HEMISPATIAL NEGLECT, ELECTROENCEPHALOGRAPHIC CORRELATES AND THE EFFECT OF SHORT WAVELENGTH LIGHT ON SPATIAL INATTENTION

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BPsych (Hons.)

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Summary

Hemispatial neglect (hereafter referred to as "neglect") is a common and disabling neurological syndrome clinically defined as the inability to detect, respond to, and orient towards stimuli on the side contralateral to cerebral damage. Contemporary models of neglect posit that the disorder is most typically the result of disruption to a right lateralised system responsible for the maintenance of arousal and vigilance, which subsequently causes reduced exploration of, and poor attention directed to, the left side of space. This deficit is asymmetrical in that responses to stimuli presented in the intact ipsilesional (i.e., right) side of space, are largely normal. Although many individuals recover, approximately one-third of patients manifest a chronic form of neglect, with a substantial proportion exhibiting clear deficits more than six months post-stroke. The presence of on-going neglect is significant as the disorder is associated with poor functional outcomes, both within and beyond rehabilitation settings. Yet despite decades of research, the disorder is not well understood. The contributing underlying physiology that influences the behavioural phenotype remains unclear and this lack of understanding has hampered the development of effective rehabilitation strategies. One perspective that could provide useful insights in neglect patients is that of perceptual decision-making. Perceptual decision-making encompasses multiple neural processing stages from representing, selecting and accumulating sensory information to preparing and executing actions. Although spatial attention and perceptual decision-making have not historically been co-examined, variation at any stage within the perceptual decision-making process could affect the ability to orient in space, suggesting this approach may provide important insights into the phenomenon of neglect.

As such, this thesis had three core aims: (1) to investigate how perceptual decision-making and specifically the neural correlates associated with orienting of attention and evidence accumulation are affected by healthy aging; (2) to investigate the role of attention orienting and evidence accumulation in accounting for the archetypal behavioural left spatial inattention observed in patients with neglect symptomatology following stroke; and (3) to investigate the utility of a non-pharmacological manipulation of alertness, ocular blue-enriched light exposure, to

remediate the pathological bias of spatial attention to left space seen in neglect patients.

The first chapter of the thesis reviews the literature, providing an overview of neglect, including a summary of associated deficits, theoretical explanations, current assessment tools, anatomical correlates, and previous electroencephalographic (EEG) investigations. The background to perceptual decision-making is presented. The various rehabilitation strategies currently available for neglect are discussed before the potential utility of using blue-enriched white light as a mode of modulating spatial inattention in neglect patients is proposed.

Chapter Two presents the first empirical study, which aimed to investigate the impact of natural aging on perceptual decision-making, including attention orienting, as measured by the $N2_{(c)ontralateral}$ and $N2_{(i)psilateral}$ components, and evidence accumulation, as measured by the centro-parietal positivity (CPP) component. To achieve this, 30 younger and 31 older healthy participants completed a bilateral version of the classic random-dot motion task in which participants detected the onset of coherent from amongst random motion that occurred in one hemifield. Findings showed significant group differences, with older participants exhibiting slower peak $N2_{(c)}$ latency, later CPP onset, and a more gradual CPP slope. These results suggest that dysfunction of target selection and evidence accumulation negatively influenced older participants ability to perform effectively on this bilateral motion detection task. We highlight that a perceptual decision-making framework can provide important insights into understanding the aging brain. Further, we contend that these processes could be appropriate targets for intervention techniques aimed at impeding the impact of cognitive decline in older adults.

Chapter Three involved investigating the same perceptual decision-making metrics ($N2_{(c)}/N2_{(i)}$; CPP) in a cohort of neglect patients, in comparison to age-matched controls. Twenty-three patients were screened for neglect and the final sample of seven were tested using simultaneous EEG and eye tracking. Behavioural results found five patients to have left neglect with slower reaction times (RTs) for left hemifield targets than right hemifield targets. The two remaining participants did not display neglect. Of the five neglect participants, two participants had more severe neglect symptomatology and were unable to complete enough trials of the perceptual decision-making paradigm to warrant RT analyses. For the remaining neglect patients (n=3), RT analyses were completed. Results indicated a reduced right hemisphere

$N2_{(c)}$ for left hemifield targets (in line with right hemisphere pathology) but an intact left hemisphere $N2_{(c)}$ for right hemifield targets (in line with preserved left hemisphere function). Linear mixed effects modelling of the effect of $N2_{(c)}$ on RT found that the left hemisphere $N2_{(c)}$ predicted RTs to the right hemifield whereas the right hemisphere $N2_{(c)}$ did not predict RTs. A pronounced left hemisphere $N2_{(i)}$ was observed for left, but not right, hemifield targets and this predicted RTs to the left hemifield. We suggest that the distinct left hemisphere $N2_{(i)}$ may represent compensation for performances in the left hemifield, helping to overcome the dysfunctional right hemisphere $N2_{(c)}$ in these patients.

Chapter Four presents previously published work by Newman et al. (2016) to which the candidate contributed. In this paper, blue-enriched light was employed to directly manipulate alertness in healthy volunteers. Results showed that exposure to higher intensity blue-enriched light, relative to lower, enhanced response-times for left hemifield targets but not right hemifield targets. This increased processing speed was mediated by a specific effect of light intensity on right-hemisphere parieto-occipital α-power. The behavioural and neurophysiological effects were sustained over task duration (~36 minutes). These data provide evidence for a direct modulatory influence of alertness on spatial attention, using a non-invasive, non-pharmacological manipulation of alertness, which highlighted the possibility of using a light-based intervention for right hemisphere disorders of spatial attention, such as neglect.

The final paper, **Chapter Five**, presents the results of a pilot study examining the effects of blue-enriched white light on spatial inattention in four stroke patients with right middle cerebral artery involvement and neglect. Participants completed a five-session protocol involving a baseline session (no light intervention), two sessions of active control (low intensity blue-enriched white light) and two sessions of the active intervention (high intensity blue-enriched white light). Results did not reveal any significant effect of blue-enriched white light on spatial inattention, as measured by RT-asymmetry in this sample. Limitations of the study are discussed including, individual differences in sleep, mood and medication effects.

Overall, this thesis provides novel contributions to the understanding of neglect and the fields of spatial attention and perceptual decision-making more broadly. For the first time, neglect has been decomposed into its component electrophysiological signatures. These same neural signatures have also been isolated and related to behaviour in healthy aging, furthering the current understanding on

perceptual decision-making as a function of age. Future studies should aim to investigate perceptual decision-making in a larger sample of neglect patients as it may ultimately have utility as a sensitive, reliable and objective test of spatial neglect. Further, investigations mapping dysfunctional dissociable EEG components to distinct lesion locations would be beneficial. Decomposing behavioural/physiological and anatomical heterogeneity is clinically important, as distinct treatments exist for different neglect phenotypes. The identification of distinct subgroups of patients whose neglect is underpinned by discrete information processing deficits would provide a principled basis upon which to target these interventions.

In line with Monash University guidelines, the experimental chapters are presented in a 'thesis by publication' format, whereby parts of the thesis have been written as manuscripts and submitted for publication (thus not in the more traditional thesis format). As such, there is some unavoidable repetition of introductory comments and methodologies. Figures, tables and headings within chapters prepared for manuscripts have been changed to maintain consistency and to facilitate the reading of this thesis.

List of publications, presentations, posters, and awards

Publications

Stolwyk, R. J., **O'Neill, M. H.,** McKay, A. J. D., & Wong, D. K. (2014). Are cognitive screening tools sensitive and specific enough for use after stroke?: A systematic literature review. *Stroke: a Journal of Cerebral Circulation*, *45*(10), 3129-3134. doi: 10.1161/STROKEAHA.114.004232 (see Appendix 1)

Newman, D. P., Lockley, S. W., Loughnane, G. M., Martins, A. C. P., Abe, R., Zoratti, M. T. R., Kelly, S. P., **O'Neill, M. H.,** Rajaratnam, S. M. W., O'Connell, R. G. & Bellgrove, M. A. (2016). Ocular exposure to blue-enriched light has an asymmetric influence on neural activity and spatial attention. *Sci Rep, 6*, 27754. doi: 10.1038/srep27754. http://www.nature.com/articles/srep27754#supplementary-information

Conference Presentations

O'Neill, M. H., Newman, D. P., Stolwyk, R. J., New, P., & Bellgrove, M. A. (2016). An Electroencephalographic Investigation of Hemispatial Neglect: Case Studies. *The College of Clinical Neuropsychologist, Postgraduate Research Symposium.* Melbourne, Victoria, October 2016

Poster Presentations

O'Neill, M. H., Loughnane, G. M., Stolwyk, R. J., New, P.W., O'Connell, R.G., & Bellgrove, M. A. (2017). Early target selection and evidence accumulation is impaired in the left hemifield after right hemisphere stroke. *The International Conference for Cognitive Neuroscience*. Amsterdam, The Netherlands, August 2017

Awards

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General Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes chapters of publications (Chapter 2 and 4) and thesis chapters (not currently submitted/published; Chapter 3 and 5). Information regarding published works can be found on the page 16.

Signature: 

Name: Megan H O'Neill

Date: 25/10/17

Declaration: Thesis Including Published Works

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis. The published works of this thesis include one peer-reviewed paper currently submitted and one previously published paper in a peer-reviewed journal. The core theme of the thesis is spatial inattention in hemispatial neglect. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Institute of Cognitive and Clinical Neurosciences under the supervision of Prof Mark A. Bellgrove. Dr Renerus J. Stolywk and Dr Daniel P. Newman. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. In the case of Chapter's 2 and 4, my contribution to the work involved the following:

Thesis chapter	**Publication title**	**Publication status**	**Candidate's contribution**	**Co-Authors**	**Monash Student (Y/N)**
Two	Altered attention orienting and evidence accumulation as a result of healthy aging	Submitted – Neurobiology of Aging	80%: Conception and design, review of literature, recruitment and testing, data analysis & manuscript write-up.	1) Daniel Newman: Data processing and data analysis (3%) 2) Gerard Loughnane: Data processing and manuscript write-up (3%) 3) Méadhbh Brosnan: Critical reviews of manuscript (3%) 4) Redmond O'Connell: Critical reviews of manuscript (3%) 5) Mark Bellgrove: Study design, critical reviews of manuscript (3%)	Y N N N N
Four	Ocular exposure to blue-enriched light has an asymmetric influence on neural activity and spatial attention.	Published	5%: Conception & design, review of relevant literature, participants testing, manuscript review.	1) Daniel Newman: Literature review, hypothesis conception and study design, recruitment and testing of participants, data processing, inferential data analysis, and manuscript write-up. (70%) 2) Steven Lockley: Study design, critical reviews of	Y N

				manuscript (2%) 3) Gerard Loughnane: Critical reviews of manuscript (1%) 4) Ana Carina Martins: Recruitment and testing of participants (5%) 5) Rafael Abe: Recruitment and testing of participants (5%) 6) Marco Zoratti: Recruitment and testing of participants (5%) 7) Simon Kelly: Paradigm programming (2%) 8) Shantha Rajaratnam: Critical reviews of manuscript (1%) 9) Redmond O'Connell: Critical reviews of manuscript (2%) 10) Mark Bellgrove: Critical reviews of manuscript (2%)	N N N N N N N

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: [redacted]

Date: 25/10/17

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: [redacted]

Date: 25/10/17

Preamble to Chapter One

The aim of this chapter is to provide the conceptual background to the empirical work presented within this thesis. The present chapter is organised in five main sections. In the first section, an overview of spatial attention and the disorder of hemispatial neglect are presented. The important role of attention networks in hemispatial neglect is highlighted within this section, with particular focus on Corbetta and Shulman's (2011) theory of neglect. The second section shifts focus to a discussion about perceptual decision-making paradigms, with specific emphasis on how this technique could be utilised as a means of evaluating aberrant spatial attention. The third section provides an overview of current rehabilitation strategies used for ameliorating spatial inattention in hemispatial neglect patients. The fourth section describes the current understanding of short-wavelength light and its potential uses as a rehabilitation technique for disorders involving alertness based deficits. These four sections then culminate in the fifth and final section, where an overall summary of the research questions and the chapter outlines are presented.

CHAPTER ONE: AN INTRODUCTION

Spatial attention refers to the selection of sensory stimuli for further processing based on location in space (Vecera & Rizzo, 2003). Generally, humans are able to shift their attention across space with little conscious awareness of a processing advantage for information presented in a particular visual field. However, decades of research has demonstrated a systematic bias, or asymmetry, in the processing of information in space, with a slight advantage for information presented in left space over that presented in the right hemifield, a phenomenon labelled pseudoneglect (Bowers & Heilman, 1980; Voyer, Voyer, & Tramonte, 2012). The preferential computing of information presented to the left hemifield is thought to reflect the right hemisphere's lateralisation for spatial attention (Bartolomeo, 2006, 2014; Benwell, Harvey, & Thut, 2014; Bjoertomt, Cowey, & Walsh, 2002; Cicek, Gitelman, Hurley, Nobre, & Mesulam, 2007; Fierro et al., 2000; Fink, Marshall, Shah, et al., 2000; Foxe, McCourt, & Javitt, 2003; Jewell & McCourt, 2000; Nicholls, Bradshaw, & Mattingley, 1999; Reuter-Lorenz, Kinsbourne, & Moscovitch, 1990; Thiebaut de Schotten et al., 2011; Thiebaut de Schotten et al., 2005; Voyer et al., 2012), a notion that is corroborated by evidence that hemispatial neglect is more severe and enduring following damage to the right, compared to the left hemisphere (Driver & Mattingley, 1998; Halligan, Fink, Marshall, & Vallar, 2003; Harvey & Rossit, 2012; Ringman, Saver, Woolson, Clarke, & Adams, 2004; Swan, 2001).

The Disorder of Neglect

Hemispatial neglect (hereafter referred to as 'neglect') is a disabling neurological syndrome clinically defined as the inability to detect, respond to, and orient towards stimuli on the side contralateral to cerebral damage (Heilman & Valenstein, 1979; Parton, Mahotra, & Husain, 2004). Neglect is more severe and enduring following stroke to the right hemisphere, resulting in inattention to the left side of space, and generally affecting the territories supplied by middle cerebral artery (Ringman et al., 2004; Swan, 2001). Patients with neglect, especially those with severe forms of the syndrome, behave as though "half of their universe has abruptly ceased to exist" (Mesulam, 1981, pg. 309), however it is important to note that the severity of the disorder lies upon a continuum from subtle to severe (Bartolomeo, 2014). In day-to-day life, this can manifest as patients eating from only the right side of their plate; ignoring people, objects or sounds on the left side of the room; or

missing words on the left half of the page when reading (Husain & Rorden, 2003; Vuilleumier, 2013). When neglect patients are asked to copy an object or scene, or draw a clock from memory, only detail from the ipsilesional side (generally the right side) is included, while the left side is 'neglected' (see Figure 1.1; Bartolomeo, 2014; Marshall & Halligan, 1993). Importantly, this occurs without any conscious awareness of the 'neglected' components.

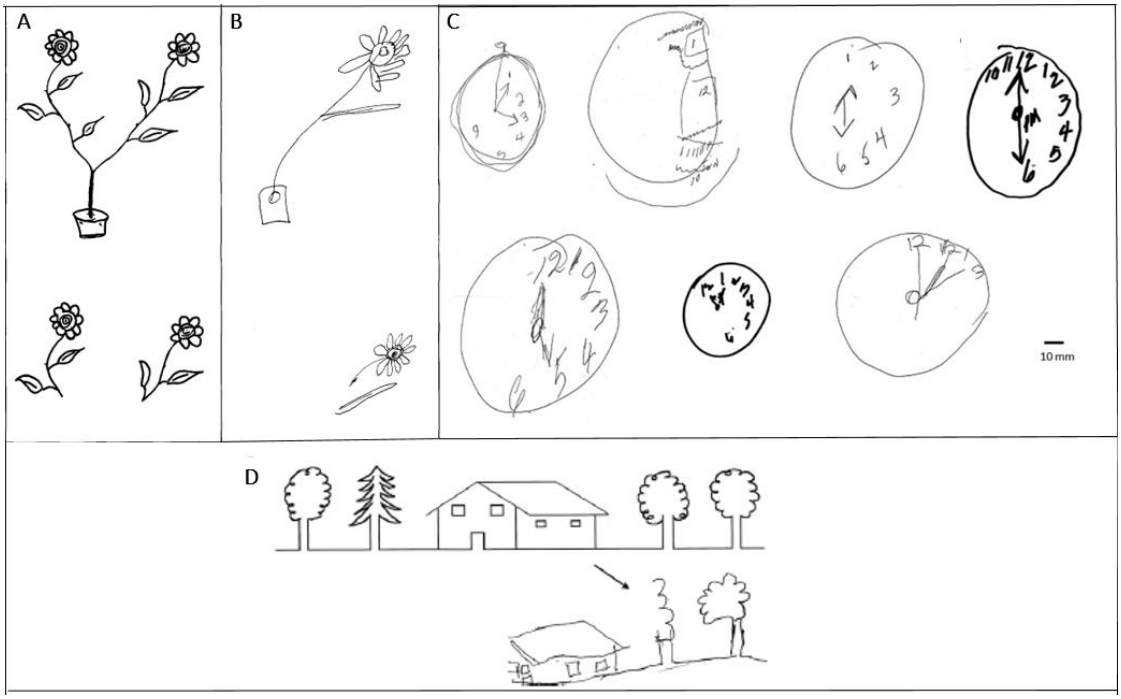

Figure 1.1. Examples of drawings completed by hemispatial neglect patients. [A] Target object to be copied; [B] Copy of object (depicted in [A]) completed by patient with unilateral right hemisphere damage with neglect (Adapted and printed with permission from Marshall & Halligan, 1993); [C] Examples of clock drawings produced by right-brain-damaged stroke patients with spatial neglect (Adapted and printed with permission from Chen & Goedert, 2012); [D] Example of a left neglect patient competing a landscape copy task (Adapted and printed with permission from Bartolomeo, 2014).

