Pseudoneglect and visual attention networks

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A thesis submitted in fulfilment of the requirements for the
Degree of Doctor of Philosophy

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September, 2015

Abstract

Pseudoneglect represents the tendency for healthy individuals to show a slight but consistent bias in favour of stimuli appearing in the left visual field. The bias is often measured using variants of the line bisection task. An accurate model of the functional architecture of the visuospatial attention system must account for this widely observed phenomenon, as well as for modulation of the direction and magnitude of the bias within individuals by a variety of factors relating to the state of the participant and/or stimulus characteristics. To date, the neural correlates of pseudoneglect remain relatively unmapped. In the current thesis, I employed a combination of psychophysical measurements, electroencephalography (EEG) recording and transcranial direct current stimulation (tDCS) in an attempt to probe the neural generator(s) of pseudoneglect. In particular, I wished to utilise and investigate some of the factors known to modulate the bias (including age, time-on-task and the length of the to-be-bisected line) in order to identify neural processes and activity that are necessary and sufficient for the lateralized bias to arise.

Across four experiments utilising a computerized version of a perceptual line bisection task, pseudoneglect was consistently observed at baseline in healthy young participants. However, decreased line length (experiments 1, 2 & 3), time-on-task (experiment 1) and healthy aging (experiment 3) were all found to modulate the bias. Specifically, all three modulations induced a rightward shift in subjective midpoint estimation. Additionally, the line length and time-on-task effects (experiment 1) and the line length and aging effects (experiment 3) were found to have additive relationships. In experiment 2, EEG measurements revealed the line length effect to be reflected in neural activity 100 – 200ms post-stimulus onset over source estimated posterior regions of the right hemisphere (RH: temporo-parietal junction (TPJ)). Long lines induced a hemispheric asymmetry in processing (in favour of the RH) during this period that was absent in short lines. In experiment 4, bi-parietal tDCS (Left Anodal/Right Cathodal) induced a polarity-specific rightward shift in bias, highlighting the crucial role played by parietal cortex in the genesis of pseudoneglect. The opposite polarity (Left Cathodal/Right Anodal) did not induce a change in bias.

The combined results from the four experiments of the current thesis provide converging evidence as to the crucial role played by the RH in the genesis of pseudoneglect and in the processing of visual input more generally. The reduction in pseudoneglect with decreased line length, increased time-on-task and healthy aging may be explained by a reduction in RH function, and hence contribution to task processing, induced by each of these modulations. I discuss how behavioural and neuroimaging studies of pseudoneglect (and its various modulators) can provide empirical data upon which accurate formal models of visuospatial attention networks may be based and further tested.

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

Christopher Stephen Yates Benwell

Acknowledgements

I would like to thank Professor Gregor Thut and Dr Monika Harvey for accepting me as their PhD student and for their excellent and invaluable supervision of the work throughout. I am very grateful to the Economic and Social Resarch Council (ESRC) for funding my PhD (ES/I02395X/1).

Thank you to my family and friends for their support throughout my PhD. In particular, I thank my Mum for the invaluable knowledge and support she imparted to me based on her experiences in academia. I will be happy if I come close to contributing as much as she did.

Thank you to Merle-Marie Ahrens for her patience and advice. I would also like to thank David Fleming for his help with data collection and discussions of analysis techniques and more. Thank you also to Gemma Learmonth, Ashley Grant, Stephanie Gardner and Maria Smithers for their help with data collection. I am grateful to have met and enjoyed the company of many friends throughout my PhD (Merle, Gemma, David, Oli, Niamh, Stephanie, Magda, Marc, Flor, Carl, Roberto, Mimma).

Previous published dissemination:

The findings reported in Chapter 1 have been published in:

Benwell, C. S. Y., Harvey, M., Gardner, S., & Thut, G. (2013a). Stimulus- and state-dependence of systematic bias in spatial attention: additive effects of stimulus-size and time-on-task. *Cortex*, 49(3), 827–836.

The findings reported in Chapter 2 have been published in:

Benwell, C. S. Y., Harvey, M., & Thut, G. (2014). On the neural origin of pseudoneglect: EEG-correlates of shifts in line bisection performance with manipulation of line length. *Neuroimage*, 86, 370-380.

The findings reported in Chapter 3 have been published in:

Benwell, C. S. Y, Thut, G., Grant, A., & Harvey, M. (2014). A rightward shift in the visuospatial attention vector with healthy aging. *Frontiers in Aging Neuroscience*, 6:113.

The findings reported in Chapter 4 have been published in:

Benwell, C. S. Y, Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralised attention bias. *Cortex*, 69, 152-165.

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General Discussion

General Introduction

The attention systems of the human brain serve to “filter” behaviourally relevant from irrelevant information based on current goals. They are crucial for perception and everyday functioning given that deficits lead to severe perceptual and behavioural impairments, as seen for instance in hemispatial neglect (Karnath et al., 2004; Vallar & Perani, 1986; Mort et al., 2003; Vallar, 1998; Harvey & Rossit., 2012; Driver & Mattingley, 1998). Several of these attentional systems have been identified anatomically and studied as to their involvement in regulating perception.

Based on lesion studies, two early prominent models of visuospatial attention processing have been the ‘right hemispheric dominance’ theory (RHDT: Heilman & Van den Abell, 1980; Mesulam, 1981) and the ‘interhemispheric competition’ theory (ICT: Kinsbourne, 1970; 1977; 1987) which differentially implicate left versus right hemispheric processes in determining spatial attention biases. The RHDT postulates that the left hemisphere (LH) only codes for input from the right side of egocentric space whereas the right hemisphere (RH) codes for input from both the left and right sides of egocentric space (Heilman & Van den Abell, 1980; Mesulam, 1981; Dietz et al., 2014). The ICT postulates that homologous regions across both cerebral hemispheres operate as opponent processors through reciprocal inhibition and hence asymmetrical activation biases attention in the direction contralateral to the preferentially activated hemisphere (Kinsbourne, 1970; 1977; Reuter-Lorenz et al., 1990; Bultitude & Aimola-Davies, 2006; Szczepanski & Kastner, 2013). Based on conflicting data from transcranial magnetic stimulation (TMS) experiments, Duecker & Sack (2015) recently proposed a ‘hybrid’ model of attentional control suggesting that the posterior parietal cortex (PPC) portion of the fronto-parietal network subserving visuospatial attention is characterized by competition between the hemispheres (ICT) whereas the frontal eye field portion shows right hemisphere dominance (RHDT).

Structural and functional brain imaging studies (in both neurologically healthy as well as in brain lesioned individuals) have revealed distinct but overlapping networks that subserve the fundamental components of visual attention. A bi-hemispheric dorsal frontoparietal network is postulated to subserve the endogenous allocation of spatial attention across the visual field, whereas a ventral frontoparietal network is implicated in the maintenance of arousal/vigilance and the reflexive re-orienting of attention to salient/unexpected stimuli (Corbetta & Shulman, 2002; 2011). The latter ventral frontoparietal network is highly right hemisphere lateralized (Corbetta & Shulman, 2011; Petersen & Posner, 2012) and because it underlies the production and maintenance of an optimal vigilance state, is thought to facilitate perception and behaviour. The combined interactivity of these networks is postulated to regulate visual performance at a given moment in time or point in space (He et al., 2007; Thiebaut de Schotten et al., 2011; Corbetta & Shulman, 2011). Importantly, any accurate model of the visuospatial attention system must account for commonly observed visuospatial phenomena. In the current set of experiments I sought to utilise psychophysical and neuroimaging measurements of a phenomenon termed pseudoneglect (a perceptual bias towards the left side of space found to occur in the majority of neurologically normal people) in order to further elucidate the functional architecture of the visuospatial attention system in the healthy brain.

Pseudoneglect

First documented by Bowers & Heilman (1980), pseudoneglect represents a visuospatial bias in favour of the left side of space displayed by the majority of neurologically normal people. Stimuli appearing in the left visual field/space tend to be responded to quicker and/or judged as larger, brighter or more numerous than comparable stimuli appearing in the right visual field (Charles et al., 2007; McCourt & Olafson, 1997; Nicholls et al., 1999; Jewell & McCourt, 2000). This subtle but robust phenomenon has been measured and replicated using a variety of different tasks requiring the distribution of visuospatial attention across the entire visual field, primarily variants of horizontal line bisection (Scarisbrick et al., 1987; Milner et al., 1992; Jewell & McCourt, 2000; Nicholls et al., 1999). Although considerable inter-individual variation exists in the direction and magnitude of lateralised spatial bias (with a common leftward asymmetry when averaged across participants), the bias displayed within individuals appears to reflect a reliable individual trait (Tomer, 2008; McCourt, 2001; Varnava et al., 2013). The pseudoneglect phenomenon has been suggested to influence everyday behavioural consequences as diverse as collisions occurring whilst navigating the environment (Nicholls et al., 2007; Nicholls et al., 2008; Nicholls et al., 2010; Thomas et al., 2009; Turnbull & McGeorge, 1998; Wilkinson et al., 2010; though see Fujikake et al., 2011 and Hatin et al., 2012 for discrepant results), driving performance (Benedetto et al., 2013), sporting performance (Roberts & Turnbull, 2010; Carlstedt, 2004; Nicholls et al., 2010; Masters et al., 2007), perception of retail displays (Massara et al., 2014) and responses on Likert scale surveys (Nicholls et al., 2006; Maeda, 2015). Additionally, pseudoneglect direction and magnitude have been suggested to predict tonic personality traits such as temperament (Tomer, 2008; Garner et al., 2012) and schizotypy (Brugger & Graves, 1997; Mohr et al., 2003; Taylor et al., 2002; Liouta et al., 2008; Ribolsi et al., 2013; though see Schofield & Mohr, 2014 for discrepant results) as well as phasic traits such as approach/avoidance motivation (Friedman & Forster, 2005; Drake & Myers, 2006; Nash et al., 2010; Roskes et al., 2011; Miller et al., 2012) and emotional state (Foster et al., 2008; Tamagni et al., 2009; Wilkinson et al., 2010; Cattaneo et al., 2014).

Neurologically, pseudoneglect is posited to arise from anatomical and functional asymmetries of the brain networks subserving visuospatial attention (Bultitude & Aimola-Davies, 2006; Corbetta & Shulman, 2011) but the phenomenon remains to be fully mapped onto brain activity/anatomy. Lateralization of cognitive functions in the human brain is well established and is thought to facilitate optimal information processing (Cai et al., 2013; Corballis, 1989). Whether a bias of attention toward the left visual field/space confers any additional adaptive advantage remains unclear (see Marzoli et al. (2014) for a recent discussion of this). However, it is apparent that the functional hemispheric asymmetry is likely to have an ancient evolutionary origin as it is also found in non-human animals such as primates (Hauser & Andersson, 1994) and mice (Ehret, 1987). Indeed, pseudoneglect has also been repeatedly documented in birds (Diekamp et al., 2005; Regolin, 2006; Chiandetti, 2011). Both behavioural and neuro-imaging studies of pseudoneglect can contribute much towards our understanding of the functional architecture of visual attention processing in the human brain. Below I provide brief reviews of both behavioural and neuro-imaging studies published to date on pseudoneglect before outlining the rationale and results of the present experiments. Furthermore, I then identify pertinent questions that remain unanswered and suggest some potentially productive methods for approaching them.

Behavioural studies of pseudoneglect

In a seminal review and meta-analysis of early behavioural studies of pseudoneglect (encompassing 73 studies with a total of 2191 participants), Jewell and McCourt (2000) documented an overall significant leftward bisection error (with an effect size of between -0.37 and -0.44) that was however significantly modulated by a number of task and participant specific variables. The leftward bias has been observed in a variety of different bisection tasks, including manual paper-and-pencil line bisection (Scarisbrick et al., 1987; Son et al., 2001; Chieffi et al., 2014), bisection-by-pointing (Hurwitz et al., 2011), rod bisection (Bradshaw et al., 1985; Bradshaw et al., 1987; Laeng et al., 1996) and bisection by visual fixation (Hurwitz et al., 2011; Cavezian et al., 2012, though see Leonards et al., 2013 for evidence of a rightward ocular bisection bias). The landmark task, originally developed by Milner et al. (1992), is a forced-choice bisection task in which participants are presented with pre-bisected lines and asked either to judge which end of the line is shorter/longer or asked to judge whether the line is correctly bisected or not (Bisiach et al., 1998; Toraldo et al., 2004). In both instances, overestimation of the left relative to the right segment of the line is usually found (Fink et al., 2002; Toba et al., 2011). The landmark task minimizes the influence of motor factors on midpoint judgement and allows for the removal of scanning eye movements through tachistoscopic line presentations (McCourt & Olafson, 1997, see Figure 1 for examples of line stimuli employed in the current experiments). Indeed, the task employed here has been termed tachistoscopic line bisection (McCourt & Olafson, 1997). Hence, the task allows for the dissociation of purely perceptual bias from motor bias during line bisection. The consistent leftward bias displayed on the landmark task thereby highlights the attentional nature of pseudoneglect, in contrast to intentional/motor accounts of the bias (Brodie & Pettigrew, 1996; Dellatolas et al., 1996; MacLeod & Turnbull, 1999).

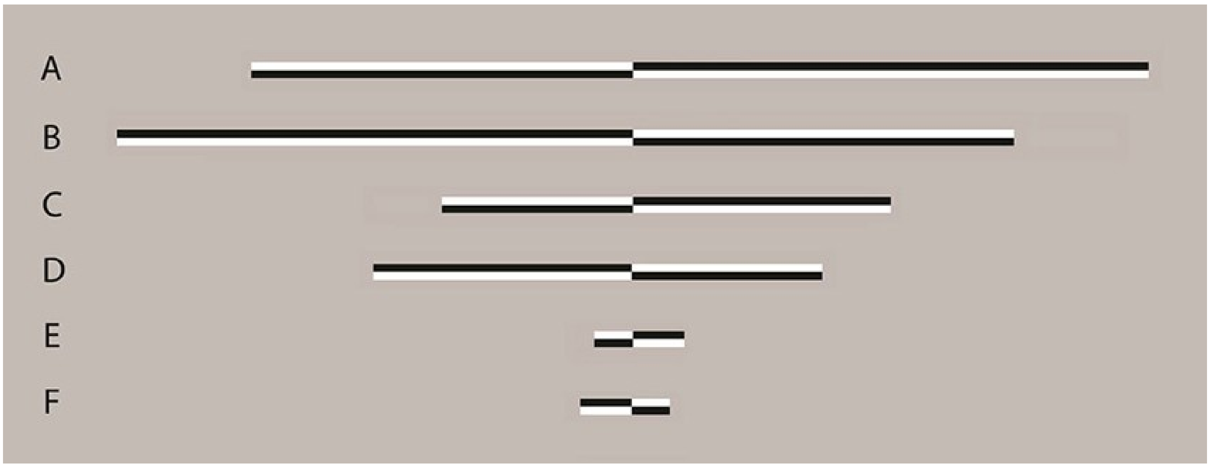

Figure 1. Examples of line stimuli used in the current experiments: Lines were transected at various locations symmetrically distributed to the left and right of veridical centre. All lines were displayed with the transector location centred on the vertical midline of the display (i.e., aligned to a central fixation cross which preceded the presentation of the lines). Lines A, C and E are transected to the left of veridical centre whereas lines B, D and F are transected to the right of veridical centre. Lines of varying contrast polarity appeared with equal frequency and the order of appearance was randomized.

Left visual field advantage is also observed in a variety of non-bisection visuospatial tasks that nonetheless involve a forced-choice decision regarding relative characteristics of stimuli presented simultaneously to the left and right visual field. Stimuli employed include chimeric faces (Levy et al., 1972; Dutta & Mandal, 2002; Bourne, 2008; Butler & Harvey, 2005; 2006; 2008), basic shapes (Milner & Harvey, 1995; Nicholls et al., 1999; Charles et al., 2007) and dot/star arrays (Nicholls et al., 1999). The greyscales task developed by Mattingley et al., (1994) requires participants to judge the darker of two simultaneously presented left-right mirror-reversed brightness gradients. Neurologically normal participants tend to choose the greyscale that is dark on the left side, even though both greyscales in a pair are always identical in overall brightness (Nicholls et al., 1999; Nicholls et al., 2004; Mattingley et al., 2004; Orr & Nicholls, 2005; Loftus et al., 2009; Loftus & Nicholls, 2012; Thomas & Elias, 2012). In a recent meta-analysis of laterality effects in non-bisection free-viewing tasks (encompassing 112 studies with a total of 19,909 participants), Voyer et al., (2012) found a large and significant left visual field bias (estimated effect size ($d = 1.024$)). In addition, left visual field advantage has also been observed during lateralised dot detection tasks (e.g. modified Posner paradigms (Posner, 1980)) employing reaction time as a dependent variable (Hilgetag et al., 2001; Koch et al., 2005; Thut et al., 2006; Thiebaut de Schotten et al., 2011).

A leftward bias also occurs for initial fixations when viewing natural visual scenes (Dickinson & Intraub, 2009; Ossandon et al., 2014; Nuthmann & Matthias, 2014; Foulsham et al., 2013). This effect has been shown to persist for roughly 1500 ms across a variety of different viewing instructions/tasks and has been attributed to pseudoneglect (Nuthmann & Matthias, 2014; Ossandon et al., 2014). However, recent analyses of fixations and saccadic eye movements during landmark task performance have revealed a tendency for average gaze direction to be biased to the right side of the line (McCourt et al., 2000; Elias et al., 2005; Thomas et al., 2012), though there is also evidence for first fixations to be biased to the left (Cavezian et al., 2012). Thomas et al. (2012) suggest that the rightward gaze bias for the landmark task may occur in order to bring the majority of the line into the left visual field and hence to facilitate visuospatial processing in the right hemisphere (see also Elias et al., 2005 for a similar effect with greyscales, stars and shapes stimuli). However, direct evidence for the link between saccadic eye movements/fixations and the pseudoneglect bias is lacking (Hurwitz et al., 2011; Foulsham et al., 2013). Indeed, pseudoneglect has consistently been displayed during tasks in which scanning eye movements are not possible and so scanning eye movements/fixations must only have a modulatory influence on the direction and magnitude of bias displayed during free-viewing or extended-viewing tasks (Chokron and Imbert, 1993; Chokron et al., 1998; Foulsham et al., 2013).

Nonetheless, the bias displayed by any given individual can be modulated by a variety of stimulus, state and experimental factors. One of the most established modulators of bisection bias is the length of the to-be-bisected line, with the magnitude of pseudoneglect reducing linearly as a function of line length (McCourt and Jewell, 1999; Hurwitz et al., 2011). In short lines (< 2 cm in length or subtending < 2° of visual angle horizontally), either symmetric patterns of midpoint judgements (Thomas et al., 2012) or even reversed rightward biases under certain experimental conditions (see Rueckert et al., 2002) have been observed. This has been reported for landmark task performance (Rueckert et al., 2002; Heber et al., 2010; Thomas et al., 2012) in line with a perceptual origin of the effect. However, the effect has proven inconsistent for manual bisection, ocular bisection and bisection by pointing, suggesting that motor/intentional factors can ameliorate the line length effect under certain experimental conditions (Rueckert et al., 2002; Mennemeier et al., 2005; Veronelli et al., 2014; Hurwitz et al., 2011). The bias has also been suggested to be modulated by the vertical and horizontal location of the stimulus relative to the observer (leftward bias strongest for upper visual field and left visual field (McCourt & Garlinghouse, 2000; Barrett et al., 2000; Thomas & Elias, 2010; 2011; Charles et al., 2007; Luh et al., 1995; McCourt & Jewell, 1999; Son et al., 2001)), stimulus presentation time (leftward bias strongest for short presentation times (Jewell & McCourt, 2000; Thomas & Elias, 2011; Thomas et al., 2012)), cueing effects (midpoint judgement shifts towards cue (Harvey et al., 2000; McCourt et al., 2005; Bultitude & Aimola-Davies., 2006; Toba et al., 2011)), viewing distance (rightward shift in spatial bias from peri- to extra-personal space (McCourt & Garlinghouse, 2000; Varnava et al., 2002; Bjoertomt et al., 2002; Longo & Lourenco, 2006; Gamberini et al., 2008; Mahayana et al., 2014)) and perceptual load (rightward shift in spatial bias with increased perceptual load (Perez et al., 2009; O'Connell et al., 2011; Newman et al., 2013)).

As well as factors relating to the stimulus, context and experimental set-up, endogenous factors related to the state of the tested participants have also been found to influence the manifestation of pseudoneglect. Over an extended period of landmark task performance (~1 hour), a rightward shift in subjective midpoint has been observed within participants (the time-on-task effect (Manly et al., 2005; Dufour et al., 2007)). The time-on-task effect has been suggested to represent an interaction between spatial orienting and arousal networks in the right hemisphere (Manly et al., 2005; Fimm et al., 2006; Dufour et al., 2007; Chica et al., 2012; Newman et al., 2013). However, Schmitz et al., (2011) found that sleep deprivation under controlled conditions did not modulate subjective midpoint estimation on the landmark task, thereby a reduction in general arousal/vigilance alone may not fully account for the observed rightward shifts in spatial bias with extended time-on-task.

Another factor that appears to modulate the direction and magnitude of the line bisection bias is the age of the participant. The group-level left bias is ameliorated (and sometimes reversed) with healthy aging, with elderly participants either displaying no consistent group-level directional bias or a systematic right bias (Schmitz & Peigneux, 2011; Veronelli et al, 2014). Additionally, some manual bisection studies have suggested that this age-related shift in bias may be gender specific, only occurring in men (Varnava & Halligan, 2007; Barrett & Craver-Lemley, 2008; Chen et al., 2011). This absence (or reversal) of pseudoneglect has been posited to reflect either general right hemisphere decline (Nagamatsu et al., 2011) and/or a reduction in hemispheric asymmetry for spatial processing in the elderly (Schmitz & Peigneux, 2011), in line with models of aging that emphasize changes in hemispheric asymmetries (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008).

Evidence from neuroimaging and brain stimulation in healthy participants

Utilising variants of line bisection, several studies have investigated the neural correlates of bisection decisions in the healthy brain. As mentioned, the landmark task minimizes the influence of motor factors on midpoint judgement and allows for the removal of scanning eye movements through tachistoscopic line presentations (McCourt & Olafson, 1997). For these reasons, the landmark task is ideal for implementation in neuro-imaging studies of spatial attention processing. In a series of fMRI and PET experiments, Fink et al. reported increased activity in right hemisphere superior posterior parietal cortex (IPS), inferior parietal lobule (temporo-parietal junction (TPJ)) and pre-frontal cortex and the left cerebellum along with increased bilateral early visual activation during landmark task performance compared to a non-spatial control task[1] (Fink et al., 2000a; Fink et al., 2000b; Fink et al., 2001; Weiss et al., 2000; Weiss et al., 2003).

Subsequent studies have revealed differences in the brain regions implicated during bisection decisions depending on task-specific factors. Fink et al. (2002)

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[1] The ‘non-spatial’ control task employed required the participants simply to indicate whether the line contained a transection mark or not (trials were included in which the line was not transected at all). This control task was employed in order to identify the neural correlates specific to the visuospatial judgement involved in the landmark ask whilst controlling for neural activity associated with the visual input and motor response preparation.

found that the instructions issued to participants modulated the pattern of task-relevant activation during landmark task performance, with the explicit instruction to compare the relative lengths of the two line segments resulting in differential activation compared to the instruction to simply respond as to whether the transection mark was correctly centred or not. Neural activation common to both strategies was observed in the inferior parietal lobes bilaterally and in right temporooccipital cortex (Fink et al., 2002). Additional neural activation specific to the relative length comparison strategy was observed in left and right superior posterior parietal cortex whereas additional bilateral lingual gyrus and anterior cingulate activation was observed for the correctly centred judgements. Cicek et al., (2009) used fMRI to assess the brain regions involved during both the landmark task and manual line bisection. A conjunction analysis of BOLD activity related to the processing of both tasks again implicated right lateralized superior posterior parietal and lateral peristriate cortex regions. Frontal eye field activation was only found during manual line bisection and not during landmark task performance (Cicek et al., 2009). Cavezian et al., (2012) compared activity between landmark task performance and an ocular line bisection task in which participants were instructed to fixate on the point of the line that they judged to be the midpoint. The results revealed mainly right lateralised superior parietal cortex, supplementary motor area (SMA) and right cerebellum activity during performance of both tasks, though less hemispheric asymmetry of parietal response was observed for the ocular bisection task along with greater recruitment of frontal areas compared to landmark task performance (Cavezian et al., 2012).

Thus, the converging evidence from fMRI and PET studies of line bisection performance is of right hemispheric dominance for task processing (in line with the model of Heilman & Van den Abell, 1980), primarily implicating regions of superior and inferior parietal cortices. However, the low temporal resolutions of both fMRI and PET do not allow for investigation of the evolution of the neural activity associated with task processing. In the first high-density electroencephalography (EEG) event-related potential (ERP) study of line bisection performance, Foxe et al., (2003) revealed a robust net negative potential from 170-400 ms post-stimulus presentation during performance of the landmark task relative to the same non-spatial control task originally employed by Fink et al., (2000a). Foxe et al., (2003) termed this electrophysiological correlate of line bisection judgements ‘the line-bisection effect’. The effect onset earlier over the right hemisphere and source analysis of the intracranial generators of the effect was in good agreement with the fMRI literature (Fink et al., 2000a; Fink et al., 2000b; Fink et al., 2001; Weiss et al., 2000; Weiss et al., 2003; Cicek et al., 2009; Cavezian et al., 2012), implicating right lateral parieto-occipital cortex (early phase of effect ~ 165-190ms) and then regions of the posterior superior and central parietal cortex (~ 190-400 ms). Also using EEG and source analysis, Waberski et al., (2008) investigated the neural correlates of landmark task processing (again as compared to the non-spatial control task (Fink et al., 2000a)) when participants were instructed to respond as to whether the transection mark was correctly centred or not (as in condition 2 of the Fink et al., (2002) study). The analysis implicated early activation of right middle occipital gyrus (~ 90 ms post-stimulus onset) followed by successive activations of right superior posterior parietal (~ 115 ms), bilateral inferior occipital (~ 135 ms (left), ~ 150 ms (right)) and right inferior posterial parietal cortex (~ 200 ms) during correctly-or-incorrectly bisected judgements relative to the non-spatial control task. Utilising magnetic source imaging (MSI), Billingsley et al. (2004) observed asymmetric activation of regions within inferior parietal, occipital and prefrontal cortices (> activation in the right hemisphere (RH)) to occur ~200-300 ms post-stimulus presentation during performance of a landmark task variant.[2]

However, a key aspect not addressed by many functional neuro-imaging studies of pseudoneglect is the link between the neural correlates of stimulus processing and the perceptual bias/behavioural performance displayed across participants. Linking brain activity and behaviour in this manner would provide more compelling evidence as to the specific role any given brain region/neural component plays in the genesis of pseudoneglect. Anatomically, Thiebaut de Schotten et al. (2011) report an association between the relative hemispheric lateralisation of a parieto-frontal white matter pathway (superior longitudinal fasciculus II (SLF II)) as measured by diffusion tensor imaging (DTI) and the direction and magnitude of spatial bias displayed during manual line bisection performance across individuals. Those individuals with a larger asymmetry in the relative lateralized volume of SLF II in favour of the RH were more likely to display a leftward bisection bias and vice versa. Individual differences in the direction and magnitude of pseudoneglect have also been suggested to be predicted by hemispheric asymmetries in dopaminergic brain systems (Slagter et al., 2010; Newman et al., 2012; Bellgrove et al., 2007; Greene et al., 2010; Tomer et al., 2013). Further exploration of the explanatory potential of these proposed predictors, as well as how they relate to each other and to functional neuro-imaging correlates of visuospatial processing, is required. Any proposed model and anatomical/neuronal predictor of pseudoneglect should also account for the observed stimulus and state modulations of bias.

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[2] The contrast employed by Billingsley et al. (2004) was between presentation of single endpoints of a line (to one side of a fixation cross) versus simultaneous presentation of both lateral line endpoints (akin to the traditional landmark task (Milner et al., 1992))

Hence, a potentially useful and relatively unexplored avenue of research is to investigate how different modulators of bias interact with each other and what the neural correlates of these modulators are. The relationship between different modulators of bias in terms of behavioural and neural outcome can provide compelling evidence as to whether each modulator arises from the same or different neural networks. Additionally, in terms of identifying the neural activity which underlies the genesis of pseudoneglect and hence the neural networks that are directly involved, established modulators of perceptual bias such as line length (Jewell & McCourt, 2000; Rueckert et al., 2002; Thomas et al., 2012) and time-on-task (Manly et al., 2005; Dufour et al., 2007) can be utilised in order to parcel out the activity that is necessary for the bias to arise. Previous controls employed in neuroimaging studies of line bisection performance may be inappropriate as they do not necessarily isolate that activity which is contributing primarily to the bias. Since the bias is stimulus dependent (i.e. the line length effect), controlling for line bisection by introducing a 'non-spatial' task with identical stimuli does not necessarily provide the best means of parcelling out the bias relevant activity.

Comparing the associated neural activity for the task between those stimulus conditions under which the bias arises and those under which the bias does not arise within the same individuals, offers a novel and potentially useful approach to the question of the neural correlates of spatial bias. Such an experimental design may provide a more appropriate control than the 'non-spatial' control task employed in previous neuro-imaging studies of pseudoneglect (Fink et al., 2000a; Fink et al., 2000b; Fink et al., 2001; Foxe et al., 2003; Waberski et al., 2008), thereby allowing for more accurate identification of the temporal and spatial locus of the bias.

Further evidence of the crucial role played by posterior parietal (particularly RH) brain regions during line bisection performance has come from studies employing non-invasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). NIBS techniques allow for causal testing of the involvement of the stimulated brain region in a given cognitive function (Walsh & Pascual-Leone, 2003). Briefly modulating neuronal firing (and hence interfering with task-relevant processing) through online single- and repetitive-pulse TMS to the parietal cortex during performance of visuospatial tasks has been shown to bias attention away from the contralateral hemifield and toward the ipsilateral hemifield (see Fierro et al., 2000; Fierro et al., 2001; Hilgetag et al., 2001; Pourtois et al., 2001; Bjoertomt et al., 2002; Ellison et al., 2004; Dambeck et al., 2006; Szczepanski & Kastner, 2013; Mahayana et al., 2014). The effect of PPC TMS on visuospatial attention appears to depend on the timing (relative to task performance) and type of stimulation. For instance, in contrast to the typical contralateral impairment observed with online studies, Kim et al., (2005) found 10 Hz offline repetitive-pulse TMS applied to the PPC to facilitate subsequent perception of contralateral stimuli.

More recently, tDCS applied to PPC has also been shown to modulate the direction of visuospatial bias (see Sparing et al., 2009; Giglia et al., 2011; Loftus & Nicholls, 2012 and Wright & Krekelberg, 2014). TDCS involves the application of weak electrical currents to the scalp through sponge-covered electrodes, resulting in modulation of membrane potentials (and thus concurrent cortical excitability) in neurons underlying the stimulated regions. Two subtypes of stimulation delivered at a constant current strength are the following: (1) *anodal stimulation* enhances neuronal firing by inducing de-polarization (neuronal excitation); and (2) *cathodal stimulation* hyperpolarizes neurons and depresses the firing rate (inhibition) (Nitsche & Paulus, 2000). There is growing interest in the potential therapeutic and neuroenhancing potential of tDCS for various cognitive functions (Brunoni et al., 2012; in particular see Ko et al., 2008; Sparing et al., 2009; Utz et al., 2010 and Oliveri 2011 for promising early investigations of the efficacy of parietal-tDCS in ameliorating symptoms of visuospatial neglect), but the mechanisms of tDCS action on brain activity are not yet fully understood and there is large intra-individual variability in the induced effects which therefore limits the efficacy of the technique (de Berker et al., 2013; Krause & Cohen Kadosh et al, 2014; López-Alonso et al., 2014; Wiethoff et al., 2014).

Outline of the current experiments

In the series of experiments presented in the current thesis I sought to elucidate the neural origins of pseudoneglect through a combination of psychophysical measurements (landmark task), EEG recordings and tDCS. More specifically, I aimed to manipulate stimulus factors, endogenous state and task-related neural activity in order to modulate the manifestation of pseudoneglect both within and between neurologically normal participants and thereby uncover the relationship between different modulators of spatial bias as well as their neural correlates.

