasting *offline* (i.e. post-tDCS) effects have been proposed to be related to synaptic plasticity, specifically long term potentiation and depression (LTP/LTD) (Stagg & Nitsche, 2011). This results in a strengthening or weakening of the physical connections between synapses, generating lasting effects on neural activity.

Modulation of Motor and Cognitive Systems using tDCS

Due to the increasingly large body of literature relating to behavioural modulation using tDCS, the following paragraphs briefly summarise some of the key findings to date. Some of the first neurophysiological studies to use tDCS were principally focused on altering the excitability of neurons within the motor cortex (e.g. Priori et al., 1998). Nitsche & Paulus (2000) applied 1mA anodal and cathodal stimulation to the left motor cortex for 5 minutes (with the return electrode on the contralateral forehead) and quantified the excitability of the underlying area by assessing TMS-induced motor evoked potentials (MEPs) at 1 minute intervals post-stimulation. Clear differences in induced excitation were found after anodal and cathodal tDCS (i.e. the classic effects of anode-excitation and cathode-inhibition), with a lasting effect of this modulation until 10 minutes after the cessation of stimulation.

With such apparent promise for use as an adjunct to patient rehabilitation, non-invasive brain stimulation was soon adopted into clinical trials. Given that the skin accommodates to the physical sensation of tDCS after a short period of time, the application of tDCS can be effectively double-blinded for use in randomised studies. This is achieved by applying a ‘sham’ tDCS protocol (typically for only 15-30 seconds) with little or no perceptual differences compared to ‘active’ stimulation reported by the individual. The effects of active stimulation can then be quantified over and above any placebo effect that might be associated with inclusion into the trial (Gandiga, Hummel & Cohen, 2006; Brunoni et al., 2011; Kessler et al., 2012). One of the first studies aimed at improving post-stroke limb weakness (hemiparesis) found that the application of 1mA anodal tDCS to the damaged cortical motor area resulted in improved motor function in all 6 patients tested and this outlasted stimulation, an effect that was not present after they had received the sham protocol (Hummel et al., 2005). Subsequent trials involving cathodal tDCS applied to the homologous region in the intact cerebral hemisphere (with an aim to reduce pathological interhemispheric competition exerted by the healthy hemisphere; Kinsbourne, 1977) have also proved successful in improving post-stroke paresis for 24 hours (Zimerman et al., 2012) and 1 week (Nair et al., 2011) after tDCS.

Given the success of modulating activity using tDCS over the motor cortex, researchers soon began to develop protocols to induce ‘neuroenhancement’ within a range of higher-level cognitive processes, such as memory (e.g. Fregni et al., 2005; Zaehle et al., 2011), language (Sparing et al., 2008; Flöel et al., 2008) and mental arithmetic (Hauser et al., 2013; Snowball et al., 2013). Likewise, clinical groups may benefit from stimulation targeting higher cognitive functions, e.g. improving the symptoms of depression (Fregni et al., 2006; Boggio et al., 2008; Loo et al., 2010), reducing the severity and frequency of hallucinations in schizophrenia (Brunelin et al., 2012; Andrade, 2013), and improving memory performance in Alzheimer’s disease (Ferrucci et al., 2008; Boggio et al., 2009, 2012). With reference to hemispatial neglect specifically, there is some evidence that tDCS may be capable of reorienting attention towards the left side of space. Sparing et al., (2009) applied 1mA tDCS for 15 minutes to 10 patients with left visual inattention. Each patient received 4 counterbalanced protocols involving i) anodal and ii) cathodal tDCS to the unlesioned left posterior parietal cortex (P3) and iii) anodal and iv) sham to the lesioned right PPC (P4), with the return electrode positioned on the vertex. Both anodal stimulation of the lesioned area and cathodal inhibition of the preserved cortex led to a reduction of pathological rightward bias on the line bisection task. Furthermore, in a single case study by Brem et al., (2014), 5 bi-parietal tDCS sessions given across consecutive days improved covert attention to the left side of space and on shape copying and line bisection subtests of the BIT. However a feasibility trial by Smit et al., (2015) using the same 5-session protocol suggested that such studies are unlikely to be feasible on a larger scale in patients with neglect due to a higher incidence of tDCS exclusion criteria in this group (e.g. post-stroke seizure, metallic implants e.g. pacemaker and other significant comorbidities). Finally, it is important to note that tDCS is not yet approved as a rehabilitation method by UK clinical guidance bodies due to a lack of robust evidence of its efficacy, mainly due to small sample sizes and differences in protocols (e.g. montages, current strength, duration), and a drive towards more convincing evidence is recommended (NICE, 2015).

Variability of Response to tDCS

Although there are some promising studies, a recent series of meta-analyses, taking into account both neurophysiological (e.g. MEP amplitudes) and cognitive effects of tDCS reported in the literature has questioned the general efficacy of tDCS beyond a small, reliable modulation of MEP amplitude (Horvath, Carter & Forte, 2014; Horvath, Forte & Carter, 2015a, 2015b). Moreover, there has been a steady reduction in the effect size of this MEP alteration since it was first reported by Nitsche & Paulus in 2000 (Horvath, Forte & Carter, 2015a). In an earlier meta-analysis Jacobson, Koslowski & Lavidor (2012) reported that the 'traditional' anodal-excitation/cathodal-inhibition dichotomy was applicable within the motor domain, but that this mechanism is not always applicable for cognitive tasks, particularly the effect of cathode inhibition. This may be due to the more widespread cortical excitation that supports higher-level processing that cannot easily be countered by focal tDCS to a single target region. Secondly, there are a number of reports of high intra- and inter-individual response to tDCS which indicates that the technique may be more effective in some people than others (Benwell, Learmonth et al., 2015; Chew, Ho & Loo, 2015; Lopez-Alonso et al., 2014; Wiethoff, Hamada & Rothwell, 2014) and/or related to complex fluctuations in responsiveness that have yet to be adequately specified, such as hormonal fluctuations, psychological status, medications and even caffeine intake (Fertonani & Miniussi, 2016; Li, Uehara & Hanakawa, 2015). These observations have recently generated an intense debate within the field of cognitive neuroscience regarding whether tDCS does indeed exert any meaningful effect on the underlying neurons that can in turn affect behaviour. If there are so many biological, psychological and neurochemical factors which influence the effectiveness of tDCS, then we must question whether is it ever possible to harness this technique in a meaningful way to be able to improve the lives of patients with cognitive disorders, or indeed in the course of cognitive aging. On the other hand, is it also the responsibility of researchers to systematically examine each of these potential modulatory factors so that we can begin to individualise tDCS doses to each person receiving it. In Chapter Four of this thesis I investigate whether young and older adults exhibit similar behavioural responses to tDCS, and I identify an additional factor which determines outcome: whether the individual is a good or poor performer in the task of interest.

TDCS in Healthy Aging

Given that tDCS has attracted such interest in terms of its potential for both cognitive enhancement and also for rehabilitation in clinical populations, it is surprising that relatively few studies have attempted to utilise tDCS to alleviate the effects of cognitive aging in healthy older adults. At a global level, the proportion of adults aged over 60 is predicted to double by 2050 to more than 2 billion individuals (United Nations, 2013). As a result of this demographic shift, age-related cognitive decline is now considered one of the most pressing issues to be addressed, if independence and quality of life are to be maintained throughout our later years (Depp & Jeste, 2006). Leaving aside the impact that pathological aging (e.g. dementia) enacts at both an individual and societal level, healthy non-pathological aging is also accompanied by neural changes that result in decreased performance across a wide range of cognitive domains. Whilst there are large individual differences in the speed and extent of cognitive aging, generally linguistic and numerical performance seem relatively spared into older adulthood, (Hedden & Gabrieli, 2004; Schaie, 1996) whereas domains such as working memory (Craik, 1994; Park et al., 2002; Wingfield et al., 1988), executive control (Dempster, 1992; Hasher, Zacks & May, 1999; Lamar, Zonderman & Resnick, 2002) and processing speed (Deary, Johnson & Starr, 2010; Salthouse, 1991, 1996) are more vulnerable to decline.

In my opinion, there are three overarching questions that researchers should address when applying tDCS in older adults: 1) to assess whether mechanisms of neuroplasticity differ in the older vs young brain, 2) to assess whether different areas of the brain are used to undertake the same tasks in both age groups and 3) to develop stimulation protocols that can successfully alleviate age-related cognitive decline.

With regard to the first of these three questions there is, at present, mixed evidence regarding whether neuroplasticity is generally reduced in older adults relative to young (Olivero, 2010). Fujiyama et al., (2014) compared the time course of corticospinal excitability changes after anodal tDCS in young and older adults. They applied 1mA anodal tDCS to the M1 cortical motor region for 30 minutes and recorded TMS-induced MEPs at baseline (pre-tDCS), immediately post-tDCS and at 10, 20 and 30 minutes after cessation of the current. Although they found no differences in the *magnitude* of the MEPs between the two age groups, there were clear differences in the *timing* of the tDCS effect. The young adults demonstrated the largest MEP increase immediately post-tDCS whereas the older adults reached a peak 30 minutes after stimulation had ended. The authors conclude that although anodal tDCS is equally effective in older adults, the neuroplastic effects are delayed, and such differences must be incorporated into the experimental design for application in this group.

With regard to the second of these questions, a number of studies have reported different tDCS outcomes for older people compared to young. Across three within-participant sessions, Berryhill & Jones (2012) applied 10 minutes of 1.5mA anodal tDCS to the left and right dorsolateral prefrontal cortex (F3 and F4), together with a sham protocol, in older adults (56-80 years), whilst they underwent both verbal and visual *n-back* tests of working memory. There was no overall effect of tDCS, but response was dependent on education: older adults benefited from both F3 and F4 stimulation across both verbal and visual tasks, but those with lower levels of education did not benefit at all. However, a recent series of literature reviews concerning non-invasive brain stimulation in cognitive aging have all offered enthusiastic opinions regarding the future of this field, indicating that there is sufficient evidence to conclude that it may prove beneficial (Antonenko et al., 2016; Perceval, Flöel & Meinzer, 2016; Summers, Kang & Caraugh, 2016). Given this growing consensus, there are still large gaps in the literature due to the relatively few studies focusing on this area; for instance Chapter Three of this thesis represents the very first attempt to modulate spatial attention in healthy older adults. Finally, studies such as Berryhill & Jones (2012) reported above, hint that the large intra- and inter-subject variability that afflicts the wider literature is also a major contributing factor to tDCS outcomes in older adults. Indeed it may be that variables which determine outcomes in young adults affect older adults in quite different ways. I present a detailed discussion of this issue in Chapter Three.

Overview of Thesis

In this thesis I present the results of three experiments, broadly divided into Part I: the investigation of pseudoneglect in young adults (Chapter Two) and Part II: changes in spatial attention asymmetries in healthy aging (Chapters Three and Four).

In Chapter Two I examine the test-retest reliability of 5 commonly used behavioural measures of pseudoneglect in a large sample of young adults. The aim of this Chapter is to assess whether each of the tasks provides a stable measure of pseudoneglect for each individual when administered on two different days. Secondly, I examine the relationship *between* each of these 5 tasks and ask whether they all provide similar measures of spatial attention bias.

In Chapters Three and Four I use two techniques (tDCS and EEG, respectively) to quantify the differences in spatial attention asymmetries between young and older adults.

In Chapter Three I use tDCS to modify spatial attention biases in both young and older adults by altering neural activity within the parietal cortex whilst completing a lateralised visual detection task.

The results of this study led to my final experiment in Chapter Four, which maps age-related changes in spatial attention using electroencephalography during landmark task performance.

Finally, in Chapter Five I discuss the thesis as a whole by outlining the theoretical implications of these findings in relation to the wider literature. I then discuss some of the methodological limitations of the experiments, and I conclude by suggesting some future directions for research into the mapping and modulating of spatial attention asymmetries in young and older adults.

Chapter Two

Intra- and Inter-Task Reliability of Spatial Attention Measures in Pseudoneglect

1. Introduction

Healthy adults display a processing advantage towards the left side of space (‘pseudoneglect’), likely as a result of right cerebral hemisphere dominance for spatial attention (Bowers & Heilman, 1980). This left-sided advantage manifests as a systematic overestimation of the magnitude of target features that are located on the left and has been observed across various experimental tasks. Yet as a result of these multiple methods of testing, a variety of task demands are introduced. It remains unclear whether the most frequently used tasks in the spatial attention literature capture a bias that is representative of a single, common underlying aspect of spatial attention bias or whether pseudoneglect is instead a multi-component phenomenon.

In the clinical setting, patients with hemispatial neglect are known to exhibit dissociations of performance across subtests of batteries that are intended to assess spatial attention deficits, e.g. the Behavioural Inattention Test (Wilson, Cockburn & Halligan, 1987; Chechlacz, Rotshtein & Humphreys, 2012; Driver, Vuilleumier & Husain, 2004; Halligan et al., 2003; Kerkhoff, 2001; Vuilleumier et al., 2007). These subtest-specific deficits are generally correlated with the location of the lesion within the brain. Verdon et al., (2010) reported that damage to the right inferior parietal lobe negatively affects the ability to direct attention to the ipsilesional hemispace on tasks involving general visuospatial perception components (i.e. the line bisection task and text reading). Damage more anteriorly within the right dorsolateral prefrontal cortex impairs visuomotor exploration (i.e. object cancellation tasks), whilst patients with temporal lobe damage perform less well for object-centred (‘allocentric’) perception (i.e. the Ota task). There is therefore strong evidence that hemispatial neglect is a multi-component disorder involving disruption to distinct aspects of the attentional network.

I reason that, analogous to the dissociations within the neglect patient population, the assorted tasks used to measure attentional bias in the healthy population represent a potential method of partitioning out pseudoneglect into distinct components. The lack of relationship between various spatial attention tasks was first documented by Luh (1995) twenty years ago, who reported no significant correlation between spatial asymmetries elicited in response to chimeric face judgements, dot-filled rectangles, Müller-Lyer shapes and manual line bisection performance in non-lesioned adults. Similarly, Nicholls, Bradshaw & Mattingley (1999) presented tasks requiring a judgement of size (the *shape* task), number (the *stars* task) and shading gradients (the *greyscales* task) and although bias measures were found to be highly consistent *within* each individual task (as indexed by split-half reliability), there was little evidence of a consistent relationship *between* the 3 tasks. This suggests that a dissociation exists between tasks which involve different cognitive demands, similar to the observations in hemispatial neglect patients. I aimed to evaluate both intra- and inter-task reliability in pseudoneglect explicitly, with a focus on tasks used in the current spatial attention literature.

One of the most commonly-used tests of hemispatial neglect and pseudoneglect, the manual line bisection (MLB) task, requires participants to place a mark at the midpoint of a horizontal line (Figure 1a). The deviation of this mark relative to the true midpoint determines the direction and extent of attentional asymmetry, which is typically deviated rightward in patients with neglect and leftward (although to a lesser magnitude) in the healthy population. The traditional paper-and-pencil version of the MLB task involves the co-ordination of both visuospatial and motor abilities (Luh, 1995), and replicating these demands on a computer screen can prove problematic, possibly inducing a rightward bias that may be due to the presentation being delivered in extrapersonal, rather than peripersonal, space (Dellatolas, Vanluchene & Coutin, 1996). Many studies have also reduced the motor demands of the MLB task by presenting a cursor at one end of the horizontal line, with instructions to incrementally move this towards the midpoint using keyboard buttons (Dellatolas, Vanluchene & Coutin, 1996; Çiçek, Deouell & Knight, 2009; Nicholls et al., 2014; Varnava, McCarthy & Beaumont, 2002). Recent studies have incorporated the computer mouse pointer to more closely replicate the motor action that is required in the paper versions (Halligan & Marshall, 1989; Foulsham et al., 2013; Sparing et al., 2009; Varnava, Dervinis & Chambers, 2013.

Performance variability has been reported in the MLB task, both within and between individuals (Manning, Halligan & Marshall, 1990; Jewell & McCourt, 2000) and the direction of the pseudoneglect bias appears to be partially dependent on the spatial location of the line along the horizontal plane (see Jewell & McCourt, 2000, for review). There is however mixed consensus on the direction of this 'positional uncertainty' effect, with some studies finding a bidirectional, centrifugal shift of bias leftward (or rightward) as the line is jittered further into the left (or right) side of space respectively (Reuter-Lorenz, Kinsbourne & Moscovitch, 1990; Milner, Brechmann & Pagliarini, 1992; McCourt, Garlinghouse & Slater, 2000). Others have shown a consistent leftward bias when stimuli are positioned in both left and right hemispace, with performance more extremely leftward-deviated when presented to the left (Luh, 1995).

A non-manual variant of the MLB task - the *landmark* task (LM), (also called ‘tachistoscopic line bisection’ (McCourt & Jewell, 1999), is a common alternative measure of spatial attention bias which also serves to reduce the requirement for complex manual (pointing) movements (Milner, Brechmann & Pagliarini, 1992; Milner et al., 1993; Harvey et al., 2000; Benwell et al., 2013a,b, 2014a,b, 2015) (Figure 1b). Subjects are instructed to make a two-alternative forced choice decision regarding the length of two halves of a pre-bisected line. Healthy young adults demonstrate a systematic leftward bias of the subjective midpoint of the landmark lines, that is consistent with an overestimation of the size of left hemispace (Benwell et al., 2013a,b, 2014a,b, 2015; Dufour, Touzalin & Candas, 2007; McCourt, 2001; McCourt et al., 2001, Rueckert et al., 2002). Given the similarity between the MLB and LM tasks, it is perhaps unsurprising that a consistent correlation in the direction and magnitude of pseudoneglect bias has been observed between the two tasks in healthy adults (Luh, 1995; Dellatolas, Vanluchene & Coutin, 1996; Varnava, Dervinis & Chambers, 2013; Milner, Brechmann & Pagliarini, 1992, but see also Fink et al., 2000b). In support of this, functional magnetic resonance imaging during LM and LB performance has indicated a similar pattern of right cerebral hemisphere recruitment for both tasks (right dorsal fronto-parietal network activation for both tasks (Fink et al., 2000b), with additional involvement of the right frontal eye fields for LB (Çiçek, Deouell & Knight, 2009)).

Although the MLB and LM tasks require a judgement of the relative *size* of a stimulus presented within the left and right hemispace, pseudoneglect has also been demonstrated in tasks involving a range of target features. The *greyscales* task (GRE) requires a comparative luminance ('darkness') judgement to be made between two parallel horizontal lines containing a mirror-imaged linear contrast gradients (Figure 1c). The bar in which the dark section is located on the left side of space tends to be perceived as darker overall, compared to when it is placed on the right (Nicholls, Bradshaw & Mattingley, 1999; Mattingley et al., 1994a, 2004; Loftus, Vijaykumar & Nicholls, 2009; Loftus & Nicholls, 2012; Okubo & Nicholls, 2006; Friedrich & Elias, 2014). Most importantly, the left side is reported darker even when the bars are equiluminant, indicating a perceptual overestimation of the darkness of the left side of the stimulus. Nonetheless, there is a large reported variation of bias in this task, with some individuals displaying a clear leftward bias and others rightward (Mattingley et al., 2004; Tomer, 2008; Tomer et al., 2013), although performance does appear to be reliable over multiple testing days, which may indicate the presence of distinct population subgroups for the GRE task (Tomer et al., 2013). In addition, in a first attempt at cross-task comparisons, contrasting the bias observed in GRE with other tasks of spatial bias, Mattingley et al., (2004) and Nicholls & Roberts (2002) found only weak correlations with LB bias, which may be related to the motor demands required for LB but not GRE task performance. Additionally, Heber et al., (2010) reported no correlation between the GRE and LM tasks, further indicating that size judgements (in response to MLB and LM tasks) and luminance judgements (GRE) give rise to distinct and separable spatial attention asymmetry effects.

The *gratingscales* task (GRA) is derived from the GRE task and exploits the observation that size and spatial frequency perception share common features (Carrasco, Figueroa & Willen, 1986; Meinhardt & Grabbe, 2002; Niemeier, Stojanoski & Greco, 2007). The GRA also involves the presentation of two mirror-imaged parallel horizontal rectangles, but comprising sine-wave gratings of increasing/decreasing spatial frequency (Figure 1d). When instructed to indicate the bar containing more ‘thin stripes’ (i.e. high frequency sine-wave gratings), subjects are more likely to indicate the bar with the target feature located on the left side of space (Niemeier, Stojanoski & Greco, 2007; Chen & Niemeier, 2014; Neimeier et al., 2008a,b; Singh et al., 2010). However, when instructed to judge the ‘thick stripes’ (i.e. low frequency gratings) instead there is a ‘cross-over’ of bias where the *right* side is favoured. Nonetheless, this rightward bias is comparatively smaller in magnitude, alluding to an overall right hemisphere dominance that is similar to the other tasks described (Singh et al., 2010; Niemeier et al., 2008b). Because this cross-over effect is positively correlated within individuals it appears to be indicative of a stable set of distinct attentional mechanisms that are responsible for the processing of high and low spatial frequencies (Singh et al., 2010). Importantly, the GRA and GRE tasks are positively correlated measures of pseudoneglect when the stimuli are presented for a short duration (240 or 500ms) but not at longer presentation times (Niemeier, Stojanoski & Greco, 2007).

Finally, the *lateralised visual detection* (LVD) task as described by Hilgetag, Théoret & Pascual-Leone (2001) is intended to provide a simple measure of sustained attention during which participants detect small dots that appear very briefly in the left and right sides of space. Stimuli sizes are typically titrated to an individual's peri-threshold (50%) accuracy to equate the difficulty of the experiment across individuals (Sparing et al., 2009; Hilgetag, Théoret & Pascual-Leone, 2001; Dambeck et al., 2006; Romei, Gross & Thut, 2011; Thut et al., 2006, and in Chapter Three of this thesis). Using this paradigm, Hilgetag, Théoret & Pascual-Leone (2001) and Thut et al., (2006) found greater detection accuracy for left- compared to right-presented stimuli, consistent with pseudoneglect.

Here I report a correlational study, where these five tasks that have been commonly used to measure spatial attention asymmetries were completed over two testing sessions on different days. I aimed to investigate whether i) the direction and magnitude of bias is correlated *within* tasks across the two days (i.e. *intra*-task reliability) and ii) if the bias is correlated *between* each of the five tasks (i.e. *inter*-task reliability).

I also aimed to update the inter-correlational studies of Luh (1995) and Nicholls, Bradshaw & Mattingley (1999), by using tasks that are used to measure spatial attention biases in the current literature. Although these previous studies found very little between-task reliability, it was hoped that a more consistent relationship would be observed amongst these more recently-used tasks. Conversely, if the results indicated a continued lack of equivalence between spatial attention tasks, we would conclude that pseudoneglect is indeed multi-component and task-dependent and an assumption of equivalence thus counterproductive to the investigation of the neural substrates of pseudoneglect and its functional implications.

2. Methods

2.1 Participants

Fifty adults were recruited (35 females, mean age = 22.56 years; SD = 4.46, range = 18-38) and a further 1 participant was excluded due to failure to complete the second session. All were right-handed and had normal or corrected-to-normal vision. The study was approved by the University of Glasgow College of Science and Engineering ethics committee and written, informed consent was obtained from each participant.

2.2 Procedure

Testing took place over two sessions (at least 24 hours apart) in a repeated-measures design. At the start and end of each session participants indicated their subjective alertness on a linear scale (0 = almost asleep, 100 = fully alert). They were seated in front of a computer screen with their midsagittal plane aligned with the screen. Five blocks were presented during each testing session (1 block per task) in an order that was counterbalanced across participants. The 5 tasks were i) *landmark* (LM), ii) *manual line bisection* (MLB), iii) *greyscales* (GRE), iv) *gratingscales* (GRA) and v) *lateralised visual detection* (LVD) and the sequence of presentation was the same on Day 1 and Day 2 per participant to control for possible task-order effects. A practice block (approximately 20 trials) preceded each task and participants were instructed to take a short break between blocks if required.

2.3 Stimuli

Stimuli were presented with E-Prime 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) using a Dell Precision 380 PC and a 19’ Dell 1908FP UltraSharp LCD flat screen monitor with a 1280x1024 pixel resolution. One pixel measured approximately 0.29mm^2. The viewing distance was fixed with a chin rest at 0.7m.