The reported incidence of neglect within stroke populations varies widely from 10%-82%, with some estimates postulating that anywhere between three and five million patients suffer from neglect post-stroke each year (Appelros, Karlsson, Seiger, & Nydevik, 2002; Chen, Hreha, Fortis, Goedert, & Barrett, 2012). Spontaneous recovery of neglect does occur, with recovery in 60-90% of patients within 3-12 months of the neurological event (Karnath, Rennig, Johannsen, & Rorden, 2011; Swan, 2001). Factors thought to predict recovery include age, the absence of visual field deficits, lesion location, premorbid atrophy, and neglect severity (Farne et al., 2004; Jehkonen et al., 2000). Unfortunately, there are a proportion of patients that

manifest a chronic form of neglect, with approximately one-third exhibiting clear deficits more than six months post-stroke (Karnath et al., 2011; Linden, Samuelsson, Skoog, & Blomstrand, 2005; Rengachary, He, Shulman, & Corbetta, 2011). This is concerning as neglect is associated with poor functional outcomes (Chen Sea, Henderson, & Cermak, 1993; Ween, Alexander, D'Esposito, & Roberts, 1996), including longer stays in hospital (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001), slower and attenuated recovery rates (Gillen, Tennen, & McKee, 2005), reduced ability to complete activities required for daily living (Di Monaco et al., 2011; Katz, Hartman-Maeir, Ring, & Soroker, 1999), and greater functional deterioration following the end of rehabilitation (Paolucci et al., 2000).

Sub-types of Neglect

It is important to note that neglect is by no means a homogenous nostological entity and it has been suggested that it may in fact represent a set of disorders (Driver, 1994). As Mesulam (1994) highlighted "depending on the personal tastes, preference, and creativity of the investigator, neglect behaviour has been divided into a number of components" (p. 173). Common distinctions are often made by subdividing neglect based on different underlying mechanisms (sensory or motor), modalities (visual, auditory, tactile), regions of space (personal neglect, near (reaching), far space, imagined space (representational neglect), and spatial coordinates (egocentric or allocentric). Regardless of the classification system, one common aspect is the observation that many patients are unaware of perceptual or motor issues, a symptom known as anosognosia (Parton et al., 2004).

Sensory and Motor Neglect.

At a mechanistic level, neglect may be categorised as sensory neglect, also known as inattention neglect, or motor neglect, also referred to as intention neglect. Inattentional neglect refers to the deficit in awareness of contralesional stimuli, however it can be more precisely clarified by the regions of space affected (personal, peri- or extra-personal) or by the modality affected. The most compelling manifestations of neglect affect vision; perhaps as this modality is most entangled with activities of daily living. However, it must be noted that inattentional neglect can involve other sensory modalities including touch (tactile neglect), audition, and

olfaction (Jacobs, Brozzoli, & Farne, 2012), with combinations of more than one modality often present. In contrast to inattentional neglect, intentional neglect is the underutilisation of one side of the body that cannot be explained by awareness deficits or physical defects in strength, reflexes or sensibility (Heilman, Valenstein, & Watson, 1994; Laplane & Degos, 1983). Intentional neglect may be categorised by a failure to move (akinesia), slowness in initiation of contralesional movement (hypokinesia), insufficient amplitude of contralesional movement (hypometria), impersistence in moving or maintaining posture and reduced spatial exploration (Heilman et al., 1994; Làdavas, 1994). All of the aforementioned intentional deficits can manifest in the limbs, eyes or head movements and can affect actions performed within or towards the effected hemi-space (Plummer, Morris, & Dunai, 2003).

It is important to note that the dichotomy between input (sensory) and output (motor) components of neglect is not absolute and it likely represents a gross oversimplification of the underlying contributory mechanisms. A more realistic hypothesis is that the systems interact in a dynamic circuit, with sensory information informing the spatio-temporal coordinates required for motion, and subsequent alterations of sensory targets are made to match or anticipate the needs of the motor system (Adair, Na, Schwartz, & Heilman, 1998). That being said, it has been suggested that patients with differing neglect subtypes respond differentially to specific rehabilitation strategies (Adair et al., 1998; Làdavas, 1994) and it is possible to dissociate between neglect *predominately* determined by sensory factors and neglect *primarily* influenced by motor factors.

Regions of space.

In addition to the categorisation of neglect based on input or output influences, neglect can also be differentiated based on the region of space impacted. As seen in Figure 1.2, neglect has been found to inhabit different areas of space including personal space (the body), extrapersonal space that is within reaching distance (near space) and extrapersonal space that is outside manual reaching (locomotor space). With respect to neglect in personal space, this manifestation is reflected by a lack of exploration on the contralesional side of the body (Bartolomeo, 2014). In day-to-day life, this form of neglect can be demonstrated by the patient simply "forgetting" about a side of their body, generally the left, during everyday tasks such as bathing, dressing

or shaving (Bartolomeo, 2014). Beyond personal space, the environment is separated into two sections – near (reaching) and far (locomotor). The distinction between near and far has been best demonstrated by Halligan and Marshall (1991) who highlighted that a severe neglect patient had dysfunctional spatial attention on a traditional line bisection (bisection presented in near space) task but intact performance when the stimuli were presented at a distance of 2.44m (bisection presented in far space). It is important to note that near versus far distinctions for neglect are thought only to occur for visuo-motor tasks, as this pattern of dysfunction is not evident when using pure perceptual tasks. This notion stems from work of Pizzamiglio et al (1989b) who were unable to demonstrate any near versus far distinction in a group of 70 right hemisphere patients on the Wundt-Jastrow illusion, a purely perceptual task. Finally, there have been instances where neglect has been demonstrated in representational, or imaginal, space. When asked to describe a well-known place from memory, patients with imaginational neglect recall more details about right sided items than left sided items (Bartolomeo, 2014; Bisiach et al 1981).

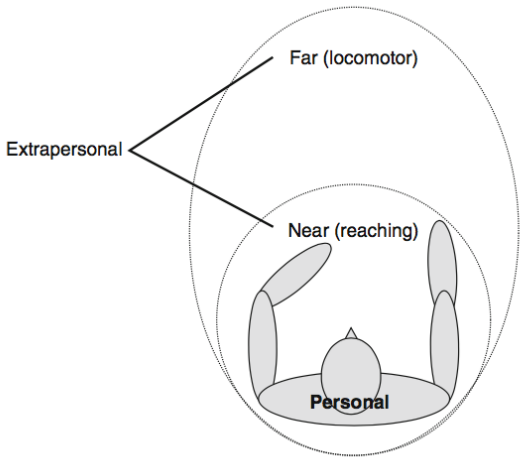

Figure 1.2. A graphic representation of the sectors of space that can be selective affected by neglect (Adapted and printed with permission from Bartolomeo, 2014). The schematic depicts personal (body) space that can be affected, near or reaching space and far space that is in the extrapersonal realm.

Spatial Coordinates.

Further classifications can also be made based on the spatial coordinators of the deficits. A classic distinction is often made between 'egocentric' and 'allocentric' neglect. Patients with egocentric neglect, also known as viewer-centred neglect, often

neglect stimuli located on the contralesional side of their spatial environment relative to their own midline (Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). In contrast, individuals with allocentric neglect or object-/stimulus-centred neglect are oblivious to the left part of each stimulus regardless of its location in space (Adair et al., 1998; Hillis et al., 2005; Yue, Song, Huo, & Wang, 2012). While the aforementioned categorisation systems are useful both clinically and in research, the distinction between left and right space should be conceptualised as fluid distinction rather than a fixed absolute division (Bartolomeo, 2014), especially considering neglect severity may differ depending on the nature and difficulty of the task.

Extinction.

When discussing neglect, it would be amiss to not highlight the similarities between neglect and perceptual extinction. As previously mentioned, neglect patients present with reduced awareness for contralesional stimuli. Similarly, patients with perceptual extinction also fail to respond to stimuli or events on the contralesional side of space but only when there is simultaneous stimulation within the ipsilesional space (Vossel et al., 2011). Similar to neglect, extinction can also manifest in a range of modalities including visual (Vuilleumier & Rafal, 2000), acoustic (De Renzi et al., 1984), somatosensory (Bartolomeo, Perri, & Gainotti, 2004), and olfaction (Bellas et al., 1988). Mattingley and colleagues (1997) have also demonstrated that extinction can occur cross modally.

Neglect and extinction are often conceptualized as associated phenomena, but the extent of the relationship remains a controversial topic and it remains unclear if they are truly distinct syndromes or if they simply lie on a continuum. Consistent with the latter, extinction is often evident in mild forms of neglect (Bartolomeo, 2014) and it can often persist as a residual symptom following recovery from neglect (Robertson & Halligan, 1999). It is has also been suggested that the two disorders may have similar underlying deficits (Posner et al. 1984), such as disordered attention (Bartolomeo, 2014). However, it is important to note that others do believe that there is some distinction between the two spatial attention difficulties, with differences in lesion locations often used as evidence of differentiation (Bisiach, Vallar & Geminiani, 1989; Vallar et al. 1994).

Component Deficits of Neglect

As previously mentioned, the mechanisms underlying neglect behaviour have prompted considerable debate. The general lack of consensus is likely due to several factors, including the heterogeneous nature of the syndrome, an inadequate theoretical understanding of visuospatial functioning, and the possibility to that several independent deficits, most likely interacting with each other, may contribute to this complex syndrome (Bartolomeo, 2014). In the past neglect has been viewed as a disorder of spatial representation, however, there is now a growing agreement that the disorder is a collection of spatial and non-spatial components (Dodds, Muller, & Manly, 2009; Van Vleet, DeGutis, Dabit, & Chiu, 2014). This notion largely stems from results suggesting that the coding of relative spatial relationships is intact in the neglected field of patients (Karnath & Ferber, 1999). Given the multitude of clinical manifestations, it is likely that neglect is the result of an interplay of many deficits together and different combinations of deficits may result in distinct clinical manifestations of neglect. Further, it is not necessary for every patient to have impairments in all putative components (Coulthard, Parton, & Husain, 2007). Dysfunction can be separated into lateralised spatial deficits, including disproportionate ipsilesional capture of right-sided non-neglected items (Natale, Marzi, Bricolo, Johannsen, & Karnath, 2007; Posner, Walker, Friedrich, & Rafal, 1984; Siéroff, Decaix, Chokron, & Bartolomeo, 2007) and impaired disengagement of attended items (Posner et al., 1984); and nonlateralised non-spatial deficits, such as impaired arousal and alertness (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta, Kincade, & Shulman, 2003; Corbetta & Shulman, 2011; Lazar et al., 2002; Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998), sustained attention (Corbetta & Shulman, 2011; Husain & Rorden, 2003), working memory (Malhotra, Coulthard, & Husain, 2009) and attentional capacity (Lavie & Robertson, 2001).

Historically, the focus of research and clinical interventions have been on the overt spatial dysfunction in neglect, however non-spatial symptoms are now increasingly emphasised given the deficits in non-spatial functioning are more accurate predictors of chronic neglect and subsequent functional disability than spatial dysfunction per se (Duncan et al., 1999; Husain, Shapiro, Martin, & Kennard, 1997; Peers, Cusack, & Duncan, 2006). The impact of non-spatial dysfunction is likely due

to the fact that lesions that produce chronic neglect are generally localised to brain regions that support non-spatially lateralised attention (Van Vleet & DeGutis, 2013).

Arousal and Alertness.

The inability to maintain focused engagement is one critical non-spatial deficit that often accompanies neglect. Decreased physiological arousal, that is a decrease in and responsiveness, has been demonstrated by reduced galvanic skin responses to electrical stimulation in neglect patients compared to controls (Heilman, Schwartz, & Watson, 1978); and irregular heart rate fluctuations following target-related cues (Yokoyama, Jennings, Ackles, Hood, & Boller, 1987). In further support for the relationship between alertness and spatial bias, Robertson and colleagues (1998) demonstrated that spatial bias could be transiently ameliorated following increases in phasic (moment-to-moment) alertness, which were triggered by an acoustic tone. This research suggested that an increase in alertness might be sufficient to reduce or even overcome the rightward spatial bias in neglect. In the same vain, sedatives which reduce alertness, have been found to result in the immediate re-emergence of neglect symptoms in patients who have previously recovered (Lazar et al., 2002). In addition to modulations of alertness, patients who have lower levels of intrinsic alertness have a greater magnitude of leftward inattention than those who are not as affected by decreased levels of arousal (Bartolomeo & Chokron, 2002; Funk, Finke, Muller, Utz, & Kerkhoff, 2010). Neglect patients have also been found to have a reduced capacity to sustain their attention. For example, neglect patients have a more severe and protracted attentional blink than healthy individuals (Corbetta & Shulman, 2011; Husain & Rorden, 2003). Further, neglect patients have significantly slower reaction times on auditory tasks and that improvement in neglect symptoms over time correlates with a reduction in these reaction times (Samuelsson et al., 1998). The deficits described here suggest that neglect is associated with an impairment in task-related sustained attention that is often attributed to decreased tonic alertness.

Interaction between spatial and non-spatial symptoms

It is important to recognise that spatial and non-spatial symptoms should not be investigated purely in isolation, as there is now a well-established interaction between these sets of symptoms (Lazar et al., 2002). Beyond investigations in neglect,

the modulation of spatial abilities by non-spatial functions has also been documented in other disorders, including attention deficit/hyperactivity disorder (ADHD). Similarly to patients with neglect, children with ADHD exhibit impairments in both spatial and non-spatial attention (Matthias et al., 2010), with considerable difficulties noted in their ability to maintain appropriate levels of alertness (George, Dobler, Nicholls, & Manly, 2005; Tucha et al., 2006). Children with unmedicated ADHD show a subtle inattention to left space, similar in nature but not severity to neglect patients (Bellgrove et al., 2005; Malone, Couitis, Kershner, & Logan, 1994; Sheppard, Bradshaw, Mattingley, & Lee, 1999). At variance with this, ADHD children medicated with the stimulant methylphenidate exhibit a reduction in the degree of rightward bias. Such results endorse the idea that non-spatial attention can modulate spatial orienting, with increases in alertness able to ameliorate neglect symptomatology (Malone, Couitis, et al., 1994; Sheppard et al., 1999; Tucha et al., 2006). Moreover, the interaction between spatial and non-spatial functioning is not confined to pathological populations and has previously been noted in healthy samples. As previously mentioned, there is a slight asymmetry in the processing of information in space for healthy individuals, with an advantage for information presented in the left hemifield. This phenomenon, termed pseudoneglect, is significantly reduced in individuals who are categorised as having poor sustained attention when compared to individuals with good sustained attention capacity (Bellgrove, Dockree, Aimola, & Robertson, 2004). In this instance, sustained attention is defined as intrinsic, long-term arousal that fluctuates over minutes and hours, but independent of external cues (Sturm et al., 1999). Further, manipulations of arousal have suggested that the leftward bias in healthy participants can be shifted rightwards under a number of conditions including increased drowsiness (Bareham, Manly, Pustovaya, Scott, & Bekinschtein, 2014), sleep deprivation (Fimm, Willmes, & Spijkers, 2006; Manly, Dobler, Dodds, & George, 2005), and long periods of repetitive task performance (Dobler et al., 2005; Newman, O'Connell, & Bellgrove, 2013), again suggesting an intricate relationship between levels of arousal and spatial orienting abilities.