In the first experiment (presented in **Chapter One**), I investigated whether the previously observed subjective midpoint modulators of line length (Jewell & McCourt, 2000; Rueckert et al., 2002; Thomas et al., 2012) and extended time-on-task (Manly et al., 2005; Dufour et al., 2007) have an interactive or additive relationship. In doing so, I tested whether bisection performance in long and short lines are governed by distinct or common mechanisms. Additionally, it was possible to assess whether the time-on-task effect occurs regardless of line length (in line with the effect occurring as a result of a reduction in general alertness per se (Manly et al., 2005; Newman et al., 2013)) or whether the time-on-task effect is stimulus specific.

In the second experiment (presented in **Chapter Two**), EEG recording is introduced during performance of the landmark task with both long and short lines in order to reveal the neural correlates of the effect of line length.

In experiment three (presented in **Chapter Three**) the development of spatial bias with healthy aging is investigated through a comparison of young and elderly participants' landmark task performance. Again, the line length manipulation was employed in order to assess the relationship between the modulators of line length and aging.

Finally, the primary aim of experiment four (presented in **Chapter Four**) was to manipulate the direction of pseudoneglect displayed within participants through bi-parietal tDCS in order to test the 'interhemispheric competition' model of spatial attention (Kinsbourne, 1977). To do so, a close replication of Giglia et al., (2011) was performed but with the introduction of an additional reversed bi-parietal polarity tDCS condition, thereby allowing for identification of potential bi-directional shifts in spatial bias depending on tDCS-polarity. Additionally, the administered current strength was modulated between two groups (1mA v 2mA) in order to assess whether differential effects would be observed depending on the level of induced noise in interaction with the participant's performance level at baseline (indexing the endogenous signal-to-noise ratio). This manipulation was adopted in order to test a recently proposed stochastic resonance model of NIBS action (Miniussi et al., 2013), the predictions of which, if found to be accurate, may facilitate the improvement of functional specificity in tDCS.

Chapter 1

Stimulus-and state-dependence of systematic bias in spatial attention: Additive effects of stimulus-size and time-on-task

Introduction

The direction and magnitude of pseudoneglect has been suggested to vary systematically within participants as a function of a number of stimulus and context factors (Jewell & McCourt, 2000; McCourt, 2001; Failla et al., 2003; Pérez et al., 2009; Heber et al., 2010 and Schmitz & Peigneux, 2011). The magnitude of the leftward bias in line bisection tends to decrease as a function of decreasing line length and has been reported to 'cross-over' to become a bias in the opposite, rightward direction in very short lines (<2 cm) (McCourt & Jewell, 1999; Rueckert et al., 2002). Previous studies investigating the robustness of this line length effect in normal participants display mixed findings, though differing bisection tasks and experimental designs have been employed (Manning et al., 1990; Luh, 1995; Laeng et al., 1996; McCourt & Jewell, 1999; Jewell & McCourt, 2000; Mennemeier et al., 2001; Mennemeier et al., 2002; Rueckert et al., 2002; Varnava et al., 2002 and Heber et al., 2010). The most commonly employed tasks include the landmark task, a perceptual line bisection judgement task designed to dissociate the contribution of perceptual and motor factors (Milner et al., 1992; Harvey et al., 2000 and Olk & Harvey, 2002), and manual line bisection, of which the former shows more reliable cross-over with short lines (Rueckert et al., 2002) suggesting perceptual bisection tasks to be optimal for detection of the line length effect in healthy participants.

Besides stimulus factors, arousal level also seems to influence spatial bias, with leftward bias associated with states of relatively high alertness and rightward bias associated with states of low alertness or fatigue (Bellgrove et al., 2004; Manly et al., 2005; Fimm et al., 2006 and Matthias et al., 2009; though see Schmitz et al. (2011) for conflicting results with the landmark task). In addition, left- to rightward shifts in line bisection judgement have been observed over the course of prolonged performance of the landmark task. This has been labelled the 'Time-on-task' effect (Manly et al., 2005; Dufour et al., 2007). These intra-individual variations indicate that visuospatial bias is a dynamic phenomenon fluctuating over time and depending on context. The aim of the present study was to probe models of spatial attention as to their ability to explain the cross-over effect using time-on-task as an experimental manipulation, detailed below.

All influential models of spatial attention assume contribution of both the RH and left hemisphere (LH) to orienting towards the contralateral visual fields, although to different extents (e.g., Kinsbourne, 1970; Heilman and Van Den Abell, 1980; Mesulam, 1981; Corbetta & Shulman, 2002; 2011; Duecker & Sack, 2015). In line with these models, predominant RH-activation during line bisection tasks (Fink et al., 2000a; Fink et al., 2000b; Foxe et al., 2003 and Waberski et al., 2008) may induce an attentional bias towards the left side of the line, thereby increasing its perceived length relative to the right side and shifting the perceived midpoint to the left of veridical centre (Bultitude & Aimola-Davies, 2006). How can the left- to right cross-over from long to short lines then be explained? One model suggests that cross-over results from the leftward attentional asymmetry coupled with a previously reported, general tendency to underestimate the absolute length of long lines and to overestimate the absolute length of short lines (Werth & Poppel, 1988; Tegner & Levander, 1991). This orientation/estimation hypothesis (Mennemeier et al., 2005) posits that once attention is preferentially oriented to one end of a line (typically the left), underestimating the absolute length of long lines leads to the bisection mark being placed short of veridical centre (i.e., to the left), whereas overestimating the absolute length of short lines leads to the bisection mark being placed beyond veridical centre (i.e., to the right). An alternative model suggests that task specific hemispheric dominance for line bisection may switch from the RH in long lines to the LH in short lines. A potential mechanism for this may be RH-dominance for lower spatial frequencies and/or global perception, in contrast to LH-dominance for higher spatial frequencies and/or local perception (Sergent, 1982; Ivry & Robertson, 1998; Monaghan & Shillcock, 2004 and Flevaris et al., 2011). Behavioural dissociations have been found in bisection tasks when participants were directed to focus on either the local or global elements of the stimulus respectively, and these differences have been suggested as a possible explanation for the line length effect (Hughes et al., 2005; Gallace et al., 2008). I call this the "Local/Global" hemispheric specialization hypothesis. Importantly, these models lead to different predictions as to the outcome of time-on-task on bisection judgement performance in long versus short lines.

The time-on-task modulation of attentional bias by arousal level has been interpreted to represent an interaction between orienting and arousal networks in the RH, which biases attention towards the left visual field in states of high alertness but results in a reduction or even reversal of this bias as RH-activation decreases with reduced alertness/increasing fatigue (Corbetta et al., 2005; Manly et al., 2005; Fimm et al., 2006 and Dufour et al., 2007). To date, the time-on-task effect in the landmark task has only been investigated using relatively long lines (Manly et al., 2005; Dufour et al., 2007). Here the influence of time-on-task on midpoint judgements in short (1 cm) as well as long lines (29 cm) is investigated for the first time. The models above would predict the following outcomes. Under both the orientation/estimation hypothesis and the “local/global” hemispheric specialization hypothesis, long and short lines should differ in directional bisection errors, with more leftward bias in long than short lines (line length effect) at the beginning of the experiment (high alertness). Under the orientation/estimation hypothesis, a rightward shift in spatial bias over the course of the experimental session should lead to a reversal of the direction of cross-over. Once attention is shifted rightwards (time-on-task effect), underestimating the length of long lines should lead to the bisection mark being placed short (i.e., to the right) of veridical centre. In contrast, overestimation of short lines should lead to the bisection mark being placed beyond (i.e., to the left of) veridical centre. Under the “local/global” hemispheric specialization hypothesis, one would expect decreasing alertness and thus RH-depletion to primarily affect the bisection of long but not short lines (due to RH-dominance for long line but LH-dominance for short line processing), therefore leading to a rightward shift primarily in long but not short lines. These predictions were tested by assessing line bisection biases for short and long lines in the landmark task at the beginning and end of the experimental session, before and after an extended practice period (about 1 h time-on-task) in which participants performed the task either exclusively on long lines or on short lines (group design).

Method

Participants

Thirty-two right-handed participants (18 male, 14 female, mean age = 22.32 years, standard deviation (SD) = 2.6) took part in the experiment. Written informed consent was obtained from each participant. All participants were volunteers naive to the experimental hypothesis being tested. All participants had normal or corrected-to-normal vision and reported no history of neurological disorder. The experiment was carried out within the School of Psychology at the University of Glasgow and was approved by the local ethics committee.

Instrumentation and stimuli

Stimuli were presented using the E-Prime software package (Schneider et al., 2002) on a CRT monitor with a 1280 × 1024 pixel resolution and 85 Hz refresh rate. Adapted from McCourt (2001), the paradigm represented a computerized version of the landmark task. Lines of 100% Michelson contrast were presented on a grey background (luminance = 179, hue = 179). Figure 1 shows examples of line stimuli used in the experiment. Two different lengths of line were presented. ‘Long’ lines measured 29 cm in length by .5 cm in height and at a viewing distance of 108 cm subtended 15.3° (width) by .39° (height) of visual angle. At the same viewing distance, ‘Short’ lines measuring 1 cm x .5 cm subtended .531° by .39° of visual angle. Both long and short lines were transected at 1 of 29 points ranging from ±4.6% of absolute line length to veridical centre. All lines were displayed with the transector location centred on the vertical midline of the display (i.e., aligned to a central fixation cross which preceded the presentation of the lines, see below).

Experimental groups

Participants were randomly split into two experimental groups of 16, a long-line prolonged (LP) time-on-task group (LP Group: 8 male, 8 female) and a short-line prolonged (SP) time-on-task group (SP Group: 10 male, 6 female). The LP Group performed the landmark task with long lines during the extended performance (time-on-task) period, whilst the SP Group performed it with short lines during the extended performance period. This was the only difference between groups as the experimental procedure was identical in every other way.

Procedure

At the beginning and end of the experimental session, all participants completed the Stanford Sleepiness Scale (Hoddes et al., 1973), a subjective measure of alertness ranging from 1 (fully alert) to 7 (asleep). Participants were then seated 108 cm from the screen and their midsagittal plane aligned with the display monitor. Viewing distance was kept constant using a chin rest.

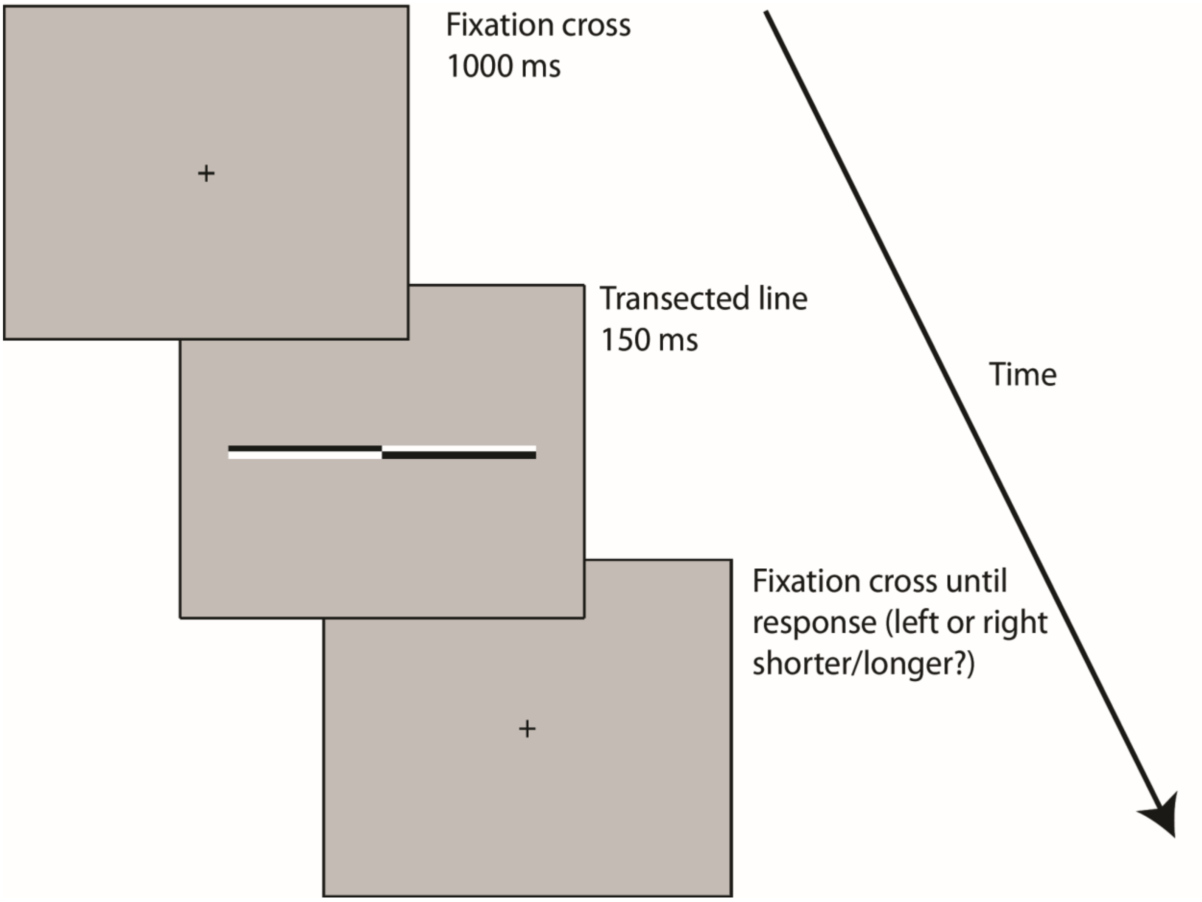


Figure 2. A Schematic representation of the trial procedure. Following 1000 ms presentation of a fixation cross, transected lines (of differing lengths in experiments 1 & 3, only long in experiment 4) were presented for 150 ms before reappearance of the fixation cross on the screen until the subject responded, by pressing either the left or right (shorter/longer?) response key. The subsequent trial began as soon as the response was made.

Each experimental block consisted of 232 trials (eight judgements at each of the 29 transector locations). Each trial began with presentation of a fixation cross [.39° (height) × .39° (width) of visual angle] for 1 sec followed by presentation of the transected line (150 msec) (see Figure 2). The transection mark was always aligned with the fixation cross (i.e., the eccentricity of the line endpoints varied across trials while the transection point always appeared at the same central position), therefore preventing use of the position of the fixation cross relative to the bisection mark as a reference point for bisection judgements. A blank grey screen followed for the response period during which participants indicated which end of the line the transection mark had appeared closest to by pressing either the left or right response key. Participants always responded using their dominant right hand (right index and middle finger respectively). The subsequent trial began as soon as the response was made. Participants were instructed to hold their gaze on the centre of the screen throughout each trial. Trials lasted approximately 2 sec with each block lasting 6–7 min. Trial type (location of transector in line) was selected at random. A block of 20 practice trials was performed immediately prior to the beginning of the experimental blocks.

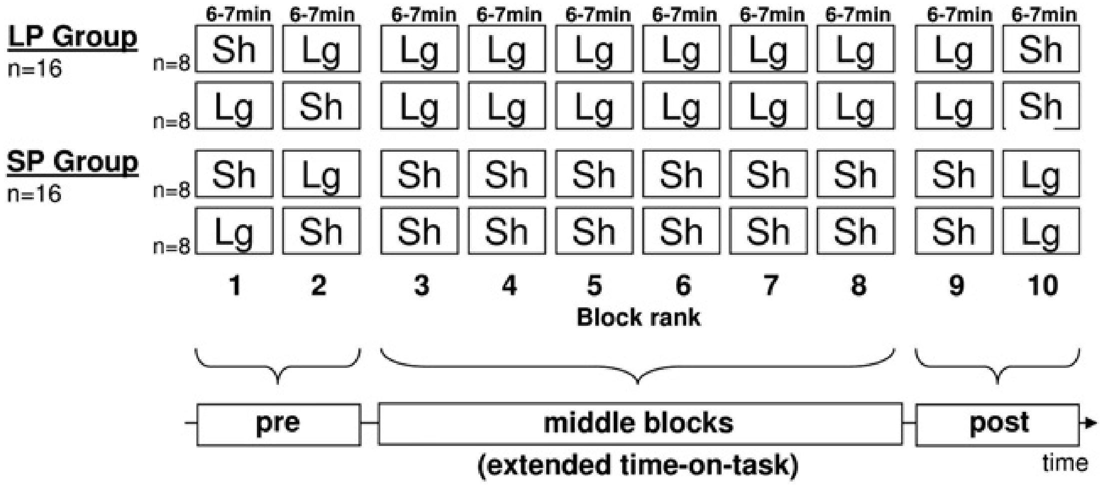


Figure 3. A schematic representation of the experimental procedure. Each block lasted approximately 6–7 min. Initially, both groups performed the landmark task in one block of long lines and one block of short lines (pre-practice blocks), the order of which was counterbalanced. During blocks 3–8 (extended time-on-task period), the LP Group performed the task exclusively with long lines and the SP Group exclusively with short lines. In the final two blocks (post-practice blocks), the LP Group performed first a block of long then short lines and the SP Group first a block of short then long lines. The order was deliberately not counterbalanced to maximize time-on-task in the practiced line length condition.

Each participant performed 10 blocks of the landmark task altogether. Figure 3 shows a schematic representation of the experimental procedure. Initially, both groups performed one block of long lines and one block of short lines (the order of which was counterbalanced across participants) to assess baseline performance (pre-practice blocks 1–2). During the middle blocks 3–8 (extended time-on-task period), the LP Group performed the task exclusively with long lines and the SP Group exclusively with short lines. In the final two blocks (post-practice blocks 9–10), both groups performed again one block of long and one block of short line bisection. Note that in these blocks the order of line length performance was not counterbalanced in order to maximize time-on-task in the practiced line length condition in each group (i.e., the LP Group finished with one block of long and then short lines, while the SP Group finished with one block of short then long lines). Participants were allowed to take as long a break as they wished between blocks. The entire experiment lasted approximately 70–80 min.

Analysis

In order to obtain an objective measure of perceived line midpoint for each block in each subject, psychometric functions (PFs) were derived using the method of constant stimuli. The dependent measure was the proportion of trials on which participants indicated that the transector had appeared closer to the left end of the line. Non-linear least-squares regression was used to fit a cumulative logistic function to the data for each block in each subject and to the group averaged proportion of left responses for each block. The cumulative logistic function is described by the equation:

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

where x are the tested transector locations, μ corresponds to the x-axis location with a 50% ‘left’ and 50% ‘right’ response rate and s is the estimated width of the psychometric curve. The 50% location is known as the point of subjective equality (PSE) and represents an objective measure of perceived line midpoint. The width of the PF provides a measure of the precision of participants’ line midpoint judgements per block. Inferential statistical analyses were performed on the individually fitted PF PSE values and estimated widths, as well as the Stanford Sleepiness Scale ratings.

Results

Subjective alertness

Stanford Sleepiness Scale ratings confirmed a reduction in subjective alertness over the course of the experimental session, with the overall mean score on the Stanford Sleepiness Scale increasing from 2.5 to 4.2. A 2 (pre *vs* post experiment) × 2 (group) factorial analysis of variance (ANOVA) confirmed a main effect of time-on-task on sleepiness rating [$F(1, 30) = 32.869$, $p = .000$] independently of group [no interaction between group and time-on-task: $F(1, 30) = .619$, $p = .438$].

Psychometric functions and subjective midpoint

Figure 4A presents group averaged PFs for both experimental groups at each line length both prior to and post extended time-on-task. Filled symbols plot mean percent left responses (±1 standard error (SE)) as a function of transector location. The smooth curves represent the best-fitting least-squares cumulative logistic PFs. Vertical dotted lines indicate the transector location corresponding to the 50% response rate (PSE) as specified for each condition adjacent to the line (in % absolute line length from veridical centre). Open symbols plot the mean PSE's (and 95% confidence intervals – CIs) of PFs fitted to the individual participants' data for each block. These are in close agreement with the group averaged PF PSE’s.

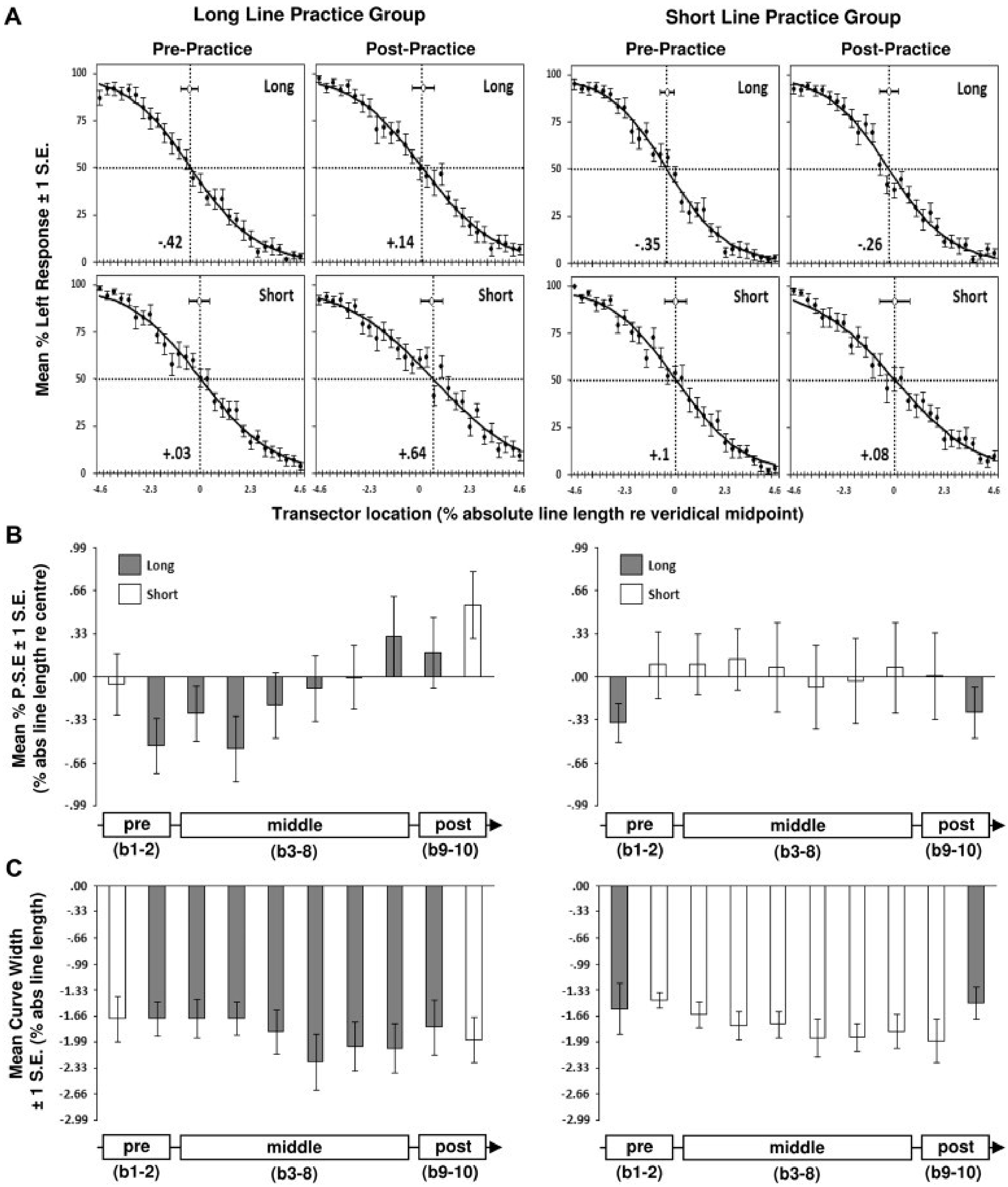


Figure 4. **Line bisection performance.** (A) Group averaged pre and post extended-practice PFs. The four panels to the left plot data for the LP Group and the four to the right the SP Group. Filled symbols plot mean % left responses (±1 SE) as a function of transector location. The smooth curves represent the best-fitting least-squares cumulative logistic PFs. Horizontal dotted lines indicate the 50% response rate. Vertical dotted lines indicate the transector location corresponding to

the 50% response rate (PSE). Open symbols plot the mean PSE's (and 95% CIs) obtained from PFs fitted to the individual participants' data as specified for each condition adjacent to the vertical dotted line (in % absolute line length from veridical centre). These are almost identical to the group averaged PSE's. Line length is displayed in the top right hand corner of each panel. (B) Group averaged PSE's (±1 SE) for each block of the experimental session. Data for the LP Group are plotted on the left and the SP Group on the right. Grey filled bars represent long line blocks and white filled bars short line blocks. (C) Group averaged width of the PF (±1 SE) for each block of the experimental session. Data for the LP Group are plotted on the left and the SP Group on the right.

In line with previous studies of pseudoneglect, mean PSE in the LP Group at the beginning of the experiment (pre-practice, Fig. 4A, 1st column) was displaced in the long lines to the left of veridical centre by −.42% (Fig. 4A: 1st column, upper row), and this leftward bias was significantly different from veridical midline (0%) (as the 95% CI does not overlap veridical centre, see Fig. 4A, 1st column) (Group averaged PF PSE: −.43%). In short lines in contrast, the pre-practice PSE was displaced slightly to the right of veridical centre by +.03% (Fig. 4A: 1st column, lower row), but this was not significantly different from veridical midline (95% CI overlaps veridical centre) (Group averaged PF PSE: +.024%). In the final two blocks after extended LP (post-practice, Fig. 4A, 2nd column), mean PSE in the long lines was displaced to the right by +.14% (Fig. 4A: 2nd column, upper row), not different anymore from veridical midline (the 95% CI overlaps) (Group averaged PF PSE: +.14%), which indicates a rightward shift of +.56% in subjective midpoint in long lines from pre- to post-practice (−.42% to +.14%). In the short lines, mean post-practice PSE was to the right of veridical centre by +.64% (Fig. 4A: 2nd column, lower row), significantly different from veridical midline (95% CI not overlapping veridical centre) (Group averaged PF PSE: +.7%), indicating a reliable rightward bias beyond veridical midline (i.e., cross-over), and a rightward shift of +.61% in subjective midpoint in short lines from pre- to post-practice (+.03% to +.64%).

In the SP Group, mean pre-practice PSE in the long lines was significantly displaced to the left of veridical centre by −.35% (Fig. 4A: 3rd column, upper row; 95% CI not overlapping veridical centre) (Group averaged PF PSE: −.36%). In short lines, mean pre-practice PSE was displaced slightly but not significantly to the right by +.1% (Fig. 4A: 3rd column, lower row; 95% CI does overlap veridical centre) (Group averaged PF PSE: +.1%). This reproduces the pre-practice pattern found in the LP Group. However in contrast to the LP Group, in the final two blocks of the experimental session, mean post-practice PSE in the long lines remained displaced to the left by −.26% (weak change of +.09% from −.35% to −.26% pre- to post-practice, with the 95% CI however overlapping veridical centre) (Group averaged PF PSE: −.23%). Similarly, in the short lines, mean post-practice PSE remained stable, being slightly but insignificantly displaced to the right of veridical centre by +.08% (weak change of −.02% from +.1% to +.08% pre- to post-practice, with the 95% CI also overlapping veridical centre) (Group averaged PF PSE post-practice: +.07%).

A 2 (Group: SP *vs* LP) × 2 (time-on-task: pre- *vs* post-practice) × 2 (line length: long *vs* short) Factorial ANOVA on individually fitted PF PSE's revealed a significant main effect of line length [$F(1, 30) = 5.235, p = .029$], a significant main effect of time-on-task (pre *vs* post) [$F(1, 30) = 5.030$, $p = .032$], no significant main effect of group [$F(1, 30) = .508$, $p = .482$], but a significant time-on-task × group interaction [$F(1, 30) = 5.149$, $p = .031$]. No other significant interaction was observed. The overall subjective midpoint was significantly more to the left in the long lines than in the short lines (as indexed by the PSE's), indicating an offset of bias from long to short lines. Analysis of simple main effects for exploring the interaction term (paired-sample *t*-tests performed between pre and post-practice subjective midpoint collapsed across line lengths within each group) revealed no statistically significant difference between pre and post-practice subjective midpoints in the SP Group [$t(15) = .019$, $p = .981$]. In contrast, the LP Group showed a statistically significant difference, characterized by a shift to the right in mean subjective midpoint from pre- to post-practice [$t(15) = -3.132$, $p = .007$], indicating time-on-task effects (irrespective of both long and short lines).

In Fig. 4B, individually fitted mean PSE's (% of absolute line length re veridical ±1 SE) are plotted as a function of block rank (including the middle practice blocks 3–8), clearly illustrating the systematic rightward shift in subjective midpoint throughout the experimental session for both line lengths in the LP Group (left panel). In contrast, the error pattern in the SP Group (right panel) deviated little throughout. Linear regression analysis performed exclusively on extended performance within each group (long lines in the LP Group, short lines in the SP Group) revealed a statistically significant linear relationship between block rank and PSE in the LP Group ($r^2 = .833$ [$F(1, 7) = 29.873$, $p = .002$]) but no statistically significant relationship in the SP Group ($r^2 = .306$ [$F(1, 7) = 2.642$, $p = .155$]).

Fig. 4C plots the mean widths of the individually fitted PFs (% absolute line length ±1 SE) for each block of the experimental session (LP Group on left, SP Group on right). Both groups displayed a slight increase in curve width over the course of the experimental session. A 2 (Group) × 2 (time-on-task) × 2 (line length) Factorial ANOVA confirmed a main effect of time-on-task on curve width [$F(1, 30) = 5.069$, $p = .032$] but no other main effects or interactions.

Discussion

The results of **experiment 1** highlight the dynamic nature of visuospatial attentional bias in healthy young participants. The direction and magnitude of bias displayed on a landmark task can be modulated by both line length and time-on-task within participants, suggesting that systematic attentional bias does not represent a static trait within individuals, but fluctuates over time and depends on context and stimulus characteristics. The results replicate those of previous studies that have found a slight but consistent overall leftward bias on the landmark task in long lines (McCourt, 2001; McCourt & Jewell, 1999; Rueckert et al., 2002 and Schmitz et al., 2011) an effect of line length on subjective line midpoint in healthy participants (McCourt & Jewell, 1999; Mennemeier et al., 2002; Rueckert et al., 2002 and Heber et al., 2010), and a time-on-task effect consisting of a left- to rightward shift in subjective midpoint after prolonged practice on long lines (Manly et al., 2005; Dufour et al., 2007), here after approximately 1 h of task performance. In addition, it is shown for the first time that this time-on-task effect transferred to un-practiced short lines (i.e., is additive across long and short lines), indicating a common denominator of line bisection performance on both long and short lines, and speaking against models which assume distinct processes (such as orientation/estimation or Local/global distinction). Finally, there was no time-on-task effect when participants practiced extensively on short lines, in spite of a similar decrease in subjective alertness over the course of the experimental session. This suggests that the time-on-task effect is not specific to declining alertness *per se*, but only shows with specific stimulus characteristics (long lines). Firstly, I discuss accounts of the time-on-task effect, before interpreting the line length effects observed on midline judgement in the light of current models of spatial attention.