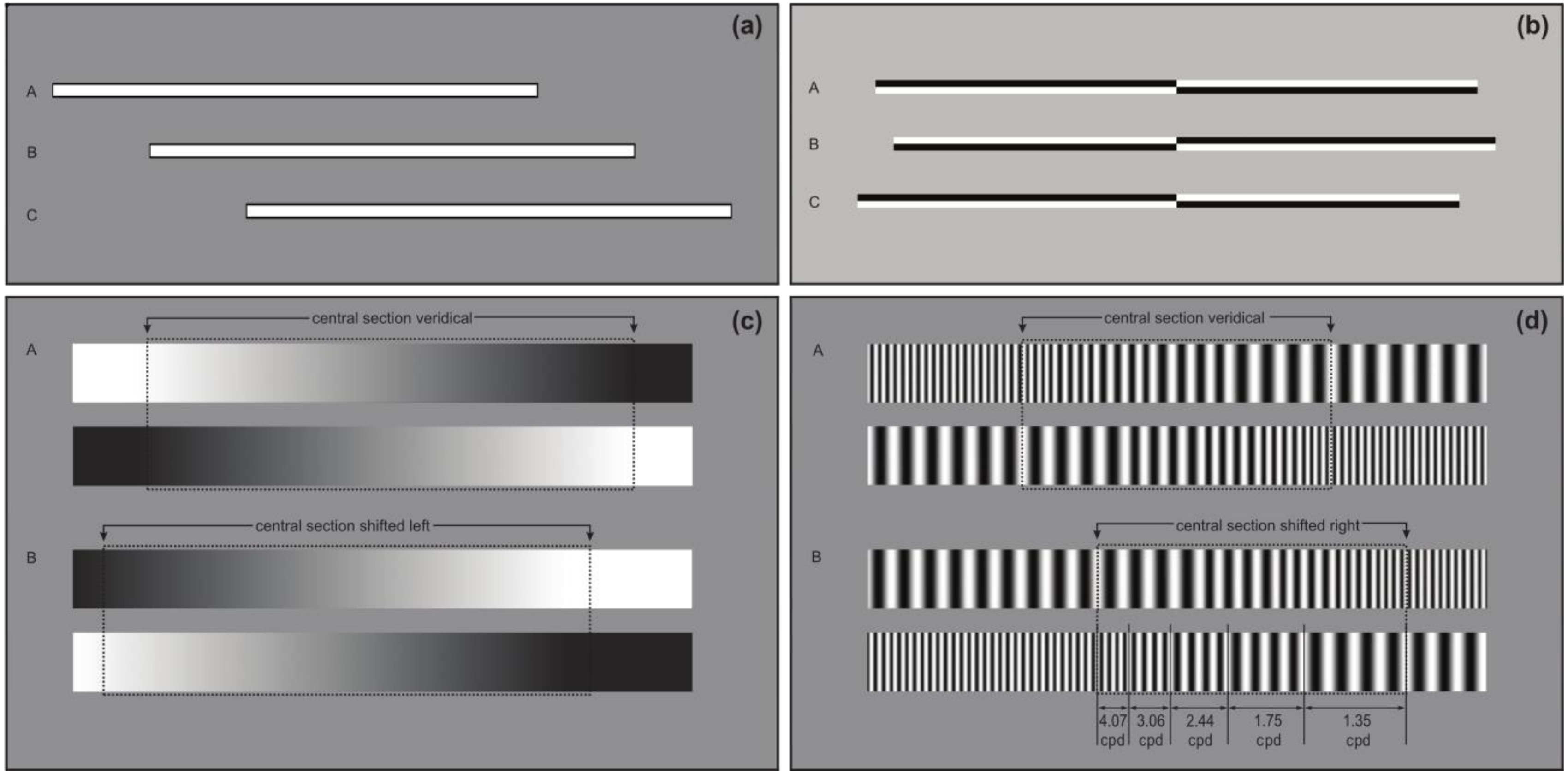

Figure 1. Examples of the (a) manual line bisection (MLB), (b) landmark (LM), (c) greyscales (GRE) and (d) gratingscales (GRA) stimuli. 1a) Stimulus B is centred at the horizontal midpoint of the screen. Stimuli A and C represent the most extremely deviated stimuli along the horizontal axis, with Stimulus A jittered 160 pixels (3.8° visual angle (VA)) leftward and C jittered 160 pixels rightward relative to centre. **1b)** The left and right sides of Stimulus A are of equal length, the left side of B is shorter by 48 pixels (0.53°) and the right side of C shorter by 48 pixels. **1c)** A central 'zone of interest' (640 pixels wide, 15.1°) was shifted in 10-pixel (0.24°) increments leftward and rightward. The shading gradient is continuous from left to right in Stimulus A and the central section is shifted leftward by -80 pixels (1.9°) in B. **1d)** A 400-pixel wide (9.47°) zone of interest was shifted in 12-pixel (0.29°) increments leftward and rightward. The zone is centred in Stimulus A and shifted rightward by 96 pixels (2.28°) in B.

2.3.1 Manual line bisection task (MLB)

The manual line bisection task was designed to closely replicate the paper-and-pencil version on a computer screen. Horizontal white lines (805 x 15 pixels) (approximately 23.5cm x 0.4cm; 19.06 x 0.33° visual angle (VA)) were presented on a grey background in the centre of the screen (Figure 1a). The outermost 2 pixels bordering the line were shaded black. The line was jittered at 9 positions along the horizontal axis on a trial-by-trial basis (0 = centred, and 40, 80, 120 and 160 pixels (0.95, 1.9, 2.85 and 3.8° VA) to the left and to the right of veridical centre). The mouse pointer was set to appear at the same starting location in the upper midpoint of the screen at the start of each trial (screen co-ordinates: X = 640, Y = 40 pixels; 11.17° above fixation). Participants were instructed to move the mouse pointer down towards the line and, using their right index finger, left-click on the horizontal midpoint of the line as accurately as possible. They were informed that the vertical co-ordinate did not matter. The line remained on the screen until a response was made, or until 6 seconds had elapsed without a response. The stimulus of the next trial appeared 1000ms thereafter (with the mouse pointer reset at the starting location). A total of 108 trials were presented (9 line positions repeated 12 times).

2.3.2 Landmark task (LM)

The LM task was adapted from McCourt (2001) and Milner, Brechmann & Pagliarini (1992) (see also Benwell et al., 2013a,b, 2014a,b, 2015). A centred fixation cross (15 x 15 pixels; 0.58° VA) appeared for 1000ms followed by a stimulus for 150ms. The fixation cross then reappeared until a response was given. Subjects indicated whether the left or right side of the line was shorter by keyboard response using their right hand. Stimuli consisted of horizontal 100% Michelson contrast lines measuring 800 x 14 pixels (approximately 23.5cm x 0.4cm; 19.06 x 0.33° VA) (Figure 1b). Each line was vertically transected at the veridical centre of the screen (i.e. at the same position as the fixation cross) but the length of the left and right sections varied across trials. The most asymmetrical (left side vs right side) stimuli differed by 48 pixels (0.53°) and the asymmetry reduced in 6-pixel (0.07°) increments until the two sides were of equal length. Thus, 17 stimuli of varying asymmetry were created. The landmark block consisted of 136 trials (17 stimuli repeated 8 times (x4 where the upper left and lower right sections were shaded black (e.g. Stimuli A and C) and x4 where the upper left and lower right were white (e.g. Stimulus B)).

2.3.3 Greyscales task (GRE)

The greyscales task was adapted from Mattingley et al., (1994a,b, 2004) and involved the presentation of two parallel horizontal rectangles, one above the other (Figure 1c). The rectangles were shaded along a smooth luminance gradient so that one end of the rectangle was fully black and the other end fully white. The rectangles were mirror-images along the horizontal and vertical axes, so that half of the trials involved upper bars that increased in luminance from left-right, with the lower bar increasing from right-left. The remaining trials contained the opposite configuration (top: right-left gradient, bottom: left-right). A centred fixation cross (15 x 15 pixels; 0.58° VA) appeared for 1000ms followed by a stimulus for 150ms. The fixation then reappeared, during which participants indicated whether the top or bottom bar was darker overall using the ‘up’ or ‘down’ keyboard arrows. The next trial began when a response was given. Each rectangle measured 800 x 100 pixels (approximately 23.5cm x 2.9cm; 19.06 x 2.37° VA), with 41 pixels (0.97°) between the two bars. As per Niemeier, Stojanoski & Greco (2007) the task was modified to allow an estimation of spatial bias with psychometric functions. A central ‘zone of interest’ section comprising 640 pixels (80% of the total length, 15.1°) was shifted in 10-pixel (0.24°) increments to the left or to the right to provide 17 different stimuli. The most extremely asymmetric rectangles differed by 80 pixels (1.9°; -10% or +10% of total length). The remainder of the bar was then filled in with solid black/white. Thus, Figure 1c Stimulus B shows the central section shifted leftwards and the participant would be likely to perceive the lower bar to be darker overall. One block comprised 136 trials (17 stimuli repeated 8 times (x4 where the upper left and lower right sections were shaded white (e.g. Stimulus A) and x4 where the upper left and lower right were black (e.g. Stimulus B)).

2.3.4 Gratingscales task (GRA)

The gratingscales task was adapted from Niemeier, Stojanoski & Greco (2007). Similar to the GRE task, two mirror-imaged, parallel horizontal bars (800 x 100 pixels: approximately 23.5cm x 2.9cm; 19.06 x 2.37° VA) were presented, but instead of a shaded gradient the stimuli contained sine-wave gratings (Figure 1d). The grating was high-frequency (‘HiSF’) at one end of the rectangle (35 pixels per cycle; 1.35 cycles per degree of visual angle (cpd)) and low-frequency

(‘LoSF’) at the opposite end (11 pixels per cycle; 4.07 cpd). A central ‘zone of interest’ measuring 400 pixels (50% of the total length, 9.47°) was shifted in 12-pixel (0.29°) increments to the left or to the right to provide 17 different gratingscales stimuli. The most extremely asymmetrical rectangles differed by 96 pixels (2.28°; -12% or +12% of total length) (Figure 1d, Stimulus B). The remainder of the line was then filled in with continuous HiSF and LoSF gratings. The zone of interest contained sine waves of 5 different spatial frequencies, with 4 sine wave cycles per frequency, which ranged from LoSF = 35 pixels per cycle, through 26, 19, 14 and the highest frequency of 10 pixels per cycle (i.e. the number of pixels per cycle reduced by a factor of approximately x0.74). A centred fixation cross (15 x 15 pixels; 0.58°) appeared for 1000ms followed by a stimulus for 150ms. The fixation then reappeared, during which participants indicated whether the top or bottom line had more ‘thin stripes’ overall (i.e. high frequency gratings) using the ‘up’ or ‘down’ keyboard arrows. Figure 1d, Stimulus B shows the central section shifted rightward and the participant would be likely to perceive the lower bar as containing more thin stripes overall. One block comprised 136 trials (17 stimuli repeated 8 times (x4 where the upper left and lower right sections were HiSF (e.g. Stimulus A) and x4 where the upper left and lower right were LoSF (e.g. Stimulus B)).

2.3.5 Lateralised visual detection task (LVD)

The task was adapted from Hilgetag, Théoret & Pascual-Leone (2001) and was similar to the task used in Sparing et al., 2009, Dambeck et al., 2006; Romei, Gross & Thut, 2011 and Thut et al., 2006. Stimuli consisted of small black squares or rectangles (with the longer edge along the horizontal axis) presented against a grey screen (luminance = 179, hue = 160). The squares were of 5 different sizes (1 x 2, 2 x 2, 2 x 3, 3 x 3 and 3 x 4 pixels; between 0.024 x 0.047° and 0.87 x 1.16° VA) and were presented either to the left (-145mm; -16.5°), or to the right (+145mm; +16.5°) of fixation (no placeholders presented). One block comprised 132 trials (12 left and 12 right for each of the 5 stimulus sizes, plus 12 blank 'catch' trials where the screen remained blank). Participants used their right hand to indicate on a keyboard when the stimulus appeared on the left (index finger) or right (middle finger) and they were instructed to withhold their response when no stimulus was detected. A centred fixation cross (15 x 15 pixels; 0.58°) appeared for 1000ms followed by a stimulus for 40ms. A blank response screen then appeared for a fixed duration of 1750ms (to accommodate false negatives and catch trials), after which a new trial began.

2.4 Analysis

2.4.1 LM, GRE and GRA tasks

The LM, GRE and GRA tasks were analysed using the same method to ensure comparability of results. Accuracy for each of the 17 stimulus asymmetries was converted into a percentage of trials where the subject perceived the stimulus to be either shorter (LM)/darker(GRE)/have more 'thin stripes' (GRA) on the *left* side of space. Psychometric functions were then fitted to the data for each individual and the point of subjective equality (PSE) for each task was obtained using the cumulative logistic function described by the equation:

$$f(\mu, x, s) = 1/(1 + \exp\left(\frac{\mu - x}{s}\right))$$

Where μ is the point on the x-axis that corresponds to 50% left and 50% right-response rate, x represents the transector locations and s is the psychometric curve width. Curve widths provide a measure of task ability, with a narrow curve width indicative of good performance (Pelli, 1985, 1987). PSEs were transformed to represent a percentage of the total line length.

2.4.2 MLB task

The x- and y-pixel co-ordinates of the screen that was clicked using the mouse were logged by E-Prime. This subjective x-co-ordinate was subtracted from the x-co-ordinate of the true midpoint location and the mean bias and standard deviation were calculated for each individual. Responses that were greater than 2.5 standard deviations above and below the individual's mean were excluded due to a few extreme values (151 trials = 1.42%), presumably made in error whilst moving the mouse towards the stimulus from the starting position. The adjusted mean was then recalculated, which provided an overall bias score (in pixels) towards either the left (negative value) or the right side (positive value) for the manual line bisection block. Bias scores were then transformed to represent a percentage of the total line length.

2.4.3 LVD task

Two methods of analysis were used to calculate spatial attention bias in the LVD task:

1. D-prime (*d'*)

This method uses visual detection sensitivity and takes into account both percentage accuracy for each side of space ('hits' when stimuli are present and 'false alarms' in response to catch trials)(Green & Swets, 1966; Macmillan & Creelman, 2005). *D'* was calculated using the function:

$$d' = z(Hits) - z(FalseAlarms)$$

where *z* represents the z-score for each side of space. Larger *d*' scores represent a greater sensitivity for detecting stimuli relative to false positives. A *d'* lateralisation index was then calculated by subtracting Left visual field (VF) *d'* from Right VF *d'*.

2. Psychometric function fitting (PF 50%)

Another method of analysis, bringing the method of analysis into alignment with the LM, GRE and GRA tasks reported here, is to fit psychometric functions for percentage accuracy on the 5 stimulus sizes. Individual curves were fitted separately for left- and right-presented stimuli, and PSEs and curve widths were extracted. To fit the curves, the 5 stimulus sizes were labelled as 1 = 1x2 pixels, 2 = 2x2, 3 = 2x3, 4 = 3x3 and 5 = 3x4 and therefore a PSE of 1.5 indicates that the participant reached 50% accuracy (PF 50%) at a stimulus size that lies half way between 1x2 and 2x2 pixels. A small PF 50% value represents better performance compared to larger PF 50% values (i.e. 50% accuracy was achieved at a smaller pixel size). A measure of lateralised spatial bias was then calculated by subtracting the Right VF PSE from the Left VF PSE. The PF 50% and *d'* methods were found to be strongly correlated on both testing days (Day 1: r=0.884, p<0.001; Day 2: r=0.965, p<0.001; Mean Days 1+2: r=0.937, p<0.001).

3. Results

3.1 Counterbalancing

A Friedman test confirmed that the tasks were adequately randomised in terms of presentation order ($\chi^2(4)=1.232$, p=0.873). Mean ranks *MLB:* 2.96 (SD=1.32), *LM:* 3.02 (SD=1.39), *GRE:* 3.04 (SD=1.48), *GRA:* 3.16 (SD=1.53), *LVD:* 2.82 (SD=1.38).

3.2 Subjective alertness

A 2x2 analysis of variance (ANOVA) (TIME: *pre-* vs *post-experiment* x DAY: Day *1* vs *Day 2*) on the subjective alertness scores found that alertness generally reduced over the course of the experiment [Mean *pre* = 74.75, SD = 11.46, Mean *post* = 64.9, SD = 15.29; main effect of TIME: F(1,49)=25.51, p<0.001] but did not differ between the two testing days. No other effects proved significant.

3.3 Task performance

While spatial bias is the primary measure of interest, it does not enable an assessment of the precision of the participants' performance, i.e. to what extent participants were actively engaged with the task. I therefore first analysed the curve width, a measure of the precision of the subjective midpoint judgement (for each block), available for all tasks employed (LM, GRE, GRA and LVD), except MLB (no psychometric functions fitted). A steep slope indicates high task precision, whereas a shallower curve is obtained when the individual is less precise (Pelli, 1985, 1987). Each task showed a slight mean reduction of curve width on the second day relative to the first, reflecting a slight improvement in precision gained by task learning, but paired samples t-tests indicated that the reduction was not significant for the LM, GRA and LVD (all p values ≥0.149). Only the mean GRE curve was significantly narrower on Day 2 compared to Day 1 [t(49)= -2.424, p=0.019]. For the LM, GRE and GRA tasks, the intra-task curve widths were correlated between Day 1 and Day 2 across participants (Pearson's r: LM r=0.312, p=0.028; GRE r=0.546, p<0.001; GRA r=0.67, p<0.001) indicating good performance consistency over the two days. Likewise, for the LVD task, curve widths obtained from curve fitting (analysis of PF 50%) were correlated across the two testing days for each visual field (Day 1 vs Day 2, Left-presented stimuli: r=0.335, p=0.018; Right-presented stimuli: r=0.380, p=0.007). An average curve width was calculated across days (Day 1, Day 2) and the curve widths for the Left versus Right stimuli were significantly correlated (r=0.452, p=0.001) indicating that participants performed the task with similar precision across both days and in both sides of space. Overall, this indicates significant performance consistency, suggesting that spatial bias values across days and tasks are interpretable (are not contaminated by poor task engagement across days or tasks).

3.4 Spatial bias per task

3.4.1 MLB task

The group-averaged MLB bias was first analysed for each of the 9 jittered line positions along the horizontal axis (averaged across the two testing days in Fig. 2). Separate one-sample t-tests against zero for each of the 9 positions confirmed a bias towards the left of the true horizontal centre when the line was positioned at the veridical centre and when jittered towards the left of the screen (position *0 veridical*: [t(49)= -3.533, p=0.001]; *-40 left*: [t(49)= -4.926, p<0.001]; *-80 left:* [t(49)= -6.286, p<0.001]; *-120 left:* [t(49)= -6.589, p<0.001]; and *-160 left*: [t(49)= -6.455, p<0.001]) but participants did not err significantly when the line was jittered towards the right (positions *+40*, *+80, +120* and *+140 right*). A repeated measures ANOVA for the 9 line positions revealed a main effect of POSITION [F(1,49) = 39.77, p<0.001, ηp^2=0.448]. Paired samples t-tests found no difference in bias between the two most extreme leftward lines (*-160 left* and *-120 left* of centre) but there was a significant incremental leftward shift between positions *0* vs *-40* [t(49)= -3.029, p=0.004], *-40* vs *-80* [t(49)= -3.897, p<0.001], both significant at corrected α=0.00625, and *-80* vs *-120* [t(49)= -2.526, p=0.015] indicating an increase in leftward bias magnitude as the line was shifted further into left hemispace, and confirming the findings of Luh et al., (1995). A compound measure of bias in this task (collapsing across all 9 line positions and the two days) revealed an overall leftward bias (one sample t-test against zero: t(49)= -3.85, p<0.001).

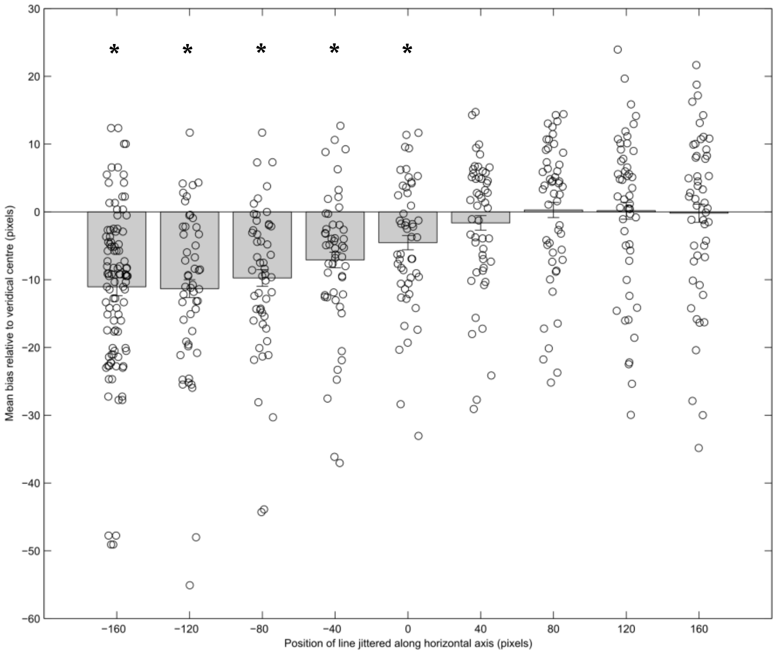

Figure 2. Mean bias for the MLB task with individual values overlaid. *represents a significant leftward bias (p<0.002).

3.4.2 LM, GRE and GRA tasks

The group-averaged psychometric function curves (mean of Day 1 and Day 2), used to calculate the point of subjective equality (PSE), and curve widths for the LM, GRE and GRA tasks are shown in Fig 3. Analysis of PSEs (PF 50%) per task (collapsed across days) revealed a consistent leftward bias only for the LM task (one sample t-test against zero: t(49)= -3.47, p=0.001). PSEs of the GRE and GRA tasks were not significantly different from zero (GRE [t(49)=1.52, p=0.136], GRA [t(49)=1.136, p=0.25], data collapsed over the two days).

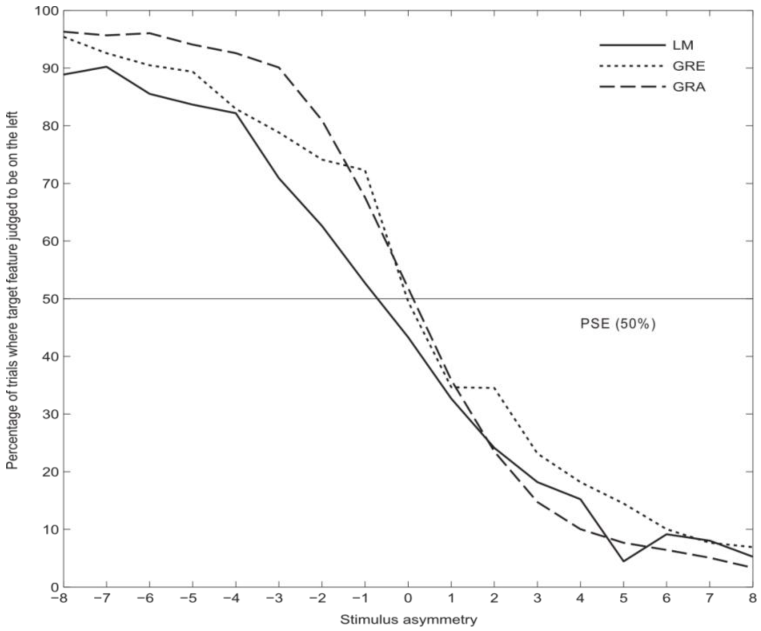

Figure 3. Mean psychometric function curves for the LM, GRE and GRA tasks. The asymmetry of the presented stimulus is shown on the x-axis, where 0 = 'both sides equal length' (LM) or 'both bars equal darkness/thin stripes' (GRE/GRA respectively). Negative asymmetry values represent trials where the target feature is located on the left side and positive values on the right side. One unit on the x-axis equates to 3 pixels (0.07°) for the LM task, 10 pixels (0.24°) for GRE and 12 pixels (0.29°) for GRA.

3.4.3 LVD task

The mean accuracy of stimulus detection is illustrated in Figure 4, per stimulus size and hemispace, revealing no apparent asymmetry between the two visual fields. Averaged across the 5 pixel sizes, stimuli presented on the left were detected with an overall mean accuracy of 52.6% and 53.7% for right-presented stimuli.

Analysis method 1: D prime (d')

88.33% of catch trials were correctly rejected, with 44.29% of the total false positives made towards the left VF and 55.71% to the right (no difference between sides, p>0.05). Mean group-average *d'* bias (*d' RVF* minus *d' LVF)* was

0.022 (collapsed across days). This was not significantly different from zero (one sample t-test, t(49)= 0.69, p=0.496), hence not revealing a lateralised bias.

Analysis method 2: Psychometric function fitting (PF 50%)

One participant was excluded from this analysis due to poor performance (18.3% accuracy on Day 1 and only 6.7% on Day 2) which resulted in an unfeasible PF 50% value. The mean (Day 1, Day 2) group-averaged PF 50% for *left*-presented stimuli was 2.81 and 2.72 for *right*-presented stimuli. A 2 x 2 (*VF* x *Day*) repeated measures ANOVA showed no PF 50% differences across stimulus presentation location (VF: F(1, 48)=2.037, p=0.160, ηp^2=0.41) or testing day (DAY: F(1,48)=2.255, p=0.140, ηp^2=0.045) and no interaction between the two factors. Accordingly, the mean group-averaged lateralised bias, which amounted to 0.09 (PF 50% *RVF* minus *LVF*) was again not significantly different from zero (one-sample t-test: t(48)= 1.420, p=0.162).

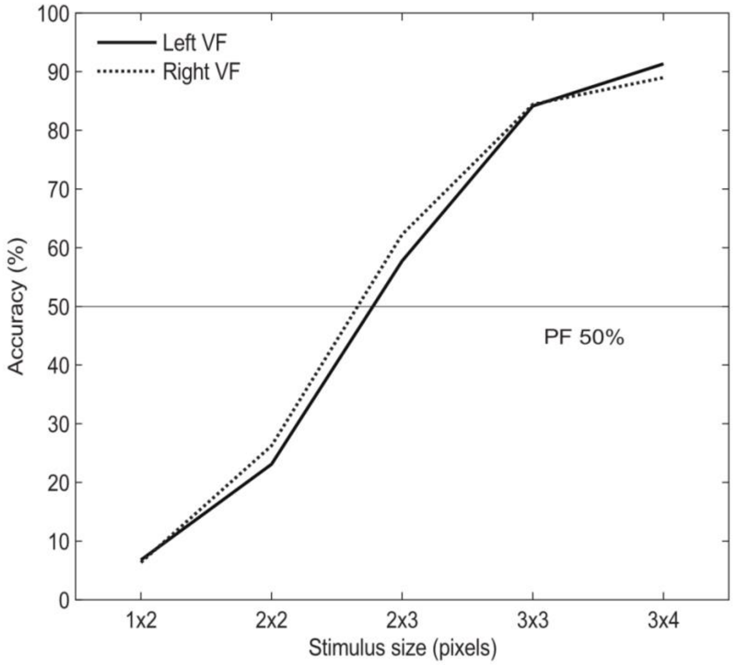

Figure 4. Mean detection accuracy for the LVD task. Separate curves for the left and right VFs are shown, across the 5 stimulus sizes.

3.5 Summary of overall task bias

The above group-level results for each of the five tasks are summarized in Figure 5, as well as split by Day 1 and Day 2. One-sample t-tests against zero confirmed an overall significant leftward bias (pseudoneglect) on both days for the MLB task [Day 1: t(49)= -4.330, p<0.001; Day 2: t(49)= -3.026, p=0.004] and LM task [Day 1: t(49)= -3.158, p=0.003; Day 2: t(49)= -3.049, p=0.004]. There was a significant, but weak, *rightward* bias for the GRE task on Day 1 [t(49)=2.098, p=0.041] which was not present on Day 2. Neither the GRA nor the LVD tasks elicited a lateralised bias on either testing day.