Attention Networks and Neglect

The intertwined nature of non-spatial functions, namely arousal and alertness, and spatial attention is a fundamental component of the contemporary model of neglect posited by Corbetta and Shulman (2002; see Appendix 2 for concept map diagrammatically exploring this model). Neuroimaging studies have suggested two largely separate and discrete attentional networks exist, a bilateral dorsal frontoparietal attention network (DAN) and a right lateralised ventral frontoparietal attention network (VAN; Corbetta & Shulman, 2002; He et al., 2007; Shulman et al., 2009; Vandenberghe & Gillebert, 2009). The bilateral DANs connect the superior parietal lobes and intraparietal sulci, with the dorsal frontal lobes and frontal eye fields. These networks are involved in goal-directed attentional selection and facilitate the exploration of space contralaterally (Ting et al., 2011). Intuitively, it would be damage to this system, particularly the right DAN that would result in neglect. However, Corbetta and colleagues (Corbetta et al., 2005; Corbetta et al., 2003; Corbetta & Shulman, 2002, 2011) have instead posited that neglect results from damage to the right lateralised VAN, a system that is associated with the maintenance of arousal, vigilance, and stimulus-driven, bottom-up attentional selection (see Figure 1.3; Corbetta et al., 2005; Corbetta et al., 2003; Corbetta & Shulman, 2002, 2011). The VAN which includes the right tempo-parietal junction (TPJ) and right ventral frontal cortex has been made analogous to a circuit breaker, as it sends interrupting signals to the DAN in order to modulate ongoing selection (Chang et al., 2013). This theory is supported by reports that the TPJ (Azouvi et al., 2002; Mort et al., 2003; Robbins, 1994; Vallar & Perani, 1986) and underlying white matter, such as the superior longitudinal fasciculus (SLF; Bird et al., 2006; Doricchi & Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005) are among the most commonly affected regions in neglect patients. The consequence of damage to the VAN is thought to be a general reduction in arousal, which therefore results in abnormal VAN-DAN interactions. The theory postulates that an interhemispheric imbalance between DAN networks results, whereby the left hemisphere becomes hyperactive, while the right becomes hypoactive, thus forcing spatial attention rightwards.

Assessment of Neglect

Currently, there are distinct difficulties in determining a diagnosis of neglect and this trouble stems from several sources. Firstly, there is a large variability in the assessments used for diagnosis (Chen et al., 2012). Menon and Korner-Bitensky (2005) identified 28 standardised and 34 non-standardised tools used to evaluate neglect symptoms. Assessments include traditional pencil-and-paper tests, which generally assess extrapersonal spatial neglect (Maxton, Dineen, Padamsey, & Munshi, 2013), and a wide range of functional assessments of neglect behaviours including the behaviour Inattention Test (Wilson, Cockburn, & Halligan, 1987), the semi-structured scale of functional evaluation of hemi-inattention (Zoccolotti & Judica, 1991), and the Catherine-Bergego Scale (Azouvi et al., 1996). The second major issue in diagnosing neglect, is that the heterogeneous nature of the disorder almost ensures that some current assessment fail to detect specific subtypes of neglect (Chen et al., 2012). It has been suggested that examinations with more than one assessment tool are useful to detect subtypes (Marsh & Hillis, 2008), different underlying mechanisms (Buxbuam et al., 2004), and assess both clinical signs and real-world functions, especially when they pertain to treatment outcomes (Vangkilde & Habekost, 2010).

Visuoperceptual Tests.

Visuoperceptual tests are popular measures, as they do not typically involve motor movement and therefore can investigate the contribution of sensory neglect in isolation. The general procedure for visuoperceptual tests is for the patient only visually analyse a pattern and provide a verbal response. Examples of visuoperceptual tasks include the Wundt-Jastrow illusion (Massironi, Antonucci, Pizzamiglio, Vitale, & Zoccolotti, 1988), overlapping figures task (Gainotti, D'Erme, & Bartolomeo, 1991; Gainotti, D'Erme, Monteleone, & Silveri, 1986; Gainotti & Tiacci, 1971), visual search for images (Chédru, Leblanc, & Lhermitte, 1973; De Renzi, Faglioni, & Scotti, 1970; Gainotti et al., 1986), reading tasks (Vallar, Burani, & Arduino, 2010) and landmark tasks (Fink, Marshall, Weiss, et al., 2000; Marshall & Halligan, 1995).

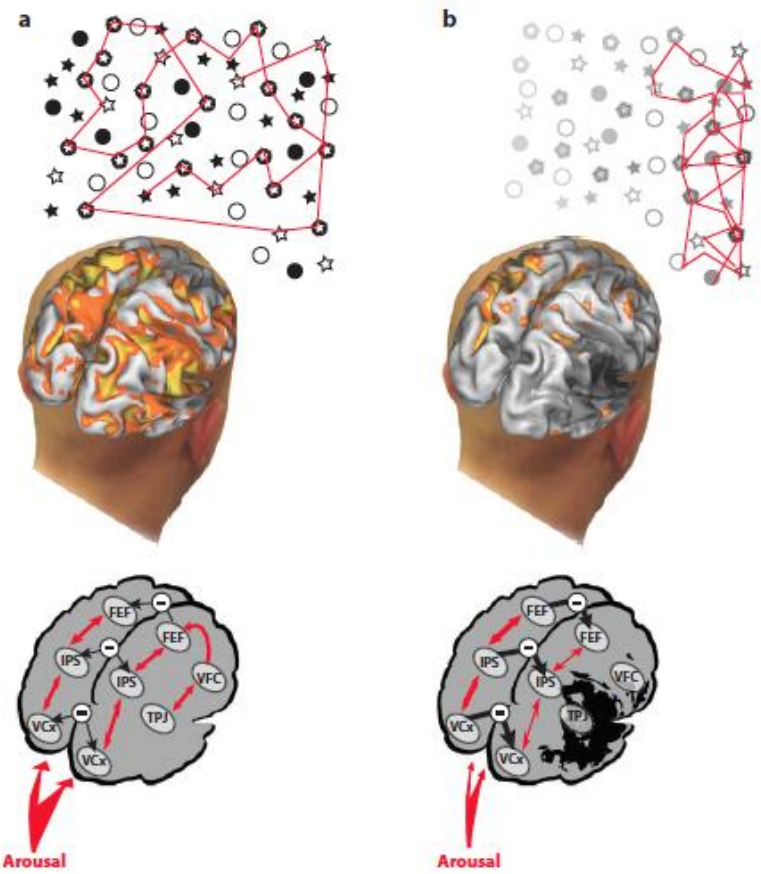

Figure 1.3. A graphic representation of the pathophysiology of spatial neglect (Adapted and printed with permission from Corbetta & Shulman, 2011). [a] depicts a representation of visual search activity in a healthy brain. During a visual search, hemispheric activity is symmetrical and interhemispheric interactions are balanced. Each of the dorsal attention network directs eye movements and attention contralaterally and this results in a relatively symmetrical search of space. Of note, under normal conditions, there is a slight advantage for information within the left hemifield due to the right lateralization of the ventral attention network. The ventral network is lateralises because of a slight asymmetry of arousal input from the brainstem locus coeruleus/norepinephrine system (right > left), which interacts with the dorsal network (right > left). [b] represents the proposed activation pattern following a right hemisphere stroke. Damage to the ventral regions encompassing the TPJ results in reduced levels of arousal, target detection and reorienting that leads to a visual field impairment. Abnormal ventral-dorsal interactions within the right hemisphere, leads to an interhemispheric imbalance between the right and left hemispheres, with attention and eye movements shifted rightward.

Visuographic Tests.

Despite the distinct advantage of visuoperceptual tasks, visuographic tests are arguably the most common form of clinical evaluation in neglect. Such tasks require the participant to draw either from memory or copy a model, with the former generally used to test for representational neglect (Agrell, Dehlin, & Dahlgren, 1997). The most commonly used figures are flowers, stars, cubes and geometric shapes. Incomplete drawings or pictures are thought to be indicative of neglect (Plummer et

al., 2003).

Line Bisection.

Line bisection is another commonly used task that requires a motor response. During line bisection tasks, the patient is asked to estimate and place a mark at the midpoint of a horizontal line. There are different variations of this task but the most common has a number of lines at different orientations on the same stimulus page. The page is centred to the patients' midline and bisection marks are made with the dominant or unaffected hand (Plummer et al., 2003). Neglect patients deviate the subjective midpoint to the right of true centre, as if they have ignored the left hand side of the line (Adair et al., 1998; Bartolomeo, 2014; Halligan & Marshall, 1989). The magnitude of the deviation can vary and the severity of neglect is an important factor in line bisection performance, as those with mild or moderate neglect can be influenced by the length and spatial position of the line relative to the observer (Koyama, Ishiai, Seki, & Nakayama, 1997), while these factors do not generally impact performance in those with more severe neglect.

Cancellation Tasks.

Cancellation tasks also involve a motor component. Cancellation tasks require patients to cross out or 'cancel' target items that are scattered on a page and interspersed with distractor items (non-target items that must be ignored). Patients with neglect typically begin scanning the stimulus sheet from the right side, unlike healthy individuals who scan from left to right (Bartolomeo, D'Erme, & Gainotti, 1994). Neglect patients fail to attend to targets on the left side, often without reaching the midline of the sheet. There are number of variations of cancellation tasks including bells (Gauthier, Dehaut, & Joanette, 1989), shapes (Weintraub & Mesulam, 1987, 1988), stars (Plummer et al., 2003), letters (Egelko et al., 1989), numbers (Wade, Wood, & Hewer, 1988), circles (Bisiach, Luzzatti, & Perani, 1979) and lines (Albert, 1973). The nature of the task, including whether it involves distractors, single or double target symbols; structured or random arrays can affect performance (Bartolomeo, 2014; Plummer et al., 2003; Weintraub & Mesulam, 1988). For example, the presence of distractors increases the sensitivity of cancellation tasks in detecting neglect, as it requires participants to first decide if the stimuli is a target before

crossing it out (Azouvi et al., 1996; Gauthier et al., 1989; Halligan & Marshall, 1989; Robbins, 1994). This is the case for Bell's cancellation, which requires participant to search for and circle 35 black ink drawings of bells (targets). The patient must scan for the 35 targets amongst 280 distractors, all of which are equally distributed across seven columns.

Line Bisection versus Cancellation.

Azouvi et al. (2002) found that the Bells Cancellation test was the single most sensitive test for detecting neglect on its own, however this still only resulted in sensitivity in 50.5% of patients. Some have suggested that cancellation tasks have greater test-retest reliability than line bisection (Kinsella, Packer, Ng, Olver, & Stark, 1995), while others have suggested that line bisection has greater (Black, Vu, Martin, & Szalai, 1990) or equal (Bailey, Riddoch, & Crome, 2000) sensitivity. Ferber and Karnath (2001) completed a comprehensive comparison of the two assessment measures by comparing a line bisection task with four variants of a cancellation task (line crossing, letter cancellation, star cancellation and bells test) in 35 patients with well-defined spatial neglect. The authors reported that line bisection missed 40% of neglect (thereby producing a large number of false negatives), whereas bells cancellation and letter cancellation missed only 6%. This suggests that these two cancellation tasks are more effective than line bisection in exploring the deficit of neglect. Further, the authors noted that "deviations in line bisection are not fundamentally related to spatial neglect but may arise from other causes (e.g. hemianopia, or which hand is used)" (Ferber and Karnath, 2001, p.599) and therefore care must be taking when interpreting these results. Despite these results, the controversy as to which test is more effective for testing neglect continues to be a source of contention in the literature. More recently, Molenberghs and Sale (2011) reported that while cancellation is more sensitive than line bisection, scores on each test correlate well (r=.76), and both can be used clinically to test for neglect. Further voxel-based symptom lesion mapping identified the angular gyrus as the critical lesion site for both tasks suggesting that both tasks reflect the same underlying mechanism.

Test psychometrics

Given the wide range of tests used in neglect assessment, it is important to highlight those that are psychometrically sound. A comprehensive review of the sensitivity of clinical and behavioural tests for neglect following right hemisphere stroke was conducted by Azouvi and colleagues (2002). This study investigated both personal and extrapersonal neglect, however, given the focus on extrapersonal neglect in this thesis, we will focus solely on the latter. Two hundred and six sub-acute right hemisphere stroke patients completed a comprehensive battery of neglect tasks, including the bells test, figure copying, clock drawing, line bisection, overlapping figures test, reading, and writing. The sensitivity of these tests was variable, ranging from 19.0% for line bisection (5 cm lines) to 50.5% for the starting point on bells test. Importantly, the entire test battery was more sensitive than any single one test, with 85.9% of participants exhibiting neglect on atleast one task. The most sensitive tests was the starting point on the bells test (50.5%). In the context of the previous cancellation versus line bisection comparison, the difference between left and right omissions (44.9%) and the total number of omissions (41.3%) on the bells test was more sensitive than 20cm (37.7%) and 5cm (19.0%) line bisection. The authors suggest that the strong visual component required to complete bells test is a contributing factor when assessing neglect as this is thought to exacerbate neglect. The ultimate conclusion of this work was that using multiple tests is more sensitive and that "normal performance on one test alone is not sufficient to rule out the presence of neglect in a given patient" (Azouvi et al., 2002, p. 164).

Anatomical Correlates

Multiple brain regions have been implicated in spatial neglect, which is an unsurprising finding given the complex range of symptoms and individual variability associated with the syndrome. Whilst there is some disagreement about the critical lesion in neglect, it is generally accepted that neglect is most common after damage to regions that receive blood from the middle cerebral artery (MCA). The major cortical regions identified as common to neglect include the right TPJ and the superior temporal gyrus (STG; Karnath, Ferber, & Himmelbach, 2001; Karnath, Fruhmann-Berger, Kuker, & Rorden, 2004; Ringman et al., 2004; Vallar, 2001). However, the anatomical debate regarding critical lesion sites in neglect remains ongoing and

additional regions beyond the TPJ and STG have been implicated (Molenberghs, Sale, & Mattingley, 2012). Lesions localised at the cortical level include angular and supramarginal gyri (Buxbuam et al., 2004; Mort et al., 2003), medial temporal lobe (Hillis et al., 2005), and the superior longitudinal fasciculus (Hayashi et al., 2013; Lunven et al., 2015; Shinoura et al., 2009; Thiebaut de Schotten et al., 2011; Vallar, 2001). Subcortically, the basal ganglia (Karnath et al., 2004; Ringman et al., 2004) and thalamus (Ringman et al., 2004) have also been implicated in the development of neglect.

Given the enduring controversy regarding the relative contribution of the different brain regions, Verdon et al. (2010) conducted an anatomo-functional study with 80 right hemisphere stroke patients. The authors concluded that different sub-types of neglect were associated with damage to different cortical and subcortical regions. Three components – allocentric neglect, perceptive/visuospatial egocentric neglect, and exploratory/visuomotor egocentric neglect were identified and all had differing corresponding anatomical correlates. Allocentric neglect, categorised by errors for the left side of words during reading tasks and the left side of targets during the Ota search, involved temporal lobe regions with peaks localised near the parahippocampal gyrus extending dorsally into white matter. The first of the two egocentric subtypes, perceptive/visuo-spatial, showed involvement of posterior brain regions, specifically the inferior parietal lobe, near the supramarginal gyrus and adjacent white matter. Patients were categorised as perceptive/visuospatial if they displayed deviations on line bisection and contralesional word omission in two reading tasks. This was markedly different from the pattern of involvement seen in patients classified as having exploratory/visuo-motor egocentric neglect. Patients were categorised as such if they displayed contralesional misses in cancellation tasks. Anterior brain regions (right inferior frontal gyrus, anterior dorsolateral prefrontal cortex, posterior sections of the middle frontal gyrus and some portions of the frontal subcortical white matter) were associated with exploratory/visuo-motor egocentric subtype. Finally and more generally, the authors noted that damage to frontoparietal white matter fibres correlated with the presence of global and severe neglect, again supporting the involvement of the SLF in the development of neglect.

Electroencephalography in Neglect

From a research perspective, a wide range of methods have been employed to investigate neglect behaviour, including imaging and EEG. The incomparable temporal resolution of EEG ensures that it is a highly advantageous method for examining specific cognitive subsystems (Luck, Woodman, & Vogel, 2000), such as those often dysfunctional post-stroke. To date, investigations using EEG in stroke and neglect can broadly be divided into quantitative EEG (qEEG) studies and those investigating specific event-related potentials (ERPs).