Time-on-task effect: no evidence for the general vigilance account but for stimulus-specific neuronal fatigue

Models of pseudoneglect in healthy participants emphasize RH-dominance in spatial attention and/or associated connectivity patterns as important factors contributing to the general leftward advantage (e.g., Reuter-Lorenz et al., 1990; Foxe et al., 2003; Thiebaut de Schotten et al., 2005; Bultitude & Aimola-Davies, 2006 and Siman-Tov et al., 2007). It is possible that this advantage is facilitated in states of high alertness by interactions between alerting and orienting networks in the RH (Sturm & Willmes, 2001; Corbetta & Shulman, 2002 and Sturm et al., 2004). It follows that with increasing fatigue, this advantage may reduce and even reverse, thereby explaining the rightward shift in attentional bias observed with temporary and chronic reduced arousal (Bellgrove et al., 2004; Manly et al., 2005; Fimm et al., 2006; Dufour et al., 2007; Robertson & Manly, 1999; Lazar et al., 2002; Matthias et al., 2009; De Gutis & Van Vleet, 2010 and Chica et al., 2012). Previous studies on the reduction or reversal of pseudoneglect (i.e., the left- to rightward bias) over the course of 40–60 min of landmark task performance have focused on long lines (Manly et al., 2005; Dufour et al., 2007). Here, it is shown that this effect depends on line length during continuous performance, but that the reduction in subjective alertness does not (alertness was equally reduced over the course of the session irrespective of line length). This is in line with Schmitz et al. (2011) who found that sleep deprivation under controlled conditions did not induce a consistent shift in landmark task midpoint estimation within participants, suggesting that it is not simply a reduction in general arousal that underlies the time-on-task effect. One potential explanation is that bisection of long lines may require more RH attentional resources than bisection of short lines. Because long lines extend into peripheral portions of both visual fields, they likely lead to a stronger need for integration of information from the periphery of both visual fields for task performance, and/or require maintaining a larger spotlight of attention. As a result, bisection of long lines is likely to be more taxing, and therefore may deplete neuronal resources for attention orienting faster than short lines.

Therefore, the time-on-task effect may be better explained by a neuronal fatigue account (than a general vigilance account), in which the neuronal resources for line bisection (likely engaging more the RH than the LH) become differentially depleted as a function of line length. This neural fatigue may not be indexed by a measure of subjective arousal level such as the Stanford Sleepiness Scale. This would overlap with the vigilance account in that it is a RH resource which decreases with fatigue (hence causes the rightward shift in attentional bias), but differs from the vigilance account in that it would be the resources that govern spatial attention *per se* which are affected, not necessarily in interaction with other RH functions.

Line length effect: no evidence for orientation/magnitude estimation account

Mennemeier et al. (2005) account for cross-over from long to short lines by positing a bias in magnitude estimation in addition to an attentional bias. The current results do not fit this hypothesis. Instead of the additive effect of time-on-task (rightward shift) irrespective of line length observed here (long line practice) the orientation/estimation hypothesis would predict an interaction of time-on-task and line length. That is, rightward orienting shifts should place subjective midpoints in long lines to the right (previously left) as a result of a tendency to underestimate line length associated with long lines; and should place midpoints of short lines to the left (previously right) because of overestimation of short line length. In fact the opposite was observed here, as post-practice mean subjective midpoints were actually biased further to the right (in % of absolute line length) in the short lines than in the long lines.

This suggests that the orientation/estimation hypothesis does not capture ‘cross-over’ behaviour in landmark task performance of a sample of young healthy participants. It has to be noted however that validation studies of this hypothesis have been limited to manual line bisection and reproduction tasks (in which line lengths are estimated and drawn from memory) in neglect patients and elderly controls (Mennemeier et al., 2005). It is therefore conceivable that accounts of line length effects may differ as a function of task demands and the studied population.

Line length effect: no evidence for the local/global hemispheric specialization account

The “local/global” hemispheric specialization hypothesis of the line length effect is based on previous research which has established functional hemispheric asymmetries in global (RH dominant) versus local (LH dominant) object processing (Sergent, 1982; Flevaris et al., 2011). The hypothesis posits that the leftward bias for bisection of long lines versus the rightward bias for bisecting short lines may originate from a RH/LH processing advantage for low/high spatial frequencies and/or global/local stimulus aspects (Monaghan & Shillcock, 2004; Gallace et al., 2008). This hypothesis would predict that as neuronal fatigue of attention resources increases, or general vigilance decreases (both cases being associated with a RH-depletion with time-on-task), long and short line bisection should not be affected to the same extent because of differential RH- versus LH-contribution to long and short line processing. While subjective midpoint should shift more rightwards in long lines (task-relevant RH resource becomes depleted), subjective midpoint in short lines should be less affected (because RH contributes less to short line judgement). Again, this would predict an interaction between time-on-task and cross-over, not the observed additive effect. The current data therefore also speak against this hypothesis, at least as an account of the line length effect. Though it may be argued that the use of only two line lengths in the current study represents a limited range, the length of the short lines (1 cm, .531° of visual angle) was well within the range of those previously found to induce a reversal of bias compared to long lines (see McCourt & Jewell, 1999 and Rueckert et al., 2002 where cross-over occurred at about 2–4°). Therefore, and because significant differences between long and short line bisection performance were observed here, as well as cross-over in short lines with time-on-task, it appears that the chosen line lengths were appropriate for testing and discarding the local/global hypothesis as an origin of the line length effect.

Alternative models explaining the line length effect

The current findings show that spatial bias modulates with state factors (time-on-task) and stimulus characteristics (line length). Moreover, because state- and stimulus-dependent changes were additive, it is concluded that one common process controls attentional bias under all tested conditions.

But how can a general offset in bias between long and short line bisection be reconciled with a unitary mechanism controlling line bisection under both conditions? If a common mechanism is to explain this offset (as suggested by the findings), this mechanism should then affect long lines more strongly than short lines due to some particular stimulus characteristics. The most straightforward candidate mechanism is that long line bisection may tap more into RH attentional resources, because of the need to integrate information from bilateral peripheral visual fields, or a large spotlight of attention (see also discussion of the time-on-task effect above). As a result, RH resources may in general be more activated with long than short lines, hence leading to a leftward shift. A second candidate mechanism is bilateral attentional competition, which should increase with increasing line length and therefore bilateral peripheral stimulation. In neglect patients, the level of inter-hemispheric competition exacerbates attentional imbalance (Doricchi et al., 2005; Urbanski & Bartolomeo, 2008; Bonato et al., 2010 and Charras et al., 2010) with right-sided stimuli having a negative impact on the processing of left-sided stimuli (Posner et al., 1984; Baylis et al., 1993; Urbanski & Bartolomeo, 2008 and Charras et al., 2010). If this extinction-like behaviour flips side in healthy participants (as does pseudoneglect), then extinction would occur more for right parts of the visual field during bisection of long lines leading to a more consistent leftward bias. This may occur to a much lesser extent with short lines, due to the lack of peripheral extensions of the lines.

Such attentional accounts of the line length effect have been formalized by Anderson (1996). In this mathematical model, observers bisect lines at the point at which the 'salience' of the two ends of a line are perceived to be equal, where salience is mapped to spatial location along the left-right continuum through the combined contribution of the left and right hemispheric attentional systems, each modelled independently. As a result, perceived salience (and subjective length) of each half of a line depends on how far the line extends into the visual field and on the modelled hemispheric contributions. Anderson (1996) showed that his model can explain cross-over for long versus short lines in neglect patients, and accordingly that purely attentional accounts may provide a unitary explanation for line length effects. In contrast to such purely attentional accounts, Savazzi et al., (2007) and Savazzi, (2008) have shown that a general left-right distortion of the mapping of external space onto an internal representation (spatial anisometry in neglect: Milner et al., 1993; Milner & Harvey, 1995; Bisiach et al., 1998 and Bisiach et al., 1999) may provide the basis for a unitary explanation of the line length effects in neglect patients, and possibly pseudoneglect in healthy subjects (though see Doricchi et al., 2008 and Binetti et al., 2011 for results contrary to the space anisometry account of cross-over).

Irrespective of what mechanism may explain the offset of line midpoint with line length, the current data provide further arguments that line bisection in healthy participants is governed by one mechanism, and that stimulus-dependent biases in line bisection are determined by how these stimulus characteristics deploy this common mechanism (rather than by distinct processes). Under this model, any change in attentional bias (e.g., with time-on-task) would transfer to both long and short lines.

Note on learning as a confound of the time-on-task effect

The rightward shifts of pseudoneglect with time-on-task have been discussed above in terms of a shift in attentional bias or spatial distortions. Could some of these changes in line bisection behaviour simply be explained by the participants becoming more accurate in line bisection performance over time (progressively converging from pseudoneglect to veridical midline judgment)? There are several aspects in the data that clearly do not support an interpretation of the time-on-task effect in terms of learning. Firstly, the rightward shift in subjective midpoint with extended time-on-task in the long lines transferred to post-practice performance in the un-practiced short lines. Secondly, psychometric curve widths, which provide a measure of the precision of participants' line midpoint judgements, increased with extended time-on-task revealing that participants did not become more accurate in their performance. Thirdly, reduced response consistency and increased variability in performance alone cannot explain the observed systematic rightward shift, since both the long and short line practice groups displayed an increase in curve width over the blocks of the experimental session, yet only the long line practice group displayed a shift in subjective midpoint. Fourthly, the observed shift cannot be attributed to the uni-manual (right hand) response across the experimental session since the shift occurred in one group only. Finally, in one condition (short line performance after long line practice), the rightward shift led to a cross-over effect crossing the veridical midline, i.e., to systematic overshoot (opposite directional error) relative to accurate performance.

Conclusion

The current findings emphasize the dynamic nature of subjective midpoint judgement in healthy participants suggesting that both line length and time-on-task can influence performance in the landmark task. The results add further weight to an interpretation of the time-on-task effect in pseudoneglect as representing an endogenous shift in attentional bias, rather than learning, and best fit a model which takes into account the dynamic nature of spatial attention and emphasizes a common mechanism for the control of long and short line bisection despite the line length effect, i.e., a systematic offset in subjective midline judgement of long and short lines.

In order to further elucidate the mechanisms and neural correlates of the line length effect, in the following chapter (using the same stimuli as in **experiment 1**) I will compare event-related potentials between long and short line landmark task performance.

Chapter 2

On the neural origin of pseudoneglect: EEG-correlates of shifts in line bisection performance with manipulation of line length

Introduction

As reviewed in the General Introduction, numerous lesion and neuroimaging studies have suggested visuospatial attention processing to be predominantly lateralized to the right hemisphere (RH) of the human brain (Driver & Mattingley, 1998; Halligan et al., 2003; Harvey & Rossit, 2012; Karnath & Rorden, 2012; Mort et al., 2003; Parton et al., 2004; Vallar, 1998; Cai et al., 2013; Cavezian et al., 2012; Çiçek et al., 2009; Fierro et al., 2001; Fink et al., 2000a; Fink et al., 2000b; Fink et al., 2001; Foxe et al., 2003; Thiebaut de Schotten et al., 2005; Thiebaut de Schotten et al., 2011 and Waberski et al., 2008) and this lateralization is thought to underlie pseudoneglect. As evidenced by the results of **experiment 1**, the degree of lateralized bias in visual processing is subject to dynamic changes within participants, being modulated by experimental manipulation of non-spatial attentional factors such as time-on-task/arousal level (Bellgrove et al., 2004; Benwell et al., 2013b; Dodds et al., 2008; Dufour et al., 2007; Fimm et al., 2006; Manly et al., 2005; Matthias et al., 2009, Newman et al., 2013 and Robertson et al., 1998) and/or attentional/perceptual load (Bonato et al., 2010; Peers et al., 2006; Perez et al., 2008; Perez et al., 2009 and Vuilleumier et al., 2008). With regard to non-clinical participants, prolonged time-on-task, reduced arousal and increased perceptual load all tend to result in a rightward shift in spatial bias and hence attenuation of the typical left bias (Bellgrove et al., 2004; Benwell et al., 2013b; Dodds et al., 2008; Dufour et al., 2007; Fimm et al., 2006; Manly et al., 2005; Matthias et al., 2009; Newman et al., 2013; Perez et al., 2008 and Perez et al., 2009). The rightward shift has been attributed to an interaction between spatial and non-spatial attention functions in the RH, localized respectively to the dorsal frontoparietal attention network (engaged in the control of spatial attention) and the ventral frontoparietal attention network (engaged in the maintenance of arousal and the detection of novel/salient stimuli). Depletion of processing capacity in the right lateralized ventral network under conditions of low arousal and/or high attentional load is postulated to reduce the left visual field advantage by causing right dorsal network downregulation (Corbetta and Shulman, 2002; 2011; Newman et al., 2013), though the results of **experiment 1** suggest that reduced arousal alone may not explain the rightward shift in bias as the time-on-task effect was stimulus-dependent.

As shown in **experiment 1**, another factor which modulates the magnitude of bias (associated with line bisection decisions) is the length of the to-be-bisected line, again both in neglect patients (Anderson, 1996; Anderson, 1997; Harvey et al., 1995; Mennemeier et al., 2005; Monaghan and Shillcock, 1998 and Ricci and Chatterjee, 2001) and non-clinical samples (Heber et al., 2010; McCourt & Jewell, 1999; Mennemeier et al., 2005; Rueckert et al., 2002 and Thomas et al., 2012). Recent studies in healthy participants, employing a perceptual computerized line bisection task (the landmark task (Harvey et al., 2000; Milner et al., 1992 and Olk and Harvey, 2002)), have shown that while long lines (subtending > 6° horizontal visual angle (VA) in length) induce a systematic (usually left) bias, short lines (subtending < 2° VA) induce no such consistent bias (**experiment 1**, Heber et al., 2010 and Thomas et al., 2012) or can even be associated with a significant right bias when combined with manipulation of non-spatial attention through extended time-on-task (**experiment 1**). Hence, as with manipulation of non-spatial attention, manipulation of line length leads to a rightward shift in spatial bias. The line length effect has been hypothesized to arise from asymmetrical hemispheric contributions (RH > LH) to the perceived salience of visual stimuli that is more pronounced for peripheral stimuli or stimulus-parts stretching into the peripheral visual field, hence a left bias arises more prominently for long rather than short lines (Anderson, 1996; McCourt & Jewell, 1999; Monaghan & Shillcock, 1998 and Monaghan & Shillcock, 2004).

While a right hemispheric dominance in spatial attention and a left spatial bias in visual processing are well documented, and the attenuation of left visual field bias with depletion of right hemispheric function would suggest a close link, relatively little is known about the information processing stages during which the bias arises. Only a handful of electroencephalographic (EEG) studies have looked at the neural correlates of line bisection per se in healthy participants (Foxe et al., 2003; Longo et al., 2015) and at the neural correlates of the above rightward shifts in bias in particular (for manipulation of time-on-task see Newman et al., 2013; for perceptual load see O'Connell et al., 2011 and Perez et al., 2009). Also, while spatial bias is shifting rightward with both manipulation of non-spatial attention (such as perceptual load and arousal) and stimulus properties (line length), it is unclear whether one common mechanism underlies both of these changes, or alternatively whether they are determined at distinct processing stages. Unlike for perceptual load (O'Connell et al., 2011; Perez et al., 2009), time-on-task (Newman et al., 2013) and viewing distance (Longo et al., 2015), to date the neural correlates of the effect of line length have not been investigated empirically using EEG. Elucidating the neural correlates of different experimental manipulations of lateralised spatial bias within participants and whether these are driven by the same or different mechanisms should help in understanding more fully the functional architecture of the visuospatial attention system.

In the present EEG study, the aim was to determine, for the first time, the neural correlates of the line length effect in healthy participants (rightward shift in line bisection performance with decreasing line length), and to interpret this in light of previous EEG studies on the neural correlates of line bisection performance per se (e.g. Foxe et al., 2003; Longo et al., 2015) and the rightward shift in spatial bias with manipulation of non-spatial attention (O'Connell et al., 2011). Foxe et al. (2003) investigated the event related potential (ERP) correlates of line bisection decisions and reported right lateralized activity with source estimates in temporo-parietal junction (TPJ) during the early phase of bisection decisions (at the latency of the N1 component), followed by right superior parietal activity (in the vicinity of the intraparietal sulcus (IPS)), in good agreement with fMRI-signatures of landmark task processing (Cai et al., 2013; Cavezian et al., 2012; Çiçek et al., 2009, Fink et al., 2000a; Fink et al., 2000b and Fink et al., 2001). O'Connell et al. (2011) examined the neural correlates of the rightward shift in bias with increased attentional load using ERPs. Employing a lateralized target detection paradigm with a simultaneous central alphanumeric target detection task, the authors manipulated the level of attentional load required at fixation. Compared to the low central load condition (unique feature detection), high central attentional load (detection of conjunction of features) led to an attenuation of the RH–N1 response to contralateral stimuli (O'Connell et al., 2011). Interestingly, the effect again source-localized to regions of the right TPJ: a key node in the ventral frontoparietal attention network thought to determine spatial bias in interaction with the dorsal attention network (Corbetta & Shulman, 2002; 2011). The implication of the N1 component in the genesis of the spatial bias is in line with previous single pulse transcranial magnetic stimulation (TMS) studies in healthy participants (Dambeck et al., 2006; Fierro et al., 2001) and ERP studies of altered visuospatial processing in neglect patients (Di Russo et al., 2008; Tarkka et al., 2011). Based on the above studies, it was hypothesized that attenuation of right lateralized TPJ-activity at the latency of the N1 component may also be a good candidate signature of the rightward shifts seen in line bisection with manipulation of line length. In line with this, the effect of line length was found to be reflected predominantly during the N1 over the RH in regions of the TPJ (source estimates). Furthermore, the data reveal how neural activity maps onto shifts in behavioral bias. The attenuation of the N1 component over the RH by line length (long v short) was found to correlate with the associated rightward shift in behavioral bias across participants. Hence, the neural correlates of rightward shifts in attention through manipulation of central attentional load (see O'Connell et al., 2011) versus manipulation of line length (the present study) have much in common, both in terms of their anatomy (right TPJ) and timing (N1). Implications for understanding the processes involved in the rightward attentional shift with these manipulations are discussed.

Method

Participants were asked to perform two tasks on lines of two different lengths: A) the landmark task and B) a control condition in which they simply indicated if the presented line was transected or not (task manipulation adopted from Foxe et al., 2003 and Waberski et al., 2008). This served to examine the electrophysiological correlates of line bisection performance and differences in the bisection bias induced by the line length modulation. Note that the focus on the line length effect emphasizes the contrast between bisection of long lines and bisection of short lines (long minus short lines) within the same participant. As well as providing the means for investigating the neural correlates of the line length effect itself, this manipulation effectively corrects for individual factors influencing the EEG signal measured over the scalp (such as overall activation influenced by arousal level and individual differences in skull thickness and volume conduction). This correction is important as these factors may confound the scalp signals and render the comparison of ERP amplitudes between participants, and in particular brain–behaviour correlations across participants, problematic.

Participants

Nineteen right-handed participants (14 male, 5 female, mean age = 24.14 years, max = 30 years, min = 20 years) received financial compensation for their participation in the experiment. However, due to poor behavioural performance on the landmark task (see the Behavioural analysis of landmark task performance section), 2 participants were excluded from the final analysis. Written informed consent was obtained from each participant. All participants were volunteers naive to the experimental hypothesis being tested. All participants reported normal or corrected to-normal vision and no history of neurological disorder. The experiment was carried out within the Institute of Neuroscience and Psychology at the University of Glasgow and was approved by the local ethics committee.

Instrumentation and stimuli

Stimuli were presented using the E-Prime software package (Schneider et al., 2002) on a CRT monitor with a 1280 × 1024 pixel resolution and 85 Hz refresh rate. The same long and short line landmark stimuli as in **experiment 1** were used. Figure 5 shows a schematic of the trial procedure. At a viewing distance of 100 cm, ‘long’ lines subtended 15.3° (width) by .39° (height) VA. At the same viewing distance, ‘short’ lines subtended 1° by .39° VA. For the line bisection task, lines were transected at 1 of 29 points ranging symmetrically from ± 4.36% of absolute line length to veridical center. All lines were displayed with the transector location centered on the vertical midline of the display (i.e., aligned to a central fixation cross which preceded the presentation of the lines, see below). For the non-spatial control task (judge whether line is transected or not), non-transected lines were intermixed with the same bisected lines used for the line bisection task.

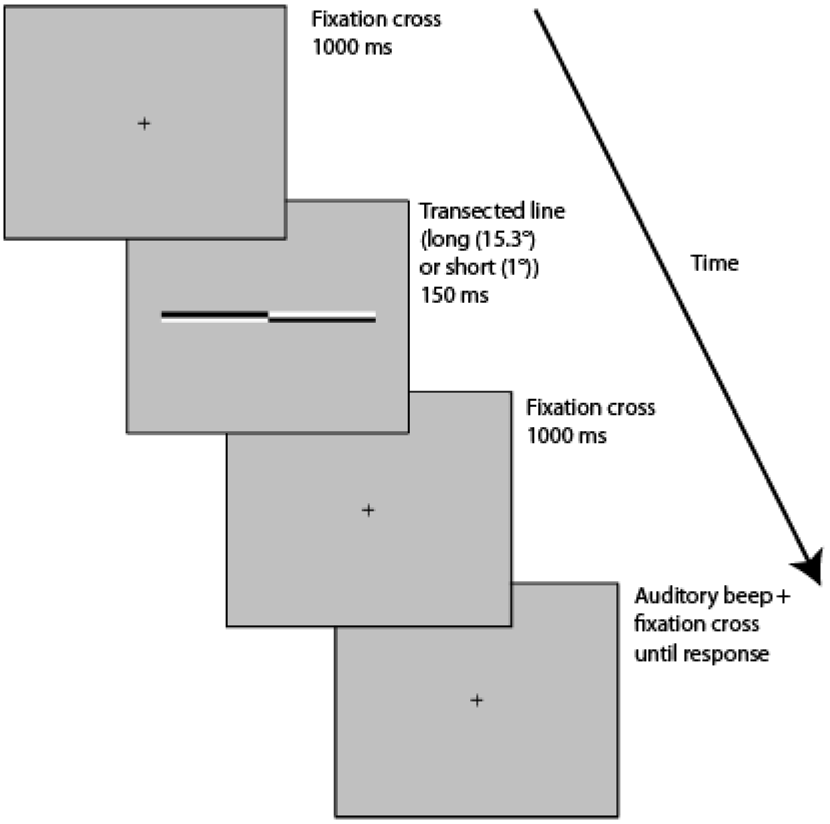


Figure 5. **A schematic of the trial procedure.** Each trial was initiated by the appearance of a fixation cross for 1000 ms followed by presentation of the line stimulus for 150 ms followed by the fixation cross, which remained on the screen until the end of the trial. Participants were requested to delay their manual response for 1000 ms following the presentation of the stimulus in order to obviate for motor artifacts in the EEG signal. The onset of the response period was indicated by an auditory beep (100 Hz). In landmark task blocks, participants were asked to judge which end of the pre-transected line appeared shortest. The long line displayed is veridically transected but lines could be transected at any 1 of 29 points ranging symmetrically from ± 4.36% of absolute line length to veridical center. Long (15.3° × .39°) and short (1° × .39°) lines were presented in separate blocks. In control task blocks, 25% of the presented lines were not transected (plain white lines) and participants were asked to indicate whether the line was transected or not.

Procedure and tasks

Subjects were seated in a comfortable chair 100 cm from the display monitor, their midsagittal plane aligned with the centre of the screen. Subjects performed two different tasks during the experiment: the landmark task in which they were asked to judge which of two ends of a pre-transected line was shorter (left or right response) and a control task in which they were asked to judge simply whether a line was transected or not. Each subject performed 4 blocks overall (174–180 trials per block): 1 block of the landmark task with long lines (Long Line LM (LL LM)), 1 block of the landmark task with short lines (Short Line LM (SL LM)), 1 block of the control task (Long Line Control (LL C)) and 1 block of the control task with short lines (Short Line Control (SL C)). Each block took 8–10 min to complete. The order of block performance was counter-balanced across subjects.

Landmark task

During landmark task performance (both for long and short lines) (see also Fig. 5), each trial began with presentation of a fixation cross (.39° height × .39° width) for 1 s followed by presentation of the transected line (150 ms). The transection mark was always aligned with the fixation cross (i.e., the eccentricity of the line endpoints varied across trials while the transection point always appeared at the same central position), therefore preventing use of the position of the fixation cross relative to the bisection mark, as a reference point for bisection judgments. Following the disappearance of the line, the fixation cross returned. Participants were instructed to delay their response for 1 s until they heard an auditory beep in order to obviate motor artifacts in the EEG signal. During the response period following the beep, participants indicated their judgment of which end of the line was shorter (which end of the line the transection mark appeared closest to) by pressing either the left or right response key on a keyboard. Participants always responded using their dominant right hand (right index and middle fingers respectively). Participants were instructed to hold their gaze on the center of the screen throughout each trial and to try to keep eye blinks/movements to a minimum. The subsequent trial began as soon as the response was made. Trials lasted between 2 and 3 s. Trial type (transector location) was selected at random within a block. During landmark task blocks, participants made 6 “left–right” judgments at each transector location (29 locations) such that estimates of perceived line midpoint were based on 174 trials.

Control task

During control task performance (both for long and short lines), trial structure was identical to the landmark task (see Fig. 5). Each trial began with presentation of a fixation cross (.39° height × .39° width) for 1 s followed either by presentation of a transected line (75% of trials) or a line of the same length with no transection mark (25% of trials) for 150 ms. Following the disappearance of the line the fixation cross returned. Again, participants were instructed to delay their response for 1 s until they heard an auditory beep. During the response period following the beep, subjects indicated their judgment of whether the line had contained a transection mark or not, by pressing either the left (transection mark present) or right (no transection mark) response key on the keyboard. The subsequent trial began as soon as the response was made. Trials lasted 2–3 s. Trial type (transector location and line type (plain v transected)) was selected at random within a block. This control task has been employed previously to dissociate EEG activity related to line bisection performance from that of an attentionally demanding non-spatial judgment (Foxe et al., 2003 and Waberski et al., 2008) and allows for equivalent button presses during landmark and control task performance. Control blocks consisted of 176 trials.

Behavioural analysis of landmark task performance

In order to obtain an objective measure of perceived line midpoint for both long and short lines in each participant, psychometric functions (PFs) were derived using the method of constant stimuli (for details of the fitted cumulative logistic function see **Analysis** section in the method of **experiment 1**). The width of the PF provides a measure of the precision of participants' line midpoint judgments per block. On the basis of extreme curve width values, two participants were excluded from further behavioural and EEG analyses: the curve widths of each of these subjects for both long and short lines were flagged as outliers by application of the median absolute deviation (MAD) rule for outlier detection. Inferential statistical analyses were performed on the individually fitted PF PSE values of the remaining 17 subjects. To test for a systematic directional bias in each condition, long and short line PSE values were separately compared to 0 (representing the veridical centre of the line) using a nonparametric 1-sample Wilcoxon’s signed rank test.

Electrophysiological measures

Continuous EEG recording was acquired from each participant at 1000 Hz through 62 scalp electrodes and 4 ocular electrodes (horizontal and vertical bipolar montage), with impedances < 10 kΩ (Brain Products). ERP-analysis was conducted using the EEGLAB toolbox (Delorme & Makeig, 2004) and the Mass Univariate ERP Toolbox (Groppe et al., 2011a). Source estimates were calculated using Cartool (Brunet et al., 2011; http://sites.google.com/site/fbmlab/cartool). Offline, the channel mean was removed from each channel, data de-trending was performed, a 0.3 high-pass filter and a 40 Hz low-pass filter were applied and the data were epoched between − 500 and 1000 ms pre- to post-stimulus onset. Thereafter, trials with abnormal activity (extreme value rejection criterion of ± 60 μV) or horizontal eye movements (based on horizontal electrooculogram) were rejected and bad channels were removed without interpolation. An independent component analysis (ICA) (Delorme & Makeig, 2004) was run using the runica EEGLAB function (Delorme & Makeig, 2004 and Delorme et al.,

2007) and components corresponding to blink activity were removed. Subsequently, data were re-epoched between − 300 and 500 ms and baseline corrected (− 300 ms to 0). Finally, previously rejected channels were interpolated using a spherical spline interpolation and the data were recalculated against the average reference. Responses to the non-transected lines in the control condition were not included in the EEG analysis as they did not appear during landmark task blocks. Consequently, the number of trials entered into the grand average per participant was equated to a common minimal denominator across conditions (taking into account only transected and artifact-free trials) which amounted to the following average number of trials entered into the grand average per condition: LL LM (103.7059 (min = 83, max = 120)), SL LM (104.1765 (min = 78, max = 123)), LL C (105.9412 (min = 89, max = 116)), and SL C (104.9412 (min = 96, max = 115)).

Mass univariate EEG analysis

The aim of the analysis was to dissociate the effect of line length (long v short lines) from the effect of task (landmark task v control task) on event-related potentials (ERPs), and to investigate whether an interaction exists between the two. To this end, main effects of line length were quantified by comparing long- versus short-line ERPs collapsed across landmark and control tasks. Then, the main effects of task were quantified by comparing landmark-task and control-task ERPs collapsed across long and short lines. Finally, line-length × task interaction effects were quantified by calculating the difference between long and short lines and comparing this difference between tasks (landmark task versus control task; double difference). Periods of amplitude modulation between conditions were identified using pairwise comparisons at each time point across all electrodes. This analysis was carried out separately for each of the two main effects (hereafter referred to as the “line length effect” and “line bisection effect”), as well as for the interaction between the two. In order to control the familywise error rate (FWER), cluster-based permutation tests (Bullmore et al., 1999; Groppe et al., 2011b and Maris & Oostenveld, 2007) were employed. The calculation of the test statistic involved the following: Based on the initial pairwise comparisons, all t-scores falling below a threshold corresponding to an uncorrected p-value of 0.01 were ignored. The remaining t-scores were formed into clusters by grouping together t-scores at adjacent time points and electrodes (this step was performed separately for samples with positive and negative t-values (two-tailed test)). The spatial neighbourhood of each electrode was defined as all electrodes within approximately 3.65 cm, resulting in a mean of 3.5 (max = 4, min = 1) and median of 4 neighbours per electrode. The t-scores of each cluster were subsequently summed to produce a cluster–level t-score. The most extreme cluster–level t-score across 20,000 permutations of the data was used to provide a data driven null hypothesis distribution. The relative location of each observed cluster level t-score within the null hypothesis distribution indicates how probable such an observation would be if the null hypothesis were true (no ERP difference between conditions). A 1% alpha level was adopted in order to strengthen familywise error rate control.

Hemispheric asymmetry EEG analysis

In order to probe hemispheric lateralization in the ERPs related to the line length and the line bisection effects, the electrode showing the largest sensitivity to each manipulation (as indexed by the largest t-score) and the equivalent contralateral electrode were selected from the time periods specific to each effect. The mean amplitudes at these electrodes during the time periods of differences between conditions were averaged and entered into a 2 × 2 (hemisphere × line length / task) repeated measures analysis of variance (ANOVA).

Correlation analysis

To further investigate the relationship between the bisection bias and right hemispheric activity related to the effects of line length or task (which both proved to be right lateralized, see the Results section), separate correlation analyses were carried out between peak ERP amplitude and bisection bias during time periods associated with both the line length effect and the line bisection effect. As behavioural measures, the individual differences in behavioural bias associated with the difference in line length (i.e. PSE for long lines minus PSE for short lines) were entered into the correlation analyses. This subtraction between conditions (but within participants) controls for inter-individual differences in arousal levels potentially confounding the behavioural bias, because bias per se depends on time-on-task whereas the relative bias (long minus short) does not (as shown in **experiment 1**). Behavioural biases were measured in pixels relative to veridical line centre. These values were correlated with the corresponding individual ERP difference associated with the effect of line length or alternatively, with the individual ERP difference associated with the line bisection effect. To determine individual ERP differences associated with the line length manipulation, the electrode showing the strongest line length effect (as indexed by the highest t-score) was selected and its peak amplitude during the line length effect period extracted for both conditions from each participant and then subtracted (long lines minus short lines). Likewise, to obtain an individual measure of ERP activity specific to line bisection, the electrode showing the strongest line bisection effect was selected, peak amplitudes (during the line bisection effect period) extracted for both conditions per participant, and then subtracted (landmark task minus control task). In analogy to behaviour, subtracting ERP data between conditions (but within participants) effectively corrects for inter-individual differences potentially confounding the EEG signals, such as arousal, skull thickness or volume conduction. Both Pearson's r and Spearman's rho were calculated for each correlation (with their 95% percentile bootstrap confidence intervals) in order to attain robust measures of association.