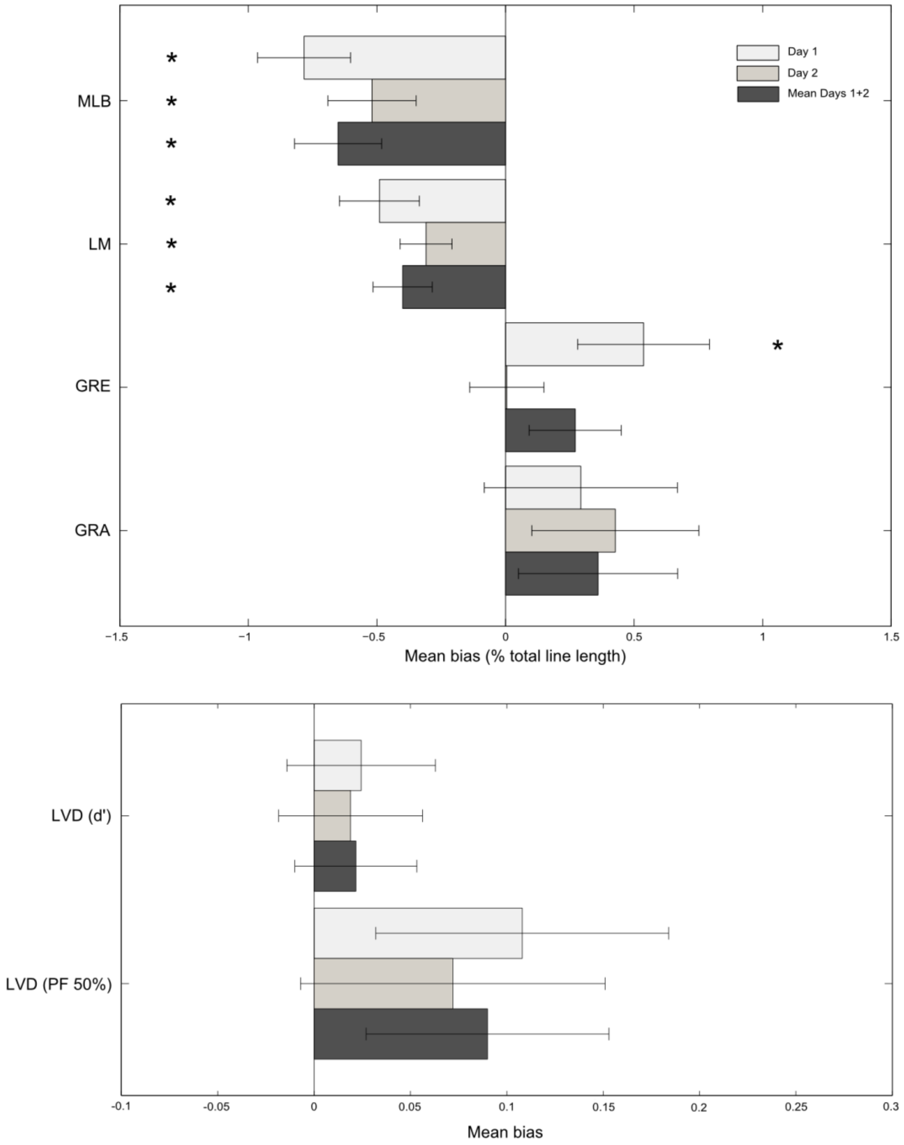

Figure 5. Grand average spatial attention bias for the 5 tasks. Negative and positive values represent leftward and rightward biases respectively. The LM and MLB tasks show significant leftward biases on both days and the GRE rightward on Day 1 only. The LVD task (d’ and PF 50%) is presented separately on the lower axes for clarity, due to smaller bias values. *represents a significant attentional bias compared to zero ($p<0.05$).

3.6 Intra-task reliability

A series of Pearson’s *r* correlation tests were used to assess the intra-task test-retest reliability of performance between Day 1 and Day 2 across participants. The biases obtained on all five tasks were correlated across testing days (Figure

6), showing that each measure is a stable indicator of individual spatial attention bias, despite some tasks not scoring an overall bias. Pearson's *r* of Day 1 vs Day 2 were: [MLB: r=0.846, p<0.001; LM: r=0.595, p<0.001; GRE: r=0.564, p<0.001; GRA: r=0.560, p<0.001; LVD (*d'*): r=0.395, p=0.005; LVD (PF 50%): r=0.342, p=0.023].

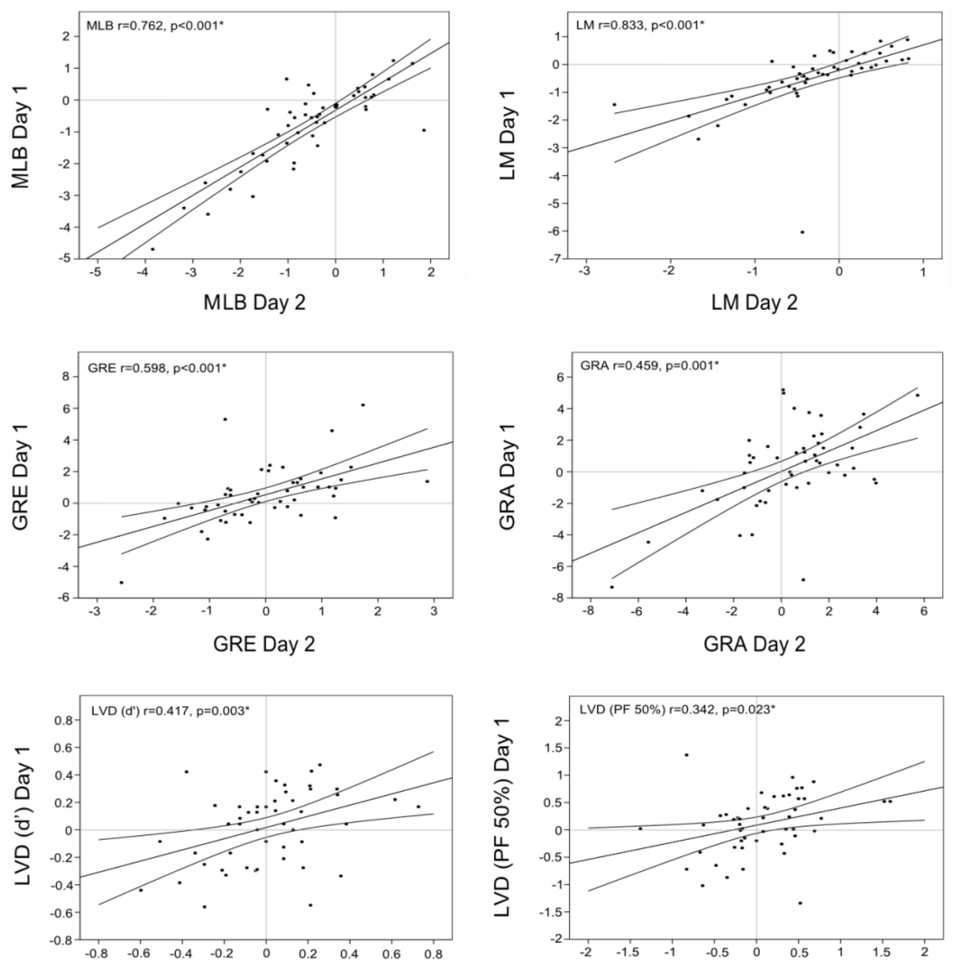

Figure 6. Intra-task correlations. Day 1 vs Day 2 biases are significantly correlated for all 5 tasks (i.e. each task provides a stable measure) over the two testing days (all p-values <0.05). Line of best fit and 95% confidence intervals are marked. *represents a significant correlation at α=0.05.

3.7 Inter-task reliability

Since each of the five tasks provided strongly correlated measures across the two testing days, further analysis was performed on the mean bias across days. Pearson's *r* correlations on these mean values assessed whether the five tasks elicited comparable measures of spatial attention bias. The correlation coefficients are provided in Table 1.

	LM	**GRE**	**GRA**	**LVD (*d'*)**	**LVD (PF 50%)**
MLB	r = 0.267 p = 0.06	r = -0.218 p = 0.128	r = -0.287 p = 0.043*	r = -0.182 p = 0.205	r = -0.183 p = 0.208
LM	--	r = -0.089 p = 0.537	r = 0.113 p = 0.436	r = -0.147 p = 0.308	r = -0.112 p = 0.445
GRE		--	r = 0.161 p = 0.264	r = -0.167 p = 0.247	r = -0.149 p = 0.305
GRA			--	r = 0.047 p = 0.744	r = 0.038 p = 0.798
LVD (*d'*)				--	r = 0.937 p < 0.001**

Table 1. Inter-task correlations performed on the mean task bias (Day 1 and Day 2 averaged). *significant p-value at α=0.05 but not significant at the Bonferroni-corrected α=0.005. ** significant at α=0.005.

Only the MLB and GRA tasks provided significant, yet negative and weakly correlated, mean measures of bias at α=0.05 that failed to maintain significance when the alpha was Bonferroni corrected for multiple comparisons (Pearson's *r*= -0.287, p=0.043, adjusted α=0.005). No other significant correlations between the five tasks were observed (see also Figure 7).

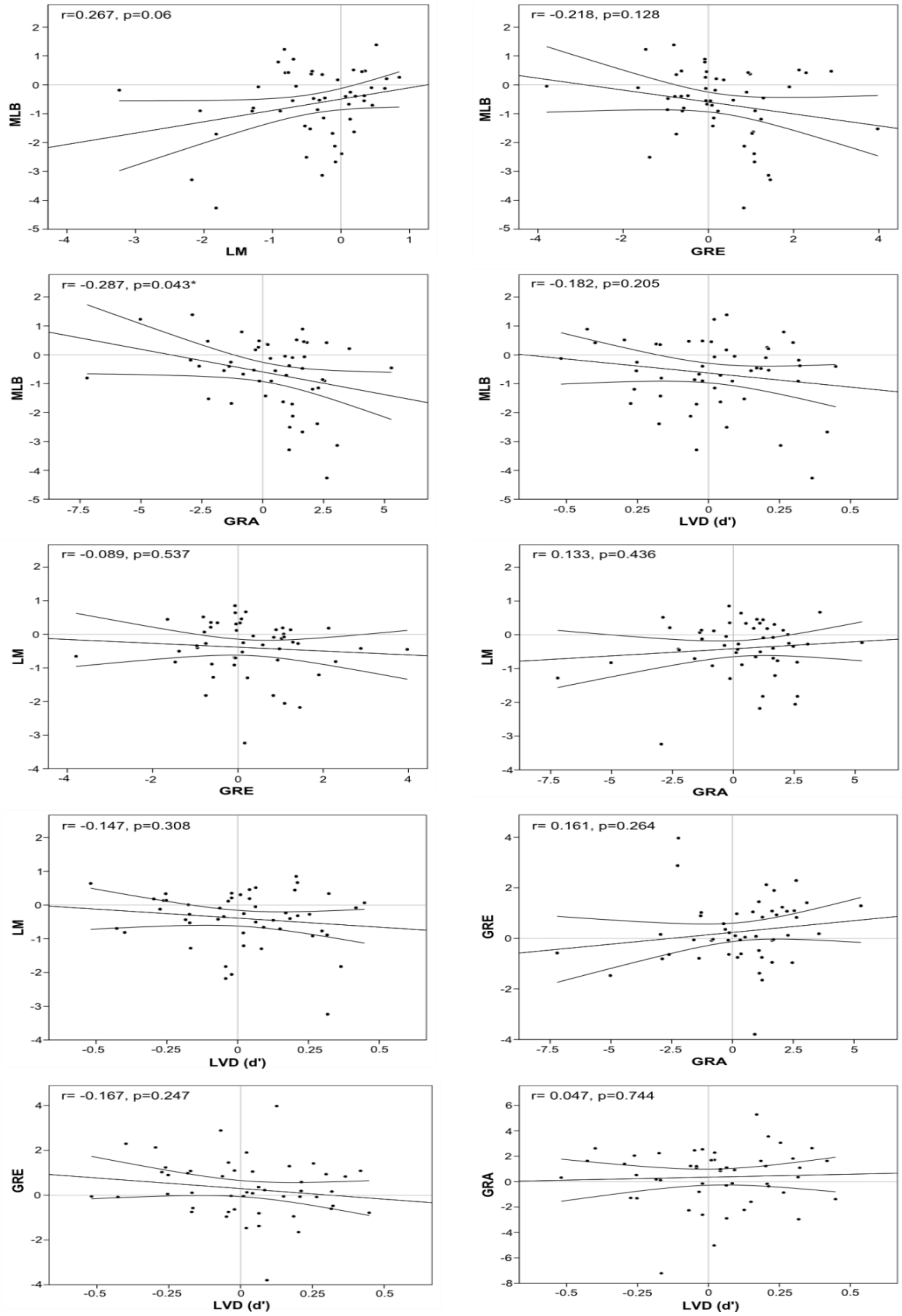

Figure 7. Inter-task correlations. Only the MLB and GRA tasks were significantly correlated at α=0.05 prior to correction, with all other comparisons p>0.05. *represents significant correlation at α=0.05, but not when Bonferroni corrected to α=0.005.

3.8 Principal component analysis (PCA)

In order to determine whether a smaller number of variables could account for the variance between the tasks, a principal component analysis (PCA) was performed on the correlation matrix using an orthogonal varimax rotation with Kaiser normalisation. Three components with an eigenvalue >1 were identified which explained 76.15% of the total variance (Table 2). A fourth component with an eigenvalue of 0.65 was forced to assess whether the LVD task loaded onto it and this 4-component model explained 89.1% of the total variance.

	PC1	**PC2**	**PC3**	**PC4**
Variance explained	**30.6%**	**24.56%**	**20.99%**	**12.95%**
Eigenvalue	1.53	1.23	1.05	0.65
MLB	**-0.62**	**0.54**	-0.18	-0.17
LM	0.11	**0.93**	-0.03	-0.05
GRE	0.1	-0.06	**0.99**	-0.09
GRA	**0.91**	0.16	0.05	-0.01
LVD (d')	0.05	-0.08	-0.09	**0.99**

Table 2. PCA loadings.

There was a strongly positive loading for the GRA task on the first principal component (PC1), whilst the MLB task loaded negatively onto this component. Both the LM and MLB tasks loaded together on PC2 and only the GRE task onto PC3. The fourth forced component (PC4) with a lower eigenvalue was found to have a strongly positive loading for the LVD task only (Figure 8).

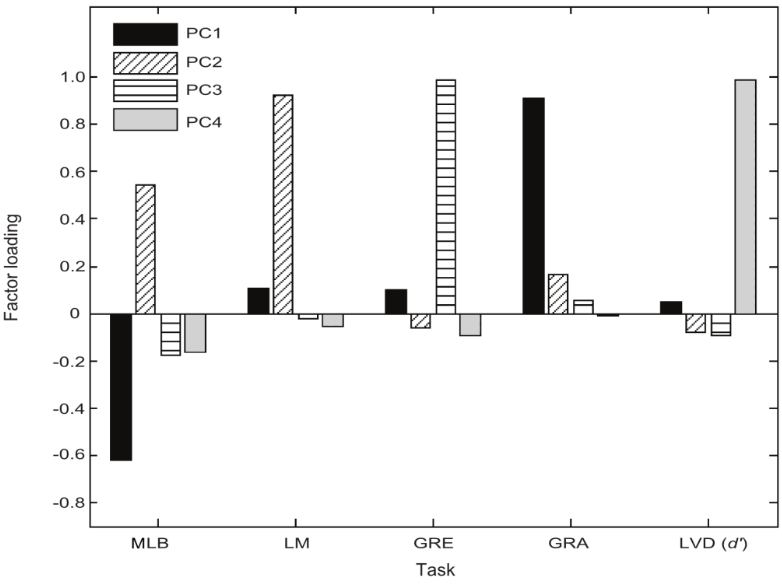

Figure 8. Visualisation of principal component analysis (PCA) loadings.

4. Discussion

The results demonstrate that each of the 5 spatial attention tasks assessed here represent consistent and reliable measures of spatial attention asymmetry when administered on different days. Individual spatial biases in each task were reliably replicated between two days of measurements, despite not all tasks showing an overall (grand-average) bias for one direction. Indeed, only two of the five tasks (MLB and LM) elicited a significant stable bias to the left side of space that is consistent with pseudoneglect. A mean *rightward* bias was found in the GRE task on the first day of testing, whereas there was no mean lateralised bias when participants were re-tested. Neither the GRA nor the LVD tasks produced a significant spatial attention bias towards either side of space. Secondly, when the tasks were inter-correlated, only a weak relationship (that did not survive Bonferroni correction) was found between the MLB and GRA tasks, with no other statistically significant relationships observed between any of the other tasks. Importantly, principal component analysis (PCA) identified 4 main components that accounted for 89.1% of the overall variance. The MLB and LM tasks both loaded onto the same component, whereas there was a negative loading relationship between the MLB and GRA tasks on another component. The GRE and LVD tasks were both explained by two further independent factors, indicating that like hemispatial neglect, spatial attention asymmetries in healthy adults involve multiple components, possibly associated with different task demands.

4.1 Intra-task correlations

The stable measures of spatial bias across testing days, as indexed by the test-retest correlations, are broadly consistent with the previous literature (Nicholls, Bradshaw & Mattingley, 1999; Benwell et al., 2013a; McCourt, 2001). I have extended the study of Nicholls, Bradshaw & Mattingley (2009) in showing consistency on a range of measures on two different testing days, rather than split-half reliability within a single testing session. Most notably, I failed to find the high performance variability that was reported by Manning, Halligan & Marshall (1990) for the MLB task: in fact the MLB task provided the strongest intra-task correlation across testing days (r=0.846). I therefore conclude that the five tasks tested here each index a consistent property of the attention network of each individual, that is stable across time.

4.2 Inter-task correlations

I predicted that if pseudoneglect manifests as a result of interhemispheric (left, right) activation differences within a single cortical location, for example the right posterior parietal cortex, that a strong correlational relationship would exist between the five tasks. Although the MLB and GRA tasks proved to hold the closest (negative) correlation between measures of asymmetry relative to the other 3 tasks (r= -0.287, p=0.043) this did not survive multiple comparison correction. I did not replicate the previously reported (although again weak) correlations between the MLB and GRE tasks (Loftus, Vijaykumar & Nicholls, 2009; Nicholls & Roberts (2002)) nor the correlation between the (procedurally similar) GRE and GRA tasks previously described by Niemeier, Stojanoski & Greco (2007). Conversely, I replicated the previous findings of Luh (1995), Nicholls, Bradshaw & Mattingley (1999) and Heber et al., (2010) showing a lack of inter-task relationship between measures of pseudoneglect and have demonstrated that tasks used in the current spatial attention literature exhibit the same lack of strong inter-task correlation that was demonstrated almost twenty years ago. It should be noted that with the sample size of 50 individuals, the within-subjects design, and the stability of all 5 measures over time as indexed by the intra-task correlations, it is most likely that the experiment provided adequate statistical power to have highlighted any relationships between tasks, should they exist.

4.3 Differences in measures of spatial bias

PCA identified four separate components which explained 89.1% of the total correlation matrix variance. Although the biases I report for the MLB and LM tasks were only very weakly correlated (r=0.267, p=0.06), the co-loading of these two tasks on to one single component (PC2) supports the behavioural (Luh, 1995; Dellatolas, Vanluchene & Coutin, 1996; Varnava, Dervinis & Chambers, 2013; Milner, Brechmann & Pagliarini, 1992) and fMRI (Çiçek, Deouell & Knight, 2009; Fink et al., 2000b) evidence that a similar pattern of neural activation underpins the completion of both of these tasks. I have chosen to label PC2 as representative of a 'global size judgement' task demand, since the MLB and LM tasks both involve an assessment of the midpoint location along a single, continuous horizontal line. This finding fits well with Verdon et al., (2010) who found that MLB task performance loaded onto a 'perceptive/visuo-spatial' component in patients with hemispatial neglect, and in which impairment on this task was closely associated with damage to the right inferior parietal lobe. Moreover, I found that only the MLB and LM tasks produced a significant mean leftward bias in both testing sessions. Tasks involving global size judgement may therefore be more sensitive to detecting asymmetries in spatial attention than tasks which require visual assessment of other stimulus features.

The relative independence of the GRE loading on PC3 (which I have labelled 'luminance judgement') is perhaps surprising, given that the GRE and GRA tasks are procedurally similar, with both requiring a comparison of the relative area containing target stimulus features between two parallel horizontal bars. Yet since they both load strongly onto different PCA components, I am confident that this highlights differences in task demands (i.e. the focus on luminance versus spatial frequency).

Similar to the GRE, the LVD task also loaded independently on to PC4 (although note that the eigenvalue was <1), which I have labelled ‘stimulus detection’. Contrary to the studies of Thut et al., (2006), Hilgetag Théoret & Pascual-Leone, (1999) and Chapter Three of this thesis, there was no grand-average visual detection sensitivity bias towards the left hemispace. Given that the two methods of analysis (*d’* and PF 50%) produced highly correlated measures of LVD bias, I conclude that this lack of bias was likely due to procedural differences rather than an artefact of analysis. Most notably, previous studies using the LVD (Hilgetag, Théoret & Pascual-Leone, 1999; Dambeck et al., 2006; Romei, Gross & Thut, 2011; Thut et al., 2006) have titrated the stimuli for each individual and presented 2 peri-threshold stimuli to ensure that the task was of equable difficulty across participants. Here instead, I chose to present a standard set of 5 stimulus sizes which may have been less sensitive to the detection of spatial bias due to reduced (or *increased* for some individuals) task difficulty that may have differentially influenced the balance of activity within the spatial attention network. Given that the LVD did not correlate with any other task and loaded independently onto PC4, I conclude that the LVD as presented here relies upon attention mechanisms that are procedurally distinct from the other tasks tested.

The *inverse* relationship between the MLB and GRA loadings on PC1 is more complex to explain. For the MLB task, participants assessed the *global* properties of the stimulus by visually scanning the entire line length and determining the midpoint location over a relatively long trial duration (maximum = 6 seconds). Conversely, the GRA involved fast stimulus presentation (150ms) during which participants were directed to assess the quantity of fine-grained, *local* stimulus features (i.e. the number of 'thin stripes') in the absence of visual scanning. Therefore, labelling PC1 as representative of '*local vs global*' processing could fit the divergent task demands of MLB and GRA presented here. This interpretation also aligns with models of spatial attention which claim that tasks involving fine-grained perceptual judgements (the processing of '*local*' stimulus features and HiSF gratings) are processed using LH resources, whereas the RH supports decisions regarding larger scale, '*global*' stimulus features and LoSF gratings (Sergent, 1982; Monaghan & Shillcock, 2004). The model would therefore predict a leftward spatial bias when LoSF gratings are assessed and a rightward bias in response to HiSF targets.

More specifically, and contrary to this model, Niemeier, Stojanoski & Greco (2007) found a leftward attentional bias for HiSF targets and a rightward bias for LoSF, possibly due to the comparatively high salience of HiSF relative to LoSF that preferentially activates the RH (Singh et al., 2010). I failed to find a spatial bias in this sample, even though participants were directed to the HiSF features. However, Niemeier et al., (2008b) have also shown that the leftward bias in the GRA task is more pronounced when the HiSF gratings span a spatial frequency range of 0.6-2 cycles per degree (cpd). Thus the stimulus choice of HiSF 4.07 cpd here may have proved less sensitive to detecting an underlying spatial asymmetry, although a weak correlation between the GRE and GRA using similar stimulus parameters (stimulus G4 in Niemeier, Stojanoski & Greco, 2007) was still noted. So if I have correctly labelled PC1 as being representative of *global vs local* feature processing, and participants show an inverse PCA loading relationship between the MLB and GRA tasks, then the results may indeed align with the RH-global / LH-local model.

4.4 Pseudoneglect as a multi-component phenomenon

In line with the current conceptualisation of hemispatial neglect as a multi-component disorder, I would argue that pseudoneglect may also be conceptualised as multi-faceted. Patients with neglect demonstrate large individual performance variability on tasks that involve different task demands (e.g. text reading, object cancellation, line bisection) and are dependent on the location of their lesions (Chechlacz, Rotshtein & Humphreys, 2012; Verdon et al., 2010; Mattingley, Bradshaw & Phillips, 1992). Correspondingly, I have shown here that the direction and magnitude of spatial bias in healthy young adults is strongly task-dependent and therefore likely to be related to partially-overlapping regions of the brain which are responsible for the completion of each task. The results demonstrate that an individual may overestimate the size of the left hemispace as measured by MLB or LM tasks, however it does not follow that they will also exhibit a strong leftward overestimation of luminance or spatial frequency on the left, nor show increased stimulus discrimination sensitivity to this side.

These results fit well with the interhemispheric competition model of spatial attention (Kinsbourne, 1970; 1977), which posits that attentional asymmetries manifest as a result of the relative differences in activation between the left and right cerebral hemispheres (LH/RH). A larger net RH activation biases attention towards the left side of space (resulting in an over-estimation of the stimulus features on this side), and net LH activity results in a preference for the right. Alternatively, this variation in bias may reflect a more complex interaction between dorsal (*endogenous*) and ventral (*exogenous*) attention networks (Corbetta & Shulman, 2002; Thiebaut de Schotten et al., 2011) that is mediated by variations in task demands. If tasks differentially activate areas within the RH and LH then this would predict the inconsistency of spatial bias as displayed here.

4.5 Potential effects of task difficulty and viewing distance

The influence of task difficulty on hemispatial neglect in patients is well documented, with the extent of inattention towards the left hemispace often accentuated as task difficulty increases (Bonato, 2012; Bonato et al., 2010; Bonato & Deouell, 2013; Rapcsak et al., 1989; Russell et al., 2013, but see also Harvey et al., 2002). Similarly in the non-clinical population, a greater overall attentional engagement with the task might be expected as a function of increased task difficulty. This may actively engage the right hemisphere leading to a leftward bias, or in some cases *deplete* RH functions leading to rightward shift in attention, such as observed with prolonged time-on-task, reduced arousal or increased perceptual load (Benwell et al., 2013a,b; Dufour, Touzalin & Candas, 2007; Bellgrove et al., 2004; Dodds et al., 2008; Fimm, Wilmes & Spijkers, 2006; Manly et al., 2005; Matthias et al., 2010; Newman, O'Connell & Bellgrove, 2013; Perez, Garcia & Valdes-Sosa, 2008; Perez et al., 2009). Aligned with this, our research group has previously reported that an increase in task difficulty (as indexed by a larger psychometric function curve width for short, compared to long, LM task lines) is accompanied by a rightward shift in PSE (Benwell et al., 2014b). However, Niemeier, Stojanoski & Greco (2007) found no influence of stimulus presentation time (where a shorter presentation time was found to be more difficult as indexed by psychometric function slopes) on the direction of the bias in the GRA task: a leftward bias was observed for both short and long durations.