The first method, qEEG, is a technique used to map electrical brain activity by extracting raw EEG signals collected from scalp electrodes and converting this information via a Fast Fourier Transformation (FFT) into pre-determined frequency bands (0.5-50 Hz; see Table 1 for overview of bands and associated behaviours; Budzynski, 2009). The resulting frequency bands include *delta* (0.5-4 Hz), theta (4-8 Hz), *alpha* (8-12 Hz), *beta* (15-18 Hz), *high beta* (20-30 Hz) and *gamma* (30-50 Hz;Budzynski, 2009; Evans, 1999; Ricker, 2000). Finnigan and colleagues (2004, 2007) have highlighted the utility of using qEEG as a predictive tool in stroke, with qEEG recorded into the acute phases post stroke associated with patient outcomes at following up (Finnigan et al., 2004; Finnigan, Walsh, Rose, & Chalk, 2007). For example, Finnigan et al. (2004) recorded EEG in 13 patients, 48 hours post stroke and assessed each patient on the National Institute of Health Stroke Scale (NIHSS), a measure of stroke-severity, in the acute phase post-stroke and again at follow-up 30 days later. Delta activity, activity that is evident during deep, non-rapid eye movements sleep, and increased delta:alpha power ratio were both highly correlated with NIHSS scores, with increased delta activity associated with poorer outcomes (as measured by NIHSS). This work is also consistent with the work of Watson, Andriola, and Heilman (1977) in neglect patients. In one of the first investigations of neglect using EEG, the Watson, Andriola, et al. (1977) investigated the pattern of qEEG patterns in 23 neglect patients (20 right hemisphere, 3 left hemisphere), comparing them to 21 left hemisphere patients with aphasia. Neglect was associated with a diffuse pattern of increased *delta* and *theta* activity across the entire damaged hemisphere, while aphasia patients had an increase in *delta* and *theta* activity but only over the focal lesion site. Changes in *delta* have also been found when comparing neglect patients to non-neglected patients (Colson, Demeurisse, Hublet, &

Slachmuylder, 2001; Demeurisse, Hublet, & Paternot, 1998) and when comparing hemispheric activity (higher delta activity in posterior regions is evident within the right hemisphere when compared to the left; Demeurisse et al., 1998).

Table 1.1. EEG frequency bands and the associated behaviours.

Frequency Band	Associated Behaviour
Delta (0.5-4 Hz):	An increase of delta waves is indicative of reduced cortical activation. Delta waves are found during sleep in healthy individuals. Abnormal levels of delta activity can reflect brain injury.
Theta (4-8 Hz)	Theta waves are evident during sleep (Stage 1, Stage 2 and rapid eye movement sleep). It has been suggested that theta activity is related to consolidation of recent memories. Apart from sleep, theta waves are also evident during waking hours. Theta is to be an indictor of alertness, with increased theta levels related to decreased alertness. Theta has also been linked to working memory.
Alpha (8-12 Hz)	Alpha activity is strongest during states of relaxation, or when the brain is not active in cognitive tasks. Alpha is also thought to be important for active inhibition processes. Of note, Alpha is often segregated into lower alpha (7-9.5 Hz), implicated in attentional processes, and upper alpha (9.5-12 Hz), implicated in semantic memory processes.
Beta (15-18 Hz)	Beta band frequencies are most often associated with high level cognitive processes such as focused attention and problem solving. There is also evidence that beta is linked to alertness and vigilance.
High beta (20-30 Hz)	Like beta, high beta activity is associated with peak cognitive performance and higher order processing.

Beyond quantitative methods, investigations have also utilised event-related potentials. Event-related potential (ERP) recordings have been used to study attention since the 1960s (Eason & Harter, 1969) and it is an advantageous method for evaluating the integrity of underlying neural processes, as neural responses associated with specific events can be extracted (Deouell, Hamalainen, & Bentin, 2000; Luck, 2014; Luck et al., 2000). Within the context of stroke and neglect, commonly studied ERPs include the C1, a primary visual cortex signal (onset 40-60ms post-stimulus, peaking 80-100 ms post-stimulus) that is sensitive to basic visual stimulus parameters, such as contrast and spatial frequency (Luck, 2014); the P1, which is largest over lateral occipital sites (onset 60-90 ms post-stimulus onset), sensitive to stimulus parameters and modulated by selective attention and arousal (Luck et al., 2000; Luck & Yard, 1995; Vogel, Luck, & Shapiro, 1998); the N1 and its subcomponents (one anterior and two posterior), all of which are influenced by spatial attention (Luck, 2014; Mangun, 1995; Vogel & Luck, 2000); the P2, a distinct wave found over anterior and central scalp regions (Luck & Hillyard, 1994); anterior and posterior N2 components (Folstein & Van Petten, 2008; Luck, 2014); and the P3 or P300 (Polich, 2007, 2012). See Figure 1.4. for a graphical representation of the aforementioned ERPs (P1 to P3).

Given the nature of the neglect symptoms, the majority of studies utilising an EEG method have focused on examining the integrity of early sensory processing signals. Yet despite considerable effort, the results are inconsistent. One of the earliest investigations was conducted by Watson, Miller, and Heilman (1977) who measured the P1, N2 and P2 in macaque monkeys, who following ablation of the arcuate sulcus (posterior prefrontal region) developed neglect. In this instance, while the three monkeys displayed neglect symptoms, no significant changes to early EEG components (P1, N1, and P2) were evident. Analogous results have been reported in human subjects, with reports that normal somatosensory and visual evoked potentials can be elicited in left neglect patients (Vallar, Sandroni, Rusconi, & Barbieri, 1991). In contrast, some have reported abnormal sensory functioning in neglect patients with smaller ipsilesional N1 components evident when visual and auditory stimuli are presented to the neglect hemifield (Deouell, Bentin, & Giard, 1998; Deouell et al., 2000; Verleger, Heide, Butt, Wascher, & Kompf, 1996). Spinelli and colleagues have also reported differences in steady state visually evoked potentials (SSVEPs) with prolonged latencies (10-30ms) for SSVEPs on the neglected side compared to those

on the ipsilesional side (Angelelli, De Luca, & Spinelli, 1996; Pitzalis, Spinelli, & Zoccolotti, 1997; Spinelli, Angelelli, De Luca, & Burr, 1996; Spinelli, Burr, & Morrone, 1994).

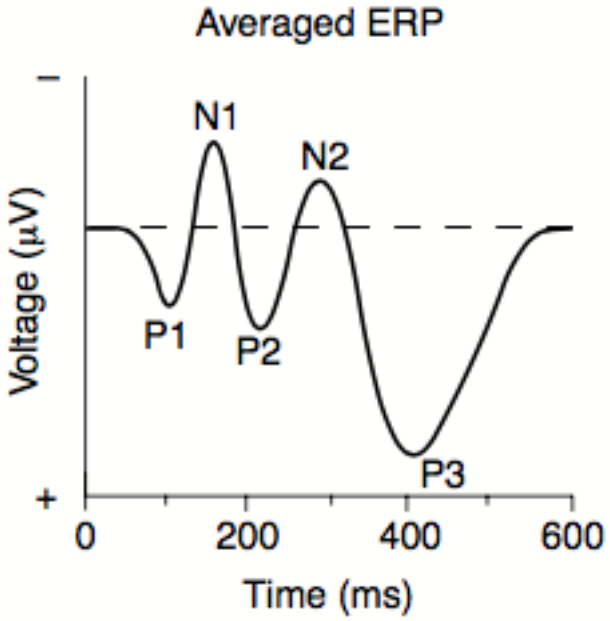

Figure 1.4. A graphic representation of ERPs commonly studied within a stroke and neglect context (Adapted and reprinted with permission from Luck et al., 2000). The P1 is evident 60-90 ms post-stimulus onset, following by the N1, P2, N2 and the P3 (P300). Not included here is the C1, which occurs 40-60ms post-stimulus, over the primary visual cortex.

Reports suggest that the dysfunction in neglect also occur further down the sensory processing system, such as in the P3 component. The P300 generally occurs 300-600ms following stimulus onset, is known to be modulated by attention (Polich & Kok, 1995), and is a signal often used to measure the allocation of attention (Sawaki & Katayama, 2008). For example, the initial monkey by Watson et al (1977) reported delays in N2 and P3 latencies and increased P3 amplitudes in the macaque monkeys with neglect. These isolated changes to later EEG components were taken as evidence for the arousal-attentional hypothesis underlying neglect. This work has since been followed up by examinations in human neglect patients. Saevarsson, Kristjansson, Bach, and Heinrich (2012) tested six chronic neglect patients on a standard random-sequence oddball paradigm and reported that on average, P300 amplitudes were smaller for targets presented in left hemifield compared to right targets. Additionally, those participants who have higher rates of missed targets, showed a larger difference in P300 amplitude between perceived and missed left targets. The authors concluded that these results not only support a general attentional

impairment in neglect patients but also suggest that the P300 adjusts as a function of the stimuli awareness.

Perhaps the most comprehensive assessment of ERP components in neglect was completed by Di Russo (2008) who recorded EEG from eleven right-hemisphere patients with neglect, using a task with focal stimuli located in four visual quadrants, and compared their results to that of six left-brain damaged patients without neglect. Stimulus processing was intact up until 130ms post onset, with no differences evident in the C1 or P1 components between groups or hemifields. Divergent processing began to emerge from this point on, with differences first noted in the N1a component. A small N1a component was evident for stimuli presented in the right hemifield in neglect patients, however no such signal was evident for left hemifield targets. Further dysfunction occurred in components believed to provide top-down feedback for visual processing, namely the N1p (140-180ms) and P2 (180-220ms) signals. A delayed latency and a reduced amplitude for the N1p and a delayed P2 signal were evident in neglect patients when stimuli were presented in the upper left quadrant compared to the upper right. Further, a reduced amplitude was noted in N1p and a delayed latency and reduced amplitude was evident for the P2 when stimuli was presented in the lower left quadrant. Ultimately, the results from this study suggested that early bottom-up processing (C1, P1) remained intact in neglect patients but signals related to visual processing in more dorsal regions adjacent to the parietal lobe (N1a, N1p, P2) are impaired.

Neglect: An Interim Summary

The literature presented to this point highlight a number of important considerations for future neglect research. First, the above highlights the need to include a range of assessment tools when assessing neglect symptomatology. Given the manifestation of neglect is variable, "several tests are more likely to uncover evidence of neglect than a single test" (Halligan, Marshall, & Wade, 1989, p. 910).

Secondly, although different sub-types of neglect can be defined (Verdon et al., 2010) such a definitive dichotomy may represent a gross oversimplification of the underlying contributory mechanisms. Indeed, it is highly probable that neglect may have multiple underlying causes including biased attention, decreased arousal, sensory dysfunction, or problems of motoric sequencing deficits (Corbetta et al.,

2005; Corbetta & Shulman, 2011; Manly et al., 2005; Mesulam, 1999; Rizzolatti & Gallese, 1988). Alternatively, it may be that these deficits are inter-related and combine to result in neglect. While much of the work to date has been focused on developing an understanding of the lesion sites, little has been done to parse out the relative contribution of possible deficits to the development of neglect.

Finally, it should be noted that the difficulty in accurately assessing neglect using current pen-and-paper tests suggests that there is a need to expand beyond this antiquated approach into more objective neurophysiologically-based measures of spatial attention. Molenberghs, Sale and Mattingley (2012) have advocated for the future incorporation of laboratory tests in clinical practice, to aid the investigation of the underlying mechanisms driving the disorder. Stagnation in neglect research and a failure to reach a consensus regarding underlying mechanisms reflects a need to shift to new perspectives. The implementation of novel techniques may provide the catalyst for new growth, providing answers that have currently eluded the research field.

Perceptual decision-making paradigms

Perceptual decision-making encompasses multiple neural processing stages from representing, selecting and accumulating sensory information to preparing and executing actions (Gold & Shadlen, 2007; Sternberg, 1969). The brain's ability to identify and process pertinent information amongst considerable amounts of irrelevant sensory information before producing an action has garnered much interest over the past two decades (Gold & Shadlen, 2007; Newman, Loughnane, Kelly, Connell, & Bellgrove, 2017; O'Connell, Dockree, & Kelly, 2012; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011). This interest stems from the appreciation that the ability to categorise sensory information and therefore make judgements about our environment is a fundamental skill required for effective day-to-day functioning. For example, consider a driver navigating through traffic on a busy road. As the driver approaches the next traffic light, they check to see if there is a green arrow to turn right and, with this information, automatically begin to move their foot to the accelerator to move forward, switch on their indicator and then slowdown in preparation to make the turn. To respond to such a scenario, neural processes need to adequately filter the relevant signals from environmental noise (Freedman & Assad,

2011; Hanks & Summerfield, 2017). Importantly, the filtering of relevant information from irrelevant noise becomes more challenging when the visual information is less legible, such as during a heavy storm (Merfeld, Clark, Lu, & Karmali, 2016). Given the brain is unable to interpret information with perfect fidelity (Merfeld et al., 2016), perceptual decision-making is vitally important as the brain must integrate the *available* information to create a perceptual decision.

The solid theoretical basis of perceptual decision-making comes from sequential sampling models (also known as integrator models; Forstmann, Ratcliff, & Wagenmakers, 2016; Smith & Ratcliff, 2004), which posit that sensory evidence is repeatedly sampled and accumulated across time until which point the evidence reaches an action-triggering threshold (see Figure 1.5; Link & Heath, 1975; Shadlen & Kiani, 2013; Smith & Ratcliff, 2004; Usher & McClelland, 2001). There are many different variants of sequential sampling models, including linear ballistic accumulation models (Brown & Heathcote, 2008), leaky competing accumulator models (Usher & McClelland, 2001), and drift-diffusion models (Ratcliff, 1978). These models are differentiated by the specific parameters used within the computation, such as whether the accumulation is thought to occur continuously or during discrete time periods (Ratcliff & Smith, 2004). One example of how these models function can be seen in Figure 1, Panel A. In this figure, the drift-diffusion model highlights that evidence is gradually and continuously accumulated until which point the evidence reaches a decision boundary (Evans & Brown, 2017; Vuckovic, Kwantes, Humphreys, & Neal, 2014). At this point, a decision would be made and in the case of behavioural paradigms, a motor response would be prepared. It is important to note that the computational models used to describe the processes underlying perceptual decision-making are thought to provide more accurate predictions of behaviour than behaviour or neural metrics alone (Turner, Forstmann, Love, Palmeri, & Van Maanen, 2017). Further, Love (2015) has suggested that these models can also be of use when integrating neurophysiological and behavioural data, as the models are able to identify the cognitive processes contributing to the behavioural response (Forstmann, Ratcliff, & Wagenmakers, 2016; Grafton & Tunik, 2011) and these can be linked with measures of neural activity (Forstmann et al., 2016; Turner, van Maanen, & Forstmann, 2015). Importantly the complementary relationship is also true, such that behavioural results and neural data are also able to

better inform theoretical models (Mack, Preston, & Love, 2013; van Maanen et al., 2011). For example, initial behavioural experimental work involving invasive recordings of monkeys during performance on sensorimotor tasks has supported the sequential sampling theoretical framework and has enabled further characterisation of neural changes during each of the processing stages required for perceptual decision-making (Gold & Shadlen, 2007; Kable & Glimcher, 2009; Schall, 2001).

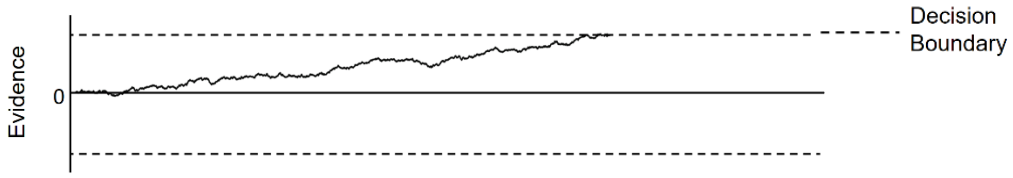

Figure 1.5. A visual depiction of the drift-diffusion model. This model demonstrates that evidence being accumulated gradually until a decision threshold (decision boundary) is reached. It is that this point that a decision is made and in the case of behavioural experiments, a motor response is prepared (Adapted and printed with permission from Evans & Brown (2017)).

As previously mentioned, current theories suggest that decision-making is a dynamic process requiring multiple neural networks (Filimon, Philiastides, Nelson, Kloosterman, & Heekeren, 2013; Twomey, Kelly, & Connell, 2016). These separate networks are believed to represent different stages of decision-making (Ding & Gold, 2013), namely the representation of sensory information (Shamir, 2014), early target selection (Goschy, Koch, Müller, & Zehetleitner, 2014), integration of building evidence (O'Connell, Dockree, & Kelly, 2012), and preparation for motor response or action (Sandrone, 2014).

While spatial attention and perceptual decision-making have not historically been co-examined, the use of such methods to investigate spatial bias in healthy participants has recently gained traction (Loughnane et al., 2016; Newman et al., 2016; Newman et al., 2017; Newman et al., 2013). It is clear that the breakdown of any stage within the perceptual decision-making process could affect the ability to orient in space, suggesting this approach may contribute significantly to the current understanding of neglect.