Source estimates and analysis

We estimated the localization of the electrical activity in the brain using a distributed linear inverse solution (minimum norm) applying the LAURA regularization approach comprising biophysical laws as constraints (Grave de Peralta et al., 2004; Grave-de Peralta et al., 2001 and Michel et al., 2004). LAURA selects the source configuration that better mimics the biophysical behavior of electric vector fields (i.e. activity at one point depends on the activity at neighboring points according to electromagnetic laws). LAURA was implemented in a realistic head model using 4024 nodes, selected from a 6 × 6 × 6 mm grid equally distributed within the gray matter of the Montreal Neurological Institute's average brain. To estimate the source of the line length effect and the line bisection effect, statistics were performed on the source estimations in the time periods associated with the effect of line length (100–200 ms; comparing source estimates of long lines versus short lines, collapsed over tasks) and with the effect of task (230–500 ms; comparing source estimates of line bisection versus control task, collapsed over stimuli).

Results

Behavioural results

Figure 6 presents the median of individually fitted PSE's (% of absolute line length relative to veridical centre ± 1 SE) as a function of line length. In long lines, median PSE was displaced to the left of veridical centre by − 0.35%, and this bias was significantly different from veridical centre (0) (Wilcoxon's signed-rank test, p = .044) indicating a systematic leftward bias. In short lines, median PSE was displaced to the left of veridical centre by − 0.15%, but this was not significantly different from veridical centre (0) (Wilcoxon's signed-rank test, p = .554) indicating no systematic bias in short lines.

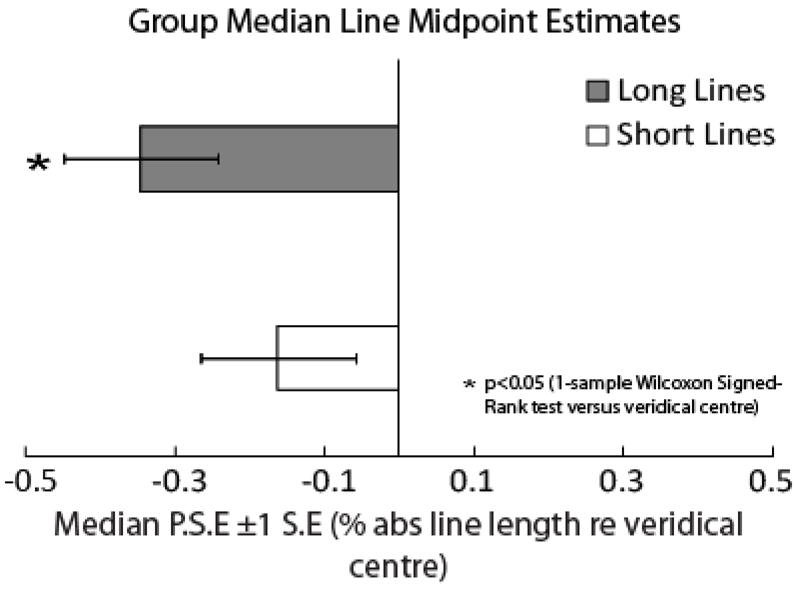


Figure 6. **Behavioural bias data.** Group-averaged (N = 17) point of subjective equality (± 1 SE) for both long (gray bar) and short (white bar) landmark task performance (in % of absolute line length relative to veridical center). Negative values indicate leftward bias. Note the typical systematic leftward error (pseudoneglect) is stronger for long than short lines.

EEG results

The group averaged visual evoked potentials for all electrodes (from − 100 to 500 ms relative to stimulus onset) are presented as butterfly plots separately for all four conditions in Figure 7. Also presented are group averaged topographies at time points corresponding to the traditional P1, N1, P2 and P3 series of ERP components. Figures 8A and 9A illustrate the corresponding global field power (GFP) plots for each of the four conditions (upper left panels, information duplicated in Fig. 8 and Fig. 10 for a better comparison with the respective mass univariate results illustrated below). These plots clearly reveal an early grouping of condition according to line length (red & blue solid lines vs. red & blue dashed lines: i.e. long vs. short lines) which occurs between 100 and 200 ms post-stimulus onset. In a later time window (300–400 ms), these conditions regroup according to task (red lines vs. blue lines: i.e. bisection vs. control task). The corresponding mass univariate analysis revealed these differences to be significant. The line length effect (long versus short lines, Fig. 8A) preceded the line bisection effect (line bisection versus control line judgment task, Fig. 10A) with no overlap of the two effects in time. In addition, no significant interaction effect between line-length and task was found at any time point during the epoch (not shown). Below, the results of the line length effect and of the follow-up analyses on source estimates and the relation to behaviour (Line length effect section) are presented, before the line bisection effect and follow-up analyses (Line bisection effect section).

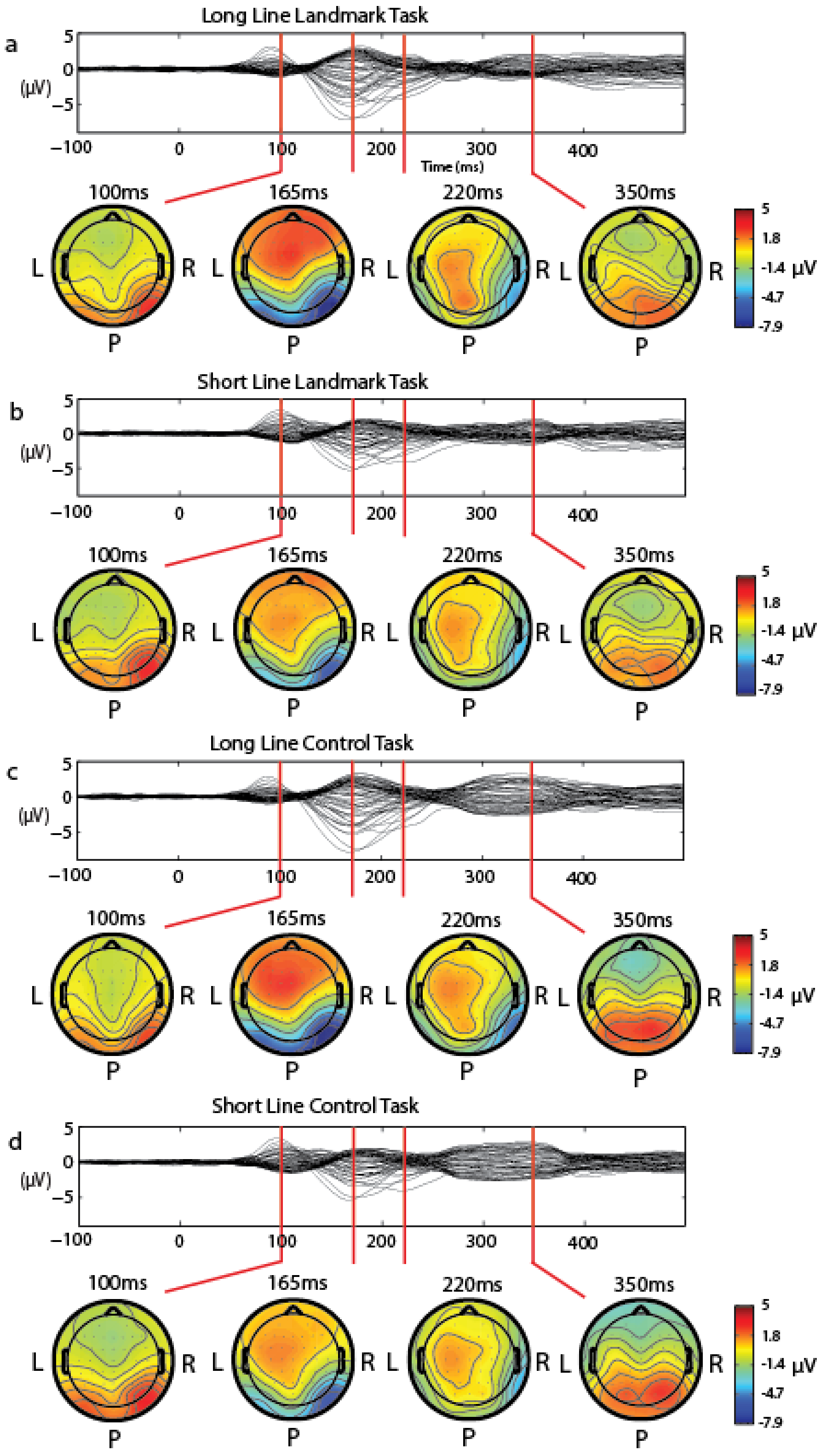


Figure 7. Butterfly plots and topographies. Group-averaged (N = 17) voltage waveforms (62-channel butterfly plot) and topographic maps at selected time points corresponding roughly to the traditional P1, N1, P2 and P3 components of the ERP. Data are shown separately for (a) long line landmark task, (b) short line landmark task, (c) long line control task and (d) short line control task performance. L: Left, R: right, P: posterior.

Line length effect

Fig. 8A (lower panel) presents the results of the mass univariate analysis of the effect of line length across time (x-axis) over electrodes (y-axis: anterior–posterior electrodes, broken down by left vs. right hemisphere: LH vs RH). The analysis revealed significant differences between long and short lines in terms of ERP amplitude from 102 to 202 ms post-stimulus onset over posterior electrodes (increased negativity in long lines compared to short lines, coded in blue tones) and frontal electrodes (increased positivity in long lines compared to short lines, coded in red tones). The peak of the effect (in terms of t-score) occurred 140 ms post-stimulus onset at RH parieto-occipital electrode PO4 (t-score = − 8.28, time point marked in Fig. 8A). Fig. 8B (left map) illustrates the topographical distribution of t-scores (long minus short) across the scalp at the selected time point (electrode of maximum difference between conditions shown in white). As well as being strongest over the RH, the increased negativity in long lines over posterior (occipital, parietal and central–parietal) electrodes was also more widespread over the right hemisphere as compared to the left hemisphere (see Fig. 8B). It is important to note that this right lateralized topography with a posterior maximum was stronger for long than short lines (line length effect) irrespective of task, as no interaction with task was found (see above), i.e. this occurred independently of whether the line needed to be mentally bisected or not.

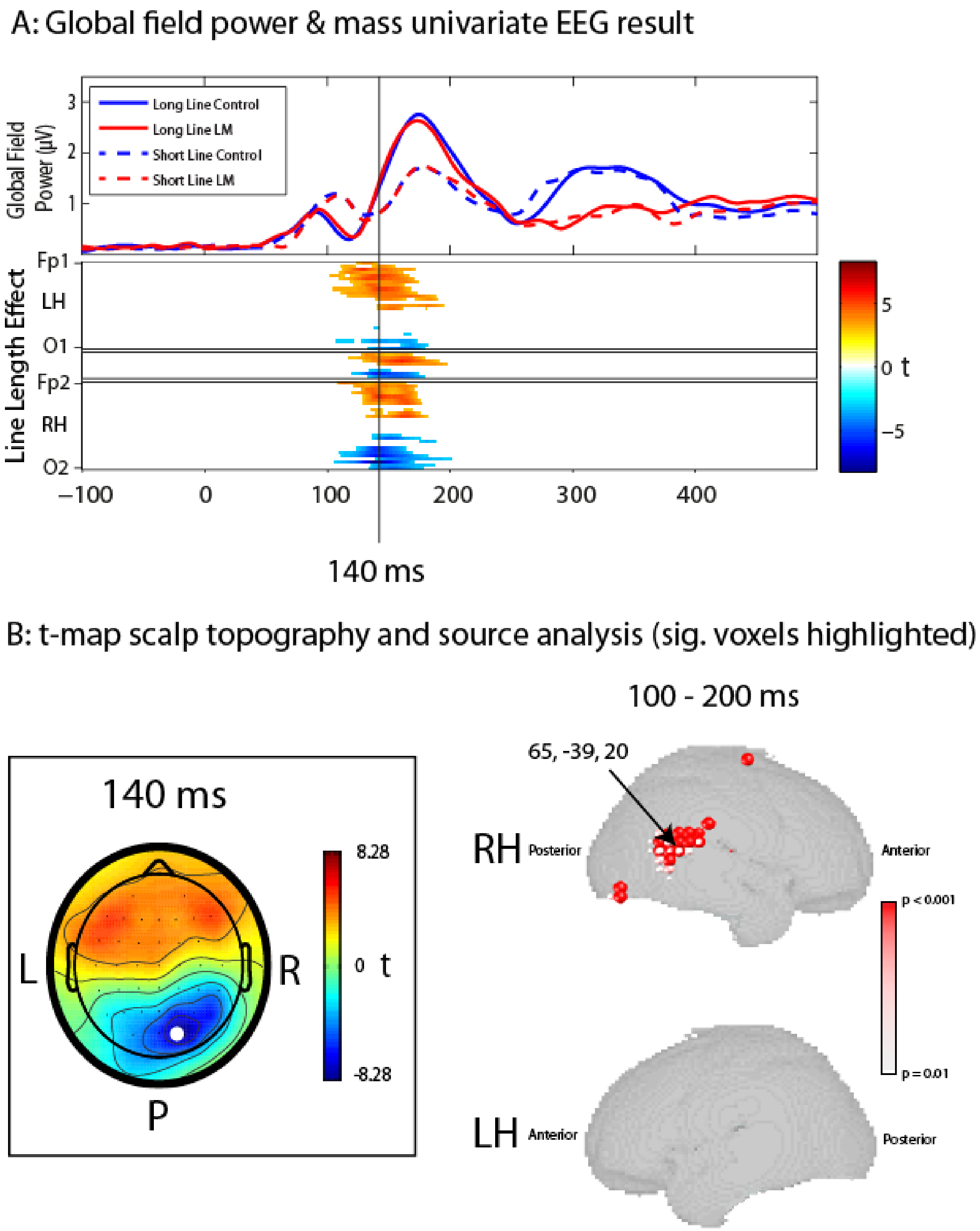


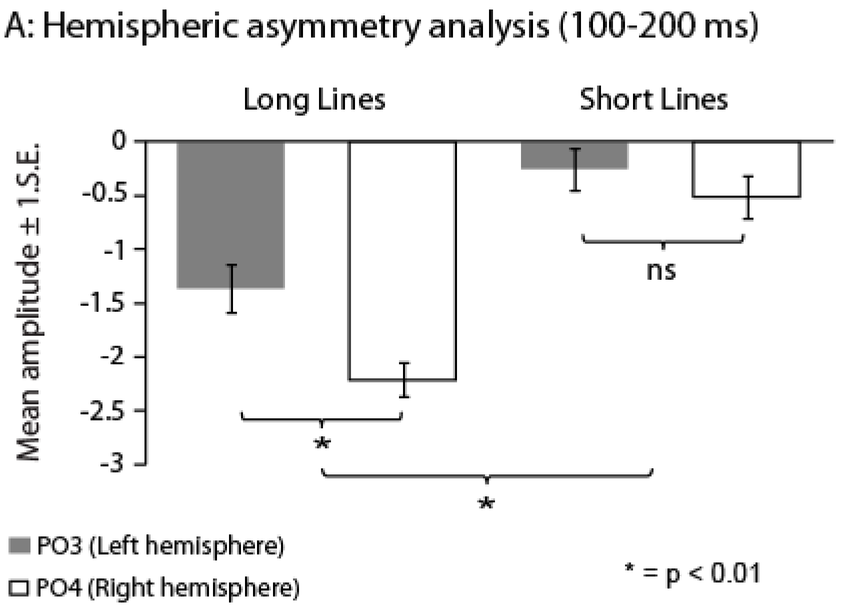
Figure 8. Line-length EEG-effects. (A) Global field power (GFP) over time for each experimental condition (upper panel) and mass univariate analysis results of the line-length effect (lower panel). Note in the GFP the early grouping of conditions according to line length (red & blue solid lines vs. red & blue dashed lines: i.e. long vs. short lines). The corresponding mass univariate analysis revealed these differences to be significant, peaking at 140 ms post-stimulus onset. (B) Topographical t-map (long minus short) across the scalp at 140 ms (left panel) and source estimate p-value maps of the effect (right panel, only p-values reaching a significance level of $p < 0.01$ are displayed, p-value coded by voxel size and color). Note that the line length effect peaked at electrode PO4 (electrode marked in white) and localized to the temporo-parietal junction of the RH (max. significant voxel: Talairach coordinate: 65, − 39, 20, peak t-value = 4.59, $p < 0.001$).

Line length topography: Hemispheric lateralization

To probe for hemispheric lateralization of the line length topography (not tested by the electrode-wise mass univariate analysis above), the mean ERP amplitude at homologous electrodes of maximum line length effects (PO3 vs PO4, 100–200 ms) were entered into a 2 (line length: long vs short) × 2 (hemisphere: PO3 left vs PO4 right) repeated measures ANOVA. The corresponding data are shown in Fig. 9A. The ANOVA revealed a significant main effect of line length [F (1, 16) = 29.534, p < .001], no significant main effect of hemisphere [F(1, 16) = 4.056, p = .061] and a significant line length × hemisphere interaction [F(1,16) = 10.176, p = .006]. Analysis of simple main effects (paired-sample t-tests performed between hemispheres for long and short lines separately) revealed that long lines induced a hemispheric asymmetry, with an increased negativity in the RH as compared to the LH [t(16) = 2.561, p = .021]. No significant difference in amplitude was observed between hemispheres during short line processing [t(16) = 1.080, p = .296]. This supports right hemispheric lateralization of the line length topography.

Line length effect: Correlation with behavioural bias across participants

The correlation analysis between the line length effect in RH-ERP (PO4) and the spatial bisection bias across individuals revealed a positive correlation in both Pearson [Pearson r = 0.544, p = 0.024] and Spearman analysis [Spearman r = 0.532; p = 0.028] and proved robust for both when bootstrapped [Pearson correlation: bootstrap 95% CI = 0.142, 0.741, Spearman correlation: bootstrap 95% CI = 0.022, 0.799] (see Fig. 9B). The larger the difference in RH peak (N1) amplitude over electrode PO4, the larger the difference in landmark task bias between short and long lines. This suggests that the level to which the RH is engaged during this time period (100–200 ms) influences the direction and magnitude of the lateralized behavioural bias.



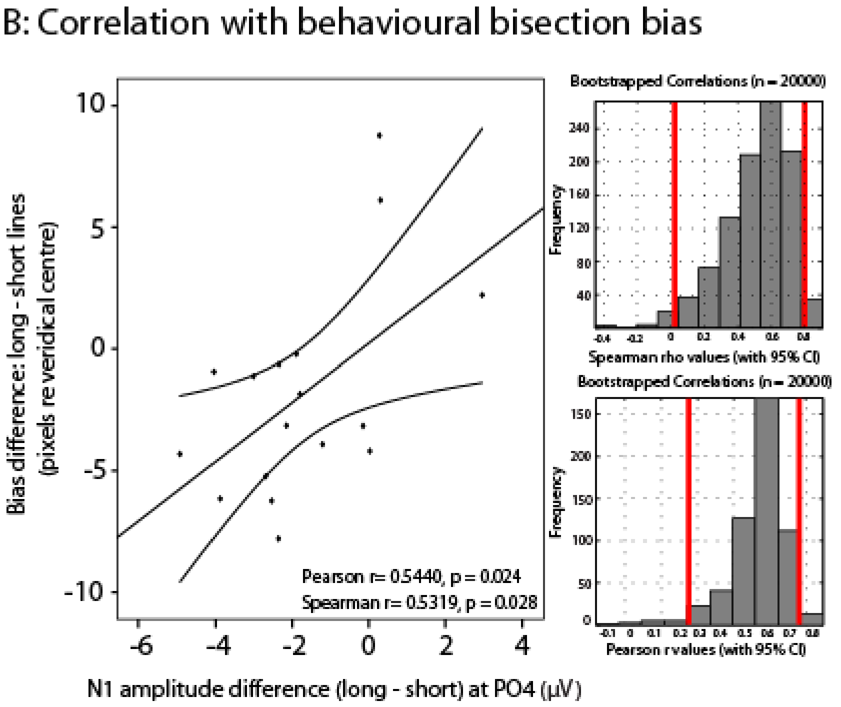


Figure 9. Line length hemispheric asymmetry analysis and brain-behaviour correlation. (A) Hemispheric asymmetry data for electrodes PO3/PO4. Long lines were associated with a hemispheric asymmetry (RH > LH), not present in short lines. (B) Relationship between the line-length effect in ERPs (long–short lines) at PO4 and the line-length effect in behavioural bias (long–short lines) across individuals (left panel), and histograms of the corresponding Pearson and Spearman bootstrapped correlation values (right panels, red bars = 95% confidence intervals). The correlation proved significant by both correlation methods ($p < 0.05$) and the bootstrapped 95% confidence intervals for both did not include 0.

The positive relationship suggests that the level to which the RH is engaged by “long” line processing during the early time period influences the direction and magnitude of lateralized behavioural bias.

Line length effect: Source estimates

In source space, voxels with maximum significant differences between the two line length conditions (long vs. short lines) in the relevant time interval (100–200 ms) were localized to the RH (see Fig. 8B). The source estimates implicated the right inferior parietal cortex and the right superior temporal sulcus in the line length effect indicating that regions of the right temporo-parietal junction (TPJ) were the likeliest generators of the line-length effect in sensor space (max. significant voxel: Talairach coordinate: 65, − 39, 20 (peak t-value = 4.59, $p < 0.001$)).

Line bisection effect

Fig. 10A (lower panel) illustrates the results of the mass univariate analysis of the effect of task (line bisection vs. control) in a time (x-axis) × electrode (y-axis) plot. The analysis revealed significant differences between line bisection and control task in terms of ERP amplitude from 231 to 500 ms post-stimulus onset over (mainly RH lateralized) centro-parietal electrodes (increased negativity in the landmark task compared to the control task, coded in blue tone) and a more widely spread difference over frontal electrodes (increased positivity in the landmark task compared to the control task, coded in red tones). Notable peaks (in terms of t-scores) were present at 280 ms post-stimulus onset at RH centro-parietal electrode CP6 (t-score = − 7.36), and at 378 ms post-stimulus onset at RH centro-parietal electrode CP4 (t-score = − 7.173, time points marked in Fig. 10A). Fig. 10B (left map) shows the topographical distribution of t scores (line bisection minus control) across the scalp at these time points (electrodes of maximum difference between conditions shown in white). Both of these topographies revealed increased RH negativity in line bisection as compared to the control task, and their maxima were located in a more superior position than the RH negativity of the line length topography (compare Figs. 8B vs. 10B, occipito-parietal vs centro-parietal positions).

Line bisection topography: Hemispheric lateralization

To probe for hemispheric lateralization of the line bisection topography (in analogy to the above analysis on line length effects), the corresponding data were subjected to 2 (task: line bisection vs control) × 2 (hemisphere: left vs. right CP electrodes) repeated measures ANOVAs. The 2 × 2 ANOVA on CP5/CP6 (230 ms–330 ms, data shown in Fig. 11A) revealed a significant main effect of task [$F(1, 16) = 11.721$, $p = .003$], no significant main effect of hemisphere [$F(1, 16) = .998$, $p = .333$] and a significant task × hemisphere interaction [$F(1, 16) = 7.893$, $p = .013$]. Analysis of simple main effects (paired-sample t-tests performed between control and line bisection task for the LH and the RH separately) revealed an increased negativity in the bisection task as compared to the control task in the RH/CP6 [$t(16) = 3.664$, $p = .002$] but no significant difference between the two in the LH/CP5 [$t(16) = 1.556$, $p = .139$]. Likewise, the 2 × 2 ANOVA on CP3/CP4 (330–500 ms, data not shown) revealed a significant main effect of task [$F(1, 16) = 26.005$, $p < .001$], no significant main effect of hemisphere [$F(1, 16) = 1.031$, $p = .325$] and a significant task × hemisphere interaction [$F(1, 16) = 7.627$, $p = .014$]. Analysis of simple main effects again revealed an increased negativity in the bisection task compared to the control task in the RH/CP4 [$t(16) = 6.179$, $p < .001$] but no significant difference in the LH/CP3 [$t(16) = .831$, $p = .418$].

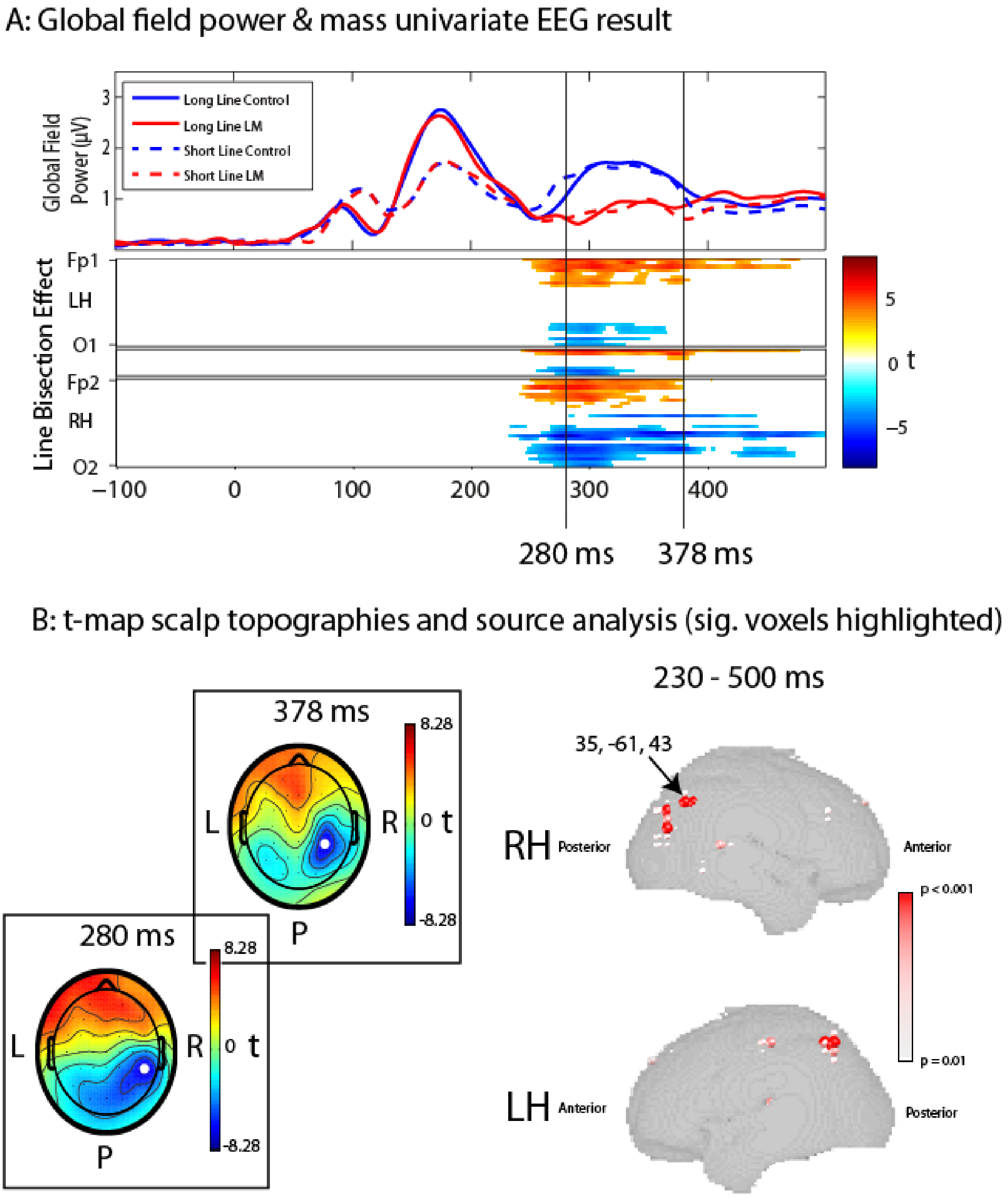


Figure 10. Line-bisection EEG-effects. (A) Global field power (GFP) over time for each experimental condition (upper panel) and mass univariate analysis results of the line bisection effect (lower panel). Note in the GFP the late grouping of conditions according to task (red lines vs. blue lines: i.e. bisection vs. control task). The corresponding mass univariate analysis revealed these differences to be significant, peaking at 280 ms and 378 ms post-stimulus onset. (B) Topographical t-maps (control minus landmark task) across the scalp at 280 ms and 378 ms (left panel) and source estimate p-value maps of the effect (right panel). Note that the line bisection effect peaked at electrodes CP6 (280 ms) and CP4 (378 ms), shown in white, and localized largely to the right superior parietal cortex (max. significant voxel: Talairach coordinate: 35, − 61, 43 (peak t-value = − 3.3, p < 0.01)).

Line bisection effect: Correlation with behavioural bias across participants

The above analysis of line bisection effects shows a stronger right lateralized centro-parietal negativity during line bisection as compared to the non-spatial control task in the later window of the epoch. However, this right lateralization occurred for line bisection independently of line length (no interaction with line length, see above), suggesting that activity during this time period is unlikely to account for pseudoneglect. In line with this view, ERP activity in this time window was not correlated with behavioural bias (see Fig. 11B). The correlation analysis between the line bisection effect in RH-ERP (CP6) and the spatial bisection bias across individuals revealed no significant association [Pearson r = − 0.220, bootstrap 95% CI = − 0.667, 0.270, p = 0.396; Spearman r = − 0.304, bootstrap 95% CI = − 0.744, 0.252, p = 0.236].

Line bisection effect: Source estimate

Those voxels with maximum significant differences between the two tasks (bisection vs control task) in the time interval associated with the line bisection effect (230–500 ms) were again localized to the right hemisphere, but with a more superior localization (see Fig. 10B). The source estimates implicated the right superior parietal cortex in the bisection effect. The maximum significant difference was observed at 35, − 61, 43 (Talairach coordinate (peak t-value = − 3.3, p < 0.01)), in the vicinity of the intraparietal sulcus (IPS).

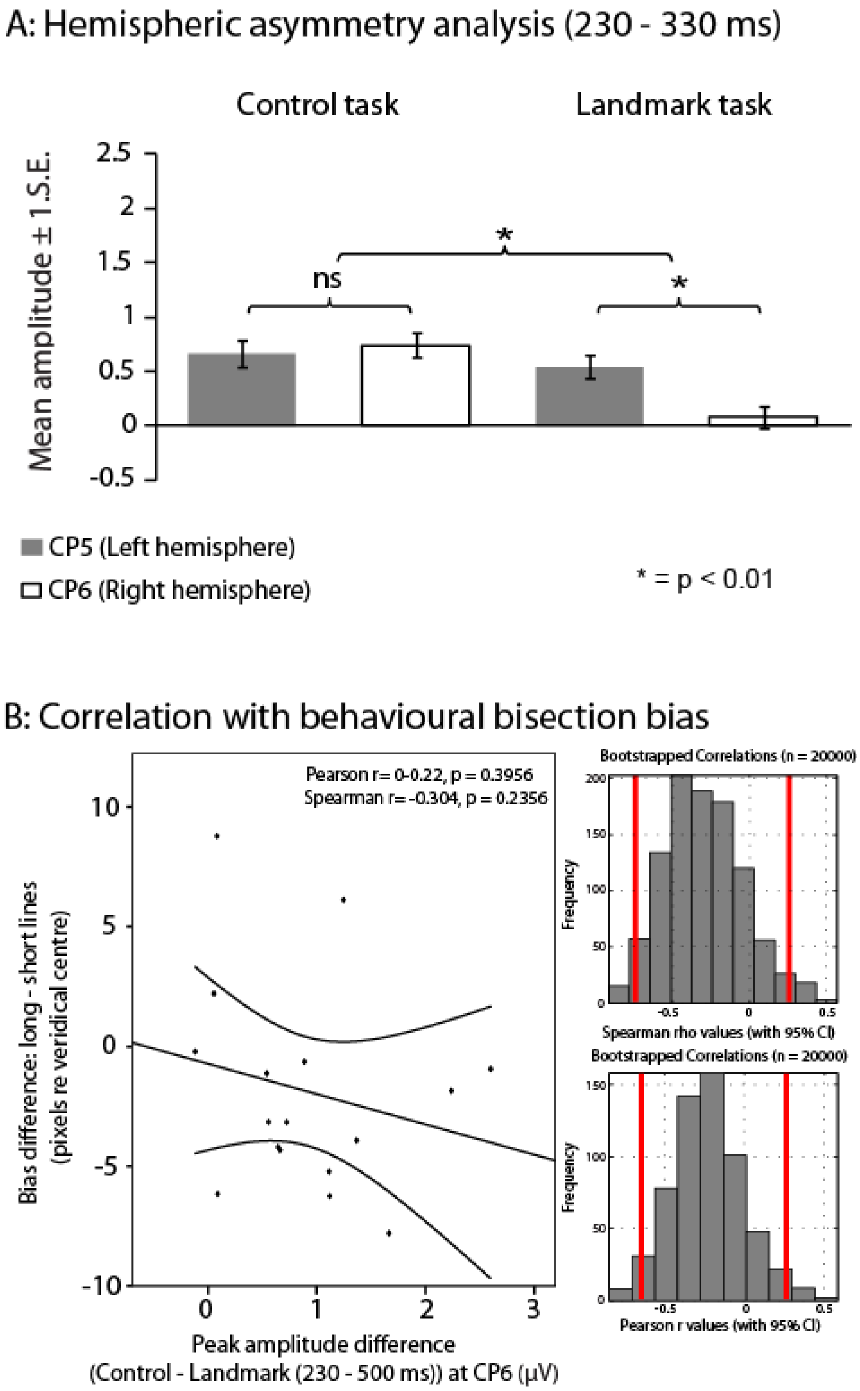


Figure 11. Line bisection hemispheric asymmetry analysis and brain-behaviour correlation. (A) Hemispheric asymmetry data for electrodes CP5/CP6. Landmark task performance was associated with a hemispheric asymmetry, not present during the control task. (B) Relationship between the line bisection effect in ERPs (control–landmark tasks) at CP6 and the length effect in behavioural bias (long–short lines) across individuals (left panel) and histograms of the corresponding Pearson and Spearman bootstrapped correlation (right panel, red bars = 95% confidence intervals). The correlation was not significant for either correlation method ($p > 0.05$) and the bootstrapped 95% confidence intervals for both included 0.