As a final consideration, the viewing distance of 0.7m here was intended to represent a compromise between the wide range of distances reported in the previous studies on which these tasks were based (approximately 0.3m for paper-and-pencil manual line bisection studies, increasing to 1.0m for some landmark task presentations (Benwell et al., 2013a,b, 2014b). It has been previously demonstrated that viewing distance can influence the spatial bias obtained in these tasks. Viewing in near space tends to elicit a leftward bias in both landmark and line bisection tasks, with a reduced bias (or slightly rightward) when viewed in far space (Varnava, McCarthy & Beaumont, 2002; Longo et al., 2015; Ferrè et al., 2013; Gamberini, Seraglia & Prifitis, 2008; Longo & Lourenco, 2006, 2007; Lourenco & Longo, 2009; Lourenco, Longo & Pathman, 2011; Bjoertomt, Cowey & Walsh, 2002, 2009). It is conceivable that the overall lack of spatial bias observed for the GRA and LVD tasks (and the GRE on Day 2) shown here was generated partially due to this aspect of the experimental design. However, given that all 5 tasks were presented at the same viewing distance, I expected to see stronger inter-task correlations than was ultimately observed. Therefore, regardless of whether the variations in perceptual asymmetry observed were related to task-dependent differences in cortical activation, task difficulty, viewing distance or otherwise, I urge caution in assuming an equivalency of tasks when designing spatial attention experiments.

In the next Chapter, I reason that if each task elicits a distinct pattern of neural activity within the brain, then this pattern may be modifiable using non-invasive brain stimulation. I also investigate whether tDCS exerts a similar modulatory effect on spatial biases in young and older adults.

Chapter Three

The Implications of State-Dependent tDCS Effects in Aging: Behavioural Response is Determined by Baseline Performance

1. Introduction

Aging brains differ from younger brains both structurally and in their functional organisation (see Fjell & Walhovd, 2010, for review; Raz et al., 2005). In functional imaging studies, young adults generally display brain activity patterns that are highly lateralised to one cerebral hemisphere, i.e. left-hemispheric dominance for language and right-sided superiority for spatial attention. This strong lateralisation diminishes with age, with activity becoming more bilaterally distributed in older adults in response to tasks involving working and episodic memory (Bäckman et al., 1997; Cabeza et al., 1997; 2004; Grady et al., 2002; Madden et al., 1999; Morcom et al., 2003; Reuter-Lorenz et al., 2000), inhibitory control (Nielson, Langenecker & Garavan, 2002), problem solving (Esposito et al., 1999), lexical decisions (Collins & Mohr, 2013) and face perception (Collins & Mohr, 2013; Grady et al., 1994).

These findings support the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model (Cabeza, 2002). This model describes a compensatory strategy, whereby a functional decline within the (previously) dominant hemisphere for a particular task is bolstered by the recruitment of neurons within the opposite hemisphere. Indeed, functional reorganisation has been positively correlated with task performance, with high-performing older adults demonstrating a greater degree of bilateral activation in working memory tasks compared to low-performing adults of the same age (Cabeza, 2002; Cabeza et al., 1997; 2002; Reuter-Lorenz et al., 2000). In corroboration, Huang et al. (2012) report superior performance on numerical and size judgement tasks in older adults who show an increased bilateral involvement of the posterior parietal cortex (PPC). Secondly, an age-related functional reorganisation from posterior to anterior regions has also been described. Analogous with the HAROLD model, a larger posterior-anterior shift appears to be positively correlated with task performance (Davis et al., 2008; Grady et al., 1994; Spreng, Wojtowicz & Grady, 2010). Thus, it seems plausible that the large individual differences in cognitive performance observed in older adults may, to some degree, be related to the extent of functional reorganisation that has taken place.

Asymmetric patterns of activity between the two cerebral hemispheres may also represent the neural substrate of ‘pseudoneglect’, a phenomenon described within the visuospatial attention literature which mirrors the left inattention resulting from right parietal lobe damage in patients with hemispatial neglect (Bowers & Heilman, 1980). Young adults typically display a processing advantage within the left visual field (LVF)/space, which is considered a consequence of right parietal involvement for spatial attention (Heilman & Van Den Abell, 1980; Kinsbourne, 1970; Malhotra, Coulthard & Husain, 2009; Thiebaut de Schotten et al., 2011; Weintraub & Mesulam, 1987). Although the magnitude of this pseudoneglect bias is small, relative to the often debilitating effects of left-sided inattention in hemispatial neglect, both phenomena highlight the crucial role of the right hemisphere for spatial attention. Moreover, this leftward preference is consistently found in a variety of lateralised visual perception tasks, such as the landmark task (Benwell et al., 2013a,b, 2014a,b, 2015; Milner, Brechmann & Pagliarini, 1992, Chapters Two and Four of this thesis), line bisection (Bradshaw et al., 1986; Varnava, McCarthy & Beaumont, 2002, Chapter Two of this thesis), greyscales (Mattingley et al., 1994a, 2004), grating scales (Chen & Niemeier, 2014; Niemeier, Stojanoski & Greco, 2007; Niemeier et al., 2008; Singh et al., 2011) and lateralised visual detection tasks (Hilgetag, Théoret & Pascual-Leone, 2001; Sparing et al., 2009; Thut et al., 2006).

Although, as described above, this leftward preference is a well observed phenomenon in young adults, older people do not consistently display a preference towards either side of space. Indeed, older adults sometimes exhibit a slight *rightward* bias in line bisection (Failla, Sheppard & Bradshaw, 2003; Fujii et al., 1995; Fukatsu et al., 1990; Stam & Bakker, 1990), landmark (Benwell et al., 2014a,b; Schmitz & Peigneux, 2011) and lateralised visual detection tasks (Nagamatsu et al., 2009, 2011, 2013). Interestingly, there is empirical evidence that older adults have a specific *deficit* in left visual field processing and that the extent of this decrement is positively correlated with an increased incidence of falls (Nagamatsu et al., 2009, 2011, 2013). This behaviour may be incorporated within the HAROLD model: a decrease in processing efficiency of the right parietal lobe that is compensated for by a recruitment of the left hemisphere, resulting in a rightward shift or elimination of the attentional bias. Alternatively, the findings are also compatible with the ‘right hemi-aging’ model in which the right hemisphere is more susceptible to the effects of age relative to the left hemisphere (Brown & Jaffe, 1975; Dolcos, Rice & Cabeza, 2002; Goldstein & Shelly, 1981), although the two models are not mutually exclusive. Functional imaging has provided mixed evidence of both increased (Grady et al., 2010; Huang et al., 2012; Madden et al., 2007; Townsend, Adamo & Haist, 2006) and decreased activity (Milham et al., 2002; Rosano et al, 2005) in the parietal lobes with age, which is likely to be highly task-specific (see Spreng et al., 2010 for review). Given the likelihood of a functional advantage gained by improving spatial attention in older adults, and specifically within the left visual field, I aimed here to boost parietal lobe activity using non-invasive brain stimulation.

Transcranial direct current stimulation (tDCS) is a safe and well-tolerated method of altering cortical activity, which allows us to examine the relationship between brain activity and behaviour (Nitsche & Paulus, 2000). The application of a small direct current to a neuronal population alters their membrane potential in a polarity-specific manner, thus rendering the neurons more (under the anode) or less (under the cathode) likely to fire (Stagg & Nitsche, 2011). Effects of stimulation last within the order of a few minutes in typical experimental designs, although longer lasting effects of up to 6 months have been reported with repeated stimulation over multiple sessions (e.g. Cohen Kadosh et al., 2010).

TDCS has proved effective in altering behaviour in young adults, as well as offering rehabilitative hope for some clinical populations (e.g. Fregni et al., 2006; Hummel & Cohen, 2006). The application of anodal tDCS (atDCS) in healthy older adults is attracting interest as a potentially promising method of alleviating age-related cognitive decline (Fertonani et al., 2014; Flöel et al., 2012; Holland & Crinion, 2011; Meinzer et al., 2013; Zimerman & Hummel, 2010). When applied to the left ventral inferior frontal gyrus, Meinzer et al., (2013) report that atDCS reinstated a more ‘youth-like’ (i.e. uni-hemispheric rather than bilateral) pattern of activation in older adults during a word generation task that could be visualised on functional magnetic resonance imaging (fMRI).

However, the efficacy of atDCS may be partly dependent on baseline individual differences that vary across the population. Berryhill & Jones (2012) aimed to improve working memory in older adults using 1.5mA atDCS to either the left or right prefrontal cortex for 10 minutes, just prior to participants performing verbal and visual *2-back* tasks. Performance improved on both tasks, independent of stimulation site, but only for individuals with a high level of education. Conversely, seniors with fewer completed years of education either did not benefit, or were in fact impaired on the task, post-tDCS.

In the present study, I administered a lateralised visual detection task (titrated to each individual's peri-threshold ability) to both young and older adults. The task was based on a protocol of Hilgetag, Théoret & Pascual-Leone (2001) who interrupted neural activity within the parietal cortices of young adults using 1Hz repetitive transcranial magnetic stimulation. Detection rates improved for stimuli that were presented *ipsilateral* to the rTMS pulse, which was indicative of each hemisphere exerting a regulatory effect on the other within the attention network (interhemispheric competition; Kinsbourne, 1977). Suppression of one parietal lobe thus effectively released the contralateral hemisphere from inhibition, resulting in an improvement in detection accuracy. In later work, Sparing et al., (2009) incorporated this titrated lateralised visual detection task within a tDCS protocol, using 1mA anodal or cathodal stimulation over either the left or right parietal lobes (P3 or P4 of the 10-20 EEG system; return electrode Cz). A tDCS-induced improvement in stimulus detection was elicited in the contralateral visual field after 10 minutes of atDCS, whereas cathodal tDCS inhibited contralateral detection.

I aimed to extend this protocol in the present study, by using atDCS to reinstate an adaptive, ‘youth-like’ pattern of right-hemispheric dominance for spatial attention in older adults. I applied 1mA atDCS in a uni-hemispheric montage over either the right or left hemisphere (P3 or P4; return over the contralateral supraorbita), plus a sham protocol, to both healthy young and older adults. The P4-Left supraorbital montage has previously been successful in reducing pathological left-sided inattention in patients with hemispatial neglect (Ko et al., 2008; Sunwoo et al., 2013) and here I extend the protocol by introducing the mirrored P3-Right supraorbital condition. I predicted that both R-atDCS and L-atDCS would facilitate detection accuracy in the contralateral visual field, relative to Sham, replicating the findings of Sparing et al., (2009). Regarding the older age group, as outlined above, there is currently conflicting evidence as to whether aging is associated with an increase or decrease in parietal activity across both hemispheres, and this is also likely to be task-dependent. However, the finding that older people do not exhibit lateralised spatial attention biases indicates that the right hemisphere may be reduced in activity and/or the left hemisphere over-recruited. Thus, I expected that older adults might show a different response profile to tDCS than young controls and I expected particular improvements within the left visual field as a result of R-atDCS, which would hopefully generate a unilateral pattern of activity similar to that observed in young adults.

2. Methods

2.1 Participants

20 young adults (11 females, mean age = 20.9 years; SD = 1.97, range = 18-24) and 20 older adults (10 females, mean age = 66.6 years; SD = 5.11, range = 60-77) were recruited. All participants were right-handed, had normal or corrected-to-normal vision and were screened for contraindications to tDCS. Written, informed consent was obtained from each participant. The study was approved by the University of Glasgow College of Science and Engineering ethics committee.

2.2 Procedure

At the beginning and end of each session, participants indicated their subjective alertness on a linear scale (0 = almost asleep, 100 = fully alert). They were seated in front of a computer screen with their midsagittal plane aligned with the screen. The stimulus titration phase (see 2.4.1) was completed at the start of Day 1, followed by an extended rest period when the tDCS electrodes were placed.

A direct current was delivered to the head using a battery-driven constant current stimulator (NeuroConn GmbH, Germany). Three experimental conditions were applied in a within-subject design: (i) Left anodal (L-atDCS), (ii) Right anodal (R-atDCS), (iii) Sham (counterbalanced L-atDCS or R-atDCS montage) stimulation (Figure 1). Each condition was applied on a different day (≥24 hours between sessions) and the order was counterbalanced across participants. The anode was placed over the left or right posterior parietal cortex (PPC) (centred on P3 or P4 of the 10-20 International EEG system) with the cathode (return electrode) placed on the contralateral supraorbita. All 3 protocols began and ended with a 30s ramp-up period. The current was then maintained at 1mA for 15 minutes in the two active tDCS sessions, followed by a 30s ramp-down period. The current was maintained at 1mA for 30s in the Sham protocol before being ramped-down, which has previously been reported as being perceptually indistinguishable from 'active' tDCS (Gandiga, Hummel & Cohen, 2006). The anode measured 5 x 5cm^2 (current density = 0.04mA/cm^2), the cathode 5 x 7cm^2 (0.03mA/cm^2) and each rubber electrode was inserted into 0.09% NaCl saline-dampened sponges.

One block of a 'landmark' task was completed (not reported here), then a baseline pre-tDCS block (Block 1) of the lateralised visual detection task. At the end of Block 1, the stimulator was turned on and allowed to ramp up to 1mA, at which point Block 2 began. The stimulation was maintained at 1mA during Block 2 and Block 3 (online), then ramped down to 0mA. Block 4 and Block 5 were undertaken post-tDCS (offline). A final 'landmark' block was then completed (also not reported here). After the electrodes were removed, a questionnaire documented the presence and severity of 5 sensory experiences during the session (headache, tingling, itching, burning, pain. Score 1 = 'Not experienced at all', 5 = 'Experienced very strongly' (modified from Brunoni et al., 2011). Days 2 and 3 began with the tDCS electrode application but subsequently proceeded in an identical manner. Participants were invited to guess which of the 3 days had involved Sham tDCS at the end of their final session.

2.3 Stimuli

Stimuli were presented using E-Prime 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) using a Dell Precision 380 PC and a 19’ Dell 1908FP UltraSharp LCD Flat Panel monitor with a 1280 x 1024 pixel resolution. The viewing distance was fixed with a chin rest at 0.5m.

2.3.1 Lateralised visual detection task

The task was adapted from Hilgetag, Théoret & Pascual-Leone (2001). Stimuli consisted of small black squares or rectangles (with the longer edge along the horizontal axis) presented against a grey screen (hue = 179, saturation = 0, luminance = 160)). Stimuli were presented either to the left of fixation (-145mm; -16.17° visual angle (VA)), to the right (+145mm; +16.17° VA), or were presented bilaterally (subtending 290mm; 32.34° VA). Blank ‘catch’ trials were randomly interspersed throughout each block.

Each trial started with a centred fixation cross (15 x 15 pixels; 0.58° visual angle) which remained on the screen for 1000ms*,* followed by a stimulus for 40ms then a blank response screen for 1750ms (see Figure 1). Participants used their dominant right hand to indicate on a keyboard whether the dot appeared on the left (index finger), right (ring finger) or bilaterally (middle finger). Participants were instructed to withhold their response when no stimulus was detected.

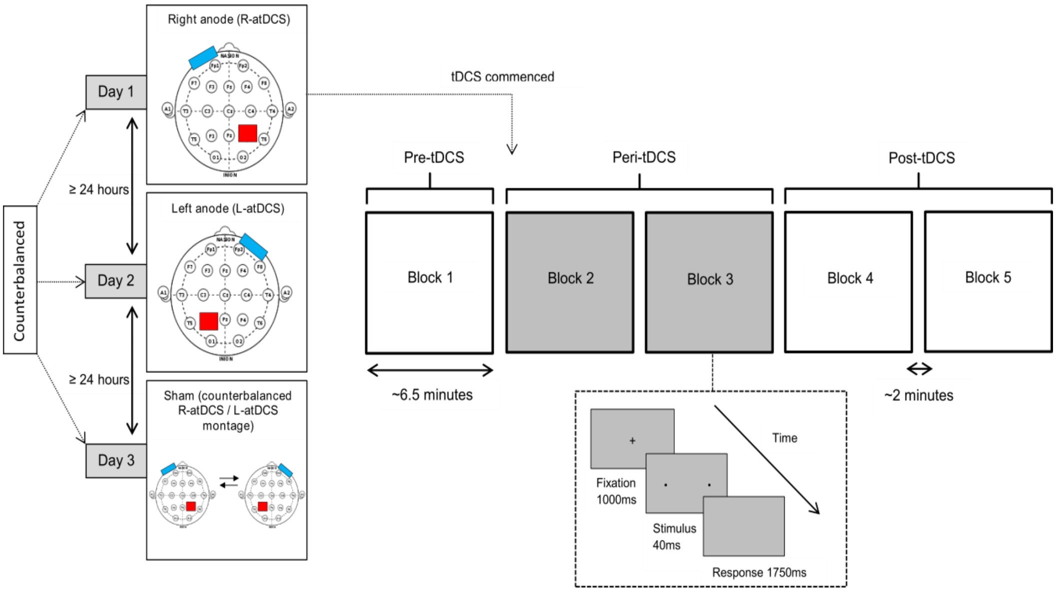

Figure 1. Schematic of the experimental procedure and the lateralised visual detection task. Three tDCS conditions (R-atDCS/L-atDCS/Sham) counterbalanced across testing days (≥24 h between sessions). 1 block of lateralised visual detection pre-tDCS. Sham tDCS applied online for 30s at the start of Block 2. R-atDCS and L-atDCS applied online for 15 min throughout Blocks 2 and 3. Blocks 4 and 5 post-tDCS.

In order to equate the difficulty of the experiment across individuals, each participant completed a *stimulus titration phase* to identify their peri-threshold stimulus sizes at the start of their first session (i.e. which stimuli they could detect with approximately 50% accuracy). To test this, a total of 270 trials were randomly presented across 3 short blocks (75 left-presented stimuli, 75 right, 75 bilateral and 45 catch trials). Each titration phase involved the random presentation of five different stimulus sizes. Based on pilot data, young adults were shown stimuli of 1x2, 2x2, 2x3, 3x3, 3x4 pixels and older adults stimuli of 3x3, 3x4, 4x4, 4x5, 5x5 pixels. One pixel measured approximately 0.29mm x 0.29mm. Similar to the titration phase of Hilgetag, Théoret & Pascual-Leone (2001), Sparing et al., (2009) and Thut et al., (2006) percentage accuracy was averaged across the left and right visual fields for each of the 5 pixel sizes. The 2 adjacent peri-threshold pixel sizes, just above (supra-threshold) and just below (sub-threshold) 50% accuracy, were selected as the stimuli to be presented in the main experiment. If participants did not achieve approximately 50% accuracy in this phase (i.e. they performed at floor or ceiling levels), the pixel size was successively titrated upwards or downwards until 50% accuracy was achieved in one further block of testing. The main experimental task was identical to the titration phase, however only the 2 individually-titrated stimulus sizes were presented. This comprised 5 blocks (1 block pre-, 2 blocks peri- and 2 blocks post-stimulation) lasting approximately 6.5 minutes each (see Figure 1). Each block contained 140 randomly-presented trials (40 left-presented stimuli, 40 right, 40 bilateral, and 20 catch trials). Participants were instructed that they could take a 1-2 minute break at the end of each block if desired.

2.4 Analysis

2.4.1 Visual detection titration

The distribution of the pixel sizes that elicited just above or below 50% accuracy across the left and right visual fields is shown in Figure 2. As expected, threshold accuracy was achieved at a smaller size in the young adults, with most titrated to 2x2/2x3 pixels. A wider range of larger pixels were required for older adults with the majority performing at comparable levels with 3x3/3x4 or 3x4/4x4 pixels. Group-level mean accuracy across left- and right-presented stimuli was 35.37% for the smaller (sub-threshold) and 65.79% for larger (supra-threshold) dots. Accuracy was similar across age groups (Young 32.5% and 68.83%; Older 38.96% and 62.41%).

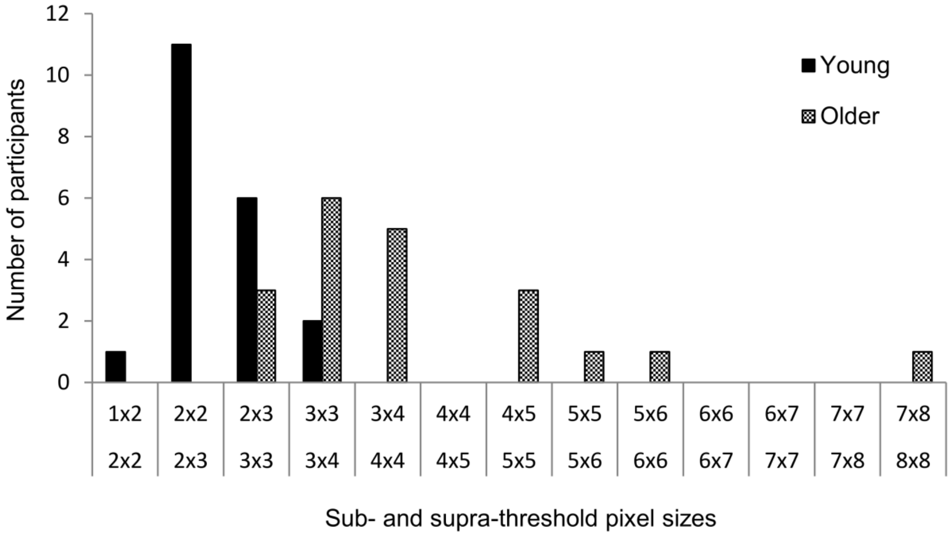

Figure 2. Distribution of peri-threshold pixel sizes determined in the titration phase.

2.4.2 D-prime (d')

Lateralised visual detection task sensitivity was calculated by computing d-prime (*d'*) scores for each visual field separately within each block of trials. In signal detection theory, *d'* is a method of assessing task sensitivity which takes into account both accuracy (when stimuli are present) and false positives (in response to catch trials) (Green & Swets, 1966; Macmillan & Creelman, 2005). *D'* was calculated using the function:

$$d' = z(Hits) - z(FalseAlarms)$$

where *z* represents the z-score for each visual field within a block. Larger *d'* scores represent a greater sensitivity to detecting stimuli relative to false positives.

3. Results

3.1 Subjective alertness

A 3 (Stimulation: *R-atDCS, L-atDCS, Sham*) x 2 (Time: *pre* vs *post* experiment) x 2 (Age: *young* vs *older*) mixed analysis of variance (ANOVA) confirmed that subjective alertness generally reduced over the course of the experiment [TIME: F(1,38)=90.9, p<0.001, mean score *pre* = 80.3 (SD = 12.3), *post* = 61.73 (SD = 17.5)]. Older adults reported higher levels of alertness overall [AGE: F(1,38)=12.1, p=0.001] (mean score *Young* = 65.4 (SD=17.3); *Older* = 76.7 (SD=16.4)). Time did not differentially affect alertness levels between groups [TIME x AGE: F(1,38)= 0.282, p=0.589] and there was no effect of stimulation on subjective alertness.

3.2 Side-effects questionnaire

Sensory side-effects were reported as ≤3 out of 5 in terms of severity in the majority of sessions (93.67%), mostly due to moderate scores on tingling or itching sensations (but low scores on burning or pain) indicating that the tDCS was generally well tolerated. A Friedman's test found small differences between the 3 stimulation sessions for reports of a slight burning sensation (χ^2= 6.031, p=0.049), but Wilcoxon's Signed Rank post hoc comparisons with a Bonferroni adjusted alpha of 0.017 did not survive correction. Of the 40 participants, only 16 correctly guessed which of the 3 sessions involved Sham tDCS, and this did not differ between age groups (Pearson $\chi^2 = 0.417$, p=0.519).

3.3 Age group split

3.3.1 Baseline sensitivity (d'): Age groups

As predicted, young adults were more sensitive to detecting stimuli in the left VF than the right VF at baseline (Block1) [t(19)=2.516, p=0.021], reflecting a leftward bias in visuospatial attention (pseudoneglect) which was not present in the older group [t(19)=0.408, p=0.688]. A one-sample t-test against zero using lateralised *d'* index (Left VF *d'* subtracted from Right VF *d'*) confirmed that older adults lacked a lateralised attentional bias [R-atDCS: t(19)= -0.601, p=0.555; L-atDCS: t(19)=1.65, p=0.871; Sham: t(19)= -0.521, p=0.608] whereas young adults were more sensitive to the left VF at baseline in the R-atDCS [t(19)= -2.114, p=0.048] and Sham sessions [t(19)= -2.326, p=0.031], with a trend towards a leftward preference in L-atDCS [t(19)= -2.007, p=0.059]. Baseline lateralised *d'* scores were compared across the 3 days by correlating performance in Block 1, and were found to be stable in the young adults [R-atDCS *vs* L-atDCS: Spearman r=0.636, p=0.03; R-atDCS *vs* Sham: r=0.567, p=0.009; L-atDCS *vs* Sham: r=0.594, p=0.006], but in only 1 of the 3 comparisons in the older adults [R-atDCS *vs* L-atDCS: Spearman r=0.456, p=0.043; R-atDCS *vs* Sham: r=0.776, p<0.001; L-atDCS *vs* Sham: r=0.304, p=0.193, adjusted α= 0.017] (Figure 3). There were no reaction time (RT) differences between the two visual fields for either age group at baseline.