Recently**,** a range of novel EEG tasks have recently been developed that allow for distinct neural signals that can be associated with discrete stages of perceptual decision-making. Perceptual decision-making paradigms typically involve monitoring

continuously presented stimuli for gradual changes in appearance, be it variations in contrast or periods of coherent motion amongst periods of random motion (Kelly & O'Connell, 2013; Kelly & O'Connell, 2015; O'Connell et al., 2012). The continuity of stimulus presentation has important implications for analyses, as it eliminates sensory-evoked deflections in the EEG signal, thereby allowing for "parallel tracking of freely-evolving sensory evidence, decision variables and motor preparation signals" (Kelly & O'Connell, 2015, p. 32). The independent measurement of discrete neural signals, whose dynamics predict the timing and accuracy of subsequent perceptual reports, is a significant advancement (Kelly & O'Connell, 2013; Loughnane et al., 2016; Newman et al., 2017; O'Connell et al., 2012). Within this thesis, we focus on the investigation of the N2, a signal representative of early target selection and spatial attention orienting (Burra & Kerzel, 2013; Eimer & Mazza, 2005; Loughnane et al., 2016; Robitaille & Jolicoeur, 2006). When attention is oriented to the left hemifield, an N2 contralateral component ($N2_{(C)}$) is evident in the right hemisphere, whereas the inverse is evident when attention is oriented to the right hemifield. Loughnane and colleagues (2016) note that the N2 signals share many of the key characteristics of the N2pc component, such as "polarity, topography, latency, contralateral dominance and contingency on task relevance..." (p.498). However, unlike the N2pc which relies on cross-condition subtractions (e.g., target-present versus target-absent trials), the N2 components can be measured using a hemispheric-specific method. This novel signal presents a unique opportunity to investigate differences in spatial orienting ability between hemifields (Kiss, Van Velzen, & Eimer, 2008; Woodman & Luck, 1999). Another novel EEG component is the centro-parietal positivity (CPP), a signal able to track perceptual evidence accumulation independent of sensory or motor requirements (Kelly & O'Connell, 2013; O'Connell et al., 2012). The CPP commences soon after target onset, increasing steadily over time as sensory evidence is accumulated, before reaching a fixed threshold at which the perceptual decision is made (O'Connell et al., 2012). Importantly, the CPP demonstrates similar evidence-dependent build-up dynamics regardless of response format (button press versus counting), modality (visual versus audition), or target features (upward or downward motion, pitch changes, intensity changes versus dot-motion detection), reflecting the supramodal nature of the signal (Kelly & O'Connell, 2013; O'Connell et al., 2012) and highlighting that this signal is able to index information processing independent of motor requirements.

The N2 and CPP, in combination with a novel bilateral dot motion detection paradigm, have recently been leveraged to trace the temporal evolution of spatial biases in the context of investigating individual differences on spatial asymmetries (Newman et al, 2017). Using the novel method, Newman and colleagues (2017) established that individual differences in spatial attention asymmetries were accounted for by asymmetries in three key neural markers: posterior alpha power, $N2_{(c)}$ peak latency and the onset of the evidence accumulation process (CPP). The development of a single paradigm that enables distinct neural processes to be measured with temporal specificity (Kelly & O'Connell, 2013; Loughnane et al., 2016; Newman et al., 2017; O'Connell et al., 2012), presents a unique opportunity to develop a deeper understanding of the neural mechanisms underpinning spatial asymmetries.

While this strategy is likely to have great clinical significance, questions remain about how particular decision-making stages are altered as a result of healthy aging. To date, much of the perceptual decision-making literature have utilised young healthy samples (Kelly & O'Connell, 2013; Loughnane et al., 2016; Newman et al., 2017; O'Connell et al., 2012) and little has been done to investigate how the dynamics of perceptual decision-making changes as a function of age. Given many neglect patients are in later decades of life (Karnath et al., 2011; Robertson et al., 1997; Tarkka, Luukkainen-Markkula, Pitkanen, & Hamalainen, 2011; Verleger et al., 1996), investigations of how these components are altered by natural aging is an important first step.

Perceptual decision-making: An interim summary

In summary, perceptual decision-making paradigms and the related EEG and ERP analyses, may significantly contribute to the current understanding of spatial inattention. The application of the above novel perceptual decision-making methods, that allow for the integrity of particular stages to be evaluated independently of each other may further our understanding of the underlying neural mechanisms of neglect. The recent discovery of the N2 and CPP components are significant and their potential utility in neglect patients should not be overlooked. While the use of these novel approaches in neglect patients is alluring, it must be noted that our current understanding of perceptual decision-making is largely based on young healthy

samples. Prior to work with patient population, an investigation of how natural aging affects these components is required.

Rehabilitation in Neglect

Over the past six decades, a variety of rehabilitation strategies have been developed to alleviate, reduce or remediate chronic neglect symptoms (Luaute, Halligan, Rode, Rossetti, & Boisson, 2006; Maxton et al., 2013; Tsai et al., 2013). Techniques have previously included top-down techniques such as visual scanning training (Kerkhoff & Schenk, 2012; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002) and bottom-up techniques such as sensory stimulation (Kerkhoff et al., 2012; Utz, Keller, Kardinal, & Kerkhoff, 2011), prism adaptation (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Ladavas, Bonifazi, Catena, & Serino, 2011; Serino, Barbiani, Rinaldesi, & Ladavas, 2009), pharmacological treatments (Danckert & Ferber, 2006; Dodds et al., 2009; Gorgoraptis et al., 2012; Lucas et al., 2013; Malhotra, Parton, Greenwood, & Husain, 2006); and brain stimulation (Brighina et al., 2003; Oliveri et al., 2001; Song et al., 2009) to name a few (see Bartolomeo (2014), Bowen, Hazelton, Pollock, and Lincoln (2013); Luaute et al. (2006), Tsai et al. (2013), Van Vleet and DeGutis (2013) for additional techniques and reviews). To date there is no widely acceptable rehabilitative strategy for chronic neglect as many techniques, while able to attenuate the severity of neglect, are impractical due to the short duration of effects, patient discomfort and poor patient cooperation (Brigida Fierro, Brighina, & Bisiach, 2006; Kerkhoff & Schenk, 2012; Kim, Chun, Kim, & Lee, 2013).

Top-down Techniques

Visual Scanning Training.

Visual scanning training is a technique still widely used in clinical settings and it aims to treat neglect by stimulating top-down processes to overcome the obvious problem that neglect patients explore only half of their visual world. The training encourages patients to actively and consciously explore the neglect side of space by giving feedback over repeated practice session (Diller & Weinberg, 1977; Van Vleet & DeGutis, 2013). A major limitation of visual scanning training is that while some

visual aspects of the disorder improve, the training fails to improve tactile search behaviour and it does not generalise well outside of the training environment (Aimola, Rogers, Kerkhoff, Smith, & Schenk, 2012; Danckert & Ferber, 2006; Robertson, Gray, Pentland, & Waite, 1990; Schindler et al., 2002). Despite this, the popularity of top-down techniques has not abated with twelve studies (Cherney, Halper, & Papachronis, 2003; Cottam, 1987; Edmans, Webster, & Lincoln, 2000; Fanthome, Lincoln, Drummond, & Walker, 1995; Ferreira, Lopes, Luiz, Cardoso, & Andre, 2011; Kerkhoff et al., 2012; Luukkainen-Markkula, Tarkkaa, Pitkanena, Sivenuisa, & Hamalainen, 2009; Robertson et al., 1990; Rusconi, Meinecke, Sbrissa, & Bernardini, 2002; Weinberg et al., 1977; Welfringer, Leifert-Fiebach, Babinsky, & Brandt, 2011; Wiart et al., 1997) investigating the effect of such approaches for neglect rehabilitation (see Bowen et al. (2013) for review and breakdown of visual training versus feedback and cueing). Practically, visual scanning training is also a very involved process, with suggestions that a minimum of 40 sessions of 50 minutes duration are required to achieve stable results (Antonussi, 1995; Kerhoff, 1998). The extensiveness of the training regime results in an expensive treatment strategy. Further, the length of treatment requires consistent commitment from both the treating clinician and the patient. Gaining consistent effort from the latter is particularly difficult to obtain given the presence of anosognosia, a lack of insight, in many patients (Adair et al., 1998).

Bottom-up Techniques.

Following the revelations regarding the limitations of top-down techniques, bottom-up techniques, which require less awareness and conscious involvement of the patient, were subsequently developed and investigated (Frassinetti et al., 2002).

Sensory Stimulation Techniques.

One group of bottom-up manipulations that requires less compliance, cooperation and active involvement from patients involve sensory stimulation, an overarching set of therapies that can include caloric and galvanic stimulation. The brain utilises cues from the vestibular, visual and proprioceptive systems to determine the body's position in space. Caloric vestibular and galvanic stimulation exploits this association. Caloric vestibular stimulation involves applying cold water to the

external auditory canal of contralesional ear or warm water to the ipsilesional ear. The stimulation stimulates the inner ear canal of the vestibular system and causes the eyes to deviate in the direction of the irrigated ear. Stimulation reduces neglect symptoms multimodally, with improvements in line cancellation and reading (Rubens, 1985); disturbances of body position, awareness of hemiplegia, and postural imbalance (Rade, Perenin, Honoré, & Boisson, 1998; Rode et al., 1992); and anosognosia (Cappa, Sterzi, Vallar, & Bisiach, 1987). Galvanic stimulation reaps similar immediate effects by stimulating the vestibular system electrically (see Utz, Dimova, Oppenlander, and Kerkhoff (2010) for review). However, the benefits of caloric- and galvanic-stimulation are often short lived, lasting for approximately 10-15 minutes, and the effects generally disappear following the cessation of the manipulation (Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Danckert & Ferber, 2006). Further, repetitive application (particularly for caloric-stimulation) is often unsuccessful as the vestibular system is able to habituate to the phenomenon (Kerkhoff et al., 2012). Despite these drawbacks, the positive effects of caloric- and galvanic stimulation suggest that simple bottom-up mechanisms are able to overcome high level cognitive dysfunction, albeit briefly (Luaute et al., 2006).

Optokinetic Stimulation.

Another form of bottom-up stimulation is that of optokinetic stimulation (OKS), which exploits the fact we use visual information, particularly information about motion, to create the perception of our body in space (Kerkhoff & Schenk, 2012). The strategy involves taking a large display that fills the patient's entire field of vision and moving it to the left, with speed of the movement ranging from 5.11/sec (Mattingley, Bradshaw, & Bradshaw, 1994) to 71.11/sec (Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990). Regardless of the speed, the movement induces the illusion that the body is rotating towards the right, and therefore the patient tries to compensate by re-orienting towards the left (Luaute et al., 2006). Pizzamiglio et al. (1990) was the first to test this rehabilitation strategy in neglect patients with positive results, however the amelioration was transient. Kerkhoff and colleagues (2002, as cited in Kerkhoff and Schenk (2012)) implemented OKS but using smaller displays and a repetitive procedure comprised of five sessions, each 45 minutes in duration, implemented over a period of 10-14 days. The technique induced

optokinetic nystagmus but did not result in trunk rotation. The authors reported that for the three patients tested neglect on visual cancellation tasks, auditory neglect and neglect dyslexia dissipated and the effects remained stable for two weeks post-intervention. This was a marked improvement on the temporary effects of top-down approaches and even that of larger OKS displays. Subsequent studies (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996; Karnath, 1996; Keller, Lefin-Rank, Losch, & Kerkhoff, 2009; Kerkhoff, Keller, Ritter, & Marquardt, 2006; Mattingley et al., 1994; Schroder, Wist, & Homberg, 2008; Thimm et al., 2009; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1997) have reported positive effects for a range of neglect behaviours, with the exception of one (Pizzamiglio et al., 2004). Pizzamiglio et al. (2004) found no significant benefit of using large full-field OKS training. However of note, in this study participants were instructed to actively refrain from using pursuit eye-movements, unlike in the aforementioned studies during which participants were encouraged to do so. These findings suggest that OKS is only effective in treating neglect if the participant can and is actively engaged in following the displayed motion (Kerkhoff & Schenk, 2012).

Pharmacological Interventions.

Several pharmacological interventions have attempted to improve functioning in neglect patients, with the majority of interventions acting on dopaminergic, noradrenergic and cholinergic systems (see van der Kemp et al. (2017) for comprehensive review; Bartolomeo, 2014; Riestra & Barrett, 2013). Evidence for the utility of pharmacological treatments stems from positive results in healthy populations. As previously mentioned, healthy individuals generally exhibit pseudoneglect, a subtle asymmetry of visual attention, with preferential processing for stimuli in left space (Bowers & Heilman, 1980). However, this slight leftward bias can be influenced by both lowered subjective alertness and time-on-task effect (Manly et al., 2005; Newman et al., 2013), which result in a rightward shift of attention, similar to that exhibited at a pathological level in neglect patients. For example, Dodds et al. (2009) investigated the effects of psychostimulant drugs on the lateralisation of spatial bias using a landmark task in healthy populations. Using a double-blind, randomised balanced design, participants ingested an oral dose of modafinil, methylphenidate, and a lactose powder placebo on three separate occasions.

There was a significant effect of modafinil, a vigilance promoting drug, on the general rightward shift that occurs due to time-on-task effects. Modafinil is a commonly used medication often used to treat narcolepsy and other disorders characterised by extreme fatigue (Minzenberg & Carter, 2008), however the underlying mechanisms remain unclear (Dodds et al., 2009). These results are consistent with the theorised relationship between arousal, alertness and spatial bias.

In neglect patients, the majority of studies have investigated the use of dopaminergic therapy (Barrett, Crucian, Schwartz, & Heilman, 1999; Buxbaum, Ferraro, Whyte, Gershkoff, & Coslett, 2007; Fleet, Valenstein, Watson, & Heilman, 1987; Geminiani, Bottini, & Sterzi, 1998; Gorgoraptis et al., 2012; Grujic et al., 1998; Mukand et al., 2001). Gorgoraptis et al. (2012) used a double-blind, placebo controlled A-B-A design to investigate the effects of 9.0mg rotigotine in sixteen neglect patients. Improvement was evident on the Mesulam Shape Cancellation test following pharmacological intervention, however, performance on all other tests remained unchanged from baseline. It is important to note that van der Kemp, Dorresteijn, Ten Brink, Nijboer, and Visser-Meily (2017) consider this study by Gorgoraptis et al. (2012) to be the only dopaminergic study of "moderate quality". The remaining six studies were considered to be of "low quality" and the results are inconsistent amongst this group, with some positive (Fleet et al., 1987; Geminiani et al., 1998) and some negative (Barrett et al., 1999; Buxbaum et al., 2007; Grujic et al., 1998) effects.

Cholinergic therapy has also been investigated in neglect patient, with three studies completed to date. Lucas et al. (2013) used a double-blind, placebo controlled within-subject study to investigate the effects of 10mg of nicotine on spatial attention in ten neglect patients. Improvement was seen in all patients on all cancellation tasks (Bells, letter, and shape cancellation). This work was consistent with the results of Paolucci, Bureca, Multari, Nocentini, and Matano (2010) who documented improvement on letter cancellation and the Wundt-Jastrow illusion following eight weeks of rivastigmine. Vossel, Kukolja, Thimm, Thiel, and Fink (2010) also found positive effects of cholinergic therapy, with reduced RTs on all trials of the Posner cueing task (improved attentional reorienting) evident following the administration of 2mg of nicotine.

Finally, one study has used noradrenergic therapy (Malhotra et al., 2006), however van der Kemp et al. (2017) notes that this study is "low quality". A single

dose of oral guanfacine (29 µg/ kg) and a placebo was administered in a counter-balanced order one-week apart. Of the three chronic neglect patients tested, only one performance significant better on a computerised space exploration task, however, no other significant differences were found on other outcomes measures or in the other two patients.

Overall, while there are some promising results for pharmacological interventions in neglect across some tasks, the results are inconsistent and there is "no clear-cut improvement of VSN [visuospatial neglect] post stroke" (van der Kemp et al., 2017, p. 697). No recommendation can yet be made about the use of pharmacological interventions in neglect, as the poor quality of the studies in combination with the different methods used across studies and the lack of an effect in some instances, limits comparability across approaches. For the moment, pharmacological treatments for neglect will remain confined to the world of research and no translation to clinical work has yet been achieved (Luvizutto, Bazan, Braga, Resende, & El Dib, 2013). Given the complexity of stroke recovery and medical intervention post-stroke, pharmacological interventions as a means of ameliorating neglect behaviour need to be considered holistically. Van Vleet and DeGutis (2013) note that drug therapies may be inappropriate for a large number of neglect patients as the efficacy of pharmacological intervention may be dependent on the functional integrity of the remaining brain regions. Further, contraindications for further medication interventions needs to be considered as many drug comes with unwanted negative side effects and may interact with other medications (Van Vleet & DeGutis, 2013).

Brain Stimulation Techniques.

Brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), theta burst stimulation (TBS) and transcranial direct current stimulation (tDCS) have been increasingly used in neglect rehabilitation to non-invasively modulate cortical activity. The aim of these techniques is to re-balance the asymmetrical activation in each hemisphere and therefore reduce spatial bias (Kim et al., 2013; Van Vleet & DeGutis, 2013). High-frequency stimulation over the lesioned hemisphere is known to increase cortical excitability, whereas low frequency stimulation over the non-lesioned, intact hemisphere lowers cortical excitability. The

aim of both approaches is to re-balance the relative activation (Kim et al., 2013). rTMS stimulation of the posterior parietal lobe of the unaffected hemisphere, has been found to temporally deactivate functioning and can ameliorate neglect symptoms both transiently (Oliveri et al., 2001; Song et al., 2009) and for weeks post stimulation period (Brighina et al., 2003). More recently, continuous TBS studies using higher frequency pulses, have reported promising results with single day applications, such that they are able to produce improvement in visual explanation in a stable manner with effects enduring for up to 32 hours (Koch et al., 2012; Nyffeler, Cazzoli, Hess, & Muri, 2009).