Discussion

In the current experiment, the neural underpinning of the line length effect in line bisection was investigated for the first time using stimulus-locked ERPs. Behaviourally, most participants displayed a systematic leftward bias (pseudoneglect) during long line landmark task performance whereas no systematic bias was observed during performance of the task with short lines, in line with the previously reported line-length effect (**experiment 1**, Heber et al., 2010, McCourt & Jewell, 1999, Rueckert et al., 2002 and Thomas et al., 2012). These EEG findings establish that an increased engagement of areas of the right lateralized ventral attention network contributes to the genesis of the spatial bias, and that this engagement is stimulus-driven (task independent because it was observed in both the line bisection and control tasks): an ERP response was found which showed higher amplitude to long than short lines, corresponded in timing to the N1-component and was right lateralized to areas of the temporo-parietal junction. Furthermore, the difference in peak N1-amplitude between long and short line processing correlated with the difference in line bisection bias between long and short lines across participants.

Neural (ERP) substrates for behavioural line bisection bias

The current findings, in combination with those of O'Connell et al. (2011), suggest a common neural substrate for the rightward shifts in behavioural bias observed with decreased line length and increased perceptual load respectively: Both experimental manipulations were associated with an attenuation of right-lateralized TPJ activity at the latency of the N1-component (O'Connell et al., 2011 and the present study). Extending the results of O'Connell et al. (2011), it is here shown in addition that the degree of this attenuation correlates with the degree of the rightward shift in behavioural bias across participants. Overall, this provides further evidence that pseudoneglect can be attributed to the predominant role played by the RH in visuospatial processing (as initially suggested by Heilman & van den Abell, 1980 and Mesulam, 1981 and later Reuter-Lorenz et al., 1990 and Bultitude & Aimola-Davies, 2006) and to areas of the right ventral attention network in particular (Corbetta & Shulman, 2002; 2011; Newman et al., 2013) especially when processing involves stimuli appearing/stretching into the periphery of the visual fields. This is in line with mathematical models of the relative hemispheric contributions to the perceived salience of visual stimuli (RH > LH) (Anderson, 1996; Monaghan & Shillcock, 1998 and Monaghan & Shillcock, 2004 and see the discussion of **experiment 1**). In light of these models, our results would suggest that the asymmetric hemispheric contribution (in favour of the RH) to the salience–perception of lateral visual stimuli can be attributed to an increased activation of areas around the right-TPJ (compared to the left) in long lines that is not present in short lines.

The question then arises as to why line length modulates the degree to which the right TPJ is activated, and how this would fit with the notion of the interplay between the right ventral arousal/re-orienting network and dorsal spatial attention network modulating spatial bias (Corbetta & Shulman, 2011, Corbetta et al., 2005,Corbetta et al., 2008, He et al., 2007 and Thiebaut de Schotten et al., 2011). Given that the right TPJ is preferentially activated during long line processing, the resources of the RH ventral network may be less engaged in processing short lines. It is conceivable that short lines may be less attentionally 'salient' and so activate the ventral network less strongly. Although this would not constitute a depletion of processing capacity in the RH ventral network with reduced line length (such as presumably achieved by increased foveal perceptual load and reduced arousal/time-on-task; see Bellgrove et al., 2004, Dodds et al., 2008, Dufour et al., 2007, Fimm et al., 2006, Manly et al., 2005, Matthias et al., 2009, Newman et al., 2013, Perez et al., 2008 and Perez et al., 2009), it would result in the same outcome (disengagement of the ventral network). Therefore, the common likely denominator of rightward shifts with manipulation of both line length and perceptual load/arousal is a disengagement of areas around the right TPJ, in line with the view that down-regulation of RH activity leads to a transient change in spatial attentional sampling at the periphery which attenuates the left visual field advantage and causes the observed rightward shifts in bias.

The above interpretation assumes that the line-length effect occurs due to a modulation of brain activity at a higher-order (visuospatial attention) processing stage. Yet, it is important to consider whether the current EEG results may alternatively be explained by a lower-level visual account related to the change in stimulus size (stronger visual evoked response to long relative to short lines). It appears that this explanation can be discarded given that the observed timing (N1), lateralization (RH only) and localization (TPJ) of the ERP effect is not in line with such a low-level account: If low-level factors alone accounted for the ERP-effect, one would expect differences between long and short lines to onset at an earlier stage of stimulus processing (such as the C1 component), with a more posterior bilateral topography and occipital source estimates (Di Russo et al., 2002; Foxe et al., 2008), and one would also not have expected a correlation with behavioural spatial bias at the latency of the N1 component.

Early versus late EEG responses in line bisection: stimulus-driven, reflexive vs. task-related, decisional stages of spatial processing

The current results reveal two main ERP-events that are modulated by the experimental manipulations, an early ERP-event occurring at around N1 showing characteristics of an automatic (reflexive) response (occurring independently of task and therefore likely primarily stimulus-driven) and a later event depending on task (spatial versus non-spatial line judgments) irrespective of stimulus properties (line length). Importantly, only the first event is correlated with line bisection behaviour, while the later is not. This dissociation strongly suggests that the two ERP events reflect different processes in task processing, further corroborated by their right hemispheric lateralization to two distinct sources, areas of the right TPJ versus right superior parietal cortex respectively. Note that the timing and localization of these two ERP-events accord with and extend the findings of Foxe et al. (2003) who report right TPJ source estimates at early phases of line bisection and right superior parietal cortex estimates (in the vicinity of IPS) at later phases, in good agreement with fMRI studies of landmark task processing (Cai et al., 2013, Cavezian et al., 2012, Çiçek et al., 2009, Fink et al., 2000a; Fink et al., 2000b and Fink et al., 2001). It is of interest to note that the time point and topography of the early effect implicate the N1, an early component of the visual ERP implicated in object discrimination and recognition (Allison et al., 1999; Doniger et al., 2001 and Vogel & Luck, 2000). In addition, pseudoneglect is stronger for solid continuous lines relative to line endpoint judgment, or lateralized segment distance/size judgments (Post et al., 2001), suggesting that behavioural biases may arise more strongly at an allocentric (object-based) level of processing (Foxe et al., 2003; Singh et al., 2011), or are strongly dependent on stimulus saliency/energy. In line with the latter view, it has been proposed that the strength of engagement of a right lateralized attention system is likely to depend on stimulus properties (see e.g. **experiment 1** and Snyder et al., 2012), such that more salient stimuli (here longer lines) may lead to a stronger engagement of this right hemispheric system, and consequently drive a stronger leftward behavioural bias.

As to the functional role of the task-related, right superior parietal cortex activation, it may rather be implicated at a decisional stage of task performance. In line with the finding of late superior parietal cortex/IPS activity-differences, previous imaging studies comparing the landmark task with a non-spatial control task have found modulation of activity to be strongly lateralized to the right superior parietal cortex (in the vicinity of IPS) both using EEG (Foxe et al., 2003, Longo et al., 2015), and fMRI (Cai et al., 2013, Cavezian et al., 2012, Çiçek et al., 2009, Fink et al., 2000a; 2000b and Fink et al., 2001). However, these studies were restricted to relatively long line task performance (> 6° horizontal visual angle). In the current study, right hemispheric dominance for landmark task processing was also found for short lines (1° horizontal visual angle) in the absence of any systematic behavioural bias, thus suggesting that the relatively late right hemispheric task effect (peaking at 280 ms post-stimulus onset in the current study and at 310 ms in Foxe et al., 2003) does not represent an activation pattern that can alone explain the genesis of spatial bias. Instead, the current finding of a correlation between the strength of RH activation earlier in time (100–200 ms) and the behavioural bias displayed across participants clearly point to an earlier temporal locus of the bias, in line with previous single-pulse TMS studies (Dambeck et al., 2006; Fierro et al., 2001) and ERP studies of visuospatial processing in neglect patients (Di Russo et al., 2008; Tarkka et al., 2011). The later, task-related activity may represent more memory rehearsal/decisional stages for task performance that occur after initial attentional engagement (and the accumulation of sensory evidence), and that do not determine the extent of the spatial bias (Duncan, 1980, Luck et al., 2000 and Philiastides & Sajda, 2006). However, it is noteworthy that Longo et al., (2015) have shown that the late ‘line bisection effect’ identified by Foxe et al., (2003), and replicated in the current experiment, scales with viewing distance (i.e. is larger in near than far space) and this perhaps suggests distinct spatiotemporal origins of differing modulators of bias (i.e. line length (early) versus viewing distance (late)).

Future directions

Interestingly, in two recent EEG studies, the rightward shifts in behavioural bias associated with time-on-task (Newman et al., 2013) and increased perceptual load (Perez et al., 2009) have also been linked to changes in oscillatory activity. These studies focused on lateralization of posterior alpha-band activity, which represents a reliable marker of the degree of spatial attentional engagement during anticipatory attention orienting prior to stimulus onset (Foxe & Snyder, 2011, Gould et al., 2011, Kelly et al., 2006, Macdonald et al., 2011, Sauseng et al., 2005, Thut et al., 2006 and Worden et al., 2000). An interesting line for future research would be to investigate the relationship between different experimental manipulations of spatial bias and both post-stimulus (as in the current study, O'Connell et al., 2011 and Perez et al., 2009) and pre-stimulus EEG activity (Newman et al., 2013), and to establish how these separate EEG measures implicated in the processing of visuospatial information relate to one another in the genesis and modulation of spatial bias.

Conclusion

The present EEG study has identified the ERP correlate of changes in line bisection bias with manipulation of line length. The results suggest that the degree to which the right hemispheric ventral attention network is engaged during the early phases of stimulus processing (~100–200 ms post-stimulus onset) modulates the degree of spatial bias displayed across individuals. Further research on experimental manipulations of spatial bias and their EEG correlates may elucidate the role played by attentional subsystems, their interactions and their contribution to the (often biased) distribution of spatial attention in both healthy individuals and post-stroke neglect patients.

Chapter 3

A rightward shift in the visuospatial attention vector with healthy aging

Introduction

Another factor that has previously been proposed to modulate the manifestation of pseudoneglect is age. Though bisection performance has proven to be less consistent in older healthy adults, the systematic leftward bias appears to be attenuated, eliminated, or even reversed with age (Fukatsu et al., 1990; Stam & Bakker, 1990; Fujii et al., 1995; Jewell & McCourt, 2000; Failla et al., 2003; Goedert et al., 2010; Nagamatsu et al., 2011; Hatin et al., 2012; Loureiro et al., 2013; Brooks et al., 2014; Veronelli et al., 2014). Additionally, recent evidence suggests potential sex-differences in age-related changes in manual line bisection performance, with aging effects being strongest in males vs. relatively intact performance with aging in females (Varnava & Halligan, 2007; Barrett & Craver-Lemley, 2008; Chen et al., 2011; however see Beste et al., 2006 for discrepant results). In order to minimize the influence of motor factors on bisection decisions, Schmitz & Peigneux (2011) recently employed the Landmark Task to investigate age-related changes in pseudoneglect. They found that young participants perceived the left side of equally bisected lines to be longer than the right side (typical of pseudoneglect), whereas elderly participants presented the opposite pattern, and were more accurate when unevenly bisected lines were divided on the left side. Overall, a rightward shift in the performance of older participants was found as compared to young participants, in line with previous studies (Sex of the participants was not distinguished in the study, Schmitz & Peigneux, 2011).

Several candidate models may account for the observed change in pseudoneglect with aging. One is that of Hemispheric Asymmetry Reduction in Older Adults (i.e., the HAROLD model, Cabeza, 2002). The HAROLD model suggests that functional recruitment of the non-dominant hemisphere for a given task helps to compensate for age-related unilateral working efficiency decline, resulting in reduced asymmetry in processing for the task at hand (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008; Li et al., 2009). The HAROLD model has largely been investigated in the context of memory tasks and its predictions have often been supported (Bäckman et al., 1997; Grady et al., 2002; Logan et al., 2002; Cabeza et al., 2004; Rossi et al., 2004; Solé-Padullés et al., 2006; Schmitz et al., 2013). Using positron emission tomography (PET), Reuter-Lorenz et al. (2000) found prefrontal cortex (PFC) activity to be lateralized to the respective dominant hemisphere for a given stimulus in young participants. However, in elderly participants the activity was bilateral for all stimulus types. Although mainly observed in the PFC, the HAROLD model may also apply to other regions and tasks (Collins & Mohr, 2013). Nielson et al. (2002) found that during an inhibition task, parietal activity was right lateralized in young participants yet bilateral in older participants. Thus in the context of visuospatial attention biases, when performing the landmark task, elderly participants may recruit supplementary contralateral (left) brain areas in a compensatory manner, resulting in the observed absence or reversal of pseudoneglect.

Another model emphasizes accelerated aging in the right relative to the LH (Brown & Jaffe, 1975; Goldstein & Shelly, 1981), which may in turn reduce the functional dominance of visuospatial attention processing in the RH. Using a test battery designed to diagnose lateralized brain injury, it has previously been found that the performance of elderly participants is analogous to that of RH damaged patients (Klisz, 1978) and more recently specific RH impairment in elderly participants has been found during performance of a variety of psychophysical tasks (Jenkins et al., 2000; Lux et al., 2008; Nagamatsu et al., 2011; Chokron et al., 2013). The absence or reversal of pseudoneglect presented by elderly participants may therefore reflect general RH decline. However, evidence supporting greater aging of the RH in comparison to the left has been mixed (Dolcos et al., 2002; Sowell et al., 2003; Raz et al., 2004).

Additionally, rightward spatial biases are often associated with states of both tonic and chronic reduced arousal (Bellgrove et al., 2004; Manly et al., 2005; Fimm et al., 2006; Dufour et al., 2007; Dodds et al., 2008; Heber et al., 2008; Matthias et al., 2009; Newman et al., 2013). It is possible that a reduction in general alertness/vigilance over the lifespan (Robinson & Kertzman, 1990; Buysse et al., 2005; Nebes et al., 2009; Goedert et al., 2010) may also contribute to the chronic attenuation of pseudoneglect in the elderly.

As shown in **experiments 1 and 2**, the degree of visuospatial bias displayed during landmark task performance is modulated within participants by stimulus properties such as line length. Recent studies employing the landmark task in healthy young participants have shown that while long lines (subtending >6° horizontal visual angle (VA) in length) induce a systematic (usually left) bias, short lines (subtending <2° VA) induce either no bias or a right bias (McCourt & Jewell, 1999; Rueckert et al., 2002; Rueckert & McFadden, 2004; Heber et al., 2010; Thomas et al., 2012). The line length effect appears to arise due to asymmetrical hemispheric contributions (in favour of the RH) to the perceived salience of line stimuli that is more pronounced for long than short lines and hence a left bias arises more prominently for long lines (Anderson, 1996; **experiment 2**). As shown in **experiment 1**, the additive effects of reduced line length and increased time-on-task suggest that both manipulations may result in down-regulation of RH attention network engagement and hence the observed rightward shifts in spatial bias. Additionally, an overall task performance decrement (as indexed by the curve width of the fitted psychometric function) was observed with prolonged time-on-task, further suggesting a degradation of attentional resources.

Elucidating how the established bias modulators of age and line length interact to influence lateralized visuospatial bias as displayed during landmark task performance will allow for a refinement of models of visual attention processing changes with healthy aging. To investigate this, landmark task performance was compared on three different line lengths (short, medium and long) between young and elderly healthy participants. In line with previous studies, a systematic leftward bias for long lines in young participants was predicted that would be attenuated with reducing line length. If hemispheric asymmetry reduction alone accounts for the attenuation of pseudoneglect with aging then one would expect to see no systematic bias for any line length in the elderly and also relatively preserved overall performance on the task. Alternatively, if reduced RH function and/or chronic reduced arousal play a role in the attenuation of bias then one would expect to see a pattern of performance in the elderly analogous to that previously observed in young participants following prolonged time-on-task: namely no bias in long lines and a systematic rightward bias for short lines along with an overall task performance decrement (as in **experiment 1**).

Methods

Participants

Twenty right-handed young (12 males, mean age = 23.25 years; SD = 2.83, max = 31, min = 18) and 20 right-handed elderly participants (11 males, mean age = 68.45 years; SD = 4.95, max = 77, min = 60) took part in the experiment. Written informed consent was obtained from each participant. All participants were volunteers naive to the experimental hypothesis being tested. All participants had normal or corrected-to-normal vision and reported no history of neurological disorder. The experiment was carried out within the Institute of Neuroscience and Psychology at the University of Glasgow and was approved by the local ethics committee.

Instrumentation and Stimuli

Stimuli were presented using the E-Prime software package (Schneider et al., 2002) on a CRT monitor with a 1280 × 1024 pixel resolution and 85 Hz refresh rate. The stimuli were similar to those employed in experiments 1 and 2. Three different lengths of line were presented. “Long” lines measured 24.3 cm in length by 0.5 cm in height and at a viewing distance of 70 cm subtended 19.67° (width) by 0.4° (height) of VA. At the same viewing distance, “medium” lines measuring

12.15 cm × 0.5 cm subtended 9.92° × 0.4° of VA and “short” lines measuring 2.43 cm × 0.5 cm subtended 1.98° by 0.4° of VA.

All three line lengths were transected at 1 of 13 points ranging from ±7.5% (distance between transector locations = 1.25%) of absolute line length to veridical center. In long lines, this represented a range of −1.48° to 1.48° of VA with a distance between transector locations of 0.25° of VA. In medium lines a range of −0.74° to 0.74° of VA with a distance between transector locations of 0.12° of VA was presented and in short lines, a range of −0.15° to 0.15° of VA with a distance between transector locations of 0.02° of VA was presented. All lines were displayed with the transector location centered on the vertical midline of the display (i.e., aligned to a central fixation cross which preceded the presentation of the lines, see below).

Procedure

Participants were seated with their midsagittal plane aligned with the display monitor. Viewing distance (70 cm) was kept constant using a chin rest. Each trial began with presentation of a fixation cross (0.4° (height) × 0.4° (width) of VA) for 1 s followed by presentation of the transected line (150 ms). The transection mark was always aligned with the fixation cross (i.e., the eccentricity of the line endpoints varied across trials while the transection point always appeared at the same central position), therefore preventing use of the fixation cross as a reference point for bisection judgments. The fixation cross then reappeared for the duration of the response period during which participants indicated which end of the line had appeared longest/shortest to them by pressing either the left or right response key. Half of the participants were asked to judge which end of each line was longest and the other half were asked to judge which end was shortest, in order to prevent any possible group-level response bias (increased likelihood of pressing either the left or right response key regardless of the visual percept, especially in cases of uncertainty (see Morgan et al., 2012; García-Pérez & Alcalá-Quintana, 2013)) from contaminating the perceptual midpoint analysis.

Participants always responded using their dominant right hand (right index and middle finger respectively) and were instructed to hold their gaze on the center of the screen throughout each trial. The subsequent trial began as soon as the response was made. Trials lasted approximately 2 s. Trial type (location of transector in line) was selected at random. Each participant completed 91 trials of each line length (Overall = 273 trials, 7 judgments at each of the 13 transector locations) split into 7 short blocks (lasting approximately 2–3 min). Participants were allowed to take as long a break as they wished between blocks. A block of 20 practice trials was performed immediately prior to the beginning of the experimental blocks. The entire experiment lasted approximately 20–25 min (see Figure 2 for a schematic representation of the trial procedure).

Analysis

In order to obtain an objective measure of perceived line midpoint for all three line lengths in each participant, psychometric functions (PFs) were derived using the method of constant stimuli (fitting the same cumulative logistic function as in experiments 1 and 2). The width of the PF provides a measure of the precision of participants' line midpoint judgments per block. A low width value indicates that the PF is steep and that the observer can discriminate differences between transector locations relatively easily, whereas a high width value indicates that the PF is shallow and that the observer can only discriminate relatively coarse differences (Fründ et al., 2011). Inferential statistical analyses were performed on the individually fitted PF PSE and width estimates.

Results

Subjective midpoint (PSE) analysis

Figure 12A–C presents group-averaged PFs for both experimental groups at each of the three line lengths. For each line length, black filled circle symbols (young participants) and gray open diamond symbols (elderly participants) plot mean percentage left response as a function of transector location. The black (young) and gray (elderly) smooth curves represent the best-fitting least-squares cumulative logistic PFs (95% confidence interval represented by black (young) and gray (elderly) dotted lines). Where black (young) and gray (elderly) vertical dashed lines cross the black horizontal dashed lines indicate the transector locations corresponding to the 50% response rates (PSEs).

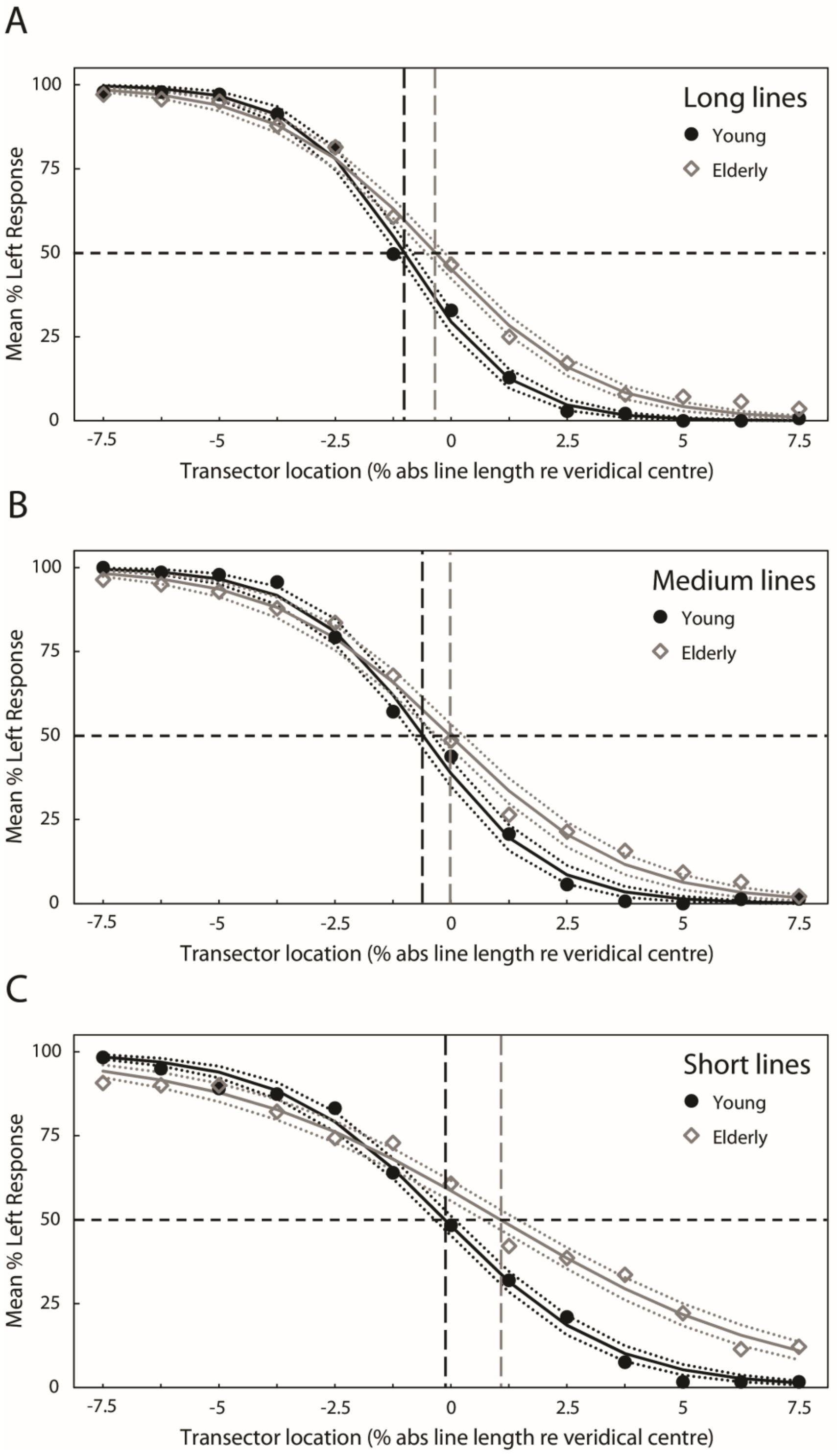


Figure 12. Group-averaged PFs for both experimental groups at each line length (A = long, B = medium, C = short). For each line length, black filled circle symbols (young participants) and gray open diamond symbols (elderly participants) plot mean percentage left response as a function of transector location. The black (young) and gray (elderly) smooth curves represent the best-fitting least-squares cumulative logistic PFs (95% confidence interval represented by black (young) and gray (elderly) dotted lines). Where black (young) and gray (elderly) vertical dashed lines cross the black horizontal dashed lines indicate the transector locations corresponding to the 50% response rates (PSEs).

Figure 13A plots the group mean PSEs (±1 standard error (S.E.), vertical dashed lines represent 95% confidence intervals (CIs)) obtained from PFs fitted to the individual participants' data for each line length. These are in close agreement with the group averaged PF PSEs. In line with previous studies of pseudoneglect, mean long line PSE in the young group was displaced to the left of veridical center by −1% of absolute line length and this leftward bias was significantly different from veridical center (95% CI does not include 0) whereas in the elderly group the mean PSE was slightly to the left (−0.14%) but not significantly different from veridical center (95% includes 0). Mean medium line PSE in the young group was displaced to the left of veridical center by −0.62% and this leftward bias was also significantly different from veridical center (95% CI does not include 0). In contrast, the medium line elderly PSE was very slightly to the right of center by 0.1% but again not significantly different from veridical center (95% CI includes 0). In the short lines, mean PSE in the young group was −0.24% to the left of veridical center but the difference from veridical center was not significant (95% CI includes 0) whereas mean PSE in the elderly group was significantly displaced to the right of veridical center by 1.1% (95% CI does not include 0).

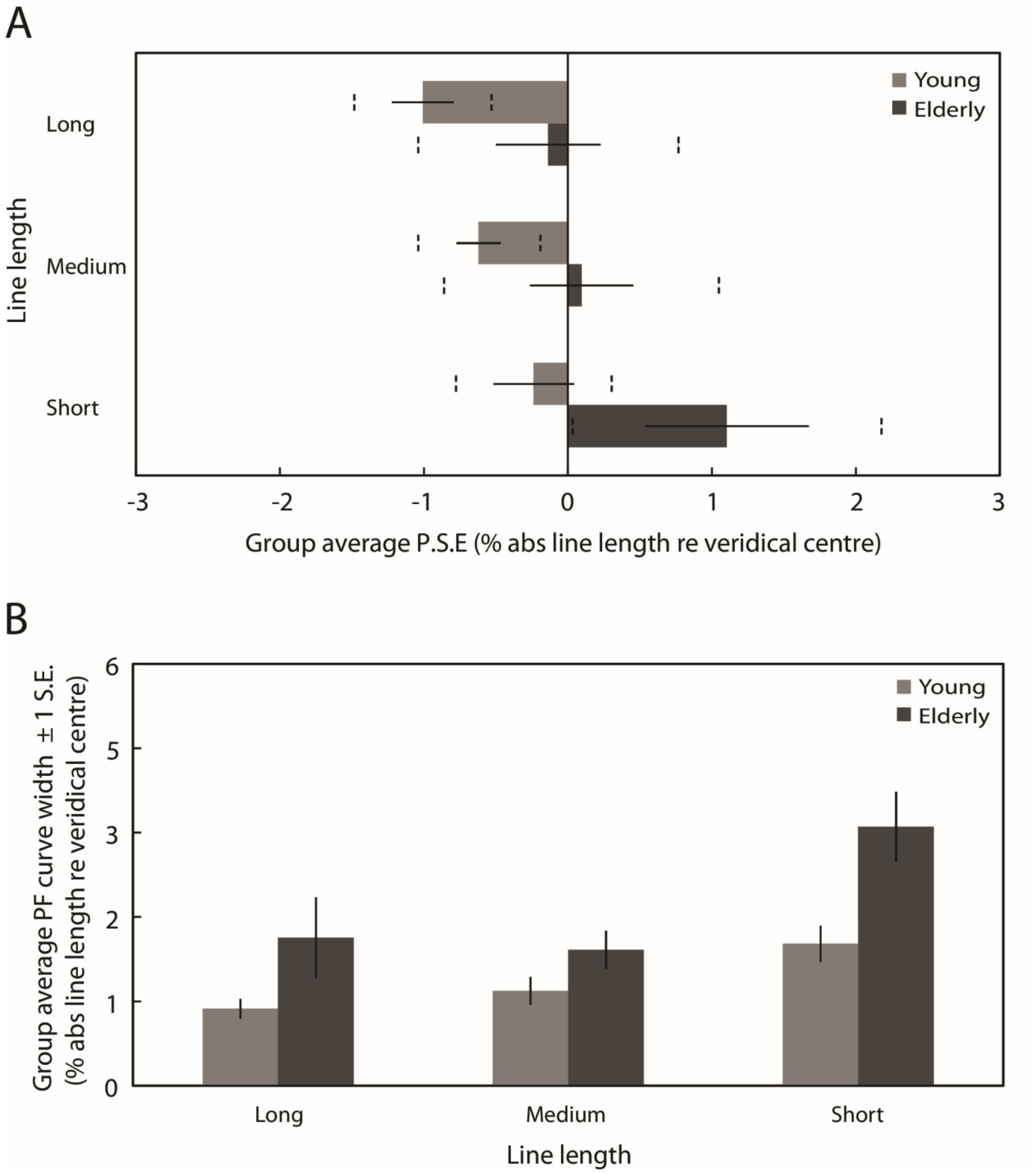


Figure 13. Group averaged psychometric function measure values. (A) Group averaged PSE values (±1 standard error (S.E.), vertical dashed lines represent 95% confidence intervals (CIs)) obtained from PFs fitted to the individual participants' data for each line length. Light gray bars represent the young group and dark gray bars represent the elderly group. **(B)** Group averaged PF curve width (±1 S.E.) obtained from PFs fitted to the individual participants' data for each line length.