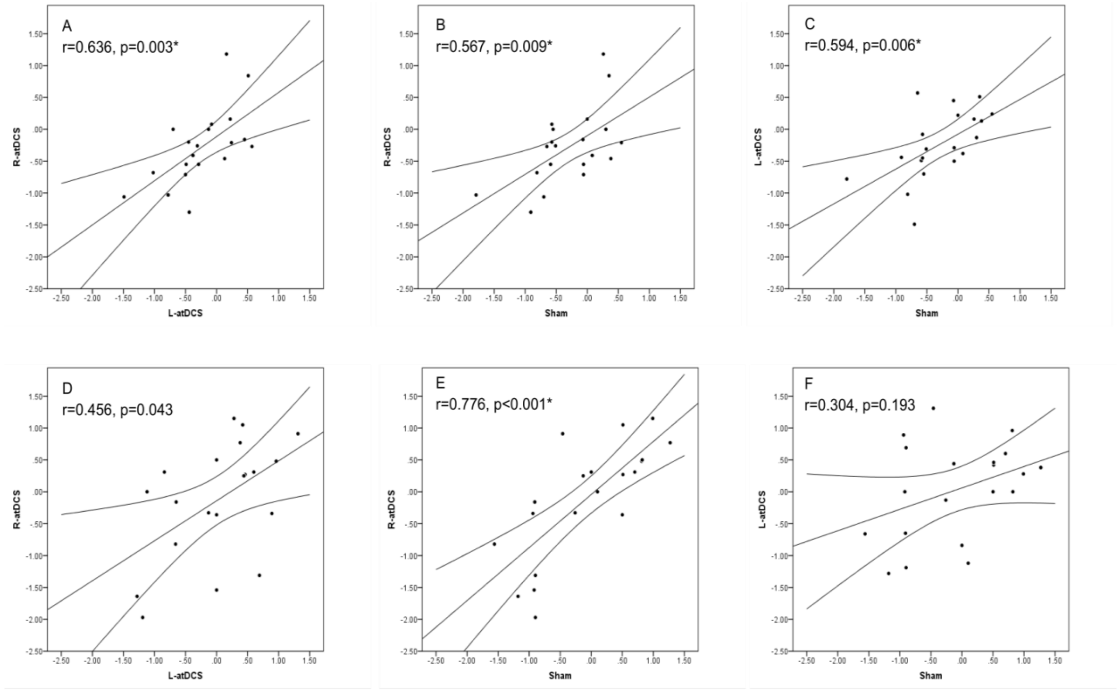

Figure 3. Correlation plots of lateralised d’ index (Left VF d’ subtracted from Right VF d’) at baseline (Block 1) over the 3 testing days. A-C: Young adults. D-F: Older adults. Young adults exhibit a stable bias across days, whereas the older group are less consistent. *significant at α<0.017.

3.3.2 D’ sensitivity: Age groups

A full-factorial mixed ANOVA (3 Stimulation types x 5 Blocks x 2 Age groups x 2 VFs) revealed generally lower *d’* sensitivity in older adults compared to young [AGE: F(1,38)=7.286, p=0.01, ηp²=0.161] and a general reduction in detection sensitivity across the 5 experimental blocks [BLOCK*:* F(4,152)=4.274, p=0.003, ηp²=0.101] (Figure 4). There were no main effects of VF or stimulation type and no significant interactions were found. Specifically, there was no Stimulation x Block x Age interaction [F(8,304)= 1.564, p=0.135, ηp²= 0.04]. The order in which the stimulation sessions were undertaken had no effect on *d’* scores.

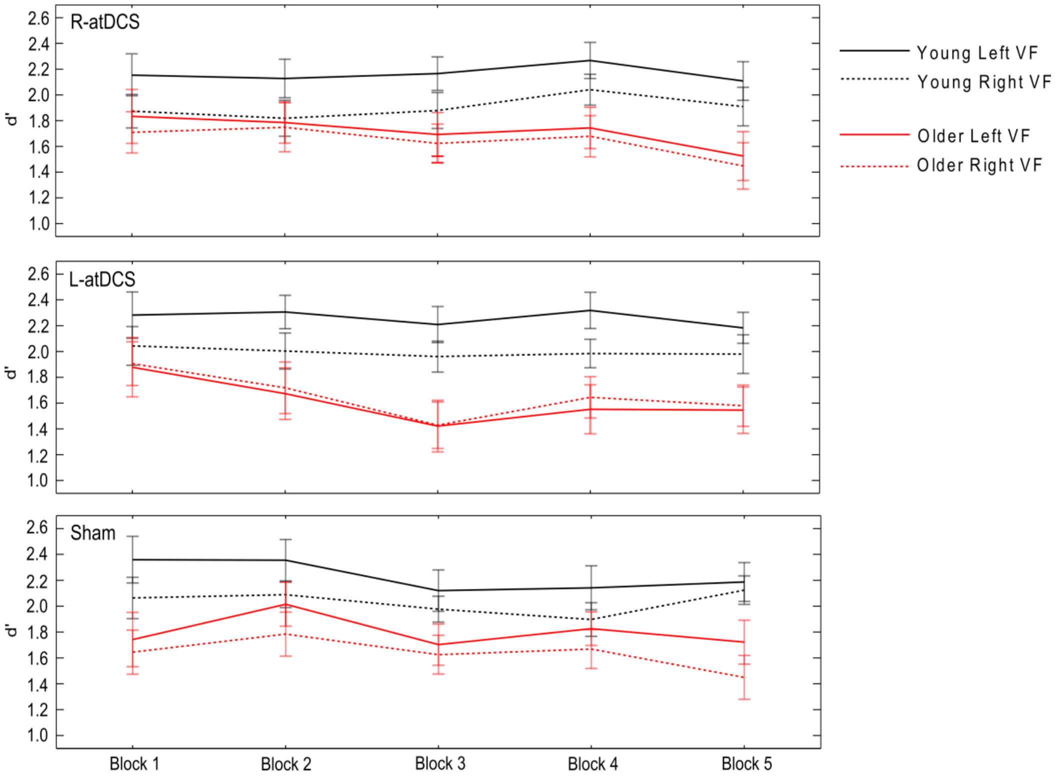

Figure 4. *D'* sensitivity scores for both visual fields (*left* and *right*), across both Age groups (*Young* and *Older*) and 3 Stimulation conditions (*R-atDCS*, *L-atDCS* and *Sham*) (± standard error of the mean (SEM)). Active tDCS was applied during Blocks 2 & 3.

3.3.3 Bilateral errors: Age groups

Accuracy for the bilaterally-presented stimuli was analysed separately from those presented to the left and right VFs. Block error rates were obtained by calculating the number of responses made to the Left or the Right when the bilateral trial was answered incorrectly. A mixed ANOVA (3 Stimulation types x 5 Blocks x 2 Age groups x 2 VFs) confirmed only an effect of AGE [F(1,38)=11.88, p=0.001 $\eta p^2=0.238$] with young adults erring on 6.36 bilateral trials per block, on average (SD=2.11), and older adults 9.27 times (SD=3.13).

3.3.4 Reaction times (RTs): Age groups

Reaction times for correct left- and right-presented trials (excluding those where RT was >2 standard deviations above the mean for each participant) were subjected to a full-factorial ANOVA (Figure 5), revealing that response times became faster overall across the experiment [BLOCK: F(4,152)=4.717, p=0.001, ηp^2=0.11] but were generally slower in older participants [AGE: F(1,38)=21.4, p<0.001, ηp^2=0.36, mean RT *Young*: 477.2ms, SD = 46.55; *Older*: 581.8ms, SD = 92.65). Paired comparisons for an Age x Block interaction [F(4, 152)=7.311, p<0.001, ηp^2=0.161] found that young adults became faster relative to baseline in Blocks 2, 4 and 5 (all p-values <0.01), whereas older adults slowed in Block 3 [t(19)= -4.138, p=0.001, adjusted α = 0.0125]. There was no effect of VF or Stimulation type on reaction times nor were there any significant interactions with these factors.

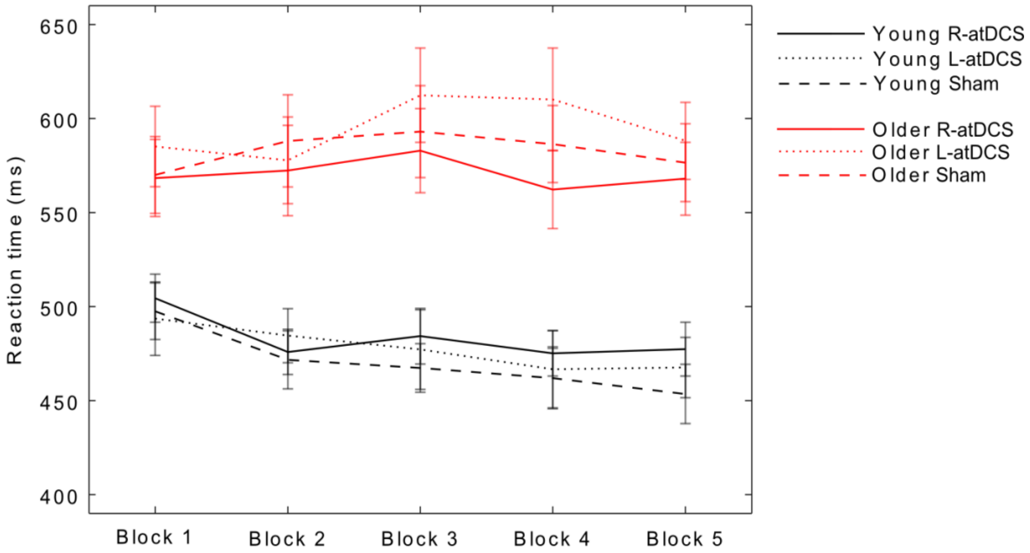

Figure 5. Reaction times for correct trials (excluding RTs >2 SD above the mean for each subject), averaged across both VFs (*left* and *right*), for both Age groups (*young* and *older*) and 3 Stimulation conditions (*R-atDCS*, *L-atDCS* and *Sham*) (± SEM).

3.3.5 Interim Discussion: No Clear Effects of tDCS in Aging

In line with the previous spatial attention literature, young adults displayed a significant leftward spatial attention bias at baseline (i.e. pseudoneglect) that was consistent across testing sessions. Older adults showed no bias towards either side, and their lateralised sensitivity scores were inconsistent across baseline blocks. Contrary to my original prediction, there were no main effects of Stimulation type in either group on any of the measures (*d′* or RT) and also no interactions between the side of stimulation, visual field or age.

However, there is now evidence that the 'traditional' anode-excitation/cathode-inhibition dichotomy may be an oversimplification of the mechanisms underpinning non-invasive brain stimulation. There is a high variability of response to tDCS both between individuals and across multiple testing sessions (Chew, Ho & Loo, 2015; Horvath, Carter & Forte, 2014; Horvath, Forte & Carter, 2015a,b; Fricke et al., 2011; López-Alonso et al., 2014; Krause & Cohen Kadosh, 2014; Wiethoff, Hamada & Rothwell, 2014). Multiple factors have been reported to influence the response to tDCS, for example the type of task (i.e. motor vs cognitive; Jacobson, Koslowsky & Lavidor, 2012; Vallar & Bolognini, 2011), task difficulty (Jones & Berryhill, 2012; Wu et al., 2014), motivation (Jones, Gönzenman & Berryhill, 2014) and baseline activity within the targeted neural network (Antal et al., 2007; Benwell, Learmonth et al., 2015; Berryhill & Jones, 2012; Dockery et al., 2009). Importantly, distinct differences in response to tDCS have been reported that are dependent on task performance. Tseng et al., (2012) found that young adults who performed poorly at a visual short term memory task at baseline benefitted from 1.5mA atDCS to the right

PPC (P4) whereas good performers did not, and this may be linked to changes in pre-stimulus alpha activity (Hsu et al., 2014). This effect of performance is also supported in the aging literature (although intriguingly, in the opposite direction) by the finding that older adults with a high level of education improved on working memory tasks whereas those with lower educational attainment were impaired after 1.5mA atDCS (Berryhill & Jones, 2012). In the present study, participants were therefore divided into two groups based on their peri-threshold pixel sizes, determined during the stimulus titration phase, rather than by age group.

3.4 Baseline Performance Split

Twenty-one participants were relatively ‘good’ at the lateralised visual detection task reaching a 50% accuracy threshold at small pixel sizes (between 1x2/2x2 and 2x3/3x3 pixels) whereas the remaining 19 required larger pixels to meet the same level of accuracy (3x3/3x4 to 7x8/8x8 pixels). Eighteen of the ‘good’ performers were young and 17 older adults comprised the ‘poor’ performance group. Thus, 3 older adults performed within the typical range for young adults whereas 2 young individuals performed relatively poorly.

3.4.1 Subjective Alertness Questionnaire: Performance Groups

The questionnaire data was re-analysed for differences in alertness and sensory experience between these two Performance groups. Subjective alertness reduced throughout the experiment [TIME: F(1,38)=90.4, p<0.001] and *Poor* performers reported higher levels of alertness overall [PERFORMANCE:

F(1,38)=5.047, p=0.031] (Mean score *Good* = 67.29 (SD=10.18); *Poor* = 75.16 (SD=11.97)). No interactions were found.

3.4.2. Side-Effects Questionnaire: Performance Groups

A Mann-Whitney U test found that side-effects were not experienced more strongly in either Performance group (all p-values >0.015, adjusted α = 0.003). The groups did not differ in their ability to guess which session involved Sham tDCS (Pearson χ^2 = 0.819, p=0.366).

3.4.3. Baseline Sensitivity (d′): Performance Groups

There were no sensitivity differences between the two Performance groups at baseline (3 Stimulation types x 1 Block x 2 VFs x 2 Performance groups). One-sample t-tests against zero using lateralised *d′* scores (Left VF *d′* subtracted from Right VF *d′*) revealed that there were no group-level visuospatial attention biases towards either visual field in either of the 3 testing days. One of the 3 baseline lateralised *d′* score comparisons were correlated in *Good* performers [R-atDCS *vs* L-atDCS: Spearman r=0.342, p=0.129; R-atDCS *vs* Sham: r=0.658, p=0.001; L-atDCS *vs* Sham: r=0.282, p=0.216] and 2 of 3 in the *Poor* performance group [R-atDCS *vs* L-atDCS: Spearman r=0.622, p=0.004; R-atDCS *vs* Sham: r=0.785, p<0.001; L-atDCS *vs* Sham: r=0.473, p=0.041, adjusted α=0.017].

3.4.4 D-prime Sensitivity: Performance Groups

The full-factorial was repeated for *d′* and RTs, but this time including Performance rather than Age as a factor (3 Stimulation types x 5 Blocks x 2 VFs x

2 Performance groups). As in the previous analysis, detection sensitivity reduced across the 5 experimental Blocks [F(4,152)=4.335, p=0.002, ηp^2=0.102] but due to the titration phase, which equated the task difficulty for each participant, there was no sensitivity difference between Performance groups. Interestingly, a significant 3-way interaction involving Stimulation x Block x Performance was then uncovered [F(8,304)=2.316, p=0.02, ηp^2=0.057] (Figure 6).

Paired comparisons for the *Poor* performance group highlighted a sensitivity difference between L-atDCS (reduced sensitivity) and Sham as a function of block [Stimulation (*L-atDCS* vs *Sham*) x Block: F(4,72)=4.836, p=0.002, ηp^2=0.212]. Further paired samples t-tests found that the sensitivity difference emerged between L-atDCS and Sham at the *end* of the stimulation period (Block 3) [t(18)= -2.568, p=0.019]. There was no difference between R-atDCS and Sham in the *Poor* performance group. The same comparisons for the *Good* performers highlighted a difference between R-atDCS (enhanced sensitivity) and Sham as a function of block [Stimulation (*R-atDCS* vs *Sham*) x Block [F(4,80)=4.635, p=0.002, ηp^2=0.188] but further paired samples tests did not reveal any specific significant differences between Stimulation conditions in any of the 5 Blocks. L-atDCS did not elicit any differences compared to Sham in the *Good* performance group. Finally, comparing the L- and R-atDCS groups directly [Stimulation (L-atDCS vs R-atDCS) x Block [F(4, 152)=2.623, p=0.037, ηp^2=0.065] showed again that the largest between-group difference appeared during Block 3 [t(38)=2.273, p=0.029]. In summary, whereas L-atDCS led to reduced sensitivity in *Poor* performers, R-atDCS seemed to maintain sensitivity in *Good* performers. These effects were most apparent during the end of stimulation (Block 3).

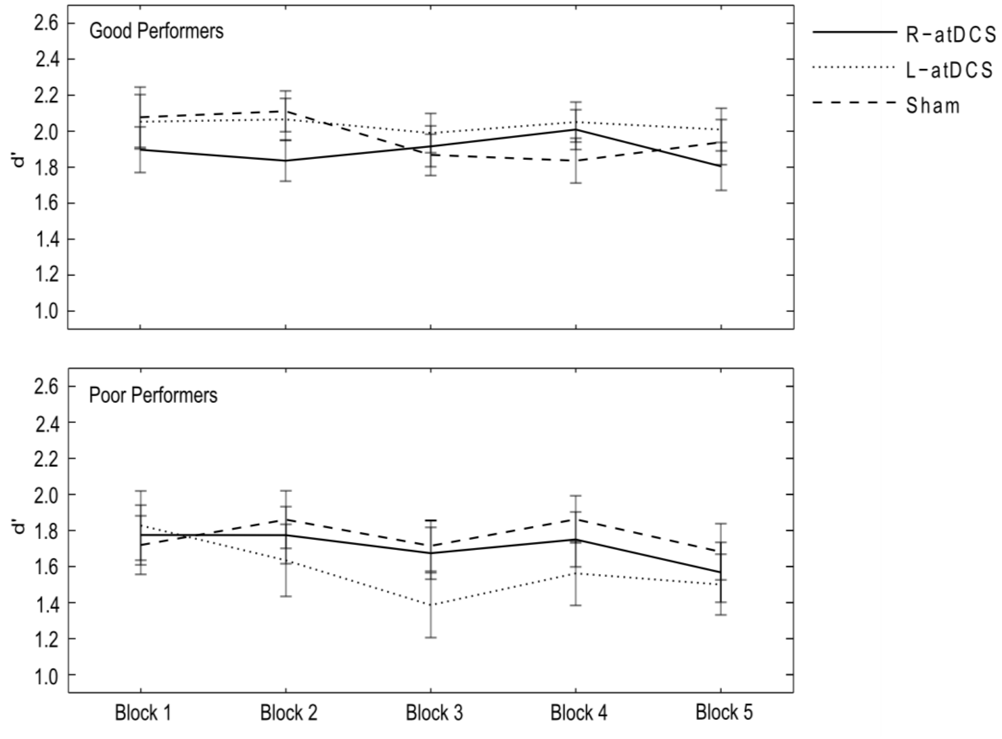

Figure 6. D' sensitivity scores averaged across both VFs (left and right), for both Performance groups (Good and Poor) and 3 Stimulation conditions (R-atDCS, L-atDCS and Sham) (± SEM).

3.4.5 Reaction Times (RTs): Performance Groups

Poor performers were slower to respond compared to *Good* [PERFORMANCE: F(1,38)=16.653, p<0.001, ηp²=0.305] (Figure 7), but mean response times generally decreased across the duration of the experiment [BLOCK: F(4,152)=4.153, p=0.003, ηp²=0.099]. These effects were modified by a significant interaction between Performance x Block [F(4,152)=4.506, p=0.002, ηp²=0.106]. Post hoc comparisons revealed that *Good* performers responded faster in Blocks 2, 4 and 5 relative to baseline (Block 1) (all p-values <0.011, adjusted α = 0.0125) whereas *Poor* performers maintained their baseline reaction time throughout the experiment. Finally, there was an interaction between Stimulation and Performance [F(2,76)=3.968, p=0.023, ηp²=0.095] with *Poor* performers slower in response to L-atDCS compared to R-atDCS, however this did not survive Bonferroni correction (paired comparisons R-atDCS vs L-atDCS: t(18)= -2.343, p=0.031; Sham vs L-atDCS: t(18)= -2.043, p=0.056, adjusted α=0.017).

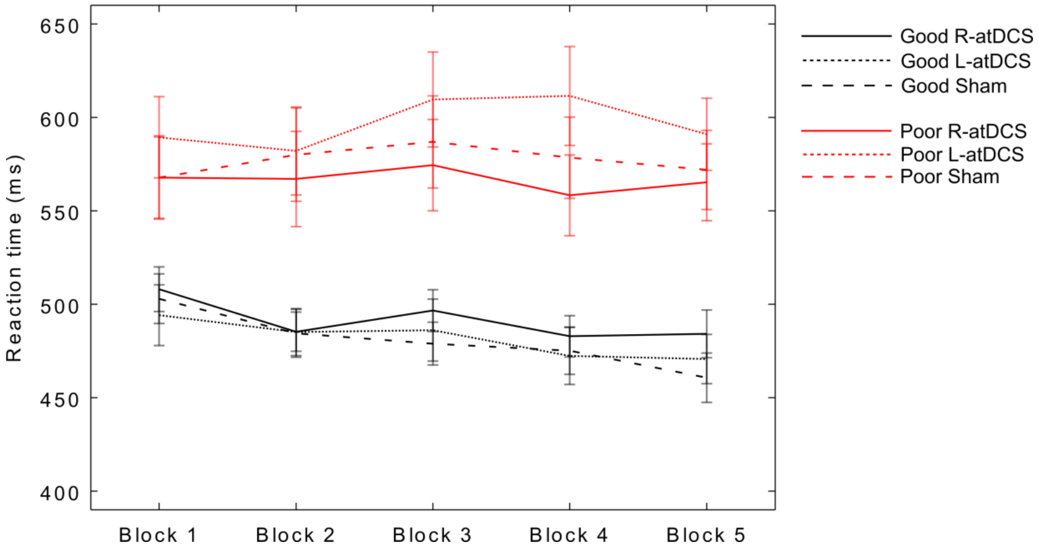

Figure 7. Reaction times for correct trials (excluding RTs >2 SD above the mean for each subject), averaged across both VFs (*left* and *right*), for both Performance groups (*Good* and *Poor*) and 3 Stimulation conditions (*R-atDCS*, *L-atDCS* and *Sham*)(± SEM).

3.4.6 Bilateral Errors: Performance Groups

Overall, *Poor* performers made more errors in response to bilateral trials than *Good* performers [PERFORMANCE: F(1,38)=13.85, p=0.01, ηp²=0.267] (Mean *Poor*: 6.35, SD = 1.89; *Good*: 9.43, SD = 3.24) and there was an interaction between Performance x Block group [F(4,152)=3.347, p=0.012, ηp²=0.081]:

although *Poor* performers made more errors overall, they did not deteriorate over the course of the experiment. Conversely, *Good* performers made more errors by the end of the experiment (Block 5) when compared to the baseline (Block 1) [t(20)= 3.41, p=0.003]. Bilateral error rates were not affected by Stimulation condition.

4. General Discussion

I predicted that anodal tDCS would elicit an improvement in stimulus detection in the visual field that was contralateral to the site of stimulation, when applied to both the left and right posterior parietal cortex. Secondly, I predicted that spatial attention might be modulated differently in young and older adults. However I did not succeed in improving either detection sensitivity or reaction times in either age group. Instead there was a (subtle) state-dependent effect of tDCS that is consistent with previous findings (Antal et al., 2007; Benwell, Learmonth et al., 2015; Berryhill & Jones, 2012; Dockery et al., 2009). Only when participants were divided into Good and Poor task performers did I find statistically significant differences between groups in response to tDCS. Detection sensitivity gradually deteriorated during the Sham condition over the course of the experiment in both *Good* and *Poor* performers, probably due to fatigue, but Poor performers were further impaired when atDCS was applied to the *left* PPC. In contrast, Good performers maintained their detection sensitivity in both visual fields as a result of anodal stimulation of the right PPC, highlighting the importance of considering baseline task performance when designing non-invasive brain stimulation protocols.

4.1 No Effects of Age in Response to Anodal tDCS

My prediction that atDCS would elicit distinct outcomes depending on the participant's age was founded on the premise that different neural populations might be recruited to execute spatial attention tasks in young versus older adults. In line with previous studies, I found a group-level, consistent leftward bias (pseudoneglect) in young adults at baseline (Bowers & Heilman, 1980) whilst older adults showed no consistent preference towards either visual field. This behavioural pattern reflects previous findings (Benwell et al., 2014a; Failla, Sheppard & Bradshaw, 2003; Fujii et al., 1995; Fukatsu et al., 1990; Jewell & McCourt, 2000; Nagamatsu et al., 2009, 2011, 2013; Schmitz & Peigneux, 2011; Stam & Bakker, 1990) and may indicate an age-related reduction of lateral asymmetry (i.e. the HAROLD model or the *accelerated aging* model). However, in the absence of functional imaging evidence with which to map age-related cortical reorganisation in the spatial attention domain, this premise remains speculative. It is also possible that a more extensive functional reorganisation had taken place in the older adults. The posterior-anterior shift in aging (PASA) model predicts that posterior regions become less active in older adults, in favour of more frontal regions of the visuospatial attention network (Davis et al., 2008). If so, the choice of electrode placement over the posterior parietal cortex, on one side only, may have proved sub-optimal in targeting the more distributed brain regions that support lateralised spatial attention in the older group. Such a shift would not be observable in the lateralised detection task data and would therefore represent a potential focus of inquiry in future functional imaging studies (see Chapter Four of this thesis).

4.2 State-Dependent (Performance) Effects of tDCS

It must be stressed that the effects found here were small. Relative to Sham, I found a sustained detection sensitivity in the Good performers during R-atDCS and reduced sensitivity in the Poor performers during L-atDCS. Reaction times also decreased over the course of the experiment, but this was similar for all three Stimulation types in the *Good* performers. The principal finding of this study - that baseline task performance determined the response to tDCS rather than age *per se* - is congruent with a growing body of research revealing state-dependent effects of non-invasive brain stimulation. Rather than exerting a homogeneous effect on each neuron underneath the electrodes and across individuals, it is likely that tDCS instead interacts with endogenous activity levels within target neuronal populations. This results in individualised effects of tDCS that are dependent on the pre-existing activation state of the targeted neurons (Antal et al., 2007; Benwell, Learmonth et al., 2015; Dockery et al., 2009; Fertonani et al., 2014; Hsu et al., 2014; Tseng et al., 2012). I found that, relative to the Sham protocol, the application of anodal stimulation to the right parietal cortex maintained stimulus detection sensitivity in the Good performance group. Given that there were no differences in the severity of sensory side-effects reported between the ‘active’ and Sham tDCS conditions, this sustained performance is unlikely to have been caused by a non-specific (i.e. sensory) effect of tDCS. These results are compatible with the finding of Berryhill & Jones (2012), who elicited an improvement in working memory, but only in older adults with high educational attainment, whereas those with a low educational background deteriorated. It is plausible that the ‘good’ performers (i.e. the highly-educated, or individuals reaching threshold accuracy at small pixel sizes in the present experiment) shared a similar baseline state that determined whether neurons responded to non-invasive stimulation.