Another recent study by Cazzoli and colleagues (2012) aimed to investigate the impact of repeated applications of continuous theta burst stimulation (cTBS) to ameliorate spatial neglect during spontaneous behaviours required for day-to-day activities. Twenty-four patients were divided into three groups: (1) cTBS followed by sham; (2) sham followed by cTBS; and (3) a no stimulation (sham only) control group. Eight trains of cTBS were applied over two consecutive days on the contralesional, left posterior parietal cortex and outcomes were measured using the Catherine-Bergego Scale (CBS), a standardized observation questionnaire that can detect the presence and severity of spatial neglect during activities of daily living. Standard neglect measures, such as the Subtask from the Vienna Test System (Peripheral perception and PVT), random shape cancellation and two-part picture test, were also collected pre- and post-intervention to investigate the effect on standardised assessment. The results showed a 37% improvement in spontaneous everyday behaviour, as measured by the CBS, after the repeated applications of cTBS. Of note, the improvement following the cTBS was robust and persisted for three weeks post-stimulation. The improvement noted in the spontaneous behaviour was also evident on the standardised neuropsychological tests. The authors highlighted that the results of this study were encouraging and the presentation of Class 1 evidence demonstrating that cTBS over the contralesional posterior parietal cortex could be used as a potential treatment for neglect symptoms was encouraging.

The culmination of these results, as highlgithed by Müri et al. (2013), is that whilemore research is required into the efficacy of stimulation techniques in neglect, the results to date are promising and suggest that brain stimulation may prove as powerful adjunct therapies for neglect.

Prism adaptation.

Prism adaptation was first introduced by Rossetti, Rode, Pisella, Farne, Boisson and Perenin (1998) and the technique aims to redistribute the biased spatial attention of neglect patients through sensory-motor remapping. The procedure requires the patient to wear prismatic goggles, which induces an optical deviation toward the ipsilesional (right) side of space. The patient wears these glasses for several minutes while they perform a task requiring them to point at targets. Initially, the visual system perceives the target to be displaced to the right of its actual position and this results in the patient overshooting to the right. With practice and over repeated trials, the patient generally learns to compensate for the right-shifting errors; a learning effect terms the adaptation effect. When the goggles are removed, the patient is left with a post-prismatic after-effect, during which they continue to make pointing deviations towards the left. It has been reported that this can occur for a period of up to two hours, an effect referred to as the post-prismatic after-effect. For further information regarding the procedure see Redding, Rossetti, and Wallace (2005) and Redding and Wallace (2006).

In the initial report, Rossetti et al. (1998) found that a short period of visuomotor adaptation to a right prismatic shift of the visual field could alleviate neglect. The improvement was observed for neuropsychological tests such as cancellation, copying and bisection and was fully maintained two hours later. Subsequent reports have reported variable benefit, with reports ranging from no significant improvement (Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003; Rousseaux, Bernati, Saj, & Kozlowski, 2006; Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010), to short term (Nys, De Haan, Kunneman, De Kort, & Dijkerman, 2008), and long-term effects (Frassinetti et al., 2002; Ladavas et al., 2011; Müri et al., 2013; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002; Serino et al., 2009). Of note, those studies reporting long-term effects implemented prism adaptation across multiple sessions, with the number of sessions generally ranging from ten to twenty. Improvements following multiple adaptation sessions are reported not only for the 'classic' neuropsychological testing but also in range of other tasks including imagination based tasks (Rode, Rossetti, & Boisson, 2001); tasks of perception but without arm movements (Farne, Rossetti, Toniolo, & Ladavas, 2002); and postural control tasks (Tilikete et al., 2001), suggesting that in some patients prism adaptation

is not only able to alter sensorimotor processing but also cognitive processing (Berberovic & Mattingley, 2003; Mattingley, 2002; Rode, Pisella, Rossetti, Farne, & Boisson, 2003). One caveat to this work is the recent study by Goedert, Zhang and Barrett (2016) who have presented a streamlined prism adaptation protocol, reducing the standard invention length. The authors investigated the effectiveness of 4-6 prism adaptation sessions noting that the usual ten sessions over a two week period is generally impractical for inpatient and outpatient rehabilitation settings (Goedert, Zhang & Barrett, 2016). The authors reported that participants receiving 4-6 sessions and the standard ten prism adaptation sessions improved similarly (48.8% for 4-6 sessions; 51.7% for 10 sessions) and this change was evident three to four weeks post-intervention. This preliminary data has been used as proof-of-concept evidence that a larger systematic randomised clinical trial is required, with particular focus on the optimisation of the dosage response for this treatment approach.

An ongoing issue within neglect literature and in prism adaptation literature more generally is the quality of the studies conducted. A recent systematic review by De Wit, Bring, Visser-Meily, and Nijboer (2016) evaluating the effect of prism adaptation on visual search in neglect highlighted this issue. Of the thirty studies included in their review, only seven were rated as of moderate-to-high quality using elements outlined by Tijssen and Assendelft (2003). The remaining twenty-three studies were characterised as low-quality. The authors noted that the general issue is that a standard protocol for treatment is lacking. Further, there is inconsistency in the reporting intervention procedures and experimental blinding; and there is significant inconsistency in the tests used as outcomes measures. De Wit and colleagues (2016) recommended that all studies need to provide clear and detailed outlines of prism adaptation procedures. This would ideally allow for a consensus to be formed regarding the most effective prism adaptation protocol and the neuropsychological tests that are best used as outcome measures. Ultimately, this would allow for better comparisons between studies and more informative evaluations.

Despite the limitations of the current literature, there are several reasons this technique has generated more interest than any other. There are distinct advantages in prism adaptation, it requires no voluntary orienting of attention, it is non-invasive, non-aversive, and simple to administer (Angeli, Meneghello, Mattioli, & Ladavas, 2004; Danckert & Ferber, 2006). Saj, Cojan, Vocat, Luaute, and Vuilleumier (2013)

investigated the mechanisms on which prism adaptation elicits its effect, assessing seven patients with left neglect on three different spatial attention tasks (line bisection, visual search and memory copying) before and after a single five-minute session of prism adaptation. fMRI demonstrated increased activation bilaterally in parietal, frontal and occipital lobes during bisection and visual search tasks and this activation was associated with a significant behavioural improvement. Saj et al. (2013) suggested that prism adaptation could restore activation in bilateral brain networks responsible for spatial inattention and reduced awareness. The authors suggest that recovery of neglect could be initiated by restoring the activation of the attention networks in the two hemispheres (Thimm, Fink, & Sturm, 2008).

Non-spatially lateralised rehabilitation interventions

One noteworthy avenue of rehabilitation strategies has aimed to capitalise on the relationship between spatial and non-spatial deficits, with the aim of utilising the latter to improve functional outcomes for patients (Van Vleet & DeGutis, 2013). Prior to discussing the interactions between spatial and non-spatial functions in neglect, there are a number of non-spatial functions that are important to define within the context of neglect and the current thesis. Firstly, it is important to highlight the role of arousal and define its function here. While arousal and alertness are often used interchangeably, this thesis defines arousal as a general wakefulness and responsiveness that is related to slow circadian rhythms **(**Bartolomeo, 2014). Secondly, it is important to define sustained attention. Here, sustained attention and tonic alertness are discussed collectively and refer to intrinsic, long-term arousal that fluctuates over minutes and hours, but independent of external cues (Sturm et al., 1999). Finally, and in contrast to tonic alertness, phasic alertness refers to brief increase in arousal that occurs in response to a short-lived event. Of note, phasic alertness is intimately involved orienting and selective attention (Husain & Rorden, 2003). To date, pharmacological manipulations have dominated the investigation of tonic alertness therapies (Hurford, Stringer, & Jann, 1998). Counter to this, a number of investigations have used bottom-up phasic alerting to impact spatial bias in neglect patients (Chica et al., 2012; Degutis & Van Vleet, 2010; Robertson et al., 1998; Van Vleet & Robertson, 2006). For example, the seminal work of Robertson et al. (1998) highlighted that the presentation of loud and unexpected tones phasically alerted the

brain and significantly ameliorated (or in some cases reversed neglect) on subsequent trials during a lateralised temporal order judgment task and reduced the protracted attentional blind. Of note, Degutis and Van Vleet (2010) have recently integrated tonic and phasic alertness into a visual sustained attention training task (TAPAT) where neglect patients were required to maintain an alert and ready state (tonic alertness), while inhibiting responses to a unexpected targets (phasic alertness). Results suggest that the TAPAT significantly improved spatial and non-spatial deficits in chronic neglect patients. This work is encouraging and ultimately Van Vleet and DeGutis (2013) suggest that "treatment approaches that more completely address non-spatial deficits and better account for their interactions with spatial attention will likely produce better outcomes" (p.327).

Neglect Rehabilitation: An Interim Summary

Despite the multitude of attempts to find an effective rehabilitation, there is currently no widely acceptable rehabilitative strategy for neglect as many techniques are impractical due to the short duration of effects, discomfort and poor patient cooperation (Brigida Fierro et al., 2006; Kerkhoff & Schenk, 2012; Kim et al., 2013). Further, a recent Cochrane review on neglect rehabilitation concluded that there was no clear evidence for preferentially using one rehabilitation strategy over another (Bowen et al., 2013). According to the Australian Clinical Guidelines for Stroke Management (National Stroke Foundation, 2010), no treatment protocol has received a grade higher than a C indicating that the "body of evidence provides some support for recommendation(s) but care should be taken in its application" (p.4). Given these limitations, there is an imperative to identify novel treatment options that are practical and effective. We suggest that ocular-light exposure may provide a non-invasive non-pharmacological treatment for neglect.

Blue-enriched Light

Light not only provides visual information but it is also crucial for regulating several circadian, neuroendocrine and neurobehavioural functions (Rahman et al., 2014; Vandewalle et al., 2013). Additionally, ocular exposure to visible light can result in behavioural improvements impacting both alertness and performance during cognitive tasks (Berson, 2003; Brainard & Hanifin, 2005; Viola, James, Schlangen, &

Dijk, 2008). These functions are often termed non-visual or non-image forming responses. The stimulation of non-visual functions using light originates from the discovery that light exposure can entrain circadian rhythms and suppress melatonin secretion in individuals who are blind and do not have any conscious perception of light (Czeisler et al., 1995).

A novel non-rod non-cone photoreceptor system is thought to mediate the non-visual effects of light, using a subset of intrinsically photosensitive retinal ganglion cells (ipRGC) that are maximally sensitive to blue light (459-483nm; Brainard & Hanifin, 2005; Foster, 2005; Gamlin et al., 2007; Hankins, Peirson, & Foster, 2008; Hatori & Panda, 2010; Schmidt, Chen, & Hattar, 2011). The sensitivity of this system to blue light is at odds with the spectral sensitivity of the 'classic' rod and cone photoreceptor systems that are responsible for vision, which are maximal for green light (550nm; Vandewalle, Maquet, & Dijk, 2009). The ipRGCs are present at low densities throughout the entire retina and utilise the photopigment melanopsin to influence the non-visual effects of light. The evidence for ipRGCs role in modulating non-visual functions are based on the fact that non-visual effects are apparent in blind individuals. Vandewalle et al. (2013) summarises the evidence linking ipRGCs to the non-visual effects of light highlighting four main lines of inquiry. The first is that ipRGC cells are undamaged in those with retinal atrophy, suggesting that their functions remain intact (Hannibal et al., 2004). The second is that the rod and cone systems cannot contribute to non-visual effects, as ophthalmological examinations confirm degeneration in the retinal pigment and there is a lack of operative responses when stimulated. The third line of evidence is that non-visual functions are more pronounced for blue monochromatic light as compared to other wavelengths, including green for which the classic rod-cone system is maximally sensitive. Finally, recent work by Gooley et al. (2012) notes that there the pupil constriction dynamics in blind individuals maps closely to what could be expected based on exclusive involvement of ipRGCs, in absence of rod and cone contributions.

The underlying brain mechanisms responsible for non-visual effects of light have not been confirmed but a number of candidate regions have been proposed (Vandewalle et al., 2009). A series of neuroimaging studies using PET and fMRI (Perrin et al., 2004; Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007) have examined modulations in brain activity following light exposure, generally while participants engaged in non-visual cognitive

tasks. The proposed target structures of ipRGCs are primarily subcortical and include the hypothalamus, in an area encompassing the suprachiasmatic nucleus (Perrin et al., 2004), and dorsal and posterior thalamus (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007), both of which are involved in the regulation of circadian and sleep-wake cycles (Gooley et al., 2012; Gooley, Lu, Fischer, & Saper, 2003; Schmidt et al., 2011). From here, ipRGCs are thought to project multisynaptically to the pineal gland, lateral geniculate nucleus and superior colliculus (Cajochen, 2007). It has been proposed that these subcortical structures are intimately connected with several of the brainstem nuclei that constitute the ascending arousal system, such as the locus coeruleus and dorsal raphe nuclei, both of which regulate cognition and project broadly throughout the cortex, particularly to prefrontal and parietal cortices (see Appendix 3 for a diagrammatically overview of the proposed mechanisms; Saper, Fuller, Pedersen, Lu, & Scammell, 2010; Vandewalle et al., 2013; Vandewalle, Schmidt, et al., 2007). Additionally cortical modulations have been documented in a range of regions involved in the top-down control of attention including dorsolateral prefrontal cortex, intraparietal sulcus and superior parietal lobule (Perrin et al., 2004; Vandewalle et al., 2006). In addition, regions related to bottom-up reorientation of attention, such as the right insula, the anterior cingulate cortex and the superior temporal sulcus (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007) also show modulation following light exposure.

Improvements in performance have been reported acutely following the onset of light exposure, both at night (Badia, Myers, Boecker, & Culpepper, 1991; Cajochen, Zeiter, Czeisler, & Dijk, 2000; Campbell & Dawson, 1990; Lockley et al., 2006) and during the day (Phipps-Nelson, Redman, Dijk, & Rajaratnam, 2003). The enhancement in performance typically occurs within 30 minutes of exposure and has been reported across a range of tasks including visual search, digit recall, serial addition-subtraction, two-column addition, logical reasoning task, letter cancellation task and simple reaction time tasks (Vandewalle et al., 2009). Not surprisingly, exposures of longer durations and/or higher intensities generate larger and longer lasting modulation of task related responses (Perrin et al., 2004; Vandewalle et al., 2006). Improved performance has also been found to reduce EEG alpha activity (8-12Hz), which as previously mentioned correlates with measures of sleepiness (Cajochen et al., 2000); and minimise the frequency of slow eye movements, which reflect inattention (Lavoie, Paquet, Selmaoui, Rufiange, & Dumont, 2003; Lockley et

al., 2006).

Historically, research investigating the alerting effects of light has generally used high irradiances (1000 lux +) of white polychromatic light. More recent work however, has documented the supremacy of short-wavelength light, particularly blue light (Cajochen, 2007; Lockley et al., 2006; Lockley & Gooley, 2006; Revell, Arendt, Fogg, & Skene, 2006; Vandewalle, Schmidt, et al., 2007). In 2005, Cajochen and colleagues compared the two-hour evening exposure to blue light (460nm) to green light (550nm) at very low intensities. The authors noted that although participant's pupils were more constricted during the blue light condition, they subjectively felt more alert. Further, blue light was able to attenuate the increase in melatonin and decrease in body temperature and heart rate that is associated with the biological night. This study was followed by that of Lockley and colleagues (2006), who exposed participants to six and half hours of light during the biological night (9.25 hours prior to normal wake-up time). Again, blue light resulted in significantly lower sleepiness ratings, as measured by the Karolinska Sleepiness Scale (KSS), when compared to green light exposure. Furthermore, the blue light condition was coupled with decreased reaction times and less attentional failures on an auditory psychomotor vigilance task (PVT), decreased EEG power density for delta-theta activity and increased EEG power density in the high alpha range. Further, Vandewalle, Schmidt, et al. (2007) aimed to investigate the impact of short-wavelength light on complex cognitive tasks. Using a fMRI protocol, the authors tested fifteen healthy participants using an auditory 2-back working memory task across three consecutive 20-minute sessions. During each session, participants were exposed to violet (430nm), blue (473nm) or green (527nm) for 50 seconds at a time, for a total of ten time per session. The authors reported that blue light resulted in increased left hippocampus, left thalamus and right amygdala activation when compared to green light exposure; and increased activation in the left middle frontal gyrus, left thalamus, and bilateral locus coeruleus when compared to the violet light exposure. The major conclusion taken from this work was that ipRGCs were able to elicit brain response almost immediately following the light exposure. Further, the non-visual effects of blue light have also shown that they can persist for more than 18 minutes post-exposure (Vandewalle, Gais, et al., 2007). Finally, the work of Rahman et al. (2014) has confirmed the dominance of blue light over other wavelengths. Sixteen healthy participants were exposed to 6.5 hours of either blue or green light during the biological day.