A 2 (Age group: young vs. elderly) × 3 (Line length: long vs. medium vs. short) ANOVA on individually fitted PF PSEs revealed a significant main effect of age group ($F_{(1,38)}$ = 5.830, p = 0.021, η2p=0.133), a significant main effect of line length ($F_{(2,76)}$ = 6.509, p = 0.002, η2p=0.146) but no significant age group × line length interaction ($F_{(2,76)}$ = 0.524, p = 0.524, η2p=0.017). The overall subjective midpoint was significantly more to the left in the young participants than in the elderly (as indexed by the PSEs), indicating a group level rightward shift in the attentional vector with age (as is clearly displayed in Figure 13A). Pairwise comparisons (Bonferroni-corrected) to analyze the simple effects of line length revealed no statistically significant difference in subjective midpoint between either long and medium lines ($t_{(39)}$ = −1.846, p = 0.226, Cohen's d = −0.292) or medium and short lines ($t_{(39)}$ = −2.163, p = 0.111, Cohen's d = −0.345) but a significant rightward shift in subjective midpoint from long to short lines ($t_{(39)}$ = −3.022, p = 0.014, Cohen's d = −0.482) regardless of age (again displayed in Figure 13A). Additionally, a within-subjects linear contrast analysis revealed a significant linear shift in bias with line length ($F_{(1,38)}$ = 9.017, p = 0.005, η2p=0.192).

Psychometric function curve width analysis

Figure 13B plots the mean PF curve width (±1 S.E.) obtained from PFs fitted to the individual participants' data for each line length. A 2 (Age group: young vs. elderly) × 3 (Line length: long vs. medium vs. short) ANOVA revealed a significant main effect of age group ($F_{(1,38)}$ = 8.674, p = 0.005, η2p=0.186), a significant main effect of line length ($F_{(2,76)}$ = 11.637, p < 0.001, η2p=0.234) and no significant age group × line length interaction ($F_{(2,76)}$ = 1.706, p = 0.188, η2p=0.043). PF curve widths were significantly shallower in elderly participants than in young participants, indicating reduced discrimination sensitivity with age. Pairwise comparisons (Bonferroni-corrected) to analyze the simple effects of line length revealed no statistically significant difference in PF width between long and medium lines ($t_{(39)} = -0.155$, $p = 1$, Cohen's $d = -0.033$) but a significant increase in width from both long to short lines ($t_{(39)} = -3.409$, $p = 0.005$, Cohen's $d = -0.542$) and from medium to short lines ($t_{(39)} = -4.845$, $p < 0.001$, Cohen's $d = -0.881$). A within-subjects linear contrast analysis revealed a significant linear shift in curve width with line length ($F_{(1,38)} = 11.56$, $p = 0.002$, η2p=0.233). Discrimination sensitivity for the task was significantly lower for short lines than for long and medium lines regardless of age (as displayed in Figure 13B).

Additional gender analysis

Recent evidence from studies employing manual line bisection has suggested potential sex-differences in age-related changes in bisection performance, with aging effects being strongest in males vs. relatively intact performance with aging in females (Varnava & Halligan, 2007; Barrett & Craver-Lemley, 2008; Chen et al., 2011; however see Beste et al., 2006 for discrepant results). In order to test for any such gender effects in age-related changes in landmark task performance, I re-analyzed *(post hoc)* the PSE and width values with an additional between-subjects factor of gender (female, male) included in the ANOVAs. The PSE re-analysis revealed no additional main effect of gender ($F_{(1,36)}= 0.019$, $p = 0.892$, η2p=0.001) and no significant interaction between either age group × gender ($F_{(1,36)}= 0.411$, $p = 0.525$, η2p=0.011), length × gender ($F_{(2,72)} = 0.337$, $p = 0.715$, η2p=0.009) nor age group × length × gender ($F_{(2,72)} = 0.608$, $p = 0.547$, η2p=0.017).

The width re-analysis also revealed no main effect of gender ($F_{(1,36)}$= 0.970, p = 0.331, η2p=0.026), no significant interaction between either age group × gender ($F_{(1,36)}$= 0.299, p = 0.588, η2p=0.008), length × gender ($F_{(2,72)}$ = 0.615, p = 0.543, η2p=0.017) nor age group × length × gender ($F_{(2,72)}$ = 0.958, p = 0.388, η2p=0.026).

Discussion

Recent studies have shown age-related changes in the expression of visual pseudoneglect (Fukatsu et al., 1990; Stam & Bakker, 1990; Fujii et al., 1995; Jewell & McCourt, 2000; Failla et al., 2003; Barrett & Craver-Lemley, 2008; Goedert et al., 2010; Nagamatsu et al., 2011; Schmitz & Peigneux, 2011; Hatin et al., 2012; Loureiro et al., 2013; Veronelli et al., 2014). I aimed to investigate, for the first time, how the established line bisection bias modulator of line length interacts with healthy aging to influence lateralized visuospatial bias as displayed during landmark task performance. For this purpose, I compared landmark task performance on three different line lengths (short, medium and long) between young (18–31 years old) and elderly (60–77) healthy participants.

As expected, young participants displayed a group-level systematic leftward bias (pseudoneglect) during long line landmark task performance. This leftward bias was reduced for the medium length lines and no systematic bias was observed for performance of the task with short lines, confirming the previously reported line-length effect (McCourt & Jewell, 1999; Rueckert et al., 2002; Rueckert & McFadden, 2004; Heber et al., 2010; Thomas et al., 2012; **experiments 1 & 2**). Moreover, the results revealed a group-level rightward shift in the visuospatial attention vector in the elderly as compared to the young participants, in line with previous findings of an attenuation or reversal of pseudoneglect with healthy aging (Fukatsu et al., 1990; Stam & Bakker, 1990; Fujii et al., 1995; Jewell & McCourt, 2000; Failla et al., 2003; Barrett & Craver-Lemley, 2008; Goedert et al., 2010; Nagamatsu et al., 2011; Schmitz & Peigneux, 2011; Hatin et al., 2012; Loureiro et al., 2013; Veronelli et al., 2014). Importantly, no interaction was observed between age group and line length suggesting that the elderly participants were subject to the line length effect in a similar manner to the young (i.e., a rightward shift in subjective midpoint with reduced line length). No effect of gender on landmark task performance was found in either the young or the elderly.

The results replicate and extend those of Schmitz & Peigneux (2011) who found suppression, and near reversal, of the leftward pseudoneglect bias in their elderly sample during long line landmark performance. In their study, the line stimuli remained onscreen until the participant responded (free-viewing). The authors note that this absence of control of ocular scanning in their study precluded them from dissociating a true perceptual bias shift with aging from a failure of inhibition of return (IOR). IOR represents a mechanism by which the viewer disengages from previously processed aspects of a stimulus in order to facilitate perception of its entirety (Posner and Cohen, 1984). Using a stimulus duration of 150 ms only (and thus preventing eye movements), it is here confirmed that the observed rightward shift in the attention vector with healthy aging is unlikely to occur as a result of a failure of IOR.

Potential Neural Mechanisms of the Rightward Perceptual Shift with Aging

Accelerated right hemisphere aging/HAROLD model

Previous studies exploring age-related variability in neurocognitive function have posited a decline in hemispheric specialization of task-related neural activity to represent a form of compensation for age-related deficits that supports task performance (Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz & Cappell, 2008; Angel et al., 2011). However, the functional significance of the observed neural activation of regions not primarily associated with task performance in young participants, and whether such “recruitment” is restricted to elderly participants, remains unclear (Reuter-Lorenz & Park, 2010; Friedman, 2013).

Though the rightward shift in the visual attention vector with age observed in the current study would support an increased involvement of the LH in task processing in the elderly compared to the young participants (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008; Li et al., 2009), the HAROLD model alone appears to be inconsistent with the findings of a significant rightward bias for short lines in the elderly in the current study along with previous reports of group-level rightward bisection biases in elderly samples (Stam & Bakker, 1990; Fujii et al., 1995). The HAROLD model would predict symmetrical bisection behavior in elderly participants but it would not predict systematic right biases beyond the veridical midline (Brooks et al., 2014). Additionally, overall performance precision (as indexed by the curve width of the fitted psychometric functions) was found to be lower in elderly participants suggesting reduced discrimination sensitivity with aging. Although the influence of low level visual deficits (such as reduced visual resolution) cannot be ruled out, elderly participants were less able to successfully discriminate between the different transector locations (for all three line lengths) and so “compensatory” recruitment of the LH for landmark task processing does not equate to preserved task performance ability equivalent to that of young participants.

Moreover, increased LH involvement could occur as a result of reduced inhibitory influence of the RH, in line with an interhemispheric competition account of spatial attention control (Kinsbourne, 1977; Duecker et al., 2013; Duecker & Sack, 2015; Szczepanski & Kastner, 2013) in combination with accelerated RH aging (Brown & Jaffe, 1975; Goldstein & Shelly, 1981; Nagamatsu et al., 2011) and/or a decline in corpus callosum integrity with age (Hausmann et al., 2003; Sullivan & Pfefferbaum, 2006; Koch et al., 2007, 2011).

Potential role of arousal and/or perceptual load

Rightward spatial biases are often associated with states of both tonic and chronic reduced arousal (Bellgrove et al., 2004; Manly et al., 2005; Fimm et al., 2006; Dufour et al., 2007; Dodds et al., 2008; Heber et al., 2008; Matthias et al., 2009; Newman et al., 2013). In fact, after 1 h of landmark task performance with long lines, a rightward shift in the attentional vector was displayed by the young participants in **experiment 1** (including a rightward bias for short lines that was significantly different from veridical centre). This pattern of bisection behaviour was remarkably similar to that displayed at baseline by the elderly sample in the current experiment. It is possible that a reduction in general alertness over the lifespan (Robinson & Kertzman, 1990; Goedert et al., 2010; Buysse et al., 2005; Nebes et al., 2009), and/or a reduction in functional interaction between RH ventral and dorsal networks subserving visuospatial attention (see Thiebaut de Schotten et al., 2011 and the discussion of Benwell et al., 2013b), may contribute to a chronic attenuation of pseudoneglect in aged individuals. Additionally, the increased difficulty of performing the task with short lines (as indexed by the shallower PF curve width values) may further hinder RH contribution to the task in states of sub-optimal function (such as with aging (Brown & Jaffe, 1975; Goldstein & Shelly, 1981; Nagamatsu et al., 2011) or reduced vigilance/increased time-on-task (Fimm et al., 2006; **experiment 1**)) and hence bring about the observed rightward biases.

Line Length Effect and Aging

Potential neural mechanisms

The current results show for the first time that, despite an overall rightward shift in midpoint judgments in the elderly, reducing line length results in the same pattern of behaviour in the elderly as in the young (i.e., a rightward shift in subjective midpoint) during landmark task performance. The rightward shifting effects of age and line length on midpoint judgment appear to be additive. In a mathematical model of bisection behaviour, the line length effect was posited to arise due to asymmetrical hemispheric contributions (in favour of the RH) to the perceived salience of line stimuli that is more pronounced for long than short lines (Anderson, 1996). In **experiment 2**, the EEG results showed that increased engagement of regions of the right lateralized ventral attention network in long relative to short lines contributes to the genesis of the spatial bias. The TPJ represents a key node in the ventral frontoparietal attention network implicated in both the orienting of visuospatial attention and the maintenance of arousal (Corbetta & Shulman, 2002, 2011). De-regulation of RH TPJ activity is thought in turn to reduce activation of the bihemispheric dorsal frontoparietal network (implicated in the distribution of visuospatial attention across the visual field) and has been linked to rightward shifts in visuospatial bias in healthy participants (O'Connell et al., 2011; Newman et al., 2013). It is plausible that these neural correlates may also underlie the length effect observed here in the elderly, over and above any age-related changes in task processing.

No evidence for gender specific effects

Varnava & Halligan (2007) employed manual line bisection to investigate the effects of age and gender on bisection performance in healthy participants on three different line lengths comparable to those used in the current study. In their study, only males showed a rightward shift in bisection bias with age and only for long line performance. This effect of gender on manual line bisection performance with aging has been supported by subsequent studies, with the effect of aging appearing to be strongest for males (Barrett & Craver-Lemley, 2008; Chen et al., 2011). A possible explanation for the discrepant finding of no sex difference in the current study could be the use of the landmark task instead of manual line bisection (Varnava and Halligan, 2007; Barrett & Craver-Lemley, 2008; Chen et al., 2011). In general, differences in experimental procedure (such as the viewing distance employed (see McCourt & Garlinghouse, 2000; Varnava et al., 2002; Longo & Lourenco, 2006)), sample demographics and analysis techniques across studies may contribute to the differential findings. Treating age as a continuous variable in a sample of participants largely over 40 years old (mean age = 58.7, only 5 out of 44 participants <40), Chen et al. (2011) dissociated “where” perceptual errors from “aiming” motor errors during line bisection and found a rightward shift in perceptual midpoint with aging in men only. Thus, further research should aim to explore, ideally in larger samples and utilizing the deployment of multiple visuospatial tasks and analysis techniques, the reasons underlying these discrepancies in gender- and age-related effects on visuospatial bias. Although the current experiment was not explicitly set up to investigate gender differences, I would propose that non-perceptual factors may contribute to the previously observed gender specific aging effects in pseudoneglect, and that both sexes appear to experience a rightward perceptual shift in the visuospatial attention vector with healthy aging.

Comparison to neglect

The pattern of the line length effect displayed by our elderly sample is in the opposite direction to that often observed in unilateral neglect patients. In these patients, a reduction in line length generally results in a systematic reduction of the severe rightward bias typically exhibited on long lines, with a leftward bias sometimes being displayed on very short lines (the “crossover” effect: Halligan & Marshall, 1988; Marshall & Halligan, 1989; Harvey et al., 1995; Anderson, 1996, 1997; Monaghan & Shillcock, 1998, 2004; Ricci & Chatterjee, 2001; Mennemeier et al., 2005; Veronelli et al., 2014). It therefore appears unlikely that the performance of elderly participants can be seen as a mild version of spatial neglect. What seems to be the case is that the elderly participants show an overall rightward shift in the attentional vector, that is most pronounced for the short lines. However, the comparison of findings from healthy participants with those in neglect patients and the “crossover” literature is complicated by the large variance of line bisection performance patterns both within and across patients (Halligan et al., 1990) and common concurrent primary visual and motor deficits post-stroke (Doricchi et al., 2005; Binetti et al., 2011; Kerkhoff & Schenk, 2011). The 150 ms landmark task presentation duration employed here minimizes the influence of non-perceptual motor components such as hand use and visual scanning on bisection decisions (Milner et al., 1992; Luh, 1995; Bisiach et al., 1998; Toraldo et al., 2004). Employing the paradigm from the current study in RH stroke neglect patients both with and without concomitant primary visual deficits would be highly informative in terms of elucidating further purely perceptual contributions to the line length effect in neglect and the potential role played by primary visual deficits in the commonly observed “crossover” effect (Doricchi et al., 2005; Binetti et al., 2011).

Future Directions

The neural origin(s) of the additive effects of aging and line length remain unclear. It is possible that two independent processes influencing spatial bias are at play, one affected by aging (leading to a rightward shift) and the other unaffected (preserving the line length effect in healthy aging). The introduction of neuroimaging techniques is likely to represent an important step with regard to answering this and many more of the open questions pertaining to visuospatial processing in the elderly. To our knowledge, neuroimaging studies of bisection task performance to date have been restricted to young healthy participants, revealing strong RH dominance for task processing (Fink et al., 2000a, 2000b, 2001; Foxe et al., 2003; Waberski et al., 2008; Çiçek et al., 2009; Thiebaut de Schotten et al., 2011; Cavézian et al., 2012; **experiment 2**). Using EEG and a passive viewing task, De Sanctis et al. (2008) showed reduced hemispheric asymmetry of early-visual processing in elderly compared to young participants. As discussed, **experiment 2** links the genesis of the landmark task bias to the RH amplitude of an early component (N1) of the visual evoked potential. In addition, the magnitude and direction of bias have also been linked to the relative anatomical hemispheric lateralization of a parieto-frontal white matter pathway (Thiebaut de Schotten et al., 2011). Investigation of these neural modulators of visuospatial bias in the elderly represents a natural and potentially illuminating next step.

Interim Conclusion

In **experiment 1** (presented in Chapter One), it was found that decreased line length and extended time-on-task have an additive effect on subjective midpoint estimation, both resulting in a rightward shift. However, the rightward shift with time-on-task (present after roughly 1 hour of task performance for both line lengths including a systematic rightward bias in short lines) only occurred for extended performance with long lines and not for extended performance with short lines. The results suggest that both long and short line bisection performance engage a common mechanism but that the magnitude and direction of lateralized bias depends on the momentary degree to which this mechanism is engaged as a function of the stimulus input and endogenous state.

The EEG results from **experiment 2** (presented in Chapter Two) showed that an asymmetric hemispheric contribution (in favour of the RH TPJ) during visual processing of long lines that is not present during short line processing represents the neural correlate of the line length effect. This effect occurred roughly 150 ms post-stimulus onset independently of the task being performed (i.e. was stimulus driven). The approach of utilising stimulus- and state-driven modulators of bias with concurrent neuroimaging during task performance offers a novel opportunity to elucidate the mechanisms of visuospatial attention bias and the neural networks involved.

The results of **experiment 3** (presented in Chapter 3) showed an overall rightward shift in subjective midpoint judgements from young to elderly participants, as well as an overall decrement in task performance precision in the elderly. Interestingly, the effects of increased age and reduced line length were found to be additive. As in experiments 1 and 2, young participants displayed a rightward shift in bias from a leftward bias in long lines to no systematic bias in short lines. In the elderly group, no bias was present for long line performance but a systematic rightward bias was displayed during short line performance.

In the final experiment, I sought to investigate the influence of hemispheric activation asymmetry on visuospatial attention processing through the employment of bilateral parietal tDCS. Additionally, tDCS-intensity was modulated and baseline performance indexed in order to assess whether the large inter-individual variability in tDCS outcome reported previously (de Berker et al., 2013, Krause & Cohen Kadosh et al, 2014, López-Alonso et al., 2014, Wiethoff et al., 2014) may be accounted for by a stochastic resonance model of NIBS (Miniussi et al., 2013).

Chapter 4

The effects of bi-parietal tDCS on visuospatial attention: an interaction between current strength and discrimination sensitivity

Introduction

Both magnetic and electrical non-invasive brain stimulation techniques are becoming increasingly established modulators of visuospatial attention function (Walsh & Pascual-Leone, 2003; Fierro et al., 2000; 2001; Hilgetag et al., 2001; Pourtois et al., 2001; Bjoertomt et al., 2002; Ellison et al., 2004; Dambeck et al., 2006; Szczepanski & Kastner, 2013; Mahayana et al., 2014; Kim et al., 2005; Sparing et al., 2009, Giglia et al., 2011, Loftus & Nicholls, 2012; Wright & Krekelberg, 2014). Transcranial direct current stimulation (tDCS) involves the application of a weak electrical current to the scalp which shifts the resting membrane potential of the underlying cortical neurons, thereby allowing for an up- versus down-regulation of the neuronal firing rate depending on the polarity of stimulation (anodal vs. cathodal), as shown in animals (Bindman et al., 1964; Creutzfeldt et al., 1962) with an analogous effect on motor cortex excitability in humans (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). In cognitive studies using tDCS, a similar a priori assumption is often made, where behavioural effects are directly mapped onto these physiological effects. However, the classic anodal-facilitation/cathodal-inhibition distinction does not always hold for cognitive functions (Jacobson et al., 2012a; Vallar & Bolognini, 2011) and the effects are dependent on differences in the initial activation state of the stimulated network (Antal et al., 2007; Dockery et al., 2009) and/or current strength (Hoy et al., 2013).

Nonetheless, along with the utility of tDCS as a research tool for investigating the functional architecture of the brain, there is growing interest in the therapeutic and neuroenhancing potential of tDCS for various cognitive dysfunctions including spatial neglect (Oliveri, 2011; Brunoni et al., 2012) despite large intra-individual variability in tDCS-outcome (López-Alonso et al., 2014; Wiethoff et al., 2014, Krause & Cohen-Kadosh, 2014).

An explanation for this outcome variability may lie in the trait- and/or state-dependent nature of tDCS effects. Previous studies have shown that tDCS outcome is not always uniform, but instead can be dependent on factors such as differences in individual trait levels (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al., 2015; Sarkar et al., 2014 and Tseng et al., 2012), the initial activation state of the stimulated network (Antal et al., 2007) and the administered current strength (Batsikadze et al., 2013; Hoy et al., 2013 and Teo et al., 2011). Failure to account for potentially subtle differences in sample characteristics and/or experimental design may hence explain the large variability in tDCS-outcome across participants and studies (Horvath et al., 2015a; Horvath et al., 2015b; Krause & Cohen Kadosh, 2014; López-Alonso et al., 2014 and Wiethoff et al., 2014). For a better understanding of tDCS effects, it is therefore of importance to map those factors, and the relationships between them, that may determine tDCS outcome across different cognitive domains.

Here, I tested the contribution of two factors in influencing tDCS outcome on visuospatial attention bias. Previous studies have independently suggested tDCS intensity (Batsikadze et al., 2013; Hoy et al., 2013 and Teo et al., 2011) and baseline task ability (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al., 2015 and Tseng et al., 2012) to be important contributing factors. In the present study, I manipulated tDCS intensity while at the same time accounting for individual differences in baseline performance. Recent papers have highlighted the dependence of non-invasive brain stimulation (NIBS) outcome onendogenous neural activity at the moment of stimulation, i.e., on baseline activity (e.g. Miniussi et al., 2013; Miniussi et al., 2010 and Ruzzoli et al., 2010). One framework in particular distinguishes between task-informative and task-uninformative neurons in the stimulated cortex at baseline (Bienenstock et al., 1982; Cattaneo et al., 2008, Cattaneo et al., 2010; Silvanto et al., 2007 and Silvanto et al., 2008), or the related concepts of signal and noise (Abrahamyan et al., 2011; Miniussi et al., 2010; Miniussi et al., 2013; Ruzzoli et al., 2010 and Schwarzkopf et al., 2011), and highlights that it is the relative activity of task-informative versus uninformative neurons (or signal-to-noise ratio) at baseline that will shape NIBS-induced perceptual/behavioural effects (for examples see Silvanto et al., 2007; or Abrahamyan et al., 2011). Accordingly, it is of interest to test measures that index the balance between these types of neuronal activities at baseline as to their explanatory potential for tDCS outcome, alongside other potentially determining factors (e.g., tDCS-intensity). One such measure is the slope of the psychometric function (PF). In PFs derived from two-alternative forced choice (2-AFC) tasks, changes in slope have been linked to changes in intrinsic uncertainty, or the ability to distinguish information from task-relevant and task-irrelevant “channels”, in guiding perceptual decisions (Gold & Ding, 2013; Kontsevich & Tyler, 1999; Pelli, 1985; Pelli, 1987 and Tyler & Chen, 2000) (see also Aihara et al., 2008 and Aihara et al., 2010 for use of the slope/width of the PF as a measure of internal noise). This intrinsic uncertainty reflected in the slope has been proposed to arise at a late readout stage of sensory information processing, and Gold et al., (2010) have identified selective neuronal pooling mechanisms in the parietal cortex that may reduce this intrinsic uncertainty and hence increase the PF slope. Based on this interpretation of the slope of the PF and the NIBS/tDCS-literature reviewed above, I predicted that tDCS effects may differ depending on the administered current intensity and the psychophysical measure of intrinsic task uncertainty at baseline, and tested for the first time for an interaction between the two. To this end, I applied tDCS at 1 mA and 2 mA (between participants) and split participant into groups according to the slope of the fitted PF (discrimination sensitivity).

These predictions are here tested using tDCS over bilateral parietal cortex, known to play a crucial role in visuospatial attention processing (Kinsbourne, 1977; Blankenburg et al., 2010; Szczepanski & Kastner, 2013; **experiment 2**). Stimulation of this network by tDCS has been shown to influence both non-spatial (Bolognini et al., 2010a; 2010b; Ball et al., 2013; Jacobson et al., 2012b; Moos et al., 2012) and spatial aspects of visual attention in healthy participants (Sparing et al., 2009; Giglia et al., 2011; Loftus & Nicholls, 2012; Wright & Krekelberg, 2014), although with inconsistent results across studies, particularly in terms of non-spatial aspects of performance. Here, I sought to investigate the influence of the administered current strength and the psychophysical metric of intrinsic uncertainty at baseline on a previously observed effect of bi-parietal tDCS on pseudoneglect as displayed during perceptual line bisection (Giglia et al., 2011). Giglia et al., (2011) showed a rightward shift in subjective midpoint during landmark task performance when participants received 1 mA, bi-parietal (Left anode/Right cathode) stimulation. Here, in a larger sample of participants, across two current strengths (1 mA and 2 mA) and accounting for baseline intrinsic task uncertainty, I sought to replicate this bi-parietal effect. Additionally, the introduction of the reversed polarity (Left cathode/Right anode) allowed for a direct test of one of the main predictions of the interhemispheric competition theory (ICT) of visuospatial attention (Kinsbourne, 1977; Sparing et al., 2009 and Szczepanski & Kastner, 2013), namely that the respective polarities should induce opposing shifts in spatial bias.

Methods

Participants

Forty right-handed participants took part in the experiment. One participant had to be excluded due to task performance not being above chance level (non-adherence to task) and another one dropped out (not returning for sessions 2–3). This led to 38 participants whose data were entered into the final analysis (19 male, 19 female, mean age = 22.9 years; SD = 3.16). All participants were naive to the experimental hypothesis being tested, had normal or corrected-to-normal vision and reported no history of neurological disorder or any other contraindication for tDCS. Each participant gave written informed consent to participate in the study, which was approved by the local Ethics Committee of the College of Science and Engineering (University of Glasgow).

Transcranial direct current stimulation (tDCS)

Bilateral tDCS was delivered over parietal cortices through a battery-driven, constant current stimulator (NeuroConn GmbH, Germany) using two 4 × 4 cm surface electrodes (placed in saline-dampened sponges). One electrode was positioned over the left and the other over the right parietal region (centred on P5 and P6 of the 10–20 International EEG system: adopted from Giglia et al., 2011). Here, three different bi-parietal stimulation protocols were administered to each participant on separate days: (i) Left anode/right cathode (LA/RC) (replicating Giglia et al.'s design); (ii) Left cathode/right anode (LC/RA) (extending Giglia et al.'s design by introducing an opposite electrode polarity) and (iii) sham stimulation (in which electrode polarity was counter-balanced across participants). Stimulation duration was 20 min (with 30-sec ramping up/down), but stimulation was discontinued after 30-sec in sham. Half of the participants (*n* = 19) received 1 mA stimulation (current density = .0625 mA/cm²) for each stimulation protocol, while the other half (*n* = 19) received 2 mA stimulation (current density = .125 mA/cm²). The tDCS sessions were separated by at least 24 h for each participant with counter-balanced ordering of the tDCS protocols across participants to control for learning and carry-over effects.

Stimuli and task

To assess discrimination sensitivity and pseudoneglect direction and magnitude at baseline as well as changes with bi-parietal tDCS, the same computerized version of the landmark task was administered as in **experiments 1, 2 and 3**. Lines measured 24.3cm in length by 0.5cm in height and, at a viewing distance of 70cm, subtended 19.67° (width) by .40° (height) of visual angle. Lines were transected at 1 of 17 points ranging symmetrically from ±4% of absolute line length relative to and including veridical centre (see 15 for an example of a line stimulus). This represented a range of −0.8° (-24 pixels) to 0.8° (24 pixels) of visual angle relative to veridical centre.

Figure 14A depicts a schematic representation of the trial procedure employed. Each trial began with presentation of a fixation cross (0.40° (height) × 0.40° (width) of visual angle) for 1 second followed by presentation of a transected line for 150 ms. The fixation cross then reappeared for the duration of the response period, during which participants indicated which end of the line the transection mark had appeared closest to, by pressing either the left or right response key. Participants always responded using their dominant right hand (right index and middle finger respectively) and were instructed to keep their gaze on the fixation cross throughout each trial. The subsequent trial began as soon as the response was made. Trials lasted approximately 2 seconds with each block lasting 3-4 minutes. Trial type (location of transector in line) was selected at random.

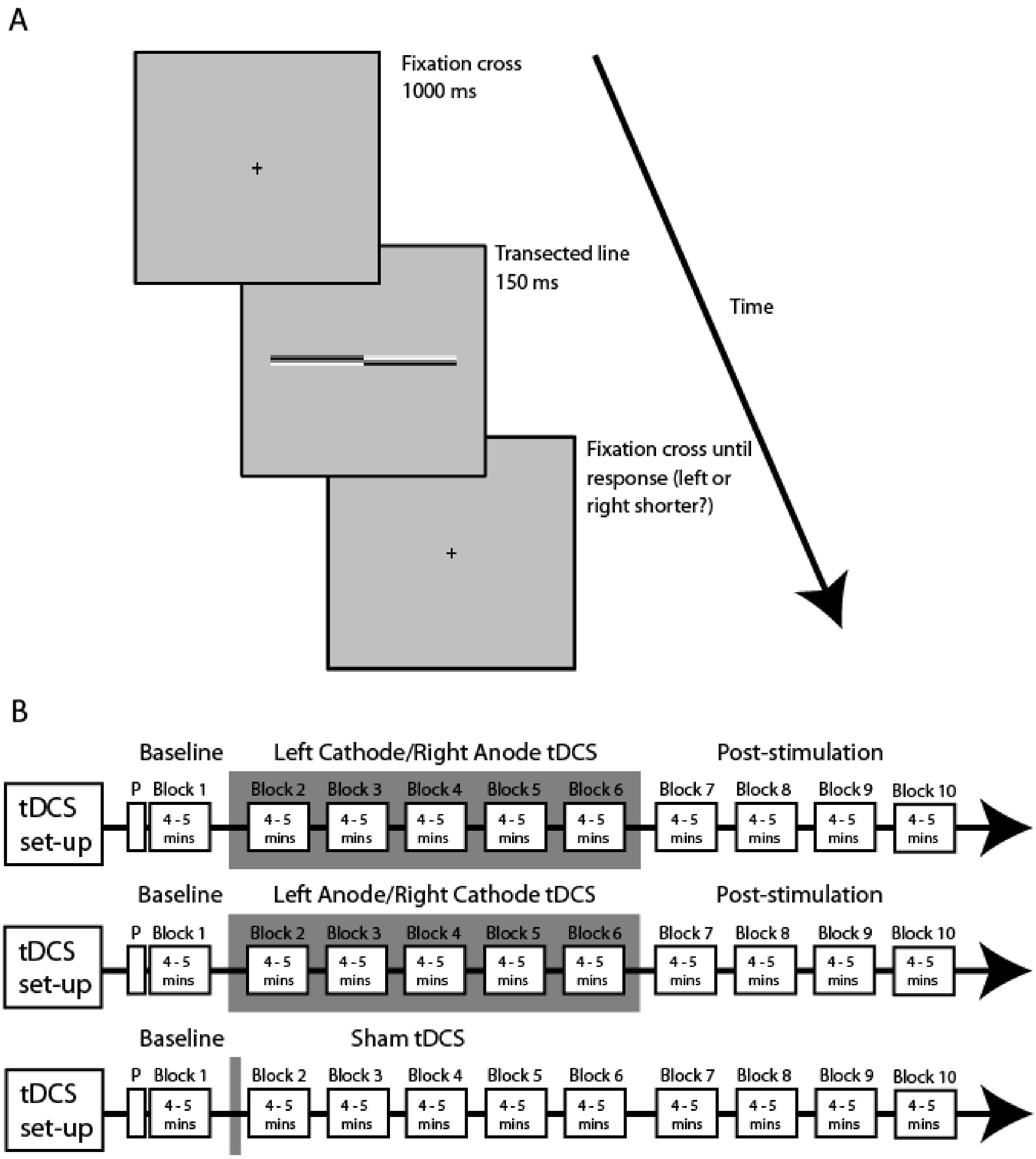


Figure 14. Schematic representations of the trial and session procedures. (A) A schematic representation of the trial procedure. Following 1000ms presentation of a fixation cross, transected lines were presented for 150ms before reappearance of the fixation cross on the screen until the subject responded, by pressing either the left or right (shorter) response key. The subsequent trial began as soon as the response was made. (B) A schematic representation of the session procedure. ‘P’ represents a set of 9 practice trials preceding each baseline block. Each participant completed all three session procedures on separate days, with the order counter-balanced across participants.