4.3 Left Anodal tDCS Impairs Sensitivity and RTs in Poor Performers

In summary, there was a reduction in visual detection sensitivity across both visual fields when atDCS was applied to the left posterior parietal cortex in Poor performers. Reaction times were also increased, although this effect did not survive multiple comparison correction. I had aimed to generate specific sensitivity improvements within each contralateral visual field, similar to the protocol of Sparing et al., (2009) (i.e. an increased left VF sensitivity with R-atDCS and vice versa), but surprisingly I did not replicate these findings. In direct contrast, anodal stimulation of the left parietal cortex resulted in an *inhibitory,* rather than facilitatory effect across both hemifields for individuals with low baseline performance. This reduction was most pronounced near the end of the stimulation period, when the effects of tDCS have previously been shown to be strongest (Nitsche & Paulus, 2000; 2001; Sparing et al., 2009; Stagg & Nitsche, 2011). These results can be explained most effectively by an interhemispheric competition account of visuospatial attention. Whilst the left cerebral hemisphere directs attention exclusively towards the right side of space, the dominant right hemisphere directs attention to both the left and right sides (Bisiach & Vallar, 2000; Kinsbourne, 1977; 1994; Mesulam, 2002; Szczepanski, Konen & Kastner, 2010). In this case, the Poor performers may have been disproportionately affected by a disruption to the balance of activity between the left and right hemispheres. Whereas the Good performers (who were likely to have utilised the right hemisphere more optimally, given their superior performance), were somewhat resistant to this increase in the left PPC, this may have impacted negatively on individuals who were already less efficient at the task.

4.4 Right Anodal tDCS Maintains Sensitivity in Good Performers

The model of competing interhemispheric attention mechanisms may also explain the subtle finding of maintained task sensitivity in Good performers. If, as predicted, the Good task performers exhibited a more optimal engagement of the dominant right PPC at baseline, then the right hemisphere may have been more amenable to the effects of tDCS than the less dominant left PPC, thus resulting in the observed maintenance of performance after right, but not left, anodal tDCS. In line with this, previous research has indicated that tDCS generates greater effects when the underlying target neuronal populations are actively engaged in a task (Antal et al., 2007; Dockery et al., 2009; Miniussi, Harris & Ruzzoli, 2013) which may have been the case for right-hemisphere neurons for this task.

However, like the effects found in the Poor performance group, the behavioural pattern in the *Good* performers is still different from the findings of

Sparing et al., (2009): neither visual field was *unilaterally* improved (nor inhibited) by atDCS. Rather than placing the return electrode on the vertex (Cz) to constrain the current flow around the parietal region, as in the protocol of Sparing et al., I chose instead to place the cathode on the forehead contralateral to the site of anodal stimulation, in order to minimise any effects of the return electrode on the surrounding cortex. This montage has been used successfully to modulate neural activity in patients with hemispatial neglect (Ko et al., 2008; Sunwoo et al., 2013) and is similar to standard electrode placements used within the motor domain (e.g. Antal et al., 2007; Nitsche & Paulus, 2001; Priori, 2003). This PPC-contralateral supraorbital placement may have diffused the current into more distant frontal regions within the opposite hemisphere. As a result, a less focal effect of tDCS may have been generated, which could have resulted in a general maintenance of alertness, rather than targeting neurons that are specifically responsible for the lateral orientation of attention.

4.5 Limitations of this Study

Yet, this interpretation may *still* represent a rather simplistic view of tDCS mechanisms, since the application of non-invasive brain stimulation in older populations must also take into account age-related differences in the plasticity of the neural system. It has recently been reported that compared to young adults, older people exhibit a delayed response to anodal tDCS within the motor domain. Peak neural excitability was reported to occur immediately post-tDCS in young adults but was delayed until 30 minutes after stimulation in older adults (Fujiyama et al., 2014). I may therefore have ended the testing session too soon after tDCS to identify any improvements in the older group, and I might also have cumulatively driven stronger and more lasting improvements with multiple stimulation sessions.

Finally, it is possible that in addition to state-dependent performance effects, anodal tDCS did indeed exert a differential effect in young and older adults yet this may have been somewhat diluted by within-group heterogeneity. As described above, the *Poor* performance group reported here consisted predominantly of older adults and *Good* performers were mostly young. Three older adults performed well enough to be reassigned into the *Good* performance group and 2 young adults performed at a *Poor* level. I acknowledge that the sensitivity effects reported here are small and that this reflects a wider debate surrounding the efficacy of transcranial electrical stimulation (e.g. Horvath, Carter & Forte, 2014; Horvath Forte & Carter, 2015a,b; Walsh, 2013). Nevertheless, these considerations give rise to questions that would be of interest to the spatial attention and brain stimulation communities: do highly-performing older adults display different patterns of cortical activity compared to poorly-performing age-matched individuals in attention tasks? Likewise, are there distinct patterns of activity in young adults with good task performance compared to less able young people?

Further neuroimaging studies would assist in answering these questions and, importantly, would help to map the extent and role of functional reorganisation for visuospatial attention in older adults. In turn, this is likely to foster a more targeted (and thus more successful) approach to improving spatial attention in the elderly using non-invasive brain stimulation. In the following

Chapter, I describe the results of my third experiment which aimed to map these age-related changes in hemispheric lateralisation using encephalography (EEG).

Chapter Four

Age-related reduction of hemispheric lateralization for spatial attention: An EEG study

1. Introduction

Young adults tend to systematically overestimate the size, luminance, number and spatial frequency of objects within the left side of space relative to the right (‘pseudoneglect’) (Bowers & Heilman, 1980). This leftward attention bias likely arises as a result of a right posterior-parietal dominance for visuospatial processing in young adults which results in a net asymmetry of activity between the right (RH) and left (LH) parietal cortices when performing spatial judgements. Specifically, the right dorsal fronto-parietal network is implicated in tasks requiring line midpoint judgements, such as the line bisection and landmark tasks (a computerised version of the line bisection task involving pre-bisected horizontal lines) (Benwell et al., 2013a,b, 2014a,b, 2015; Çiçek et al., 2009; Fink et al., 2000a,b, 2001, 2002; Foxe, McCourt & Javitt, 2003; Galati et al., 2000; Longo et al., 2015; Weiss et al., 2000; 2003).

In terms of the timing of the right-lateralisation of activity within the parieto-occipital cortex during landmark task performance, a distinct time course has been reported using electroencephalography (EEG) (the ‘line bisection effect’: Foxe, McCourt & Javitt, 2003), which broadly consists of three phases after stimulus onset: Compared to a control landmark task that required a non-spatial decision, Foxe, McCourt & Javitt (2003) found a net right-lateralized negativity relative to the control during an early phase (~165-190ms) involving the right lateral occipital cortex and the right temporo-parietal occipital junction (TPJ). The second phase (~190-240ms) also comprised this right parietal cortex negativity, with additional involvement of the superior right central parietal cortex. Finally, the peak landmark task effect was observed at ~310ms where the right central parietal negativity dominated. Using a similar task, and comparing posterior regions of interest (ROI) across the two cerebral hemispheres, Longo et al., (2015) found no strong right-lateralisation differences (landmark vs control) within an early time window (170-190ms) but found a significant effect of hemisphere in the 190-240ms window, with a larger negativity in the right vs left parieto-occipital electrodes. Finally, our research group has also recently reported an increased right central parietal negativity for the landmark task vs a control in a window of 231-500ms, with a peak bisection effect at 280ms (Benwell et al., 2014b). Therefore, when compared to a non-spatial control task, line bisection performance consistently elicits a larger negativity in the right parieto-occipital region, which probably reflects the engagement of lateralised attention networks localized to the right hemisphere for this task.

In addition to the ‘line bisection effect’, our research group has shown a further right parieto-occipital activation that is stimulus-dependent (the ‘line length effect’). In Benwell et al., (2014b), long vs short landmark lines were compared in young adults, and the two line lengths were found to be maximally differentiated in the right TPJ (electrode PO4) at 140ms post-stimulus, regardless of the task being performed (i.e. landmark versus control). Specifically, there was a larger right-lateralized negativity for long vs short lines in the right parieto-occipital cortex that corresponded to the P1-N1 component window and this was associated with a group-level leftward behavioural bias (pseudoneglect) for long but not short lines (Benwell et al., 2014b). These distinct behavioural and neuroimaging differences between line lengths reveal a behaviourally relevant hemispheric asymmetry in young people in terms of right hemispheric involvement, and therefore this experimental manipulation (line length) lends itself well to the study of hemispheric asymmetries across age groups.

In older adults, evidence for changes in spatial attention processing as assessed by the landmark/line bisection task has been provided by many studies reporting a reduction (and sometimes directional reversal) in pseudoneglect for this group relative to young participants (Benwell et al., 2014a; Failla, Sheppard & Bradshaw, 2003; Fujii et al., 1995; Fukatsu et al., 1990; Nagamatsu et al., 2009, 2011, 2013; Schmitz & Peigneux, 2011; Stam & Bakker, 1990, Chapter Three of this thesis, but see Brooks et al., 2016, for maintained pseudoneglect into older age). This intriguing finding might be indicative of a reduction of right-hemisphere dominance for spatial attention with advancing age, or perhaps even a shift towards an asymmetry favouring the *left* hemisphere.

This age-related rightward shift in spatial attention is consistent with a number of models that describe a widespread reorganisation of brain function in later life. The principal differences between these models lie in the extent to which the left and right hemispheres are considered to increase and decrease in engagement throughout the lifespan. Although none of these models specifically describe the changes that occur within the spatial attention domain (indeed, many were developed from observations regarding episodic and working memory (Bäckman et al., 1997; Cabeza et al., 1997, 2004; Grady et al., 2002; Madden et al., 1999; Morcom et al., 2003; Reuter-Lorenz et al., 2000)), I can extrapolate from these models to predict both the EEG and behavioural outcomes that might be expected in the present experiment. Firstly, the 'right hemi-aging model' claims that cognitive functions which draw upon right hemisphere resources deteriorate faster than those confined to the left hemisphere (e.g. language in the left hemisphere, attention in the right) (Brown & Jaffe, 1975; Dolcos, Rice & Cabeza, 2002; Goldstein & Shelly, 1981). Following this reasoning, I would predict to observe distinct differences in EEG signals in older adults compared to young, showing either a reduced hemispheric asymmetry or indeed reversed (i.e. stronger left vs right hemispheric activation), depending on the extent of this right hemisphere deterioration. If these cortical changes then go on to influence behavioural bias, then I would expect to observe either an elimination of spatial bias or a distinct rightward bias in the right hemi-aging model scenario. The related model of 'hemispheric asymmetry reduction in older adults' (HAROLD model) (Cabeza, 2002; Cabeza et al., 1997; 2002; 2004; Huang et al., 2012; Reuter Lorenz et al., 2000) proposes that cognitive functions that are highly lateralised to one cerebral hemisphere in young adults become generally less lateralised in older adults. This bilateral recruitment may be a compensatory mechanism to support maintained cognitive performance in the elderly, given that PET and fMRI studies have shown a more pronounced bilateral recruitment in difficult tasks (Cabeza, 2002; Cabeza et al., 1997, 2002; Huang et al., 2012; Reuter-Lorenz et al., 2000). This model would predict that older adults exhibit an eliminated hemispheric asymmetry compared to young adults as a result of reduced lateralisation, but would not allow for a shift entirely into rightward space as per the right hemi-aging model. In this scenario, I would expect to observe no lateralised EEG and behavioural bias for the older group. Finally, the 'compensation-related utilization of neural circuits hypothesis' (CRUNCH model) (Reuter-Lorenz & Cappell, 2008) proposes that older adults recruit 'different' neural pathways (i.e. pathways that are not used by young adults) to undertake difficult tasks as their neural resources diminish, although these additional resources are not necessarily drawn from the contralateral cerebral hemisphere. It has been proposed as a more general, but related, version of the HAROLD model (Berlingeri et al., 2013) in which the age-related changes that occur do not necessarily lead to a reduction of hemispheric asymmetry. In this scenario the EEG results should show a clear increase of activity in older adults compared to young, but these changes could occur at any location within the cortex. However, given that this model is not specific about the location of such changes, it does not allow for predictions in terms of behavioural bias.

Few EEG/MEG studies have specifically investigated age-related changes in spatial attention, instead focusing on mapping attention in healthy young adults and in certain clinical groups (e.g. hemispatial neglect: Di Russo et al., 2008, 2013; Rastelli et al., 2013; Sasaki et al., 2013; Spinelli et al., 1994). Nevertheless, the EEG studies that have been performed in older adults are broadly consistent with the corpus of behavioural evidence showing a reduced preference for left hemispace, and provide an intriguing insight into the aging spatial attention network. In a cued target detection task, Nagamatsu et al., (2011) found that seniors have a specific deficit in the top-down allocation of attention to the left side of space as indexed by the attention directing anterior negativity (ADAN) component (375-430ms post-cue). Young adults exhibited a larger ADAN amplitude for contralateral targets relative to ipsilateral, which was observed for targets presented in both the left and right visual fields. Seniors, however, only demonstrated this contralateral advantage for targets presented in the right visual field. Targets that were presented in the left hemifield only showed a very minor amplitude increase in the right vs left hemisphere, indicating a possible age-related decline in right-hemisphere function. Importantly, left visual field deficits were also associated with an increased risk of falls (Nagamatsu et al., 2009) indicating that these neural changes may have important consequences for maintained functional performance as we age.

Overall, the consistent reports of right-lateralised EEG activity for the landmark task in young adults, combined with distinct behavioural changes observed for this task in older adults, make this an ideal paradigm in which to formally investigate changes in hemispheric asymmetry in healthy aging.

Here I aimed to assess, for the first time, whether an age-related functional reorganisation of neural activity can be observed using EEG during a spatial judgement task. I expected older adults to exhibit a rightward behavioural shift on the landmark task relative to young adults, and I investigated whether this shift would be accompanied by a reduction of right-hemispheric lateralisation during landmark task processing (as measured by event related potentials; ERPs). Secondly, I predicted that the effect of age would interact with line length, anticipating more right vs left hemisphere asymmetry for long lines in young adults relative to short lines (in line with Benwell et al., 2014a) but expected this difference to be less pronounced or absent in the older age group.

2. Method

2.1 Participants

Twenty young adults (10 females, mean age = 20.8, SD = 2.17, range = 18-25) and 20 older adults (10 females, mean age = 68.75 , SD = 6.29, range = 60-80) were recruited. Based on task performance, 2 participants (1 young, 1 older) were excluded after application of the median absolute deviation method of outlier detection for curve width and PSE values, leading to 19 participants per group. All were right-handed and reported normal or corrected-to-normal vision. The study was approved by the University of Glasgow College of Science and Engineering ethics committee and written, informed consent was obtained from each participant.

2.2 Procedure

Participants were seated at a fixed distance of 0.8m in front of a computer screen in an electrostatically shielded room with their midsagittal plane aligned with the screen. A short (3 minute) computerised visual screening assessment was administered at the beginning of the session (see 2.2.1) to ensure adequate vision, before proceeding with EEG preparation and the experiment. Two experiments were then performed in a counterbalanced order between participants. Each experiment lasted about 30 min. One of these experiments will form the subject of a separate publication and is therefore not reported here.

2.2.1 Visual Acuity Screening

Small black 10 x 10-pixel squares were briefly presented individually at one of 36 locations (extending to 10.0° above and below fixation, and 12.13° to the left and right) for 150ms. A total of 72 trials (36 locations x 2) were randomly interspersed with an additional 24 'catch' trials, where the screen remained blank, to measure adherence with the task. Participants were requested to press the space bar if a stimulus had been detected and to withhold their response when undetected. None of the participants (all having reported normal or corrected-to-normal vision during recruitment) had to be excluded based on performance in this visual screening test.

2.2.2 Landmark Task

Participants then performed the landmark task, adapted from McCourt (2001) and Benwell et al., (2014b), whilst EEG was recorded from 64 channels. The landmark task (also called 'tachistoscopic line bisection' (McCourt & Jewell, (1999)) is a two alternative forced-choice version of the line bisection task. As in Benwell et al., (2014b), horizontal lines of 100% Michelson contrast were presented on a uniform grey background (luminance = 179, hue = 160). Half of the lines were shaded black in the upper left/lower right quadrants and half shaded black in the lower left/upper right (see Figure 1). Two line lengths were presented: long lines measured 800 x 14 pixels (14.88° x 0.27° visual angle) and short lines 80 x 14 pixels (1.48° x 0.27°). Each line was transected vertically at the veridical centre of the screen (i.e. at the same position as the fixation cross).

The length of the left and right sections varied across trials, with 13 different stimuli for each line length (6 where the left side was longer than the right, 6 where the right was longer than the left and 1 where both sides were of equal length). For the long lines, the most asymmetrical (left vs right side) stimuli differed by 120 pixels and the asymmetry reduced in 20-pixel increments until the two sides were of equal length. For the short lines the largest asymmetry was 12 pixels with a reduction of 2 pixels per stimulus.

Each landmark block consisted of 156 trials (13 long lines and 13 short lines presented 6 times each in a random order). A centrally located fixation cross appeared for 1500ms, followed by the landmark stimulus for 150ms. The fixation cross then reappeared until a response was given. Participants were instructed to press the left or right response key using their right index or middle finger if they perceived the left side of the line to be shorter (half of the participants were instructed to indicate the *longer* side, to control for potential response bias (Toraldo et al., 2004)). Five blocks were presented in total, each lasting approximately 6 minutes.

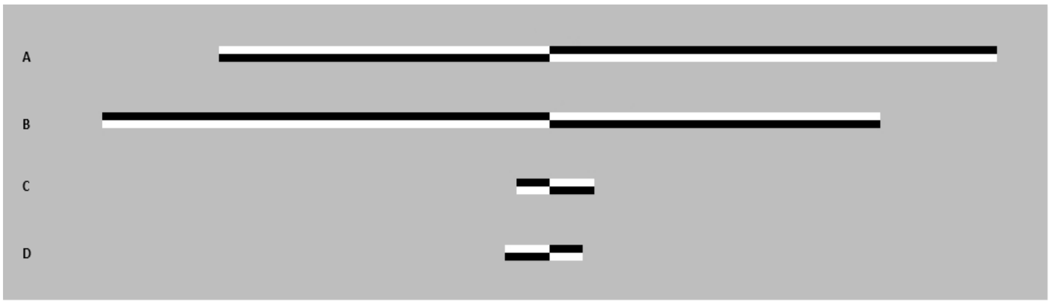

Figure 1. Example of the landmark task stimuli. Stimulus A: Long line where the left side is shorter by 120 pixels relative to the right. Stimulus B: Long line where the right is shorter by 120 pixels. Stimulus C: Short line where the left is shorter by 12 pixels. Stimulus D: Short line where the right is shorter by 12 pixels.

2.3 Data Recording and Analyses

2.3.1 Landmark Task

Stimuli were presented and manual responses recorded using E-Prime 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) with a Dell Precision T3400 PC and 19.5' Sun Microsystems CRT monitor (with 1280 x 1024 pixel resolution and 100Hz refresh rate). The percentage of trials where the left side was perceived as shorter was calculated for each of the 13 stimuli. Psychometric functions were fitted for each individual per line length per block using a cumulative logistic function:

$$f(\mu, x, s) = 1/(1 + \exp\left(\frac{\mu - x}{s}\right))$$

where μ is the point on the x-axis that corresponds to 50% left and 50% right-response rate, x represents the transector locations and s is the psychometric curve width. The point of subjective equality (PSE) and curve widths were extracted and transformed to represent a percentage of the total line length rather than an absolute number of pixels. The PSE provides a measure of the subjective midpoint of the landmark lines for each block and is used to quantify spatial attention bias, whereas the curve width estimates the precision of these judgements. A narrow (small) curve width value indicates high precision and a wide (large) curve width value low precision.

2.3.2 EEG Acquisition and Preprocessing

Data were recorded using a BrainVision EEG system (MR plus) with a 64-channel BrainCap array (62 scalp electrodes and 2 ocular electrodes, placed on the outer canthi to detect blinks and lateral eye movements). Sampling rate was set to 1000Hz. Preprocessing and subsequent analyses were conducted in Matlab using the EEGLAB toolbox (Delorme & Makeig, 2004) and customised scripts. Raw EEG signals were de-trended, segmented into epochs of 1500ms duration (500ms pre-stimulus to 1000ms post-stimulus onset) and then re-referenced to an average reference. A finite impulse response filter was applied between 0.3 and 40Hz. Epochs containing extreme artifacts were identified and removed by visual inspection and channels containing prolonged periods of extreme artefact were rejected. Further artifact elimination was performed using independent component analysis (to remove blink and eye movement artifacts) and previously rejected channels were interpolated using a spherical spline method. The resultant signal was then re-epoched to a 700ms window (-300 to 400ms) and finally, baseline corrected. The following mean number of trials per person were included in the statistical analyses: Young adults: Long lines $\bar{x}$ = 368.74 trials (range = 322-387), short $\bar{x}$ = 370.89 (325-389). Older adults: Long $\bar{x}$ = 365.68 (285-385), short $\bar{x}$ = 369 (314-388). The two age groups did not differ in the number of trials included [Age: F(1,36)=0.17, p=0.69; Age x Length F(1,36)=6.37, p=0.59] but slightly more trials were included for short relative to long lines [Length: F(1,36)=6.71, p=0.014].

2.3.3 EEG Statistical Analyses

EEG data were statistically analysed in the time domain using the Mass Univariate ERP toolbox for Matlab (Groppe, Urbach & Kutas, 2011a,b). Two-tailed cluster mass permutation tests were performed to identify clusters of electrodes and time points which differed between the conditions being compared (Bullmore et al, 1999; Maris & Oostenveld, 2007). Two approaches were used to assess different aspects of the hypotheses:

1*. Full-Scalp Cluster Analysis:* i) I first aimed to test the main effect of line length (long vs short lines) across the whole head using repeated-measures t-tests for each of the 62 scalp electrodes and time points in the 0-400ms window. Neighbouring t-scores corresponding to an uncorrected p-value of <0.01 were formed into clusters according to their temporal and spatial adjacency (separately for negative and positive t-values). Electrodes were defined as spatial neighbours if they were located within approximately 3.7cm of each other, which resulted in a mean of 3.55 channels per neighbour (min=1, max=4). The sum of all t-scores within each cluster provided a cluster-level t-score (the 'cluster mass'). The same clustering procedure (and cluster mass extraction) was then performed across 20,000 random permutations of the data in order to build a data driven null hypothesis distribution. The relative location of each observed *real* cluster mass t-score within the null hypothesis distribution indicates how probable such a score would be if the null hypothesis were true. An alpha level of 5% was adopted for cluster-level statistics. Within-group cluster tests were then repeated separately for ii) Young and iii) Older adults to assess the line length effect as a function of age. iv) The main effect of Age was then investigated using the same methodology, but using independent-samples t-tests for the between-groups comparison (Young vs Older, both line lengths collapsed). Finally, between-groups cluster tests assessed the effect of age as a function of line length (Young vs Older, separately for v) long and vi) short lines).

2. ***Lateralised Electrode Cluster Analysis****:* In addition to the full-scalp analysis, to answer the principal question of whether differences in hemispheric asymmetry exist between age groups, cluster permutation tests were performed again on the *lateralised* EEG signal. This was generated by pairing each of the 27 electrodes on the left side of the head with its corresponding homologous electrode on the right side (e.g. P1/P2, O1/O2 and excluding the 8 midline electrodes). For each trial per subject, and at each time point in the -300 to 400ms window, the EEG amplitude from the LH electrode in each pair was subtracted from the amplitude at the RH electrode. This created a lateralised (RH-LH) EEG signal for each of the 27 pairs which was then subjected to cluster mass permutation testing as per the method outlined above.

i) A series of 4 cluster mass permutation tests were first performed to assess whether either line length or age group was significantly lateralised to one hemisphere at any consecutive time points or electrodes during the 0-400ms window. This was achieved by performing one-sample t-tests against zero (i.e. the null hypothesis = no lateralisation) during the cluster identification stage, with the subsequent estimation of the null hypothesis distribution proceeding as described above.

ii) The interaction between line length x age was tested by performing a between-subjects cluster analysis (using same method as above but on the lateralised EEG data) on a long vs short line difference wave, created by subtracting the mean EEG signal in the short lines from the long lines for each participant. This interaction was followed by two within-subjects cluster tests to identify lateralised differences in the line length effect as a function of age (long vs short, separately for iii) Young and iv) Older adults) and between-subjects cluster tests to assessed the effect of age as a function of line length (Young vs Older, separately for v) long and vi) short lines).

3. Results

3.1 Visual Acuity Screening

Both age groups were highly accurate for stimulus detection, with a 96.13% overall hit rate (Figure 2). Although young adults were slightly more accurate overall (mean = 98.25%) when compared to the older group (mean = 94.01%) [t(36)=2.9, p=0.006], the majority of detection errors in the older group occurred in the extreme periphery and not in the vicinity of the landmark lines. When these peripheral trials were excluded (and only the space in which the landmark lines were positioned was analysed), both age groups performed with similar accuracy [t(36)=0.23, p=0.82]. Only 0.38% of catch trials returned false positives (young: 0.22%, older: 0.55%) [t(36)= -1.03, p=0.31].