Participants' alertness, EEG activity and performance were assessed on an auditory PVT. Results were compared between the light groups but were also retrospectively compared to the night-time exposure results reported in Lockley et al. (2006). Results indicated that blue light was superior to green for both daytime and night-time exposure, with improvements in auditory RTs, reduced attentional lapses noted. Further, the blue light conditions were able to improve EEG activity in the theta and low alpha frequency band compared to green ocular light exposure. Additionally, the blue light exposure which occurred at night was able to improve alertness to levels that were nearly comparable to that observed in the day-time.

The culmination of this evidence suggests that blue-light exposure can positively influence the alerting system of the brain and possibly provide a useful, efficacious treatment for disorders of alertness. The application of this potential treatment has been assessed in a randomised, placebo-controlled trial by Sinclair, Ponsford, Taffe, Lockley, and Rajaratnam (2014). The study investigated the efficacy of a 45 minute/morning home-based blue light (465nm) treatment to combat fatigue in traumatic brain injury patients (Sinclair et al., 2014). Compared to participants receiving a yellow (574nm) or no light treatment, those receiving blue-light exposure reported significantly less fatigue and daytime sleepiness.

Newman et al. (2016) recently investigated the effect of blue-enriched light on spatial attention in healthy individuals, using a bilateral perceptual decision-making paradigm and simultaneous electroencephalography (EEG). Previous work with this task has demonstrated that healthy adults are faster to detect targets in the left, compared with right, hemifield targets (i.e., the task elicits pseudoneglect; Newman et al., 2017; Newman et al., 2013). Using a dose-response within-subjects method, pre-task exposure to high intensity blue-enriched light (~1400 lux) was found to speed detection of left hemifield targets. Newman et al. (2016) reported that the reduced response times for left-hemifield targets was driven by an enduring effect of the light exposure on right-hemisphere parieto-occipital α-power, a robust measure of spatial attention (Thut, Nietzel, Brandt, & Pascual-Leone, 2006). These results suggest the possibility of using of blue-enriched light to overcome the persistent and aberrant right spatial bias in neglect patients.

Conclusion

In summary, many questions remain regarding exactly where the deficits in neglect lie. The possible contribution of biased attention, decreased arousal, sensory dysfunction or motor deficits, or indeed a combination of these deficits, is not well understood and our current conceptualisation of the disorder is rather simplistic. The use of perceptual decision-making paradigms and related EEG analyses may provide a new perspective in which to frame neglect investigations, allowing for discrete stages to be distinguished from each other and may provide a unique perspective regarding the mechanism of neglect. Further, despite decades of research and numerous attempts, an efficacious rehabilitation strategy has so far eluded those interested in treating neglect. Inadequate rehabilitation results suggest a need to move beyond the current strategies.

Research Aims

Broadly, this thesis aims to further understand the underlying mechanisms of visuospatial attentional asymmetry, with investigations focused on the specific changes that occur as a function of age and brain injury. Further, the potential for blue-enriched light as a treatment for neglect is also explored. This thesis is separated into four sections. Experimental **Chapter Two** explores how perceptual decision-making is affected by natural aging. This is a necessary first step as to date; the current understanding of perceptual decision-making and the related EEG components is based on younger healthy individuals. Experimental **Chapter Three** investigates the underlying neural mechanisms responsible for aberrant spatial attention in hemispatial neglect patients. **Chapter Four**, Newman et al. (2016), is a previously published peer-reveiwed paper investigating the effect of blue enriched light on alertness and visuospatial attention asymmetry in healthy individuals. A significant contribution was made the conceptualisation and study design for this research study and it has been included as it provides the rationale for experimental Chapter Five. **Chapter Five** investigates the use of blue-enriched light to as a potential non-invasive treatment approach to ameliorating the significant right bias observed in neglect patients.

CHAPTER TWO: ALTERED ATTENTION ORIENTING AND EVIDENCE ACCUMULATION AS A RESULT OF HEALTHY AGING

CHAPTER TWO

Declaration for Thesis Chapter Two

Declaration by candidate

In the case of Chapter Two, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution (%)
Literature review, hypothesis conception and analysis design, recruitment and testing of participants, data processing, inferential data analysis, and manuscript write-up.	85%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of Contribution	Extent of contribution (%) for student co-authors only
Dr. Daniel Newman	Data processing and data analysis.	
Dr. Gerard Loughnane	Data processing and manuscript write-up.	
Dr. Méadhbh Brosnan	Critical reviews of manuscript.	
Dr. Redmond O'Connell	Critical reviews of manuscript.	
Prof. Mark Bellgrove	Study design, critical reviews of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

Candidate's Signature:	[redacted]	Date: 19/10/17
Main Supervisor's Signature	[redacted]	Date: 19/10/17

Preamble to Chapter Two

In Chapter One, we highlighted that the broad aim of this thesis was to investigate the underlying mechanisms of visuospatial attentional asymmetry in stroke. Prior to conducting this work, however, a more thorough understanding of how perceptual decision-making is affected by natural aging was required. This is the focus of Chapter Two. This work represented a necessary first step as to date the current understanding of perceptual decision-making and the related EEG components is based on younger healthy individuals.

The global population is aging rapidly (Samanez-Larkin & Knutson, 2015; UNFPA & Help Age International, 2012) and the proportion of older individuals (those over 65 years of age) is estimated to double between 2000 and 2050 (Nations, 2007; Treasury, 2015). Along with healthy aging, come a myriad of changes, including cognitive decline (Riddle, 2007). Cognitive decline is common among the elderly, with the majority of studies estimating the prevalence to be between 16-20% (Roberts & Knopman, 2013). As the population ages, the proportion of the population suffering from cognitive decline and accompanying functional impairments will likely increase, which is concerning given cognitive difficulties are associated with increased social, personal and financial burden (Deary et al., 2009). Continued research focused on identifying strategies that enable older individuals to maintain adequate levels of cognitive function during the healthy aging process is integral, both for the individuals and the wider community. We contend that a perceptual decision-making framework could be harnessed to investigate the potential underlying mechanisms contributing to cognitive difficulties in older adults.

In this chapter, we investigated the integrity of two key decision-making components, the $N2_{(c)ontralateral}$/$N2_{(i)psilateral}$, known to index attention orienting and the CPP, a signal measuring evidence accumulation over time, in a group of younger and older healthy participants. Results suggest that there are significant behavioural differences between the groups, with slowed reaction times and lower accuracy in older participants. Older participant also demonstrated significant changes in neural metrics, with later peak $N2_{(c)}$ latency and CPP onset; more gradual CPP slope, indicating slower evidence accumulation; and smaller CPP amplitudes. We suggest the changes in slowed evidence accumulation rates in older participants relate to the well-documented, generalised reduction in processing speed.

Abstract

Perceptual decision-making encompasses multiple neural processing stages and is vital for efficient and safe behaviour in everyday scenarios, such as driving. Although much work has recently explored the neural processes in younger adults, little is known about how healthy aging affects these processes. Thirty younger and thirty-one older healthy participants completed a bilateral motion detection task with EEG. Decision-making components indexing target selection (N2) and evidence accumulation (centroparietal positivity; CPP) were measured. Behaviourally, older adults had slowed reaction times and lower accuracy. Older participants demonstrated: (1) later peak $N2_{(c)}$ latency and CPP onset; (2) slower CPP build-up rate, and (3) smaller CPP amplitudes. Results indicate that both delayed target selection and slowed evidence accumulation contribute to slowed perceptual decision-making in older adults, which may be related to the generalised reduction in information processing that occurs with age. We contend that perceptual decision-making processes could have utility as targets for intervention approaches and the metrics may provide a method of monitoring intervention efficacy.

Aging is associated with changes in the processing of external information (Ceponiene et al, 2008). As such, the efficiency with which older adults process and make decisions about information in their environments is increasingly considered as a biomarker of age-related cognitive decline (Deary, Johnson, & Starr, 2010; Ritchie, Tucker-Drob, & Deary, 2014). Although a range of mechanisms have been proposed to account for changes in stimulus processing (e.g. dedifferentiation, higher order compensation of inefficient lower-level processing, impaired local/lateral inhibition, prefrontal cortico-cortical facilitation, and pre-frontothalamo-cortical gating; Allman, Miezin, & McGuinness, 1985; Cabeza, Anderson, Locantore, & McIntosh, 2002; Chao & Knight, 1998; Dustman, Emmerson, & Shearer, 1996; Dustman & Snyder, 1981; Knight, 2001; Knight, Staines, Swick, & Chao, 1999; Zikopoulos & Barbas, 2006), there is currently no consensus regarding the neural mechanisms underpinning processing difficulties in the aged. Many cognitive intervention strategies aimed at enhancing sensory processing in older adults have documented positive results with improved cognition reported post-intervention (Ball, Berch, Helmers, Jobe, et al., 2002; Edwards et al., 2002; Edwards et al., 2005; Elliott, O' Connor, & Edwards, 2014). Importantly, these gains also improve functional skills, such as those required for instrumental activities of daily living, driving mobility and driving safety (Ball, Edwards, Ross, & McGwin, 2010; Edwards, Delahunt, & Mahncke, 2009; Edwards, Myers, et al., 2009; Edwards et al., 2005; Elliott et al., 2014; O'Connor, Hudak, & Edwards, 2011; Rebok et al., 2014; Roenker, Cissell, Ball, Wadley, & Edwards, 2003; Willis et al., 2006). Nevertheless, we contend that a more comprehensive understanding of the underlying mechanisms responsible for age-related cognitive changes may result in more efficient, effective and targeted intervention approaches. One theoretical framework that could be harnessed to investigate the potential underlying mechanisms contributing to cognitive difficulties in older adults is that of perceptual decision-making.

Perceptual decision-making

Perceptual decision-making encompasses multiple neural processing stages from representing, selecting and accumulating sensory information to preparing and executing actions (Gold & Shadlen, 2007; Heekeren, Marrett, Bandettini, & Ungerleider, 2004; Siegel, Engel, & Donner, 2011; Sternberg, 1969). The brain's

ability to transform sensory input into action has garnered much interest over the past two decades (Bogacz, Brown, Moehlis, Holmes, & Cohen, 2006; Bogacz, Hu, Holmes, & Cohen, 2010; Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010; Forstmann et al., 2011; Gold & Shadlen, 2007; Newman, Loughnane, Kelly, Connell, & Bellgrove, 2017; O'Connell, Dockree, & Kelly, 2012; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011; van Maanen, Grasman, Forstmann, & Wagenmakers, 2012). The theoretical basis of perceptual decision-making derives from sequential sampling models, also known as integrator models (Forstmann, Ratcliff, & Wagenmakers, 2016; Smith & Ratcliff, 2004; Summerfield & De Lange, 2014), which suggest that sensory evidence is repeatedly sampled and accumulated over time to a point at which evidence reaches an action-triggering threshold (Link & Heath, 1975; Shadlen & Kiani, 2013; Smith & Ratcliff, 2004; Usher & McClelland, 2001). In day-to-day life, accurate and efficient perceptual decision-making is essential. Driving, an activity that necessitates continuous perceptual decisions about the environment is a pertinent example of the impact that impaired perceptual decision-making has on older adults. Over the past three decades, the rate of drivers aged over 70 has increased 13% in the United States (Ball et al., 2010) and it is estimated that one in five drivers will be aged over 65 years in Western countries in the coming years (Eby & Molnar, 2009). When involved in accidents, older drivers are more likely to be found at fault in multiple vehicle accidents (McGwin & Brown, 1999) and are more likely to be seriously injured or killed (Meuleners, Harding, Lee, & Legge, 2006). It is therefore vital to explore and develop a clear understanding of the mechanisms contributing to the safe completion of such activities in the aged.

Modeling perceptual decision-making and healthy aging

The vast majority of research on perceptual decision-making and aging has been limited to psychophysical modeling. Studies using this approach report that older adults have slowed reaction times (RTs; Forstmann et al., 2011; Ratcliff, Thapar, & McKoon, 2007) and in some cases are more inaccurate, although the latter appears to be somewhat task dependent (Ratcliff, McKoon, & Thapar, 2001; Ratcliff, Thapar, & McKoon, 2003). It has been proposed that the observed slowing in older adults is the result of a more cautious response style (Baron & Mattila, 1989; Botwinick, 1969; Hertzog, Vernon, & Rypma, 1993; Salthouse, 1979; Smith & Brewer, 1985; Smith &

Brewer, 1995), and a hesitancy to commit errors (Rabbitt, 1979). Further, it has been suggested that older individuals have a higher boundary criterion than younger adults and therefore require more evidence to be accumulated before committing to a decision (Ratcliff et al., 2001; Ratcliff, Thapar, Gomez, & McKoon, 2004; Ratcliff et al., 2003; Ratcliff, Thapar, & McKoon, 2004, 2006; Starns & Ratcliff, 2010; Thapar, Ratcliff, & McKoon, 2003). It has been suggested that this restrained threshold setting is potentially due to reduced white matter integrity in the cortico-striatal tracts that connect pre-supplementary motor areas and the striatum (Forstmann et al., 2010; Forstmann et al., 2011). Yet, despite an understanding of the potential neuroanatomical connections, little is known about the mechanisms underlying these decisions.

Understanding perceptual decision-making using human electrophysiology

Recently, a range of novel behavioural/EEG tasks have been developed that allow for distinct neural signals associated with discrete stages of the perceptual decision-making process to be measured independently of each other. These tasks involve monitoring stimuli for subtle feature changes, such as variations in contrast or periods of coherent motion amongst periods of random motion (Kelly & O'Connell, 2013; Kelly & O'Connell, 2015; O'Connell et al., 2012). The continuity of stimulus presentation in these paradigms has important implications for perceptual decision-making analyses, as it eliminates sensory-evoked deflections in the EEG signal, thereby allowing for the "parallel tracking of freely-evolving sensory evidence, decision variables and motor preparation signals" (Kelly & O'Connell, 2015, p. 32). This approach has led to the recent discovery of two noteworthy neural signals, the N2 and central parietal positivity (CPP).

The N2 is a signal representative of early target selection and spatial attention orienting (Burra & Kerzel, 2013; Eimer & Mazza, 2005; Loughnane et al., 2016; Robitaille & Jolicoeur, 2006). When attention is oriented to the left hemifield, an N2 contralateral component ($N2_{(c)}$) is evident in the right hemisphere and a later N2 ipsilesional component ($N2_{(i)}$) is evident in the left hemisphere (Loughnane et al., 2016). The inverse pattern is observed when attention is oriented to the right hemifield. The N2 signals share many of the key characteristics of the N2pc component, such as "polarity, topography, latency, contralateral dominance and

contingency on task relevance..." (Loughnane et al., 2016, p. 498). However, unlike the N2pc, which relies on cross-condition subtractions (e.g. target-present versus target-absent trials), the N2 components can be measured separately over each hemisphere. Given this, the novel $N2_{(c)}$/$N2_{(i)}$ signals present a unique opportunity to investigate differences in contralateral versus ipsilateral detection processes (Kiss, Van Velzen, & Eimer, 2008; Woodman & Luck, 1999).

The second component, the CPP, tracks perceptual evidence accumulation independent of sensory or motor requirements (Kelly & O'Connell, 2013; O'Connell et al., 2012). The CPP commences approximately 250 – 300ms after target onset, increasing steadily over time as sensory evidence is accumulated, before reaching a fixed threshold at which the perceptual decision is made (O'Connell et al., 2012). A number of lines of evidence provide support for the classification of the CPP as a decision signal, that is, a variable that integrates noisy sensory evidence and determines action through a boundary-crossing criterion (O'Connell et al., 2012). First, the CPP demonstrates similar evidence-dependent buildup dynamics regardless of response format (button press versus counting), modality (visual versus audition), or target features (upward or downward motion, pitch changes, intensity changes versus dot-motion detection), reflecting the supramodal nature of the signal (Kelly & O'Connell, 2013; O'Connell et al., 2012). Second, the CPP is highly sensitive to changes within the stimuli, with the build-up rate increasing in proportion to the strength of signal (e.g. higher levels of coherent motion result in faster evidence accumulation; Kelly & O'Connell, 2013). Third, the CPP is able to predict performance, with larger amplitudes associated with higher detection probability (O'Connell et al., 2012). Finally, CPP build-up is evident even when participants falsely identify a target or when they fail to make a response, highlighting that this signal is not simply an antecedent of the motor response but rather reflects a "more central detection process" (O'Connell et al., 2012, p. 1734).