Procedure (see Figure 14B)

At the beginning and end of each experimental session, all participants completed the Stanford Sleepiness Scale (Hoddes et al., 1973). Participants were then seated and their midsagittal plane aligned with the display monitor. Viewing distance was kept constant using a chin rest. The electrodes were then attached to the participants scalp by the experimenters and held in place by a rubber band. After tDCS set-up was complete, the task was explained to the participant and a block of 9 practice trials was performed immediately prior to the beginning of the experimental blocks. During the practice block, only the most lateral transector locations to both the left and right of veridical centre were presented (i.e., ± 4% of absolute line length). Accordingly, participants were able to perform the task without difficulty. Upon completion of the practice block, all participants indicated that they understood the task and were ready to begin the experiment (that no further practice was required). In each of the three days testing LA/RC-, LC/RA- and sham-tDCS respectively, each participant completed 10 experimental blocks of the landmark task. Each experimental block consisted of 136 trials (8 judgments at each of the 17 transector locations). The first block was performed with no tDCS and served as a baseline against which performance in the subsequent 9 blocks (#2–10) was compared. After performance of the first block, participants were instructed to wait while tDCS was turned on by the experimenter. Once the stimulation was initiated, participants were instructed to begin the second block and continue at their own pace with the rest of the experiment. Participants were allowed to take short breaks between blocks. During active tDCS sessions, stimulation ended for the majority of participants between blocks 6 and 7. The entire experiment lasted approximately 40–50 min. At the end of every session, each participant completed a questionnaire assessing their subjective experience of possible side effects associated with tDCS (Kessler et al., 2012). The side-effects assessed were headache, tingling, itching, burning and pain, on a scale of 1 (not experienced at all) to 5 (experienced very strongly). In addition, at the end of their final session, each participant was asked to guess in which of the three experimental sessions they had received sham stimulation. Both the side-effect questionnaire and the sham identification question were used to investigate any potentially confounding differences in the experience of tDCS between our four experimental groups (see O'Connell et al., 2012 and Russo et al., 2013).

Data Analysis

Psychometric function (PF) measures

The two dependent variables were the width and PSE of the individually fitted psychometric functions (fitting the same cumulative logistic function as in experiments 1, 2 and 3). The curve width of the fitted PF provides a measure of the precision of the participants' line midpoint judgments per block (visual discrimination sensitivity) and hence was adopted here as an index of baseline intrinsic uncertainty (curve width in block 1 without tDCS: High width values indicate high intrinsic uncertainty, low width values indicate low intrinsic uncertainty). PF measures were obtained for all ten blocks of each of the three sessions in every participant. However, since I was interested in replicating (and extending) the previously observed effects of tDCS on subjective midpoint estimation (Giglia et al., 2011), PSE was the tDCS outcome measure of interest whilst curve width was primarily employed as a measure by which to split participants according to intrinsic performance level at baseline.

Experimental group assignment

In order to investigate whether participants' baseline discrimination sensitivity would influence the effects of tDCS on the PSE of the psychometric function, participants were split into 4 groups. Group assignment was based on the participants' baseline PF curve width estimates (averaged over the baseline data from all three sessions). Separately for each current intensity (1 mA, 2 mA), participants displaying baseline PF curve width below the group average were assigned to the 'high discrimination sensitivity' ('HDS') groups and those displaying widths above the average were assigned to the 'low discrimination sensitivity' ('LDS') groups. The group demographics were as follows: (i) 1 mA 'HDS' group (5 male, 5 female, mean age = 23 yrs, range: 20–29) (ii) 1 mA 'LDS' group (5 male, 4 female, mean age = 24.2 yrs, range: 18–35), (iii) 2 mA 'HDS' group (5 male, 6 female, mean age = 22.27 yrs, range: 17–26), (iv) 2 mA 'LDS' group (4 male, 4 female, mean age = 22.28 yrs, range: 20–25).

Baseline data (block 1, no tDCS): Test-retest reliability of PF curve width and PSE between sessions

In order to assess the consistency of the measures (PF width and PSE) within participants, robust correlation analyses were performed between the values obtained during the baseline blocks of the three testing sessions. This analysis was performed separately for width and PSE values respectively using Spearman’s rho and Shepherd’s pi. Shepherd's pi is a robust test of statistical association between two variables. Outliers are detected by first bootstrapping the Mahalanobis distance of each data point from the bivariate mean and then excluding all observations whose distance is ≥6. Shepherd's pi is equivalent to Spearman's rho after outlier removal. The p-value is doubled because the removal of outliers can inflate false positive rates (Schwarzkopf et al., 2012).

TDCS-effects on PSE values between the baseline block (#1) and the subsequent 9 blocks (#2–10) were analysed using repeated measure analysis of variance (ANOVA). Shifts across the course of each experimental session were isolated by subtracting the PSE of baseline block 1 from each of blocks 2–10 within each participant. In order to isolate tDCS induced behavioural effects during the active sessions, the raw shift values obtained for each block of the sham session were then subtracted from each corresponding block of the active sessions (LC/RA and LA/RC respectively). This allowed for subtraction from the data of the potentially confounding influence of the time-on-task effect observed during extended landmark task performance with long lines in **experiment 1** (see also Benwell et al., 2013b and Manly et al., 2005). The ANOVA then comprised the between-subjects factors tDCS-intensity [2 levels: 1mA vs. 2mA] and Baseline performance level [2 levels: good vs. poor performers] and the within-subject factors tDCS-polarity [2 levels: LC/RA vs. LA/RC] and Block-rank [9 levels: blocks 2:10]. The dependent variable was the PSE.

Results

Baseline performance and sham data across groups

Figure 15A illustrates group-averaged PFs fitted to baseline data (block 1 collapsed across all three experimental sessions) for all four groups of participants (resulting from the 2 × 2 between-subject aspect of our design), consisting of either participants with steep slope/narrow curve width of the individually fitted PFs ("high discrimination sensitivity") or shallow slope/large curve width ("low discrimination sensitivity"), before undergoing either 1 mA- or 2 mA-tDCS. All four experimental groups displayed pseudoneglect at baseline. This is illustrated in the left-biased subjective midpoint judgments (see dotted lines in Fig. 15A, corresponding to 50% left/right-responses, hence PSE), which are all significantly displaced to the left of veridical centre, as the 95% confidence intervals of the group-averaged PSEs do not overlap zero (veridical centre) for any of the groups [*1 mA- 'high discrimination sensitivity' group*: mean: −2.05 pixels/confidence interval (CI): −2.33 to −1.78; *1 mA- 'low discrimination sensitivity' group*: mean: −1.24 pixels/CI: −1.79 to −.60; *2 mA- 'high discrimination sensitivity' group*: mean: −2.13 pixels/CI: −2.44 to −1.81; *2 mA- 'low discrimination sensitivity' group*: mean:−3.43 pixels/CI: −3.96 to −2.90].

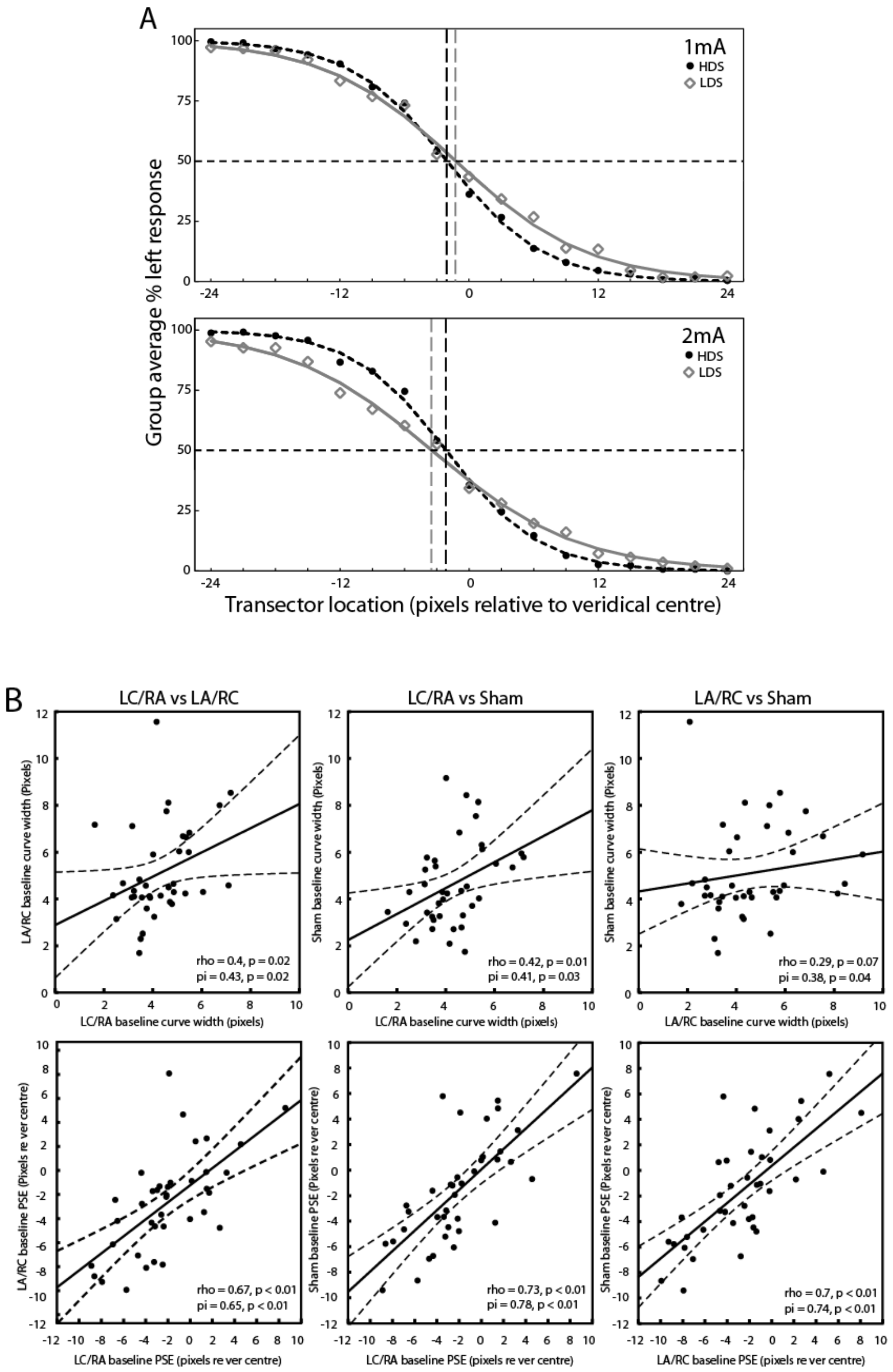


Figure 15. Baseline performance (block 1 before tDCS). (A) presents group averaged baseline psychometric functions (PFs) averaged over all three testing sessions (LA/RC, LC/RA, sham). Symbols plot mean percent left responses as a function of transector location per group ('high discrimination sensitivity' (HDS) vs. 'low discrimination sensitivity' (LDS) performers: black vs. grey symbols) and tDCS intensity (1mA vs. 2mA: upper vs. lower panel). The grey black (HDS performers) and grey (LDS performers) smooth curves represent the best-fitting least-squares cumulative logistic PFs. The points at which the vertical

dashed lines (black: HDS performers; grey; LDS performers) cross the black horizontal dashed line indicate the transector locations corresponding to the 50% left response rate (PSE's). (B) (upper panels) plots correlations between the individually fitted baseline PF widths from each of the three experimental sessions (dashed lines represent the upper and lower limits of the 95% confidence interval (CI) for the fitted slope (solid line)). (B) (lower panels) plots the correlations (slope = solid line, 95% CI = dashed lines) for individually fitted baseline PF PSE values from each of the sessions. Corresponding correlation analyses (Spearman's rho and Shepherd's pi) revealed all of the tested correlations to be significant, indicating high test-retest reliability of the employed measures.

Fig 15B (upper panels) illustrates the consistency of baseline values within participants across the three sessions (i.e., for the repeated baseline measures before LC/RA-, LA/RC- and sham-tDCS) for visual discrimination sensitivity (curve width). Fig. 15B (lower panels) plots the same data but for visuospatial attentional bias (PSE values). To probe test-retest reliability across the three baseline sessions, consistency was estimated for both psychometric measures of line bisection performance between all session-combinations (LC/RA *vs* LA/RC; LC/RA *vs* sham, LA/RC *vs* sham) using correlation analysis (see Fig. 15B, bottom right hand corner of each scatter-plot). The results replicate previous studies showing lateralized landmark task bias to be a stable, predictable trait within participants (McCourt, 2001; Benwell et al., 2013b; Tomer et al., 2013 and Varnava et al., 2013), and extends this in the first instance also to visual discrimination sensitivity during landmark performance.

To exclude that any effects of tDCS may be driven by group differences at baseline, or across sham conditions (given the 2 × 2 between subject design), it was first established that there were no baseline or sham differences across these groups. In terms of the individually fitted PSE values at baseline across the 2 × 2 groups (i.e., baseline performance level × tDCS-intensity), there was no significant difference.

There were no effects of tDCS-intensity [$F(1,34) = .814$, $p = .373$], of baseline performance level [$F(1,34) = .015$,$p = .902$], and no interactions between these factors [$F(1,34) = .749$, $p = .393$]. In terms of curve width at baseline, there were likewise no effects of tDCS-intensity [$F\ (1,34) = .07$, $p = .793$] nor any interaction with baseline performance [$F(1,34) = 1.054$, $p = .312$], while the performance groups differed [as this was the splitting criterion: $F\ (1,34) = 110.244$, $p < .001$]. Additionally, there was no difference between groups in baseline sleepiness rating scales [Kruskal–Wallis test: X2 (3) = .639, $p = .887$]. The absence of any difference at baseline on the dependent variable (PSE) between the 2 × 2 groups rules out that any effect of tDCS on PSE (baseline corrected) originates in a baseline difference. Similarly, analysis of sham PSE data (baseline corrected) did not reveal any effect of tDCS-intensity [$F(1,34) = .06$,$p = .808$], baseline performance [$F(1,34) = .932$, $p = .341$] nor any interaction between these factors [$F(1,34) = .522$, $p = .475$], ruling out that any effect of tDCS on PSE (additionally sham corrected) originates in a sham difference between groups.

Questionnaire data: discriminability of tDCS protocols (1 mA *vs* 2 mA, active minus sham) based on subjective experience across groups

Active tDCS was well tolerated with low mean difference-ratings (active minus sham) of <0.5 (out of 5) across all assessed side effects (headache, tingling, itching, burning, pain). No significant differences in tDCS associated side-effects were found between groups (Kruskal–Wallis tests performed for each side-effect separately, all *p*'*s* > .05) indicating that protocols were similar in associated (low) discomfort. Overall, 50% of the participants correctly identified in which of the three sessions they had received sham tDCS. Broken down by intensity, correct guess rate was

47% versus 53% in the 1 mA versus 2 mA groups respectively. No significant difference in the proportion of correct guesses was found between the four experimental groups (Pearson Chi-Square = 1.429, *p* = .735). Hence, the discriminability of the active protocols (compared to sham) based on subjective experiencewas not different between the experimental groups.

Effects of bi-parietal tDCS on lateralized visuospatial attentional bias

I then examined the effects of tDCS on lateralized visuospatial attention bias (indexed by the estimated PSE of the fitted PF). To this end, a 2 × 2 × 2 × 9 ANOVA on baseline and sham-corrected data (factors: tDCS-polarity, tDCS-intensity, Baseline performance level, Block-rank) was employed. See Fig. 16A for baseline corrected data across all blocks and conditions, and Fig. 16B for baseline/sham corrected data collapsed across blocks. I expected a polarity specific effect of tDCS on visuospatial bias (replicating Giglia et al., 2011), possibly as a function of the two contributors of tDCS outcome, i.e., tDCS intensity and baseline performance levels.

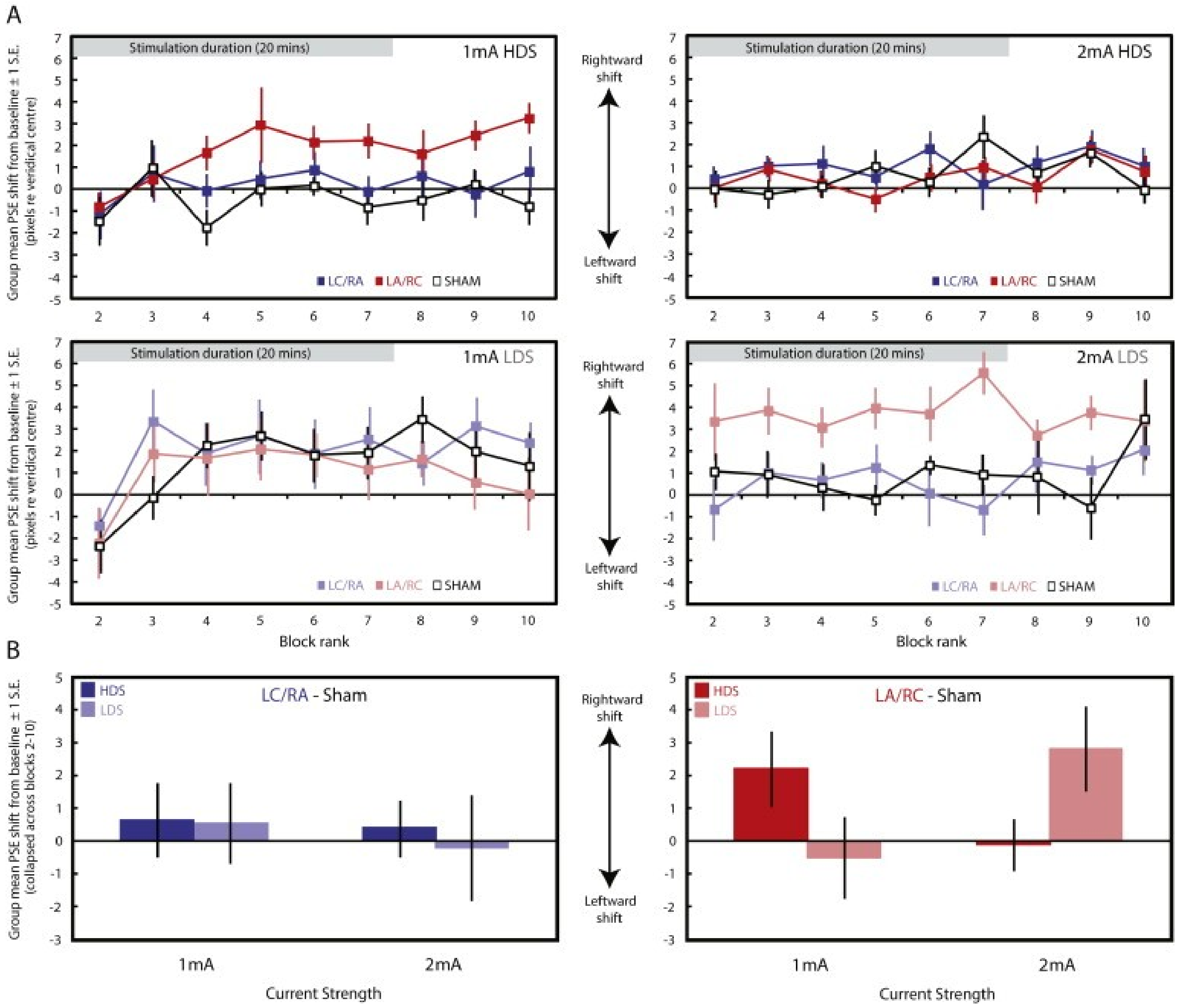


Figure 16: Effects of bi-parietal tDCS on visuospatial attentional bias during line bisection. Negative values (plotted downwards) on the *y*-axis represent a leftward shift in subjective midpoint whereas positive values represent a rightward shift in subjective midpoint relative to baseline (Fig 16A) and sham (Fig. 16B). (A) presents the mean shifts in pixels (±1 S E.) of landmark task PF point-of-subjective-equality (PSE) from baseline (block 1) across the subsequent 9 blocks of the experiment (*x*-axis) for the LC/RA condition (dark and light fill blue squares and lines), the LA/RC condition (dark and light fill red squares and lines) and the sham condition (white squares and black lines) in the 1 mA ‘high discrimination sensitivity’ (HDS) performers (top left panel), the 1 mA ‘low discrimination sensitivity’ (LDS) performers (middle left panel), the 2 mA ‘HDS’ performers (top right panel) and the 2 mA ‘LDS’ performers (middle right panel) respectively. The solid grey horizontal bars represent the stimulation duration (20 min). (B) presents the group average (‘HDS’ performers = dark fill/colour bars, ‘LDS’ performers = light fill/colour bars) shifts in PSE (baseline-corrected and sham-normalised) averaged over blocks 2–10 across both current strengths (*x*-axis) for the LC/RA condition (bottom left panel) and the LA/RC condition (bottom right panel) respectively. LA/RC-tDCS led to a rightward shift in visuospatial attention bias in the 1 mA ‘HDS’ group (high baseline signal/noise ratio) and in the 2 mA ‘LDS’ group (low baseline signal/noise ratio) whereas no shifts in spatial bias were observed in either the 1 mA ‘LDS’ group or in the 2 mA ‘HDS’ group.

The ANOVA revealed no significant main effects of the two tDCS manipulations, i.e., tDCS-polarity [$F(1, 34) = 1.796$, $p = .189$, $\eta p^2 = .05$] and tDCS-intensity [$F(1,34) = .001$, $p = .993$, $\eta p^2 = .001$] as well as no main effects of baseline performance level [$F(1,34) = .016$, $p = .9$, $\eta p^2 = .001$] or block-rank [$F(8, 272) = .51$, $p = .848$, $\eta p^2 = .015$]. In addition, tDCS polarity did not show a two-way interaction with either of the two potential contributors to tDCS outcome investigated here (tDCS-intensity or baseline performance, both F'*s* < .759, *p*'*s* > .390, ηp^2'*s* < .022), nor was there any interaction of this factor with block rank [$F(8,272) = .793$, $p = .609$, $\eta p^2 = .023$]. Hence, when considering tDCS-polarity independently of any other factor, or as a function of tDCS-intensity and baseline performance separately, there was no discernible effect of tDCS-polarity in our sample of 38 participants.

Crucially however, tDCS outcome (polarity-specific) depended on both tDCS-intensity and individual performance level at baseline, as revealed by a significant 3-way interaction between tDCS-polarity × tDCS-intensity × Baseline performance level [$F(1,34) = 7.221$, $p = .011$, $\eta p^2 = .175$], that was independent of block-rank [no 4-way interaction with factor block: $F(8,272) = .602$, $p = .776$, $\eta p^2 = .017$] (illustrated in Fig 16B). Post hoc analysis revealed a significant tDCS-intensity × Baseline performance interaction for the LA/RC-montage [$F(1,34) = 8.465$, $p = .006$, $\eta p^2 = .199$, Fig. 16B, right panel] not present for the other polarity-reversed (LC/RA) montage [$F(1,34) = .041$, $p = .842$, $\eta p^2 = .001$, see Fig. 16B, left panel]. 1 mA LA/RC tDCS led to a larger rightward shift in PSE in the ‘high discrimination sensitivity’ group compared to the ‘low discrimination sensitivity’ group that almost reached significance [$t(17) = 1.757$, $p = .097$, Cohen's $d = .8$] whereas 2 mA-tDCS led to the opposite pattern: a larger rightward shift in PSE was observed in the ‘low discrimination sensitivity' group than in the 'high discrimination sensitivity' group [*t*(17) = −2.503, *p* = .023, Cohen's *d* = −1.08].

To test whether the observed rightward shifts in midpoint judgment with LA/RC-tDCS differed significantly from what would be expected with extended time-on-task alone (whether differing significantly from sham), one-sample *t*-tests (versus 0) were performed on the shift values for each group separately. 1 mA LA/RC tDCS led to a significant rightward shift in visuospatial attentional bias in the group with steep slope/narrow curve width ('high discrimination sensitivity') [*t*(9) = 2.866, *p* = .019, Cohen's *d* = 1.91] and 2 mA LA/RC tDCS led to a significant rightward shift in the group with shallow slope/wide curve width ('low discrimination sensitivity') [*t*(7) = 3.274, *p* = .014, Cohen's *d* = 2.47]. No shift was observed in the other groups [1 mA LA/RC, 'low discrimination sensitivity': *t*(8) = −.351, *p* = .735, Cohen's *d* = .25; 2 mA LA/RC, 'high discrimination sensitivity': *t*(10) = −.141, *p* = .891, Cohen's *d* = .09]. Hence, when tDCS intensity and baseline performance levels were considered, polarity specific effects with large effect sizes >>1 (consisting of a statistically significant rightward shift with LA/RC-tDCS) became evident even in small groups of 9–10 participants. In contrast, a *t*-test against zero on LA/RC data, not differentiating between tDCS intensity and baseline performance (i.e., considering the whole group of all 38 participants), only revealed a trend [*t*(37) = 2.003, *p* = .052] with a medium effect size (Cohen's *d* = .66), despite the large number of participants. For the same comparison in the LC/RA condition, no shift was observed [*t*(37) = .664, *p* = .511, Cohen's *d* = .22].

Effects of bi-parietal tDCS on discrimination sensitivity

I also subjected visual discrimination sensitivity (indexed by the estimated width of the fitted PF) to the above 2 × 2 × 2 × 9 ANOVA on baseline- and sham-corrected data as well as to one sample t-tests against zero. In brief, the interaction of interest (tDCS-polarity × tDCS-intensity × Baseline performance level) was not significant [$F(1,34) = .05$, $p = .824$, $\eta p^2 = .001$], but Baseline performance level and tDCS-intensity were found to interact [$F(1,34) = 13.36$, $p < .001$, $\eta p^2 = .282$; see Figure 17 for the corresponding data]. This may be suggestive of tDCS also affecting discrimination sensitivity (not only attentional bias) depending on the potential contributors to tDCS outcome (i.e., tDCS intensity and individual baseline performance level). However, these changes were inconclusive for two reasons. First, while there was a trend for active tDCS to show a Baseline performance × tDCS-intensity interaction [LA/RC: $F(1,34) = 3.871$, $p = .057$, $\eta p^2 = .102$: LC/RA: $F(1,34) = 3.679$, $p = .064$, $\eta p^2 = .098$], this interaction was also present (with inverted directionality) in the sham data [$F(1,34) = 4.793$, $p = .035$, $\eta p^2 = .124$] (unlike for the attentional bias). Hence, the results may have been driven to some degree by the sham data and to a lesser extent by tDCS. Second, one sample t-tests did not provide clear evidence for changes during tDCS relative to sham [LA/RC: $t(1,37) = -.394$, $p = .696$, Cohen's $d = .13$: LC/RA: $t(1,37) = 1.337$, $p = .190$, Cohen's $d = .44$] (again unlike for the attentional bias). Potential tDCS-effects on visual discrimination sensitivity were hence clearly weaker (if present at all) than the effects on attentional bias.

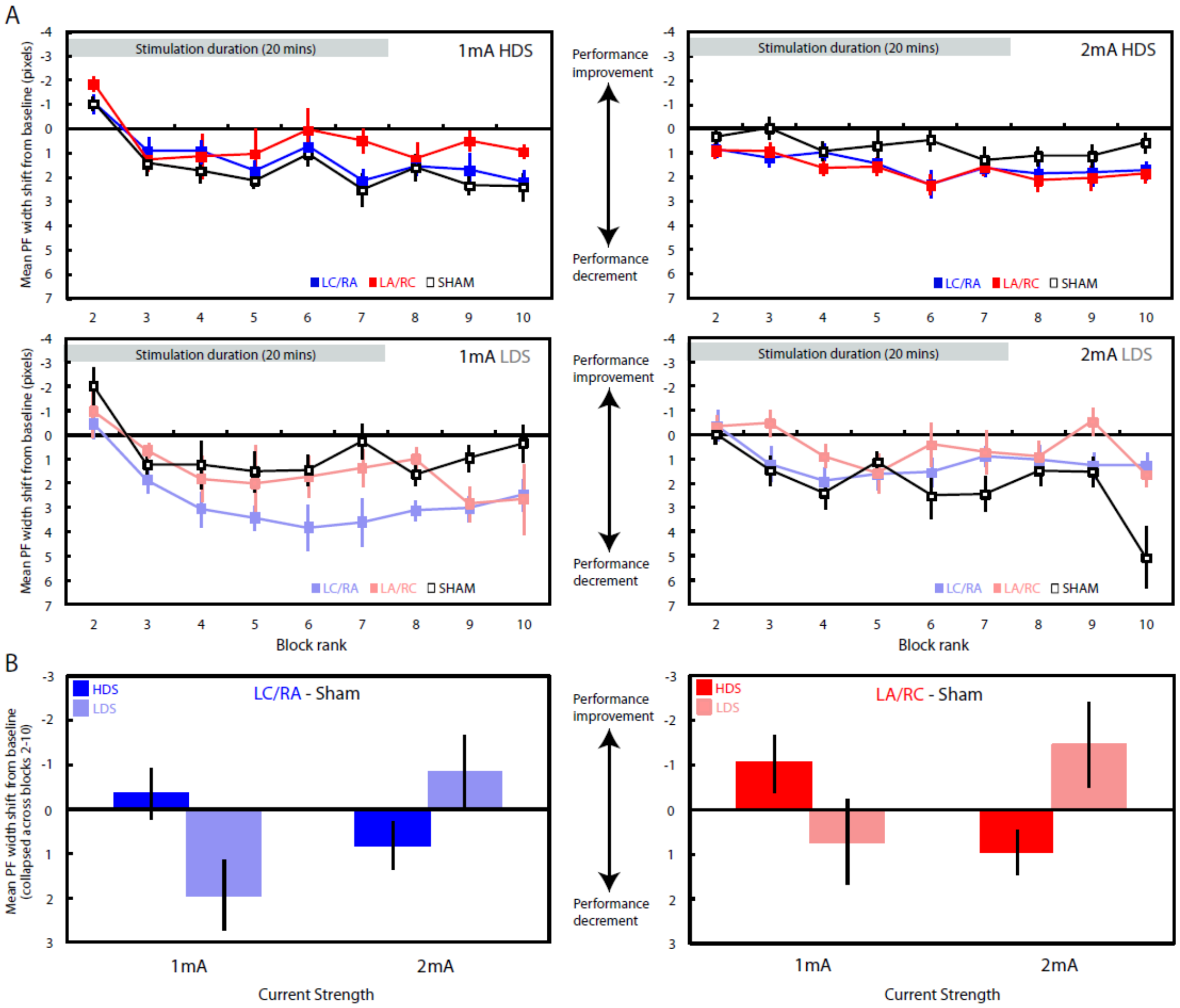


Figure 17: Effects of bi-parietal tDCS on visual discrimination sensitivity during line bisection. Negative values (plotted upwards) on the Y-axis represent an improvement in performance whereas positive values represent a decrement in performance relative to baseline (A) and sham (B). (A) presents the mean shifts in pixels (±1 S.E.) of landmark task PF curve width from baseline (block 1) across the subsequent 9 blocks of the experiment (x-axis) for the LC/RA condition (dark and light fill blue squares and lines), the LA/RC condition (dark and light fill red squares and lines) and the sham condition (white squares and black lines) per group/condition (1mA 'HDS' performers: top left panel, 1mA 'LDS' performers: middle left panel, 2mA 'HDS' performers: top right panel, 2mA 'LDS' performers: middle right panel). The solid grey horizontal bars represent the stimulation duration (20 minutes). (B) presents the group average ('HDS' performers = dark fill/colour bars, 'LDS' performers = light fill/colour bars) shifts of PF curve-width (baseline-corrected and sham-normalised) averaged over blocks 2-10 per current strengths (x-axis) for the LC/RA condition (bottom left panel) and the LA/RC condition (bottom right panel) respectively. Observers with high baseline discrimination sensitivity (high signal-to-noise) benefitted from 1mA-tDCS (low amount of added noise) relative to low discrimination sensitivity observers, while observers with low baseline discrimination sensitivity (low signal-to-noise) benefitted from 2mA-tDCS (high amount of added noise) as compared to high discrimination sensitivity observers.