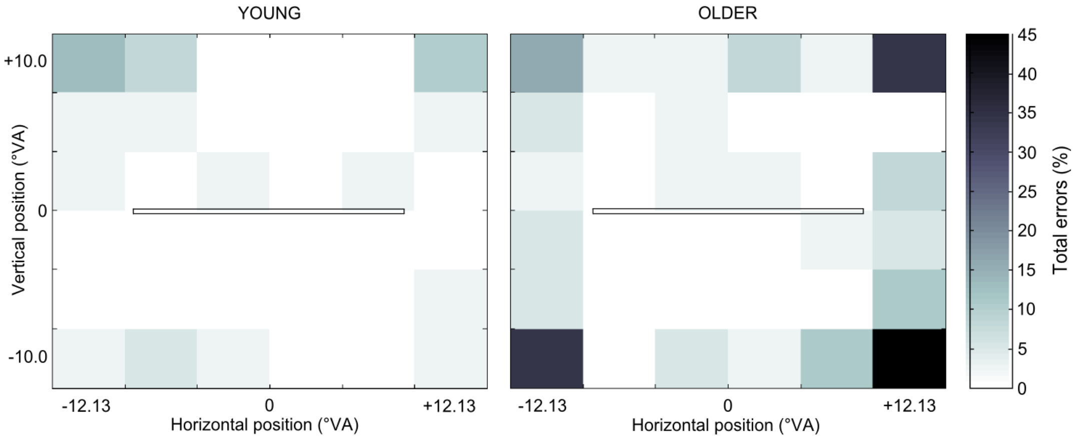

Figure 2. Heat maps of the total percentage errors for each stimulus location, as assessed by the visual screening task. Shown here in degrees of visual angle relative to the central fixation cross. The maximum display range of the landmark stimuli (long lines) is overlaid.

3.2 Behavioural Results: Landmark Task

One-sample t-tests on the PSE values for each block highlighted a significant, but transient, spatial bias in young adults towards the left side of space for long lines at the beginning of the experiment [Block 1: t(18)= -2.48, p=0.023], that is consistent with pseudoneglect. There was however no significant bias when all 5 blocks were averaged together, and no bias was evident for short lines in the younger age group in any block. Older adults displayed no group-level spatial bias for either long or short lines during any of the experimental blocks (see Figure 3a, illustrating PSE performance over all blocks). The corresponding 2 x 2 x 5 (*length x age x block*) mixed ANOVA found no significant PSE differences between young and older adults [AGE: F(1,36)=0.645, p=0.427, ηp^2 = 0.018], no differences between long and short lines [LENGTH: F(1,36)=0.676, p=0.416, ηp^2 = 0.018], no main effect of block [BLOCK: F(1,144)=0.932, p=0.477, ηp^2 = 0.025] and no interactions between factors.

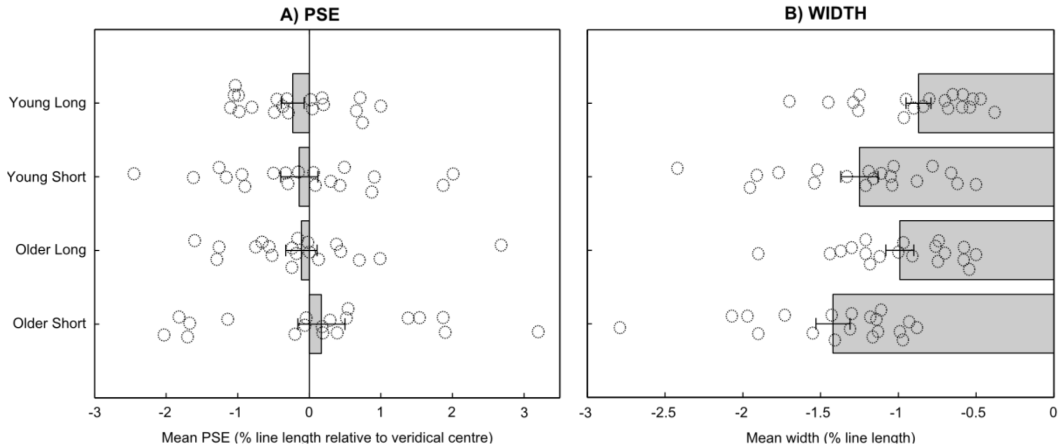

Figure 3. Group-averaged A) PSEs and B) curve widths over all blocks. Mean values for each subject are overlaid.

The psychometric function curve widths (Figure 3B) were also subjected to a 2 x 2 x 5 (*length x age x block)* mixed ANOVA, showing greater precision for long relative to short lines [LENGTH: F(1,36)=24.39, p<0.001, ηp² = 0.4]. There were no age-related differences in task precision [AGE: F(1,36)=1.56, p=0.22, ηp² = 0.042], no main effect of block [BLOCK: F(1,144)=1.27, p=0.28, ηp² = 0.034] and no significant interactions.

3.3 EEG: Line Length Effect

Cluster mass permutation tests for the main effect of line length (long minus short, data of young and older adults collapsed) revealed 2 temporally distinct positive clusters in the frontal electrodes that spanned both cerebral hemispheres (occurring between 67-304ms and 270-400ms respectively), indicating a significantly larger frontal positivity for long compared to short lines (Figure 4a). These were accompanied by 2 simultaneous negative clusters: within the posterior electrodes bilaterally at 64-241ms, and within the right posterior region at 263-400ms. The peak of the line length effect (in terms of t-value) was localised over the right parieto-occipital cortex (electrode PO4) at 139ms post-stimulus (t = -8.13). This closely replicates our research group's previous finding (Benwell et al., 2014b) where the peak line length effect was identified at 140ms over PO4 in a sample of young adults. Long lines therefore elicited a larger parieto-occipital negativity relative to short lines, which was most prominent in the right hemisphere during the P1-N1 complex. This analysis was repeated separately for the young and older groups to identify any age-related differences in the line length effect.

3.3.1 Line Length Effect: Young

Two positive clusters were identified in the bilateral frontal electrodes. The first was in a short time period between 111-172ms and the second within a longer window of 245-374ms, with the peak positivity occurring at 149ms (t = 7.1) at electrode FC1 (Figure 4b). There was a single negative cluster in the 113-178ms window over the posterior electrodes bilaterally, though with the maximum t-value (observed at 141ms) peaking over right parieto-occipital sites (electrode PO4).

3.3.2 Line Length Effect: Older

One positive cluster was identified within a sustained time period of 96-246ms, with a peak t-value at 191ms (t = 6.12) over the right temporo-parietal cortex (electrode TP9: Figure 4C). One negative cluster was identified, again within a distributed window of 75-227ms but with less apparent asymmetry (t = -5.56) occurring at 84ms over the central posterior region (CPz).

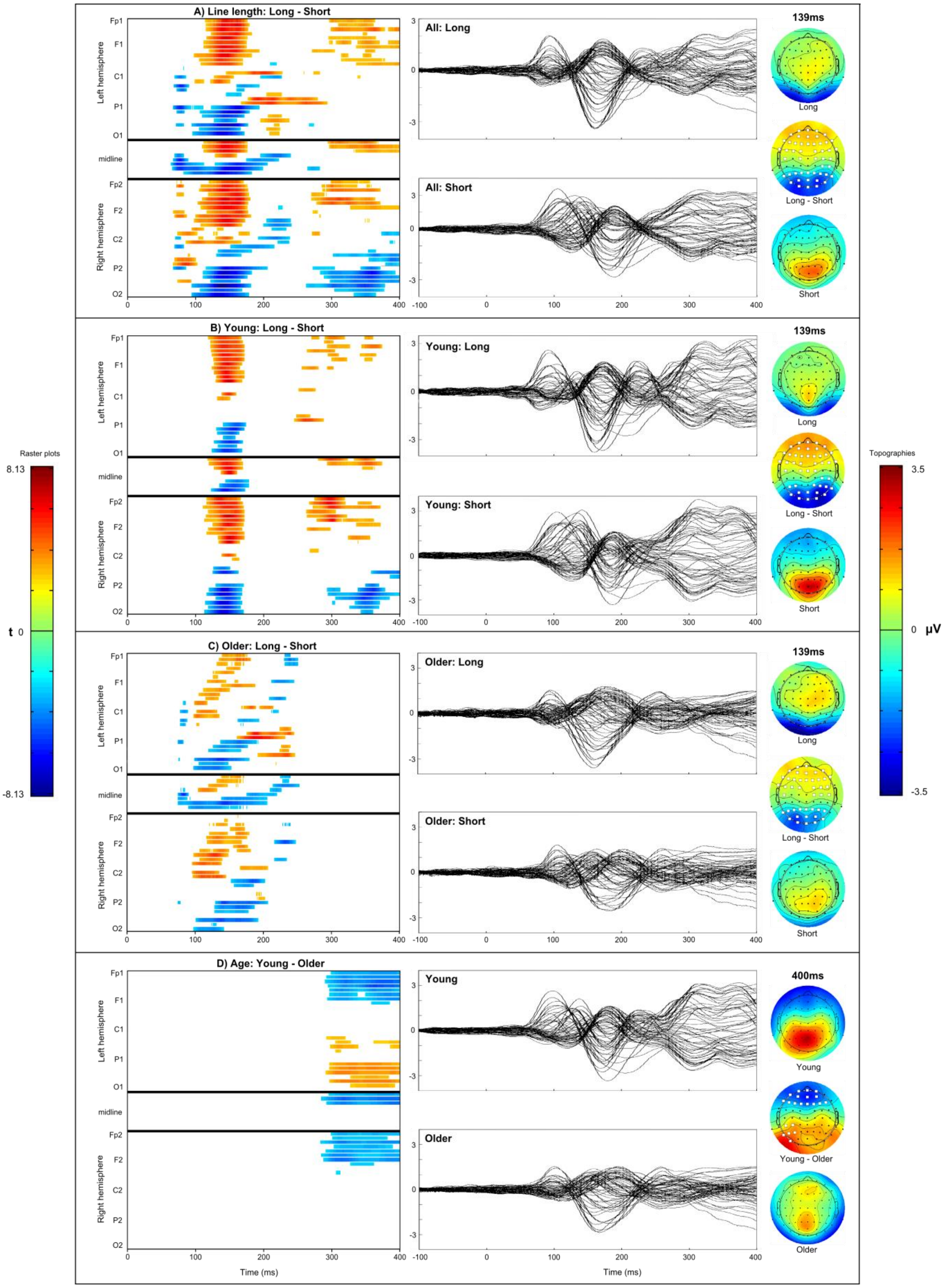

Figure 4. Raster plots highlighting the significant t-values after cluster correction. For the line length effect (long minus short lines): A) All subjects (Young and Older), B) Young adults only and C) Older adults only. Butterfly plots show the grand average voltage waveforms for the 62 channels, and the topographies for A-C show the voltage distribution at the peak long-short difference time point of 139ms. The main effect of age (young minus older) is shown in D and the topographic maps show the scalp distribution at 400ms. Significant electrodes are highlighted in white.

3.3.3 Age Main Effect: Young *vs* Older

Between-groups cluster mass permutation testing found one significant cluster in the frontal electrodes across both hemispheres corresponding with the P300 component window, where young adults had a more negative frontal amplitude compared to older participants (193-400ms, peak t = -5.11 at electrode F7 at 363ms) (Figure 4d). A second significant cluster was identified during a similar time period (180-400ms) in the posterior electrodes, mostly bilaterally represented, where the amplitude was more positive for young adults (peak t = 4.0 at electrode P7, 313ms).

3.3.4 Age-Related Changes in the P300 Component

Age differences in the topography of the P300 component have previously been well described, with many reports of the peak P300 amplitude (located at posterior electrodes in young adults), shifting to a more anterior topography in older adults (O'Connell et al., 2012; Fjell & Walhovd, 2004; Friedman, 2003; Polich 1997; West, Schwarb & Johnson, 2010). To investigate age-related changes in this dataset, the peak amplitude was first identified for each subject within two separate regions of interest (frontal and posterior) within the 280-400ms window. As per O'Connell et al, (2012) the frontal ROI comprised electrodes F3, Fz and F4 and the posterior ROI P3, Pz and P4. A 2 x 2 x 2 (length x ROI x age) ANOVA revealed a small main effect of Age [F(1,36)=4.16, p=0.049, $\eta p^2 = 0.1$] where amplitude was generally more positive in young vs older adults. The P300 was also more positive overall in the posterior ROI relative to the frontal ROI [F(1,36)=16.92, p<0.001, $\eta p^2 = 0.32$] and was more positive for short lines compared to long [Length: $F(1,36)=5.46$, $p=0.025$, $\eta p^2 = 0.13$]. Importantly, there was an Age x ROI interaction [$F(1,36)=13.31$, $p=0.001$, $\eta p^2 =0.27$], with subsequent paired t-tests revealing a large positivity in the posterior relative to frontal ROI in young adults [$t(18)= -4.6$, $p<0.001$]. There was no amplitude difference between the frontal and posterior ROIs for older adults [$t(18)= -0.44$, $p=0.67$]. Independent samples t-tests between the two age groups found significant age-related differences in both the frontal ROI [$t(36)= -2.84$, $p=0.007$] (more positive for older adults) and in the posterior ROI [$t(36)= 3.68$, $p=0.001$] (more positive for young adults).

3.4 Hemispheric Lateralisation

My main motivation for performing this study was to investigate whether any differences exist in the hemispheric contributions (i.e. right vs left hemisphere) to spatial attention judgements in young vs older adults. Given that the peak negative t-value for the line length effect (section 3.3) was located at the right parieto-occipital (PO4) electrode in young adults, but was located in the midline (CPz) for older adults, this hints that the right parietal cortex may contribute proportionally more than the left in the young adults, and that this hemispheric asymmetry may be less pronounced in the older group. In order to formally test this hypothesis, the cluster mass permutation tests were performed once again, but using the *lateralised* EEG signal derived from the RH-LH electrode pairs (see section 2.3.3 for method).

3.4.1 Identifying Hemispheric Asymmetries

One-sample cluster mass permutation tests were performed using the lateralised EEG signal, separately for the two line lengths and age groups (Figure 5). One cluster ($p=0.078$) was identified in young adults for long lines between 185-239ms, involving the electrode pairs FC1/2, FT7/8, C1/2, C3/4, C5/6, T7/8, CP1/2, CP3/4, TP7/8, indicating a small right hemisphere asymmetry for longer lines. Unexpectedly, this cluster did not involve the asymmetrical activation of any posterior parietal or occipital electrodes but did involve the more anterior, centro-parietal electrodes. There were no significantly lateralised clusters for short lines in the young group (all clusters $p>0.28$). Neither the long nor short lines were lateralised at any time point for the older group (long $p>0.16$, short $p>0.33$).

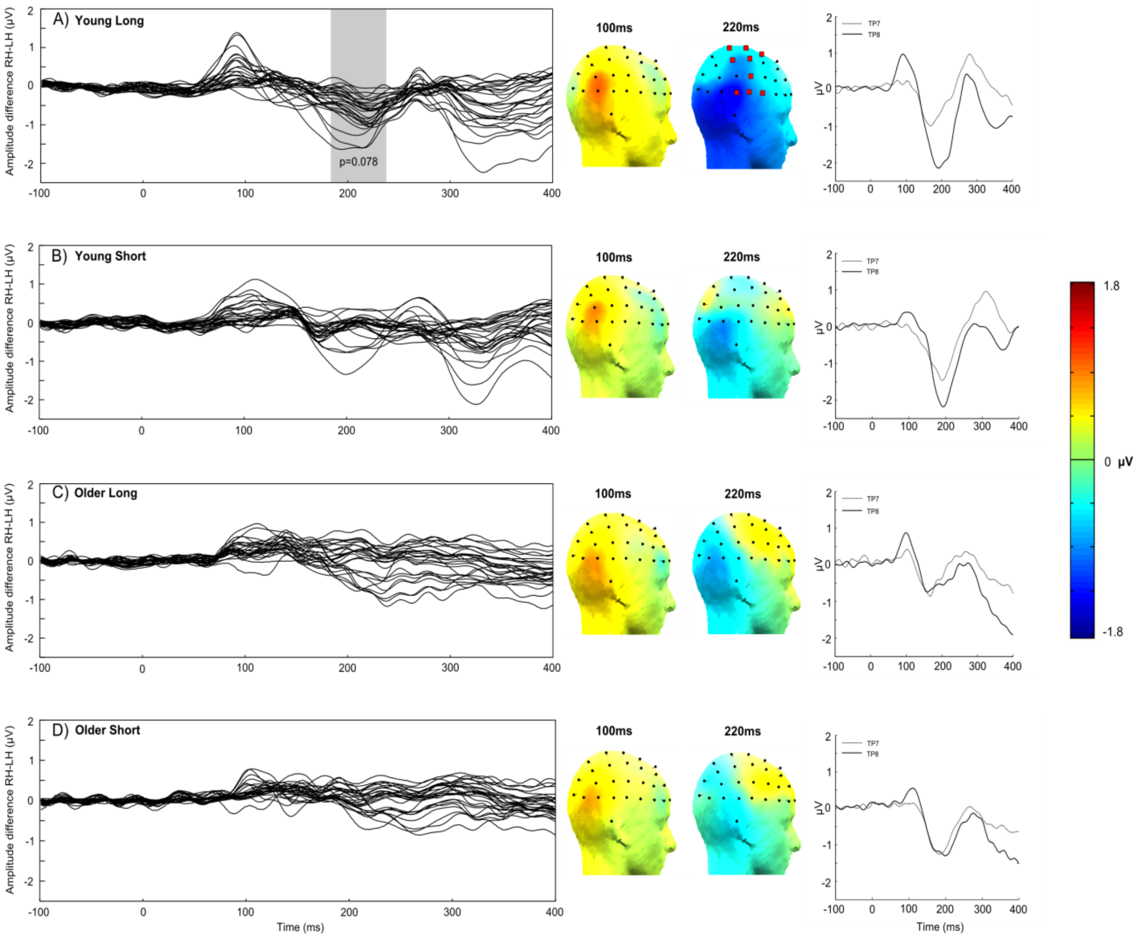

Figure 5. Butterfly plots showing the lateralised (RH-LH) grand average EEG waveforms for the 27 electrode pairs, separately for the two line lengths and age groups. The amplitude difference at each time point in the -100 to 400ms window is shown (RH electrode minus its homologous LH electrode pair). Half-scalp topographies are then plotted for the RH-LH difference at 100ms and at 220ms post-stimulus. Here, warm colours represent a larger RH vs LH amplitude during the positive-going time points (e.g. P1, ~100ms). At the negative-going time points (e.g. N1, ~200ms), cool colours represent a larger RH vs LH amplitude. Cluster analysis identified a RH lateralisation for long lines in the young group during the 185-239ms window (shaded in Fig 5a). The electrodes involved in the cluster are highlighted in red on the sagittal topography plot. The waveforms for TP7 and TP8 (identified in the cluster shown in 5a) are then shown separately in the panels on the right.

3.4.2 Hemispheric Lateralisation as a Function of Age

Within-subject cluster testing for the main effect of line length identified no lateralised cluster differences between long and short lines (all p>0.12, Figure 6a). Between-group comparisons for the main effect of age (Figure 6b) identified one lateralised cluster (p=0.051) occurring at stimulus onset (0-81ms) involving frontal, fronto-central and central electrode pairs F3/4, F5/6, F7/8, FC1/2, FC3/4, FC5/6 and C3/4. This cluster was slightly more positive in the LH vs RH for young adults during this early window. Figure 6B indicates that this effect is likely to have been present during the baseline period, although statistical tests were performed on the 0-400ms window only. The length x age interaction was then tested using between-group (young vs older) comparisons of the long-short difference wave (Figure 6c), which revealed a significant cluster during the 201-230ms window (p=0.041), involving electrode pairs F7/8, FC1/2, FC3/4, FC5/6, FT7/8, C1/2, C3/4, C5/6, T7/8, CP1/2, CP3/4 and CP5/6. There was a more pronounced right-lateralisation of the long-short difference in young adults compared to the older group at this time.

To follow up this interaction, a separate within-group cluster test for the line length effect in the young group found one cluster (p=0.0068) involving electrode pairs AF3/4, F3/4, F5/6, F7/8, FC1/2, FC3/4, FC5/6, FT7/8, C1/2, C3/4, C5/6, T7/8, CP1/2, CP3/4, CP5/6 and P1/2, indicative of right-lateralisation during the 198-237ms window (Figure 6d). It is important to note that most of the electrodes involved in this cluster of electrode asymmetry are not over posterior parietal or parieto-occipital sites (aside from the CP1/2, CP3/4, CP5/6 and P1/2 pairs), and that this cluster was identified at a later window than expected given the results of the full-scalp cluster tests (peak long-short difference at PO4, 139ms). There was no long vs short difference in the older group (Figure 6e). Finally, separate between-groups (young vs older) comparisons for long and for short lines did not reveal any significant differences (Long p>0.24, Short p>0.11).

To summarise these results, I found that long lines differentially engaged the RH more than the LH in young adults, and that this hemispheric asymmetry in favour of the RH was significantly more pronounced for long lines relative to short in the younger group. There was no lateralised activity for either line length in older adults.

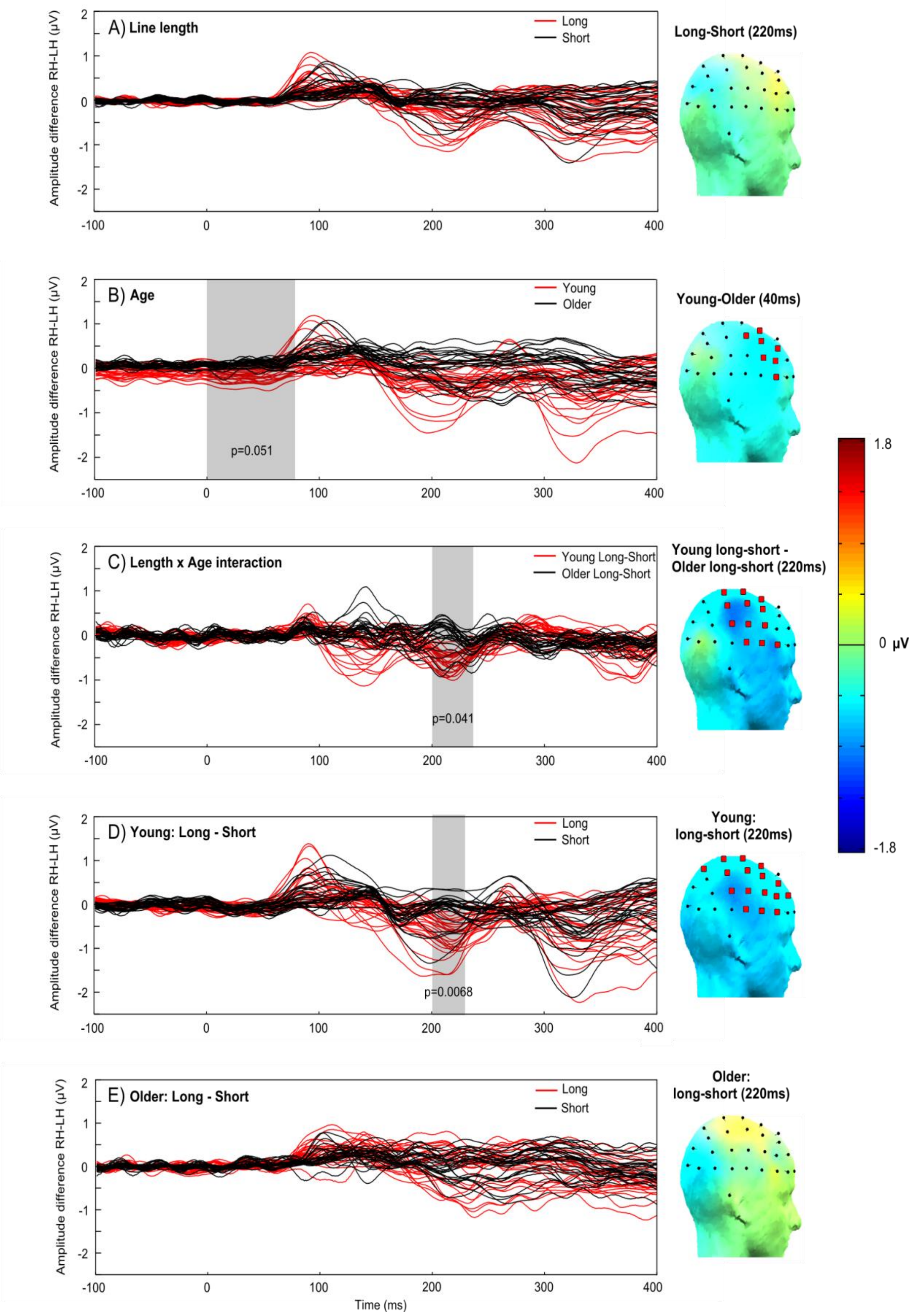

Figure 6. Butterfly plots showing the lateralised (RH-LH) grand average EEG waveforms for the 27 electrode pairs: A) the main effect of line length, B) the main effect of age and C) the line length x age interaction (young vs older comparison of the long-short difference wave). The within-group line length effect (long vs short) comparisons are then shown separately for D) Young and E) Older adults.

4. Discussion

The purpose of this study was to assess age-related changes in the cortical distribution of neural activity for spatial attention tasks. Here I present evidence of a stimulus- (i.e. line length) dependent, asymmetric engagement of the right hemisphere in young adults, accompanied by a baseline leftward spatial bias for long lines, that is representative of pseudoneglect. For the first time, I provide evidence of reduced hemispheric lateralisation in an older age group for visuospatial processing, which I hypothesise may be a contributing factor to the age-related attenuation of spatial attention biases (Benwell et al., 2014b; Failla, Sheppard & Bradshaw, 2003; Fujii et al., 1995; Fukatsu et al., 1990; Nagamatsu et al., 2009, 2011, 2013; Schmitz & Peigneux, 2011; Stam & Bakker, 1990 and Chapter Three of this thesis).

4.1 Right-Lateralisation for Spatial Attention in Young Adults

The behavioural results from the landmark task show that young adults exhibited a significant leftward behavioural bias (pseudoneglect) at baseline for long lines that was absent for short lines. This was accompanied by an asymmetry of cortical activity in the lateralised (half-scalp) EEG cluster analysis favouring the right hemisphere in the 185-239ms window which, akin to the behavioural bias, was absent for short lines. Interestingly, the electrodes involved in the asymmetric cluster were located predominately around the central gyrus, only extending posteriorly as far as the centro-parietal electrodes, but not indicating any strong posterior parietal or occipital lateralisation per se.