Discussion

The main findings from **experiment 3** were three-fold. First, the polarity specific effect of bi-parietal tDCS with a LA/RC electrode montage leading to a rightward shift in subjective midpoint (Giglia et al., 2011) was replicated, but the opposite effect with LC/RA-tDCS was not found, i.e., this montage did not shift attention leftward. Second, only a weak overall effect was found in a group of 38 participants in line with recent meta-analyses of weak effects of tDCS on cognitive outcome measures (Horvath et al., 2015b and Jacobson et al., 2012a), yet the effect was found to be strong in a subset of participants when they were split according to individual baseline discrimination sensitivity; a measure associated with intrinsic uncertainty during perceptual decision making (Gold & Ding, 2013). Third, a non-linear interaction between this measure of intrinsic uncertainty at baseline and the administered tDCS current strength was found. This extends previous studies which have separately shown tDCS-effects to depend on the relative expertise/performance level of participants (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al., 2015 and Tseng et al., 2012) and the administered tDCS-intensity (Batsikadze et al., 2013; Hoy et al., 2013 and Teo et al., 2011). These three points are discussed in more detail below.

Polarity-specific effects of bilateral tDCS on lateralized visuospatial attention bias

In the data set, polarity specific effects were expressed in a rightward shift of spatial attention after LA/RC tDCS, in accordance with the classical cathodal-inhibition and anodal-facilitation dichotomy of tDCS (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). These findings are also in line with previously reported polarity-specific effects of parietal tDCS on lateralized visuospatial attention. Anodal tDCS has been found to bias attention towards the contralateral visual field and/or cathodal tDCS to bias attention away from the contralateral visual field, both in animals (Schweid et al., 2008) and humans (Giglia et al., 2011; Loftus & Nicholls, 2012; Sparing et al., 2009 and Wright & Krekelberg, 2014). In the current study, only the LA/RC-montage shifted attention. Because right parietal dominance for visuospatial processing is thought to underlie pseudoneglect, a downregulation of right parietal activity through LA/RC tDCS may have corrected here for the leftward spatial bias and hence driven a rightward shift in the distribution of visuospatial attention. Note that Giglia et al. (2011) directly compared bi-parietal LA/RC-tDCS (as applied here) with unilateral RC-tDCS and observed a rightward shift in bias in both conditions (relative to sham), albeit stronger for bilateral parietal tDCS.. Interestingly, the reversed polarity tested here for the first time during landmark task performance (LC/RA) induced no shift in subjective midpoint relative to sham, a finding that appears at odds with the ICT (Kinsbourne, 1977; Szczepanski & Kastner, 2013). Perhaps tDCS cannot enhance the leftward bias further outside of an advantageous range for perception, in analogy to Goedert et al., (2010) who observed a similar 'ceiling effect' during prism adaptation in healthy participants. In contrast to the current results, Sparing et al., (2009) found polarity-specific bidirectional shifts in visuospatial attention bias displayed during a lateralized dot detection task, with unilateral parietal anodal versus cathodal tDCS enhancing versus impairing perception of stimuli in the contralateral visual field. Though both tasks (lateralized dot detection and the landmark task) putatively index lateralized visuospatial bias, the lack of an effect for the LC/RA configuration in the current study may suggest differences in the neural networks subserving the respective tasks, or alternatively could be explained by differences in the effects induced by unilateral versus bilateral stimulation (see for instance Sehm et al., (2013)).

TDCS outcome scales with a psychometric index of intrinsic uncertainty (related to signal-to-noise ratio), in interaction with tDCS current strength

Whilst the results of Giglia et al., (2011) for the LA/RC tDCS montage were here replicated, this effect was weak (Cohen's *d* = .66) across our entire sample (*N* = 38). However, taking into consideration baseline discrimination sensitivity (i.e., the width of the PF) and the administered current strength as factors in the analysis revealed that these two factors together strongly modulate tDCS-efficacy, with the response to tDCS differing between groups. ‘High discrimination sensitivity’ participants only responded to 1 mA-tDCS (Cohen's *d* = 1.91), whereas ‘low discrimination sensitivity’ participants responded only to 2 mA-tDCS (Cohen's *d* = 2.47). The potentially strong influence of subtle differences in sample characteristics and/or experimental protocols on tDCS outcome highlighted by these results may contribute to the large outcome variability observed across tDCS studies (Horvath et al., 2015a, Horvath et al., 2015b, Jacobson et al., 2012a, Krause & Cohen Kadosh, 2014, Krause et al., 2013, López-Alonso et al., 2014, Vallar & Bolognini, 2011 and Wiethoff et al., 2014). Conversely, research aimed at mapping the factors that influence tDCS outcome (and the relationships between them) across brain regions and cognitive domains may lead to the improvement of tDCS efficacy and specificity for both research and clinical purposes.

The finding that tDCS outcome depends on discrimination sensitivity further highlights state/trait dependency of NIBS (e.g., in TMS (Siebner et al., 2009)). Within this framework, it has been proposed that the relative balance between task-relevant and task-irrelevant neurons at baseline (e.g., Silvanto et al., 2007 and Silvanto et al., 2008), or the related concept of signal and noise (e.g., Miniussi et al., 2010; Miniussi et al., 2013 and Ruzzoli et al., 2010), is a determining factor of NIBS outcome. Note that the concept of the relative activity profile of subpopulations of neurons influencing NIBS outcome is primarily based on studies using TMS (Abrahamyan et al., 2011; Cattaneo et al., 2008; Cattaneo et al., 2010; Schwarzkopf et al., 2011; Silvanto et al., 2007 and Silvanto et al., 2008; see Miniussi et al., 2013), but is herein suggested to apply also to tDCS. The slope of the PF was employed here as a measure of the degree of intrinsic uncertainty (Gold & Ding, 2013; Kontsevich & Tyler, 1999; Pelli, 1985; Pelli, 1987 and Tyler & Chen, 2000), which in turn has been related to the degree of pooling of task-relevant neurons during perceptual decisions (Gold et al., 2010). By extension, the data suggest that the level of intrinsic uncertainty/task relevant neuronal pooling modulates tDCS outcome. On a cautionary note, the measures by which participants were split into subgroups were behavioural. Hence I have not measured from task-relevant neurons (“signal”) or task-irrelevant neurons (“noise”) directly and can only speculate as to the mechanisms through which tDCS may interact with baseline signal-to-noise ratio. In addition, this measure is indirect and can only provide an approximate estimate of neurophysiological makeup. To develop a mechanistic understanding of the relationship between tDCS and behavioural outcome, biophysical models tested through appropriate physiological and behavioural measures should be implemented (de Berker et al., 2013 and Bestmann et al., 2015, also see the **general discussion** for an expansion of this point with regard to visuospatial attention). Regardless of the mechanism underlying tDCS trait/state dependency as observed in the current study, the results suggest that current theories of state-dependency of NIBS can be extended to tDCS and that tDCS specificity and efficacy may be improved by selecting dose as a function of a person's task performance level/endogenous signal-to-noise ratio.

Non-linear interaction between baseline performance groups and tDCS current strength: potential explanations

The polarity specific effects were modulated by a complex interaction between tDCS-intensity and baseline task ability. I characterize the nature of this interaction as non-linear because one subset of participants responded to one dose whereas another subset responded to another dose. Accordingly, these effects are incompatible with floor or ceiling effects where ’high discrimination sensitivity’ participants simply show stronger effects than ‘low discrimination sensitivity’ participants (or vice versa), or with linear dose response accounts where effects should be stronger for 2 mA-than 1 mA-tDCS independent of group. How can the nonlinear dose-dependent effects of tDCS on behavioural performance then be explained?

One possible nonlinear mechanism that has been associated with NIBS outcome is stochastic resonance (Abrahamyan et al., 2011; Miniussi et al., 2010; Miniussi et al., 2013; Ruzzoli et al., 2010 and Schwarzkopf et al., 2011). Stochastic resonance has been posited in various theoretical cognitive models and has also been observed empirically in experimental neuroscience (Faisal et al., 2008; McDonnell & Ward, 2011; Moss et al., 2004 and Simonotto et al., 1997). It denotes a phenomenon in which the relative modulation of signal-to-noise (either by the addition of a given level of input noise, or by the disproportional activation of “noise” channels) can paradoxically improve information processing. Stochastic resonance may fit our data because it is inherently non-linear and predicts NIBS outcome to depend on the endogenous signal-to-noise ratio of the participant for a given task. Yet, whether stochastic resonance could explain the present non-linear effect remains elusive, and would require a better understanding of the degree to which tDCS can be considered a source of physiological noise, and a design more suited to test the specific predictions of the stochastic resonance model. Another mechanism associated with NIBS that shows non-linearity and state-dependency is homeostatic metaplasticity (Ridding & Ziemann, 2010; Siebner, 2010 and Siebner et al., 2004). However, homeostatic metaplasticity serves to maintain neuronal functions within predefined optimal ranges to avoid extreme dysfunctional levels of neural activity following prolonged periods of excitation/inhibition (Turrigiano & Nelson, 2004). Consequently, homeostatic metaplasticity pertains to compensatory mechanisms following plasticity-inducing protocols (Ziemann & Siebner, 2008) rather than the online effects of NIBS observed here. Hence, homeostatic metaplasticity can be excluded here, at least empirically, as an explanation for the observed non-linear effects.

It should be emphasized that there are other possible non-linear mechanisms alongside stochastic resonance (and metaplasticity) which could underlie the findings. While this study contributes to support models of state-dependency of NIBS as well as to characterize the nature of the interaction with other tDCS factors (namely intensity), it cannot resolve which mechanisms are at play.

Potential limitations of study

Despite there being no evidence of differences in the subjective somatosensory perceptions associated with stimulation between groups (as measured by a side-effects questionnaire), stimulation of peripheral nerves in the skin underlying the electrodes will vary systematically with stimulation intensity and even unconscious differences between the 1 mA and 2 mA groups may have affected behaviour. However, this could not explain the observed interaction between baseline discrimination sensitivity and current strength. Rather, a difference between current strength groups only would be expected under such a scenario, regardless of baseline performance level.

Finally, it is notable that stimulation intensity is not calibrated to individual cortical excitability in tDCS studies, including this study, while this is common in TMS studies. Therefore across participants potentially different stimulation intensities may be effectively delivered to the brain. Additionally, different current intensities potentially induce differential current distributions within the brain. Future studies may take into account these factors by incorporating models of current distribution based on individual physical differences (bone structure, tissue properties etc.) and the administered current density to titrate effective stimulation intensity and focality across participants.

Conclusion

The current results show that bi-parietal left anodal/right cathodal tDCS can drive a rightward shift in subjective midpoint estimation during performance of the landmark task. However, this effect depends on the baseline task performance level of participants, in interaction with the administered tDCS-intensity. The opposite polarity (left cathodal/right anodal) resulted in no change in subjective midpoint estimation. The results highlight that individual differences and dose interact to influence tDCS outcome. I conclude that it is of importance to map and understand the factors that determine tDCS outcome across different cognitive domains, and the relationships between them, if tDCS is to be developed as a useful clinical and research tool in cognitive sciences.

Additionally, it appears that lateralized visuospatial attention bias can only be shifted to the right by LA/RC tDCS (and cannot be shifted to the left using the reversed tDCS montage (LC/RA)), perhaps due to a rebalancing of the typical hemispheric asymmetry in favour of the RH during task processing. This finding accords with the results of **experiment 2** that implicate RH activation as primarily contributing to the genesis of pseudoneglect, and more broadly with the ‘right hemispheric dominance’ theory of spatial attention processing (Heilman and Van den Abell, 1980, Mesulam, 1981).

General Discussion

In the current set of experiments, it has been shown that both spatial and non-spatial attention measures are modulated by stimulus- and state-factors, as well as by neuromodulation through tDCS, during performance of the landmark task.

In experiment 1 (presented in **Chapter One**), both decreased line length and increased time-on-task were found to induce a rightward shift in spatial bias. However, the time-on-task effect was found to be stimulus-dependent, only occurring with extended performance with long lines and not for short lines. Extended performance of the task with long lines induced a rightward shift in subjective midpoint in both long and short lines suggesting a partially common denominator for line bisection performance regardless of line length.

In experiment 2 (presented in **Chapter Two**), EEG recording during landmark task performance in both long and short lines revealed the 'line length effect' to be reflected in right hemisphere lateralised neural activity during an early time window (100-200 ms) post-stimulus onset. Hence, increased right hemisphere engagement at early processing stages contributes to the genesis of pseudoneglect.

In experiment 3 (presented in **Chapter three**), an overall rightward shift in spatial bias was found in elderly participants relative to young, with no systematic bias in long lines for elderly participants versus the typical leftward bias present in young participants. The line length effect (rightward shift in bias with decreasing line length) was replicated in both young and elderly participants, with a systematic rightward bias being present for the shortest lines in elderly participants.

Finally, in experiment 4 (presented in **Chapter Four**) pseudoneglect was found to be ameliorated by the application of left anodal/right cathodal (LA/RC) tDCS during landmark ask performance. The opposite polarity (LC/RA) had no effect on spatial bias. Moreover, the degree to which LA/RC tDCS was effective in shifting spatial bias rightward was found to be modulated by an interaction between baseline discrimination sensitivity and the administered current strength, suggesting that complex interactions between individual differences and stimulation parameters influence tDCS outcome and must be harnessed in order to improve tDCS efficacy.

In terms of lateralized spatial bias, Figure 18 summarises the effects on subjective midpoint of the various modulators of bias investigated throughout the four experiments. As suggested in the introduction, any accurate model of the visuospatial attention system must account not only for the commonly observed pseudoneglect phenomenon, but also for inter- and intra-individual variations in the magnitude and direction of bias such as those reported here. In the final section, I wish to summarise how the data from the current set of experiments informs previous theories and also to identify pertinent open questions and potentially productive methods for approaching them.

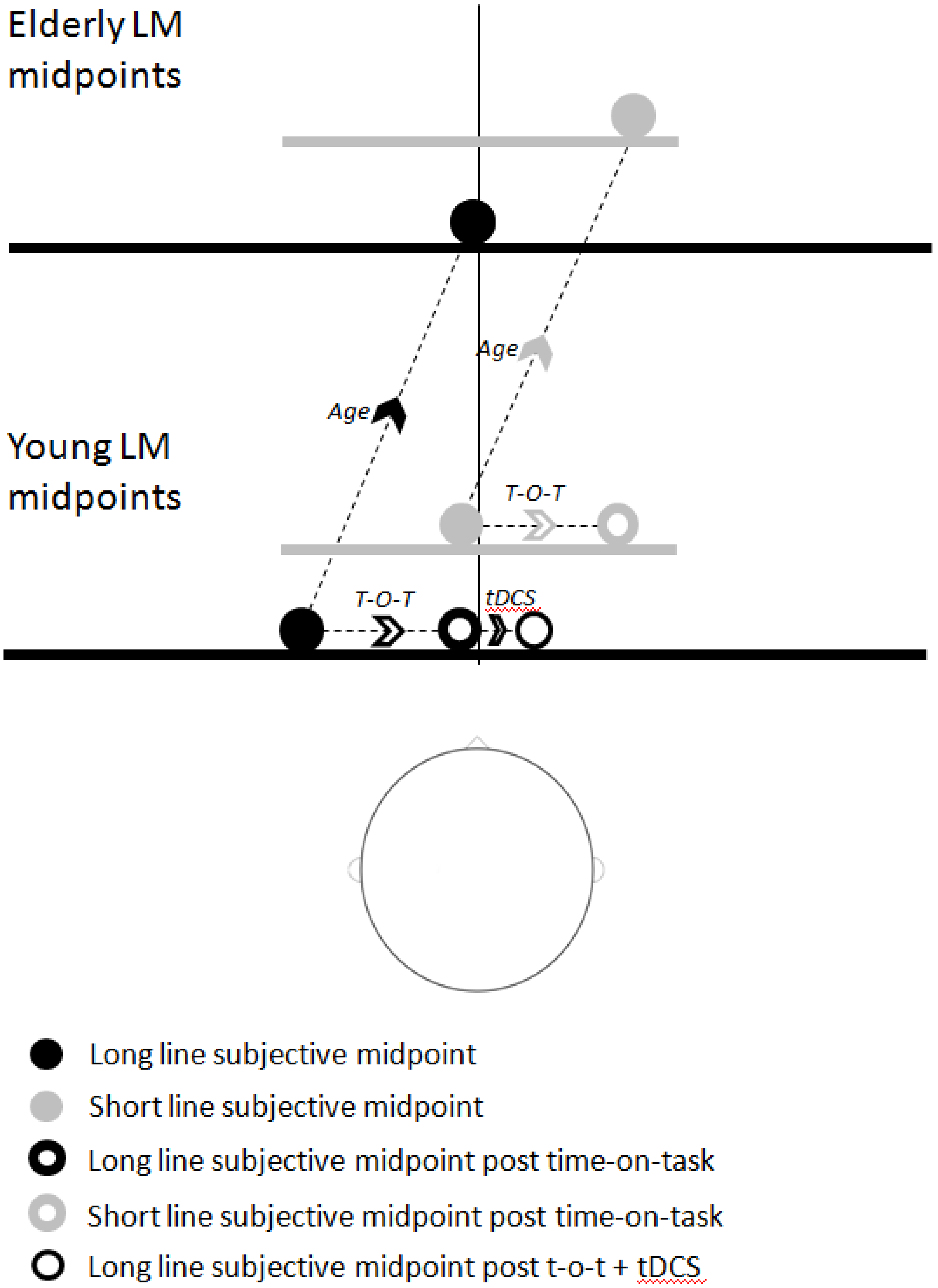


Figure 18. **A schematic of pseudoneglect modulators**. The solid vertical black line represents veridical centre relative to the ‘observer’ (head facing upwards). Dots represent group-level subjective midpoints in various ‘states’ based on the data from the current set of experiments employing the landmark task (LM). Conditions represented by each colour/fill are indexed at the bottom of the figure. The horizontal lines represent long (black) and short (grey) lines for both elderly participants (top) and young participants (bottom) respectively. Dashed lines connecting ‘midpoint’ dots represent the rightward shifts in spatial bias induced by the different modulators of bias (age, time-on-task (T-O-T) and left anodal/right cathodal tDCS labelled accordingly) investigated in the current experiments.

Neuroimaging and pseudoneglect modulators

The stimulus modulation (line length) investigated in three of the four experiments here shows a robust group-level effect on line bisection performance, in line with previous findings (McCourt & Jewell, 1999; Hurwitz et al., 2011; Thomas et al., 2012; Rueckert et al., 2002; Heber et al., 2010). Specifically, a rightward shift in subjective midpoint is observed with decreasing line length. A novel finding here is that state-modulations which also result in a group-level rightward shift of the subjective midpoint, both through extended time-on-task (experiment 1; Manly et al., 2005; Dufour et al., 2007) and healthy aging (experiment 3, Schmitz & Peigneux, 2011), interact with line length in an additive manner (see Fig. 18). Such modulators of bias (and the relationships between them) offer clues as to the functional architecture of the visuospatial attention system and the neural networks subserving spatial biases in healthy and clinical populations. As mentioned in the introduction, they provide a particularly powerful avenue of research in combination with neuroimaging measures in terms of identifying that neural activity which is necessary and sufficient for the genesis of spatial bias without having to rely on comparison of task related activity with that of a not necessarily appropriate ‘control’ condition.

In **experiment 2**, the behavioural ‘line length effect’ on subjective midpoint was found to be reflected in stimulus-evoked neural activity (as measured by EEG) source-localised to regions in and around the right temporoparietal junction (TPJ) at approximately 100 – 200 ms post-stimulus onset. The timing of the effect is in line with chronometric studies investigating single-pulse PPC TMS induced shifts in spatial bias (Fierro et al., 2001; Dambeck et al., 2006). A potentially informative next step would be to investigate the neural correlates of the other established modulators of spatial bias (such as age, time-on-task, tDCS, TMS etc.) and hence to discover whether the same neural networks are at play or whether distinct spatiotemporal contributors to the bias exist. For instance, a recent study by Longo et al. (2015) investigated the influence of viewing distance on the 'line bisection effect' identified initially by Foxe et al., (2003) and replicated here in **experiment 2**. Previous studies have found a rightward shift in spatial bias when viewing distance shifted from peri- to extra-personal space (McCourt & Garlinghouse, 2000, Varnava et al., 2002, Bjoertomt et al., 2002, Longo & Lourenco, 2006, Gamberini et al., 2008, Mahayana et al., 2014, Longo et al., 2015)). The right-parietal negativity associated with line bisection performance relative to a non-spatial control task (the 'line bisection effect' (Foxe et al., 2013, **experiment 2**) was found to scale with viewing distance, being largest in near space and reduced in far space (range: 30, 60, 90, 120 cm). The effect of viewing distance occurs relatively late in task processing (240-400 ms) and so there is tentative converging evidence that the effects of viewing distance (Longo et al., 2015) and line length (**experiment 2**) on bisection performance arise from neural substrates that are at least temporally dissociated. This line of research offers much promise in terms of mapping the spatiotemporal architecture of the visuospatial attention system. Further neuroimaging studies may incorporate different modulators of bias within the same experimental design in order to directly assess the level of independence/relatedness between the variables modulating line bisection performance and their neural substrates. Additionally, by developing biologically plausible formal models based on previous studies of visuospatial bias and its modulators, more intelligent experimental paradigms may be developed in order to help bridge the gap between neuro-imaging measurements and behavioural data. This point is expanded on in the final section. First, I wish to discuss the contribution of the current set of experiments to theories regarding hemispheric contributions to lateralised visuospatial bias.

Right hemisphere role in the genesis of pseudoneglect

The combined data from the current set of experiments broadly supports models that highlight the dominant role of the RH in the functional architecture of the visuospatial attention system and the genesis of pseudoneglect (Heilman & Van den Abell, 1980; Heilman et al., 1987; Mesulam, 1981; Dietz et al., 2014; Corbetta & Shulman, 2002; 2011). The line length effect (amelioration of pseudoneglect with decreasing line length) appears to depend on the level to which the right hemisphere IPC/TPJ is differentially engaged by long and short lines. A parsimonious explanation for the amelioration of pseudoneglect by time-on-task in long lines (**experiment 1**; Manly et al., 2005; Dufour et al., 2007), healthy aging (**experiment 3**; Schmitz & Peigneux, 2011) and bi-parietal tDCS (**experiment 4**; Giglia et al., 2011) would be that these modulators also downregulate RH contribution to task processing.

With regards to time-on-task, the interaction between RH ventral and dorsal fronto-parietal networks has been postulated to underlie the relationship between arousal level and spatial attention (Corbetta & Shulman, 2011; Newman et al., 2013). In line with the results of experiments 1 and 2, prolonged bisection performance with long lines may deplete resources in the RH ventral fronto-parietal network which in turn would reduce overall RH contribution to task processing and drive a rightward shift in spatial attention. RH downregulation also provides a potential explanation for the observed rightward shift in spatial attention with healthy aging (experiment 3), whether through hemispheric asymmetry reduction (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008; Li et al., 2009), accelerated RH aging (Brown & Jaffe, 1975; Goldstein & Shelly, 1981; Nagamatsu et al., 2011) or chronically reduced arousal (Robinson & Kertzman, 1990; Goedert et al., 2010; Buysse et al., 2005; Nebes et al., 2009).

Experiment 4 provides interesting additional evidence regarding the critical role played by downregulation of RH activity in amelioration of bisection bias through the application of tDCS. In line with a previous study by Giglia et al., (2011), left anodal (LA)/ right cathodal (RC) bi-parietal tDCS induced a rightward shift in subjective midpoint. Giglia et al., (2011) employed a unilateral right cathodal stimulation condition which also induced a rightward shift in subjective midpoint, though the effect was stronger for bilateral stimulation. Cathodal stimulation is typically thought to reduce neuronal excitability beneath the electrode, with the opposite being the case for anodal stimulation (Nitsche & Paulus, 2000). Interestingly, the reverse polarity (LC/RA) introduced in **experiment 4** did not modulate spatial bias as would be expected under the ICT (Kinsbourne, 1970; 1977; Reuter-Lorenz et al., 1990; Bultitude & Aimola-Davies, 2006; Szczepanski & Kastner, 2013) and the 'hybrid' model (Duecker & Sack, 2015). An additional study that is relevant to this point is that of Wright & Krekelberg (2014) in which the effects of bi-parietal tDCS on a centroid extraction task in healthy participants were investigated. A rightward visual mis-localization was found to be induced by LA/RC relative to LC/RA stimulation. The authors interpret the results to be partially in line with the ICT however they acknowledge that certain predictions of the ICT were not met in their data. Namely, though mis-localizations induced by LA/RC stimulation were consistently shifted to the right of mis-localizations induced by LC/RA stimulation, the sign of the shifts (negative vs. positive) relative to sham for each stimulation condition tended to be the same within participants. Under the ICT, opposite polarities (LA/RC vs. LC/RA) should induce opposite directional shifts relative to sham.

It should be noted that previous TMS and tDCS studies in healthy participants and neglect patients have induced changes in lateralised visuospatial perception consistent with the 'bi-directional shift' prediction of the ICT (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Kim et al., 2005; Koch et al., 2005; Thut et al., 2005; Dambeck et al., 2006; Sparing et al., 2009; Cazzoli et al., 2009; Sczepanski & Kastner, 2013) and the predictions of the ICT have also been met in various other neuroimaging studies in both healthy participants and neglect patients (Corbetta et al., 2005; Thut et al., 2006; Sylvester et al., 2007; Romei et al., 2010). However, in other studies only TMS applied to the RH PPC (and not the LH PPC) modulated visuospatial bias (Fierro et al., 2000; Brighina et al., 2002; Müri et al., 2002; Muggleton et al., 2006). Moreover, recent TMS-EEG (Bagattini et al., 2015) and TMS-fMRI (Ricci et al., 2012) studies cast doubt on the role of interhemispheric imbalance as an explanation for 'neglect-like' behaviour in healthy participants after unilateral RH PPC inhibitory-TMS. In both of these studies, strong evidence is provided for bilateral cortical hypo-activation after unilateral RH PPC inhibitory-TMS stimulation rather than the LH hyper-activation that would be expected under the ICT and the 'hybrid' model. Additionally, Umarova et al., (2011) have recently shown that left-right parietal imbalance (i.e. relative increase in LH activation) in acute RH stroke patients is not predictive of visuospatial deficits, being present in control participants, patients without neglect and patients with neglect. The authors propose that dysfunction of the right parietal and lateral occipital cortex, and not relative hyperactivation of the LH parietal cortex (as suggested by Corbetta et al., (2005)), are characteristic of neglect in acute RH stroke patients.

Hence, overall the evidence for a causal role of inter-hemispheric rivalry in the genesis of lateralised spatial bias is mixed. One intriguing and relatively unexplored possibility is that inter-hemispheric competition predominantly influences spatial bias only under certain conditions and hence the predictions of the ICT may be met for certain tasks/circumstances and not for others. For instance, perhaps maladaptive cortical re-organization post-stroke may modulate inter-hemispheric imbalance and hence neglect symptoms, in line with the ICT, as shown by Corbetta et al., (2005). Thus, this relationship between inter-hemispheric imbalance and lateralised spatial bias would not necessarily be found in acute stroke patients (Umarova et al., 2011) or in healthy participants after modulation of parietal cortex activity through for instance time-on-task (Manly et al., 2005; Dufour et al., 2007; **experiment 1**), healthy aging (Schmitz & Peigneux, 2011; **experiment 3**) or the application of brain stimulation (Bagattini et al., 2015; Ricci et al., 2012; **experiment 4**). Additionally, interhemispheric rivalry may influence behaviour on some tasks (i.e. extinction tasks (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Koch et al., 2005; Bien et al., 2012) and lateralised dot detection (Thut et al., 2005; Thut et al., 2006; Sparing et al., 2009)) more strongly than on others (i.e. variants of line bisection (Fierro et al., 2000; Brighina et al., 2002; **current experiments**)). Another possibility is that the predictions of the ICT may be met during certain cognitive states such as under high cognitive load (see Sheramata et al., 2010). In the current set of experiments, shifts to systematic rightward biases (as would be predicted under the ICT) were observed after time-on-task in healthy participants (**experiment 1**) and at baseline in elderly participants (**experiment 3**) but only in short lines. In long lines, all modulations of subjective midpoint investigated throughout the current experiments (time-on-task, line length, healthy aging and tDCS) resulted only in a reduction or amelioration of bias, not a cross-over to a systematic rightward bias. The systematic rightward biases observed in short lines post time-on-task and in the elderly at baseline were unexpected and are difficult to interpret in terms of inter-hemispheric competition, as the short line (subtending < 2º of visual angle horizontally and presented at the midline) condition is the one in which processing of lateral visual field portions (and hence presumably distinct contributions from each hemisphere to visual processing) is minimised. Such unexpected observations may help to inform more refined models of pseudoneglect and visuospatial attention functions.

Modelling pseudoneglect and visuospatial attention networks

It appears that some of the empirical data is not straightforward to interpret in line with current theories of visuospatial attention network organisation, with evidence in favour of the ICT and RHDT theories respectively (as well as the 'hybrid' model) being mixed. Additionally, current theories often share predictions and hence experimental outcomes can be ambiguous with regards to providing support for one theory over another. Refinement of the current models can provide new and more specific testable hypotheses for further research. However, functional-anatomical models alone may not be optimal in terms of adequately capturing all of the cognitive processes underlying visuospatial attention. Formal mathematical models of visuospatial attention function can help to bridge the gap between functional-anatomical models, neuroimaging measurements and behavioural data (Forstmann & Wagenmakers, 2015). Apparently contradictory and/or unexpected empirical data may arise due to interactions of latent cognitive processes in a non-unitary system that may not be captured by purely descriptive or functional-anatomical models. Hypotheses regarding the different cognitive processes that contribute to a given visuospatial task can be formalised in model form and then simulations and suitable experimental manipulations can be employed to test the predictions of the model (see Anderson, 1996; Mozer et al., 1997; Pouget & Sejnowski, 2001; Monaghan & Shillcock, 1998; 2004; Brandt et al., 2012; Leigh et al., 2015 for tentative examples).

For example, Anderson (1996) proposed a mathematical model of line bisection behaviour in spatial neglect in which the perceived midpoint of a line represents the point at which the salience of the right and left end of the line appears to be equal. The salience of any point of the line is determined by the combined contribution of two separate attentional processors: one in the right hemisphere and one in the left hemisphere. The contribution of each processor is represented by a saliency ‘curve’ mapped along the horizontal spatial dimension and the combined area under the curve of the two processors determines the salience at any given point. Crucially, saliency across the horizontal dimension is calculated as a function of several biologically plausible latent variables: the contra-lateral points at which saliency ‘peaks’ for the LH and RH processors, the ‘width’ of the saliency curve for each processor and the ‘height’ of the saliency curve for each processor. Such nuanced latent variables are not necessarily captured by purely functional-anatomical models and it is possible that different modulators of perception (such as brain injury, healthy aging, brain stimulation, state factors or other experimental manipulations) may influence distinct latent contributors to visuospatial attention function. After ‘lesioning’ the contribution of the RH processor to the model output (by reducing the ‘height’ and ‘width’ of the RH saliency curve but keeping the saliency ‘peak’ locations constant for each hemisphere), Anderson’s (1996) model successfully captures some of the apparently paradoxical behaviours exhibited by neglect patients during line bisection performance (such as right-to-left cross-over of spatial bias from long to short lines (Halligan & Marshall, 1988; Marshall & Halligan, 1989; Harvey et al., 1995; Anderson, 1996; 1997; Monaghan & Shillcock, 1998; 2004; Ricci & Chatterjee, 2001; Mennemeier et al., 2005; Veronelli et al., 2014) which appeared hard to explain under any of prevailing theories of spatial neglect at the time of publication of the model). Such an approach may also provide explanatory potential for other unexpected findings, such as the systematic rightward bias in short lines observed post time-on-task and at baseline in the elderly in the current set of experiments.

Whilst it is outside of the scope of the current set of experiments to formally evaluate competing models of line bisection behaviour in normal participants, this may prove to be an informative future direction. One could assess (through simulations) whether alterations in the parameters chosen for a given set of latent variables can approximately match the observed line bisection data in healthy participants and whether manipulation of each variable, either alone or in interaction, can approximate observed changes induced by established modulators of behaviour. Thus, formal models based on previously observed data would allow for the development of very specific testable hypotheses and in turn iterative refinement of the models based on new data. Such a process would allow for the identification of distinct cognitive contributors to visuospatial attention function which could then be investigated through means of neuro-imaging measurements combined with suitable experimental designs.

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