Although this asymmetry for long lines in the young group only showed a trend (p=0.078) in the one-sample t-test analysis compared to zero (i.e. a null hypothesis of no significant lateralisation), there was a clear lateralisation difference when long and short lines were compared directly. Long lines elicited a stronger right-lateralisation relative to short lines in the young group. Similar to the one-sample cluster analysis, this long-short difference also mainly involved a lateralisation of the central and centro-parietal electrodes rather than the posterior parietal and occipital channels as predicted. These results were somewhat unexpected in terms of both the topography and the latency of the lateralised line length effect, given that the results of the full-scalp cluster analysis identified the maximum long vs short line difference in the young group to be earlier (at 141ms, during the P1-N1 complex) and distributed more posteriorly over the right parieto-occipital cortex (PO4), although electrodes of both hemispheres tended to show responses at this time point. Although I have successfully replicated the line length effect from our previous study (Benwell et al., 2014b), here I show that the peak *lateralisation* difference for long vs short lines in young adults actually occurs slightly later (198-237ms) and involves the asymmetrical activation of more anterior electrodes. Collectively, the data suggests a two stage time course of the line length effect during landmark task performance which differs in terms of topography and lateralization (posterior, less lateralized followed by more central, right lateralized).

It is tempting to compare this time course to the time course of line bisection judgment identified by Foxe, McCourt & Javitt (2003), with the caveat that these are based on different comparisons to isolate activity associated with spatial bias in the landmark task (long vs short lines in this case, landmark task vs non-spatial control task in Foxe et al.). The later window of lateralised activity here does align with the second distinct topographic phase of activity occurring between 190-240ms of Foxe et al. This phase involved the emergence of a larger right lateral parieto-occipital and central parietal negativity for the spatial judgement task relative to the non-spatial control. However, this distribution was more posterior than the lateralised cluster observed for long lines compared to short here. Moreover, I found no clusters of asymmetry corresponding to the first phase window (170-190ms) nor their third phase (240-400ms), even though their stimuli were almost identically proportioned with respect to my long landmark task lines. These results also agree with Longo et al., (2015) who found no lateralisation in an early window (170-190ms) but a significant right-lateralisation of activity for the landmark task compared to a control task. My data therefore add to these previous studies to now show that this later latency window indexes the largest clustered lateralisation differences between long and short landmark lines for young adults.

4.2 Age-Related Reduction of Hemispheric Lateralisation

As expected, the lack of hemispheric lateralisation in older adults was accompanied by a lack of behavioural bias for both long and short lines in the landmark task. Although I did find long vs short differences in the full-scalp cluster analysis for older adults, the peak t-value was located over the midline (Cz). Corroborating this, the long vs short cluster analysis performed on the *lateralised* EEG signal found no asymmetric RH vs LH activity differences for either long or short lines in this older age group. I tentatively propose that this reduced EEG lateralisation may correspond with the lack of behavioural bias for older adults observed here. I did not find any significant age differences within this ~200ms post-stimulus window when the young and older group were directly compared against each other - for either long or short lines - but this could be due to a lack of sensitivity of the cluster analysis method in detecting small, between-group differences that are localised to few electrodes or time points (Groppe, Urbach & Kutas, 2011a,b).

I did however find evidence of an interaction between age and line length for the lateralised EEG signal in the 201-230ms window. Specifically, this shows a complex, stimulus-dependent response where young adults exhibit a more pronounced long-short differentiation in the right-hemisphere compared to the older group. I therefore conclude that cognitive aging is indeed accompanied by a significant reduction of dynamic RH engagement for spatial attention, although this is only apparent when taking into account the relative difference between stimulus characteristics, in this case line length.

4.3 Age-Related Reduction of the Parietal P300

The largest between-group difference was found during the P300 component time window (280-400ms post-stimulus). This was temporally distinct from the main line length effect which occurred earlier at 139ms. In terms of topography, I found a large positivity with a parietal distribution for young adults (with a corresponding frontal negativity) but there was a significant reduction of both the parietal positivity and the frontal negativity for the older group. Indeed, the topography plot for the older group (Figure 4d) appears to show a small *positivity* at the anterior electrodes, which could corroborate previous reports of a posterior-anterior shift in P300 topography for older adults (Fjell & Walhovd, 2004; Friedman, 2003; O'Connell et al., 2012; Polich 1997; West, Schwarb & Johnson, 2010).

Given that this P300 shift has been observed across a range of different tasks (Kuba et al., 2012; Pfefferbaum et al., 1984; van Dinteren et al., 2014; Walhovd & Fjell, 2003) and that it has been variously associated with decision making, context-updating and stimulus processing (see van Dinteren et al., 2014 for review), this finding may reflect age-related changes for a non-spatial aspect of the landmark task in this study. However the functional significance of both the amplitude reduction and topographic change of this the P300 component is still under debate, particularly in relation to whether the recruitment of anterior regions may help to facilitate behavioural performance in older adults, similar to the CRUNCH model (Davis et al., 2008; Grady, 2012). It is worth noting that compared to the young adults, the older group performed the task with no reduction in precision, and therefore this shift could potentially represent a mechanism whereby their performance was maintained.

4.4 Models of Neurocognitive Aging

How then might models of cognitive aging explain this change in hemispheric lateralisation as individuals get older? Firstly, I found no strong evidence for the CRUNCH model of a compensatory recruitment of additional neural circuits (Reuter-Lorenz & Cappell, 2008) that might explain the previous behavioural findings of age-related rightward shifts of lateralised spatial attention bias. However I did find tentative evidence of later additional anterior recruitment as indexed by the P300 component described above. These results indicate that age-related neuro-plastic changes for spatial attention biases are likely to be confined to more subtle, stimulus-driven changes in activation within the left and right hemispheres. Secondly, I expected to observe a *rightward* behavioural bias for short lines in the older group, as per Benwell et al., (2014b), but bias was primarily lacking for this group, rather than shifted entirely into the right hemispace. A clear shift into right space, accompanied by an asymmetry of cortical activity favouring the *left* hemisphere for short lines in this group, could conceivably have occurred in case of a strong right hemispheric change, rendering activity *lower* in the right vs left parietal cortex, and thus providing evidence for the right hemi-aging model. However, this model can also accommodate the scenario observed here of an eliminated (rather than rightward) bias, in which the RH has indeed declined in function but is not (yet) less functional than the LH. I cannot therefore exclude that these findings may be explained, at least in part, by an account of premature right hemisphere aging.

Overall, I conclude that the results align most closely with the hemispheric asymmetry reduction (HAROLD) model of cognitive aging, given that I found both a lack in behavioural bias and a lack of cortical lateralisation in the older group. To date, the bulk of evidence supporting the HAROLD model has been gained from memory studies, which report bilateral activity predominately within the frontal cortex in cognitive aging (Cabeza, 2002). Here I present evidence of a posterior asymmetry reduction, and in doing so add to a handful of studies which find HAROLD-compatible effects for tasks involving posterior regions (e.g. Berlingeri et al., 2010; Benwell et al., 2014a; Collins & Mohr, 2013). Further, as it stands the HAROLD model asserts that asymmetry reduction occurs as a *compensatory mechanism* whose purpose is to sustain cognitive performance within the aging brain in response to increased task difficulty and/or lower performance. This could explain the finding by Brooks et al., (2016), who found maintained pseudoneglect in older adults for visual, tactile and number line bisection. In those versions, without titration or time limit, the tasks are likely to have been less cognitively challenging, and therefore did not elicit the bilateral engagement seen in more difficult versions of the task. In support of this, highly-performing older individuals are known to exhibit a more extensive bilateral frontal recruitment in memory tasks compared to their lower-performing counterparts (Berlingeri et al. 2010; Cabeza, 2002; Cabeza et al., 1997, 2002; Huang et al., 2012; Reuter-Lorenz et al., 2000). I show here in the analysis of psychometric curve widths that, contrary to our previous study (Benwell et al., 2014a), older adults did *not* perform the landmark task with any less precision compared to the young adults for either line length. I cannot exclude the possibility that our sample of older adults simply represents a more 'highly functioning' subset of the general older population in terms of task performance, and that the neural changes observed here are unrelated to performance requirements. Alternatively it may be the case that their good performance was a direct result of this more bihemispheric recruitment, reflecting the compensatory mechanisms specified by the HAROLD model. In either case, these results indicate that models of neurocognitive aging remain under-specified and are as yet unable to account fully for asymmetry reduction within the spatial attention domain.

4.5 Methodological Considerations

The lack of strong group-level spatial biases on the behavioural level in the current study may be explained by methodological factors. Firstly, the leftward pseudoneglect bias in young adults for long lines was transient and limited only to the baseline experimental block. Spatial bias tends to drift rightward as time-on-task increases, probably as a consequence of depleted right ventral network resources driving a reduction in general arousal (Benwell et al., 2013a,b; Bellgrove et al., 2004; Dodds et al., 2008; Dufour et al., 2007; Manly et al., 2005; Newman, O'Connell & Bellgrove, 2013). I hypothesise that this time-on-task effect might have been hastened by a prolonged EEG setup period, and by participants undergoing the visual acuity screening. As a result, I may have observed both a less pronounced pseudoneglect bias, and thus a weaker lateralisation of EEG signals given that the analysis was performed on the pooled trials from all 5 experimental blocks.

The fixed viewing distance of 0.8m (due to laboratory restrictions) may also have contributed to this reduced bias. The magnitude of the leftward pseudoneglect bias tends to increase as stimuli are presented in close peri-personal, rather than extra-personal, space (Longo et al., 2015; Longo & Lourenco, 2006, 2007, 2010; Lourenco & Longo, 2009) and indeed Longo et al., (2015) report a larger asymmetric engagement of the right (vs left) parietal cortex for peri- vs extra-personal landmark task judgements. However we have reported both pseudoneglect and a right parieto-occipital asymmetry at a viewing distance of 100cm previously (Benwell et al., 2014b) and therefore this is unlikely to be the sole contributing factor to this reduced spatial bias.

In conclusion, I report an age-related reduction of right hemispheric control for spatial attention in older adults. This effect was stimulus-driven, with a strong differentiation of long and short lines in the right hemisphere observed in young adults, which was absent in the older group. Although the results most closely align with the HAROLD model of neurocognitive aging, current models are underspecified in fully accounting for our findings. Based on these observations, I propose that aging models need to incorporate stimulus-driven asymmetry reductions and also a reduced lateralisation within the posterior, in addition to the frontal, cortex.

Chapter Five

General Discussion

I had two main objectives for this thesis: firstly to map the behavioural and neural correlates of spatial attention asymmetries in young and older adults, and secondly to modulate these asymmetries, with an aim to move towards a reliable method of maintaining cognitive performance in older age. To achieve this, I carried out three experiments involving a combination of behavioural methodology, non-invasive brain stimulation and electroencephalography.

In Chapter Two I found that five commonly-used spatial attention tasks exhibit a strong test-retest reliability across two testing sessions on different days, indicating that each task measures a specific and stable property of the spatial attention network. However, in line with previous findings, the tasks did not correlate well with each other, suggesting that each task involved partially unique patterns of activation within the spatial attention network. I argue that pseudoneglect is differentially elicited by the various demands of each task, and that we should be cautious in directly translating the results of neuroimaging and non-invasive brain stimulation studies when different tasks are used.

In Chapter Three I found that there were no overall behavioural benefits of either right or left parietal anodal tDCS during a lateralised visual detection task, and there were no differences in response between young and older adults. However, the participants' baseline visual detection sensitivity did affect outcome: 'good' performers maintained their sensitivity to detecting stimuli across both visual fields during right atDCS, whereas 'poor' performers were impaired in both visual fields during left atDCS. The ability of tDCS to modulate neuronal activity, and therefore behaviour, is at least partly dependent on a complex set of experimental parameters and individual differences, which at present remain underspecified.

Finally in Chapter Four, using a novel method of lateralised EEG cluster analysis, I found that young adults exhibited a period of right-lateralised neural activity during the landmark task when long lines were presented (198-237ms post-stimulus), but short lines did not. No lateralisation was present for older adults for either long or short landmark lines. I argue that this reflects the first neuroimaging evidence of an age-related reduction of hemispheric lateralisation for spatial attention, which may underlie the rightward behavioural shift that is often observed in this group.

I will now address some of the wider theoretical implications of these Chapters, together with a discussion of potential future avenues of enquiry that might answer the questions that have been generated by this thesis.

Consistency of Pseudoneglect in Young Adults

Chapters Two, Three and Four are all remarkably consistent in corroborating the previous pseudoneglect literature, showing a stable, group-level leftward behavioural bias in young adults (Bowers & Heilman, 1980). The leftward bias was present on both testing days for the landmark and line bisection tasks in Chapter Two (*task-correlations*). There was a leftward bias for the long landmark lines at baseline in Chapter Four (*EEG*), and this was associated with EEG evidence of a right-hemispheric lateralisation of neural activity. In Chapter Three (*tDCS*), young adults were also more sensitive in detecting stimuli presented on the left during a *titrated* version of the lateralised visual detection task (although intriguingly, they did not show a bias for the *non-titrated* task in Chapter Two), and this was consistent across all three testing days. Taken together, all three chapters add to the previous behavioural and neuroimaging literature which implicates the right cerebral hemisphere in the genesis of spatial attention asymmetries, particularly in young adults (Bowers & Heilman, 1980; Corbetta & Shulman, 2002, 2011; Kinsbourne, 1970, 1977, 1994; Mesulam, 1999).

The Importance of Task Choice

Although I observed a leftward pseudoneglect bias in three different spatial attention tasks in Chapter Two, I found that the spatial attention asymmetries did not correlate *between* the different tasks, suggesting that they each tested slightly different aspects of spatial attention. I found that the landmark task and line bisection both produced a consistent and significant leftward bias, but the non-titrated lateralised visual detection task did not correlate with any other task in Chapter Two. Furthermore, the lateralised visual detection task loaded independently onto a single factor in the principal component analysis, indicating that it reflected unique task demands. I nevertheless chose to use a titrated version of the lateralised visual detection task in Chapter Three, to build on previous TMS and tDCS studies (Dambeck et al., 2006; Hilgetag, Théoret & Pascual-Leone, 2001; Thut et al., 2006) and also because the task is a relatively simple test of the allocation of spatial attention across space. However, this choice of ‘low-level’ visual detection task may have led to a lower engagement of the parietal cortex which was the target site for brain stimulation. Given the strong neuroimaging evidence of right dorsal frontoparietal attention network activation for the line bisection and landmark tasks (Marshall et al., 1997; Fink et al., 2000b; Çiçek, Deouell & Knight, 2009), and the consistent and significant leftward biases generated in these tasks in Chapter Two, it is possible that the task was non-optimal for reflecting shifts of spatial attention induced by parietal tDCS. Indeed, I concluded Chapter Two by urging caution in making generalised statements about spatial attention asymmetries in light of data that is gained from just one task, and using the landmark task in Chapter Three would have kept the tasks consistent throughout this thesis.

Age-Related Changes in Spatial Attention

Also in line with previous literature (Barrett & Craver-Lemley, 2008; Benwell et al., 2014a; Failla, Sheppard & Bradshaw, 2003; Fujii et al., 1995; Fukatsu et al., 1990; Nagamatsu et al., 2009, 2011, 2013; Schmitz & Peigneux, 2011; Stam & Bakker, 1990), older adults consistently *lacked* a spatial attention asymmetry, and this was observed in both the titrated lateralised visual detection (Chapter Three) and landmark tasks (Chapter Four). This reduced behavioural asymmetry was associated with an absence of lateralised EEG activity for both long and short landmark lines. Therefore, I conclude that Chapter Four suggests an affirmative answer to the question I posed in the introduction to this thesis: ‘does the aging brain undergo specific neuroanatomical changes that might cause the observed rightward shift in spatial bias?’. However, although Chapter Four shows an *association* between the behavioural and neurophysiological asymmetry reduction, future studies must be undertaken to determine whether the two observations are *causally* related.

In addition, it is clear from the behavioural results of Chapters Three and Four that, although there is a group-level rightward shift in bias with age, some older adults *do* retain a leftward bias. Indeed, some exhibit a more pronounced leftward bias than many of the young adults, and further show no decrement in their overall task precision (as indexed by both *d′* (Chapter Three) and curve width (Chapter Four) measurements). A question that remains is thus: how does a loss of spatial attention asymmetry affect older adults functionally on a day-to-day basis? Aside from the evidence uncovered by Nagamatsu et al., (2009), who found that older adults with a specific left hemispace visual processing deficit have a higher risk of falls, there is a distinct lack of evidence that a rightward shift exerts any negative influence on, for example spatial navigation in complex environments, safe driving (i.e. maintaining lane position), and general quality of life in older age. Put simply, should we be *concerned* if an older adult begins to exhibit a rightward shift of spatial bias, or is does it merely represent a harmless by-product of the healthy aging brain? To answer this, it would be valuable to assess whether these lab-based measures of spatial attention asymmetry correlate with performance on more ecologically valid tasks, such as driving, and navigating within a complex environment. It is also important to repeat the intra- and inter-task correlation experiment reported in Chapter Two in a large sample of older adults to quantify the normal range of spatial asymmetries in healthy aging. Together with administering a more detailed assessment of general cognitive performance (e.g. the Mini Mental State Exam) and collecting demographic information (e.g. educational background and quality of life assessment), this would enable us to link these changes in spatial attention bias to functional performance.

Finally, as discussed in Chapter Four and briefly in Chapter Three, it is unfortunate that these findings lack the specificity to allow me to formally assess whether the current models of cognitive aging (i.e. the HAROLD, CRUNCH and right hemi-aging models) are applicable within the spatial attention domain. In Chapter Four I chose to use electroencephalography to assess age-related differences in the *line length effect* (long *vs* short lines) previously described by our research group (Benwell et al., 2014b). Although EEG enables a precise assessment of the *timing* of stimulus-evoked neural activity, it is less well suited to *localising* the neuroanatomical activity within the brain. Thus, the difference in right-lateralised activity in response to long lines vs short identified for young adults in Chapter Four, was spatially distributed across a cluster of sixteen scalp electrodes, making it difficult to assess precisely where the differences occurred. It would be very useful to repeat the experiment using a different neuroimaging method, such as fMRI (or integrated EEG/fMRI), which would likely enable a more precise examination of the locus of these age-related changes in neural activity and, in turn, facilitate a more precise assessment of the different models of cognitive aging. This is an important question, because the models can potentially provide a framework for mapping the neural changes that take place in older age more generally. This information might then be used to develop interventions to prevent and/or rehabilitate age-related cognitive decline, for example with non-invasive brain stimulation. Alternatively, if we find that none of the models apply to spatial attention, then we must question why (and precisely how) spatial attention is anomalous in this respect, compared to other cognitive domains such as episodic and working memory.

Baseline Performance, Task Difficulty and Sustained Attention

Although this thesis provides good evidence for age differences in spatial attention asymmetries, there are likely to be a highly complex set of additional factors that contribute to the genesis of, and changes in, spatial bias. These include fluctuations in sustained attention throughout the course of an experiment, coupled with inter-individual differences in functional ability and baseline performance, with the additional influence of the cognitive load exerted by the choice of spatial attention task. These issues are highly interlinked and are, at present, underspecified with respect to precisely how they each might modulate spatial attention asymmetries. The role of baseline performance and task difficulty are paramount in the CRUNCH and HAROLD models: both models predict that difficult tasks cause a depletion of cognitive resources, which then forms the catalyst for the recruitment of alternative neural populations. In general, older adults have a lower baseline performance level for visual attention tasks (Madden, 2007; Chapter Three), they find the tasks more difficult to perform (Benwell et al., 2014a), their performance is more negatively affected by increased task difficulty (Swan et al., 2015) and they may experience a greater degree of fatigue over the course of an experiment.

Our research group, and others, have previously reported a rightward shift of spatial attention in young adults, that is driven by reduced arousal

(Benwell et al., 2013a,b; Dufour, Touzalin & Candas, 2007; Bellgrove et al., 2004; Dodds et al., 2008; Fimm, Wilmes & Spijkers, 2006; Manly et al. 2005; Matthias et al., 2010; Newman, O'Connell & Bellgrove, 2013; Perez, Garcia & Valdes-Sosa, 2008; Perez et al., 2009). This is attributed to a depletion of right-hemisphere attention resources caused by increased time-on-task, which then disrupts the balance of interhemispheric activity in favour of the left hemisphere, thus driving the rightward shift of spatial bias. For older adults, who already have a reduced neural and behavioural asymmetry, does a further depletion of right hemisphere resources via reduced sustained attention, influence spatial biases? Are older adults more negatively affected by extended time-on-task compared to young adults? Might older adults experience greater fluctuations in sustained attention over the course of an experiment? Could these effects be masked by collapsing each 5-6 minute experimental block together, as I did in Chapter Four? For example, young adults were consistently biased to the left across multiple testing sessions in both Chapter Two and Chapter Three, but the bias in older adults was less stable across days (Chapter Three), hinting that older adults might be more susceptible to the influence of these additional variables. It would be useful to perform a follow-up experiment involving single trial analysis to assess these subtle trial-by-trial fluctuations in alertness and task engagement.

Given that these issues are all of central importance, how did I attempt to control these variables in the three studies presented in this thesis? In Chapter Three I controlled the *difficulty* of the lateralised visual detection task by titrating stimulus size according to each participant's ability (i.e. everyone received stimuli that they could perceive with approximately 50% accuracy). Yet, there were clear differences in response to tDCS depending on *performance* (i.e. whether the participant reached this 50% threshold with larger or smaller stimuli). This concurs with our previous tDCS study which uncovered an interaction between current strength and performance, with 1mA tDCS inducing a rightward shift on the landmark task in good performers, and 2mA inducing the same rightward shift in poor performers (Benwell, Learmonth et al., 2015). Thus, it is likely that the neural substrates differ for spatial attention in good and poor performers: either different neural populations are being utilised, different strategies for undertaking the task are used, and/or neurons are closer to the action potential threshold in those with high ability.

Contrast this with Chapter Four, in which I chose *not* to titrate the landmark task difficulty across participants. Interestingly, and contrary to Benwell et al., (2014a), I found that older adults did in fact not perform with any less precision (as indexed by psychometric function curve width) compared to young adults. I also failed to replicate the expected shift of spatial bias into the right hemispace with short landmark lines. Due to the differences between the two studies in both behavioural asymmetry and task precision, the role of task difficulty, and performance also remain unaccounted for in this Chapter. Did the older adults in Chapter Four actively generate this high task precision by recruiting bilateral neural resources? Alternatively, were they simply a higher-functioning sample of older adults and their high precision was unrelated to the bilateral activity observed on EEG? These questions remain open at present. To test this more thoroughly, an interesting future line of enquiry would be to replicate the EEG experiment performed in Chapter Four, but instead of presenting two different line lengths (which are perceptually very different), to instead present the same line length but with different levels of difficulty (e.g. one condition where there are relatively obvious size differences between the left and right sides of the landmark line, and another where the left vs right judgements are more difficult). This modification would allow me to disentangle the effects of line length and task difficulty in older adults, and observe how task difficulty impacts upon the spatial attention networks.

Implications for Non-Invasive Brain Stimulation

Finally, the results of Chapter Three are consistent with a growing body of literature which finds no overall effect of transcranial direct current stimulation, but instead highlights that specific characteristics of the participants tested, determine response (Antal et al., 2007; Benwell, Learmonth et al., 2015; Berryhill & Jones, 2012; Bortoletto et al., 2015; Dockery et al., 2009; Li, Uehara & Hanakawa, 2015; Tseng et al., 2012).

The results of Chapter Three diverged quite profoundly from the results of Sparing et al., (2009), on whose study I based the experiment. Both studies utilised a titrated lateralised visual detection task and applied 1mA tDCS to the left and right parietal cortices. Although I chose to use a slightly different return electrode placement, I expected to replicate the improvement of spatial attention in the contralateral visual field, at least in the young adults. To find instead that anodal stimulation was in fact *detrimental,* across both visual fields, when applied to the left hemisphere, was both surprising and concerning, particularly given that the this effect was observed in the group of individuals who would likely have drawn the greatest benefit from a boost in their detection sensitivity (i.e. those with poor baseline performance). These results bring to light just how little we still understand about the specific mechanism of action in non-invasive brain stimulation, and how this technique is likely to be influenced by a large range of modulatory variables.

With respect to the experimental methodology of Chapter Three, the division of participants into two performance groups (good *vs* poor) was, admittedly, performed as a post-hoc consideration, due to the overall lack of tDCS effect. In doing so, it highlighted that the original hypotheses may have been overly simplistic. Specifically, that the aim of eliciting a unilateral pattern of ‘youth-like’ right parietal cortex activity in older adults might, in fact, be counterproductive, given our lack of understanding about the influence of baseline performance, task difficulty, sustained attention and aging on the spatial attention networks, as per the discussion above. Taken together with the results of Chapter Four, it is likely that older adults *require* a different pattern of activity, compared to young adults, to complete these spatial attention tasks. If this is the case, then the one-size-fits-all approach to the application of non-invasive brain stimulation, which is found overwhelmingly in the current tDCS literature, is greatly lacking in individual specificity.

I posed the question in the introduction of this thesis: ‘is it ever possible to harness tDCS to improve the lives of patients with cognitive disorders or in the course of cognitive aging?’. At present, consistent with the guidelines endorsed by National Institute for Clinical Excellence, there are to my knowledge no tDCS protocols which elicit reliable effects that might recommend it for use in clinical populations, such as patients with hemispatial neglect, nor in cognitive aging. In general, tDCS studies suffer from low sample sizes, small effect sizes and heterogeneity of stimulation parameters. Thus, although meta-analyses have been performed (Horvath, Carter & Forte, 2014; Horvath, Forte & Carter, 2015a, 2015b; Jacobson, Koslowski & Lavidor, 2012; Summers, Kang & Caraugh, 2016), these factors make comparing the effects in the wider literature extremely difficult. In my opinion, tDCS researchers must now work towards performing robust, large-scale replication studies to confirm that these identified grouping characteristics (such as baseline performance, identified in Chapter Three) are indeed a reliable determinant of response. In parallel, It is possible that a widespread adoption of more targeted stimulation methods, such as HD-tDCS aided by MRI-guided neuronavigation to locate the cortical areas of interest, might improve the future prospects for non-invasive brain stimulation. Given that there remains a possibility that the technique may be effective for some individuals and not others, I conclude that it remains worthwhile for researchers to try to better understand precisely how tDCS interacts with different patterns of neural activity to elicit these beneficial effects.

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