More recently it has been demonstrated that the CPP is functionally equivalent to the classic P300 or P3b. Both signals have the same polarity, have a peak that co-varies with RT, and are supramodal (Hillyard, Squires, Bauer, & Lindsay, 1971; Kelly & O'Connell, 2015). Twomey et al (2015) further demonstrated that build-to-threshold dynamics can be observed for the oddball P3b in response-aligned analyses

(Twomey, Murphy, Kelly, & O'Connell, 2015). This observation calls for a change to how we think about and measure the P300. In contrast to the CPP, the P300, often elicited using traditional ERP paradigms, is generally measured as a discrete neural event rather than a dynamically evolving one that unfolds gradually over time. The P300 has been extensively discussed in the context of aging, with the focus largely on amplitude differences (Ashford, Coburn, Rose, & Bayley, 2011; Kuba et al., 2012; Pinal, Zurrón, & Díaz, 2015; Rossini, Rossi, Babiloni, & Polich, 2007; van Dinteren, Arns, Jongsma, & Kessels, 2014; Walhovd, Rosquist, & Fjell, 2008). An important caveat of this work is that the P300 has traditionally been measured in stimulus-aligned averages. The demonstration that the P300 is a decision signal presents a potential complication since the stimulus-aligned average amplitudes of signals that closely abut a decision commitment are heavily influenced by differences in response time variability (Kelly & O'Connell, 2013; O'Connell et al., 2012), thereby potentially complicating interpretation.

Here, we leverage recent advancements in the perceptual decision-making literature to provide valuable insights into the underlying mechanisms in healthy aging. The ability to isolate and discretely measure neural metrics that reflect distinct stages in the perceptual decision-making process is significant. Further, the ability to look beyond amplitude differences to other aspects of the neural metrics such as onset, peak latency, and slope provides a unique framework whereby we can establish a mechanistic neurophysiological account of aging. We focus on two discrete stages of the perceptual decision-making process, attention orienting ($N2_{(c)}$/ $N2_{(i)}$) and evidence accumulation (CPP). By harnessing this approach, a more comprehensive understanding of how perceptual decision-making processes contribute to cognitive changes observed in older adults can be established. We assert that investigations into how perceptual decision-making processes change with healthy aging are vital, and may allow for enhanced targeting of interventions.

Method

Ethical approval was obtained from the Monash Health and Monash University Human Research Ethics Committee prior to the commencement of the study. The experimental protocol was approved and carried out in accordance with the

approved guidelines. All participants were volunteers naive to the experimental hypothesis being tested and each provided written informed consent.

Participants

Data were collected from a total of 61 healthy volunteers, 30 younger participants aged 18 to 28 years (17 female; *M*=23.68 years, *SD*=2.14) and 31 older participants aged 57 to 90 years (17 female; *M*=73.29 years, *SD*= 7.11). Three older participants were excluded from analysis: one was ambidextrous, one was experiencing a current depressive episode and one had a Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) score < 26, suggesting possible cognitive impairment. All remaining participants (30 younger; 27 older) were right-handed, as determined by a handedness inventory (Nicholls, Thomas, Loetscher, & Grimshaw, 2013), had normal or corrected to normal vision, had no history of neurological or psychiatric disorder, had no head injury resulting in loss of consciousness and were not medicated with steroids, tranquilizers or any other medication that would affect arousal levels. Years of education were comparable between younger participants (*M* = 16.00 years, *SD* = 2.24 years) and older participants (*M* = 15.30 years, *SD* = 3.69 years), with no statistical difference between the groups, 95% [-2.36, 0.95], $t(42.027) = -.859$, $p = .395$.

Materials & Procedure

Assessment of Perceptual Decision-making

Participants were seated in a dimly lit sound-attenuated room, supported by a chin rest, at a viewing distance of 57 cm. A 21 inch CRT monitor (85Hz, 1024 x 768 resolution) was used and participants were asked to perform a bilateral variant of the random dot motion task (Loughnane et al., 2016). A bilateral perceptual decision-making paradigm, which is a novel variant of the random dot motion task (Britten, Shadlen, Newsome, & Movshon, 1992; Loughnane et al., 2016; Newsome, Britten, & Movshon, 1989; Shadlen, Britten, Newsome, & Movshon, 1996) was used to investigate the distinct stages of perceptual decision-making. The use of a bilateral measure allowed for subtle spatial asymmetries to be investigated. Before beginning the task, participants read on-screen instructions and the task was also explained

verbally to ensure adequate comprehension. Participants were required to fixate centrally and were discouraged from blinking or moving during each trial. Participants monitored two peripheral circular patches (one in each of the lower quadrants) of 150 moving dots. Participants were required to identify targets, defined by a seamless transition from random motion to coherent motion in an upward or downward direction (see Figure 2.1). Once a target was detected, participants made a speeded button press with their right index finger (dominant hand) using the left mouse click. The responding hand was kept constant across trials. Participants completed 8-9 blocks, with each block consisting of 24 trials (total trial no. = 192-216 trials). The number of blocks completed varied based on participant fatigue. Given the large number of trials and the trial-by-trial analysis, this variation was not expected to detrimentally impact results. A short break (15-60 seconds) interleaved each block. Each trial consisted of a period of random motion (initiated on fixation and lasting 1800ms, 2800ms or 3800ms) followed by a coherent motion target (90% of the dots moved coherently), which ceased following a response or after 3000ms. Targets (coherent motion) only appeared in one of the two patches on any given trial. If a fixation break occurred during a trial (either a blink or a gaze deviation >4° left or right of centre, detected via EyeLink1000, SR Research Ltd), the task halted (stationary dots). Once fixation returned to the central fixation dot, the trial restarted. The 12 possible trial types (each a combination of one of the 3 periods of random motion, 2 target locations, and 2 coherent motion directions) occurred in a pseudorandom order with the constraint that each different trial type arose twice every 24 trials. The paradigm was run on a 32-bit windows XP machine using MATLAB (MathWorks) and the Psychophysics Toolbox extensions (Brainard, 1997; Cornelissen, Peters, & Palmer, 2002; Pelli, 1997).

Bilateral motion detection task parameters

Stimuli appeared white (RGB: 221) against a black background and a red (RGB) fixation mark was a 6×6 pixel square placed centrally. The circular dot patches were 8 degrees diameter with the centre of each patch situated 6 degrees below and 8 degrees to either the left or right of the central fixation point. During random motion, 150 dots per patch (each dot = 6x6 pixels) were placed at random and independent positions within each patch and moving at a flicker rate of 20.0 frames/s. During

coherent motion targets, 90% of dots (135 total) were randomly selected and displaced in either a downward or upward direction on the following frame, resulting in a motion speed of 5 degrees/s. The fixation dot remained on screen throughout the entire task; however, the two peripheral patches were only present when the trial was initiated by the participant's fixation on the central point.

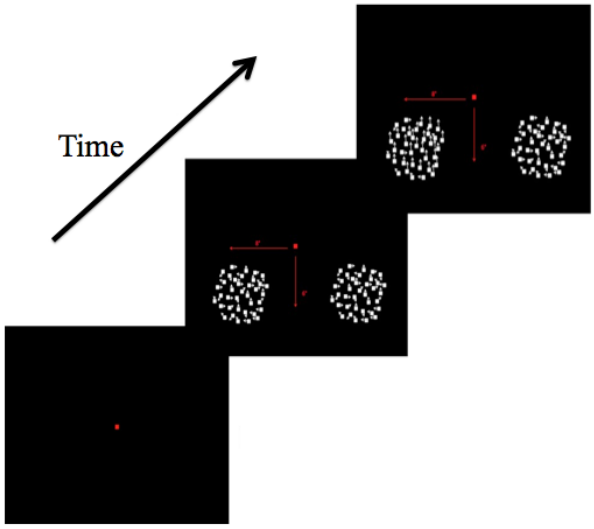

Figure 2.1. Schematic of a single trial. The screen remained blank (apart from the fixation dot) until the trial was manually started by the examiner, at which point two peripheral patches of randomly moving dots appeared. Participants monitored these patches for instances of coherent motions (either upward or downward). Participants responded to motion targets via a speeded button press. Coherent motion only occurred in one of the two patches per trial. The pre-target random motion lasted either 1800ms, 2800ms or 3800ms, chosen pseudorandomly on a trial-by-trial basis.

Analysis

EEG Acquisition and Preprocessing

EEG was simultaneously acquired from 64 scalp electrodes using a Brain Products BrainAmp DC system digitized at 500Hz. Data were processed using a combination of custom scripts and EEGLAB[64] (Delorme & Makeig, 2004) routines implemented in MATLAB (MathWorks). A 35Hz low-pass filter was applied offline

using 4th order Butterworth filters, noisy channels were interpolated (spherical spline) and the data were re-referenced to the average reference. Epochs were then extracted from the continuous data from -1000ms to 1880ms around target onset, and baselined with respect to -100 to 0ms before target onset.

Data exclusion

Trials were excluded from analysis if: (a) RTs were < 150ms (pre-emptive responses) or >1800ms (responses after coherent motion offset); (b) RTs were beyond 3*SD* from the mean; (c) EEG from any channel exceeded +/- 100μV during the interval from -100ms before target onset to 100ms after RT for the ERP analysis; (d) if central fixation was broken by blinking or eye movement >4° from the centre, during the interval between 100ms before target onset and 100ms after response for the ERP analysis.

EEG Data Extraction

The $N2_{(c)}$ and $N2_{(i)}$ components were measured contralaterally and ipsilaterally to the target location, respectively, at peak electrodes P7 and P8 (Loughnane et al., 2016), whereas the CPP was measured at peak electrodes CPz (Kelly & O'Connell, 2013; Loughnane et al., 2016; O'Connell, Dockree, & Kelly, 2012). The $N2_{(c)}$, $N2_{(i)}$ and CPP signals were aggregated to average waveforms as a function of target hemifield for each participant, as per Newman et al. (2017). N2-latency was identified as the time-point with the most negative amplitude value in the stimulus-locked waveform between 150-400ms for the $N2_{(c)}$ and $N2_{(i)}$, whereas the N2-amplitude was measured as the mean amplitude inside a 100ms window centred on the stimulus-locked grand average peak ($N2_{(c)}$: 266ms; $N2_{(i)}$: 340ms; Loughnane et al., 2016). CPP build-up rate was defined as the slope of a straight line fitted to the response-locked waveform (Kelly & O'Connell, 2013; Loughnane et al., 2016; O'Connell et al., 2012) with the time window defined individually for each participant as 100ms prior to the maximum CPP amplitude pre-response. Onset latency of the CPP was measured by performing running sample-point-by-sample-point t-tests against zero across each participant's stimulus-locked CPP waveforms. CPP-onset was defined as the first point at which the amplitude reached significance at the 0.05 level for 25 or more consecutive points (Foxe & Simpson, 2002; Kelly, Gomez-Ramirez, & Foxe, 2008;

Loughnane et al., 2016). CPP peak amplitude was defined as the maximum value pre-response and this was measured using a window that was individually defined for each participant.

Inferential Analysis

Inferential statistics were calculated using a combination of SPSS, custom Matlab scripts and packages in R. To begin, we used ANOVA to investigate the effect of Group (Younger, Older) on target Accuracy. A two-way mixed model ANOVA was used to investigate the effect of Group (Younger, Older) and Hemifield (Left, Right) on the number of misses. Analysis of the effects of Group (Younger, Older) and Hemifield (Left, Right) on RT, $N2_{(c)}$, $N2_{(i)}$ and CPP were conducted using two-way mixed model ANOVAs. In cases where the assumption of normality was violated, the p-value ("$p_{permuted}$") of a permutation test based on 1000 permutations is also reported. Finally, a binomial logistic regression was used to ascertain which of the neural metrics ($N2_{(c)}$latency, CPP onset, CPP slope and CPP amplitude) maximally discriminated between the groups.

Results

Behavioural Results

The mean target detection accuracy for the overall sample on the bilateral motion detection paradigm was greater than 90%, however younger participants had significantly higher mean accuracy (*M* = 97.77%, *SD = 2.57;* range 88-100%) than older participants (*M* = 94.78%, *SD = 6.87;* range 71-100%), $F(1,55) = 4.93$, $p=0.031$, $\eta_G^2 = 0.082$, $p_{permuted} = 0.026$. There was no significant main effect of Hemifield $F(1,57) = 1.38$, $p=.25$. There was no statistically significant Group x Hemifield interaction, $F(1,57) = 0.021$, $p=.89$.

Younger participants had significantly faster mean RTs compared to older participants, $F(1,55) = 52.39$, $p<0.001$, $\eta_G^2 = 0.49$, $p_{permuted} = p<0.001$. There was a significant main effect of Hemifield, with significantly faster mean RTs for left hemifield targets than right hemifield targets, $F(1,55) = 5.89$, $p=0.019$, $\eta_G^2 = 0.002$,

$p_{permuted}$ =0.014. There was no Group x Hemifield interaction on RT, F(1,55) = 0.69, p=0.42, $p_{permuted}$ = 0.42.

EEG Results

$N2_{(c)}$ and $N2_{(i)}$ amplitude

There was no significant main effect of Group on $N2_{(c)}$ amplitude, F(1,55) = 2.48, p=0.12. There was a main effect of Hemifield, such that $N2_{(c)}$ amplitude was significantly larger for left hemifield targets than right hemifield targets F(1,55) = 5.35, p=0.024, η_G^2 = 0.027 across both groups. There was no Group x Hemifield interaction, F(1,55) = 2.69, p=0.11. For the $N2_{(i)}$ amplitude, there was no significant main effect of Group, F(1,55) = 3.13, p=0.083, or Hemifield, F(1,55) = 0.82 p=0.37, and no Group x Hemifield interaction F(1,55) = 1.88, p=0.18.

$N2_{(c)}$ and $N2_{(i)}$ latency

$N2_{(c)}$ latency occurred significantly earlier in younger participants than it did in older participants F(1,55) = 7.79, p=0.003, η_G^2 = 0.11, $p_{permuted}$ =0.001. The time to peak $N2_{(c)}$ latency occurred significantly earlier for targets presented in the left hemifield as compared to the right hemifield F(1,55) = 7.79, p=0.007, η_G^2 = 0.046, $p_{permuted}$ =0.007. There was no Group x Hemifield interaction, F(1,55) = 0.91, p=0.35, $p_{permuted}$ = 0.32.

For the $N2_{(i)}$ latency, there was no significant main effect of Group, F(1,55) = 1.03, p=0.32, $p_{permuted}$ =0.33, or Hemifield, F(1,55) = 0.92, p=0.31, $p_{permuted}$ =0.34; and no Group x Hemifield interaction F(1,55) = 0.065, p=0.80, $p_{permuted}$ =0.81.

CPP onset, slope and amplitude

The CPP occurred significantly earlier for younger participants than older participants F(1,55) = 29.83, p<0.001, η_G^2 =0.31 (see Figure 2.2, Panel A & C). There was no significant difference in CPP onset between left and right hemifields, F(1,55) = 0.43, p=0.51 (see Figure 2.2, Panel A & C). There was no significant Group x Hemifield interaction F(1,55) = 0.17, p=0.68.

With respect to CPP slope, younger participants exhibited a significantly steeper CPP slope compared to older participants, $F(1,55) = 14.93$, $p<.001$, $\eta_G^2 = 0.21$, $p_{permuted} <0.001$ (see Figure 2.2, Panel B & D). There was no significant difference in CPP slope when comparing Hemifields, $F(1,55) = 0.40$, $p = 0.53$, $p_{permuted} =0.54$. There was no significant Group x Hemifield interaction for CPP slope $F(1,55) = 0.49$, $p = 0.49$, $p_{permuted} =0.51$.

There was a significant difference in CPP amplitude between the younger and older groups, with a significantly larger amplitude for younger participants, $F(1,55) = 9.62$, $p= 0.003$, $\eta_p^2 = .15$. There was no significant difference in CPP amplitude between left and right hemifields, $F(1,55) = .13$, $p=.73$. There was no significant Group x Hemifield interaction $F(1,55) = .76$, $p= 0.39$.

The discriminatory power of neural metrics between age groups

Next, we used a binomial logistic regression to ascertain which signals could maximally discriminate between older and younger adults. $N2_{(c)}$ latency, CPP onset, CPP slope and CPP amplitude were investigated. These signals were chosen as previous analyses indicated that there were significant groups differences. Given the scale and units differed between variables, all predictor variables were standardised (z-scores; Field, 2013) and the regression was subsequently completed using these variables.

The logistic regression model was statistically significant, χ^2 (4) = 53.86, $p < .001$. The model explained 81.6% (Nagelkerke R^2) of the variance in group and correctly classified 87.7% of cases. Sensitivity was 90.0%, specificity 85.2%, positive predictive value was 88.46% and negative predictive value was 87.09%. Of the four predictor variables only three were statistically significant: $N2_{(c)}$ peak latency, CPP onset, and CPP slope (as shown in Table 2.1). Odds ratios indicated slower peak $N2_{(c)}$ latency, later CPP onset and a shallower CPP slope were associated with an increased likelihood of being an older participant.

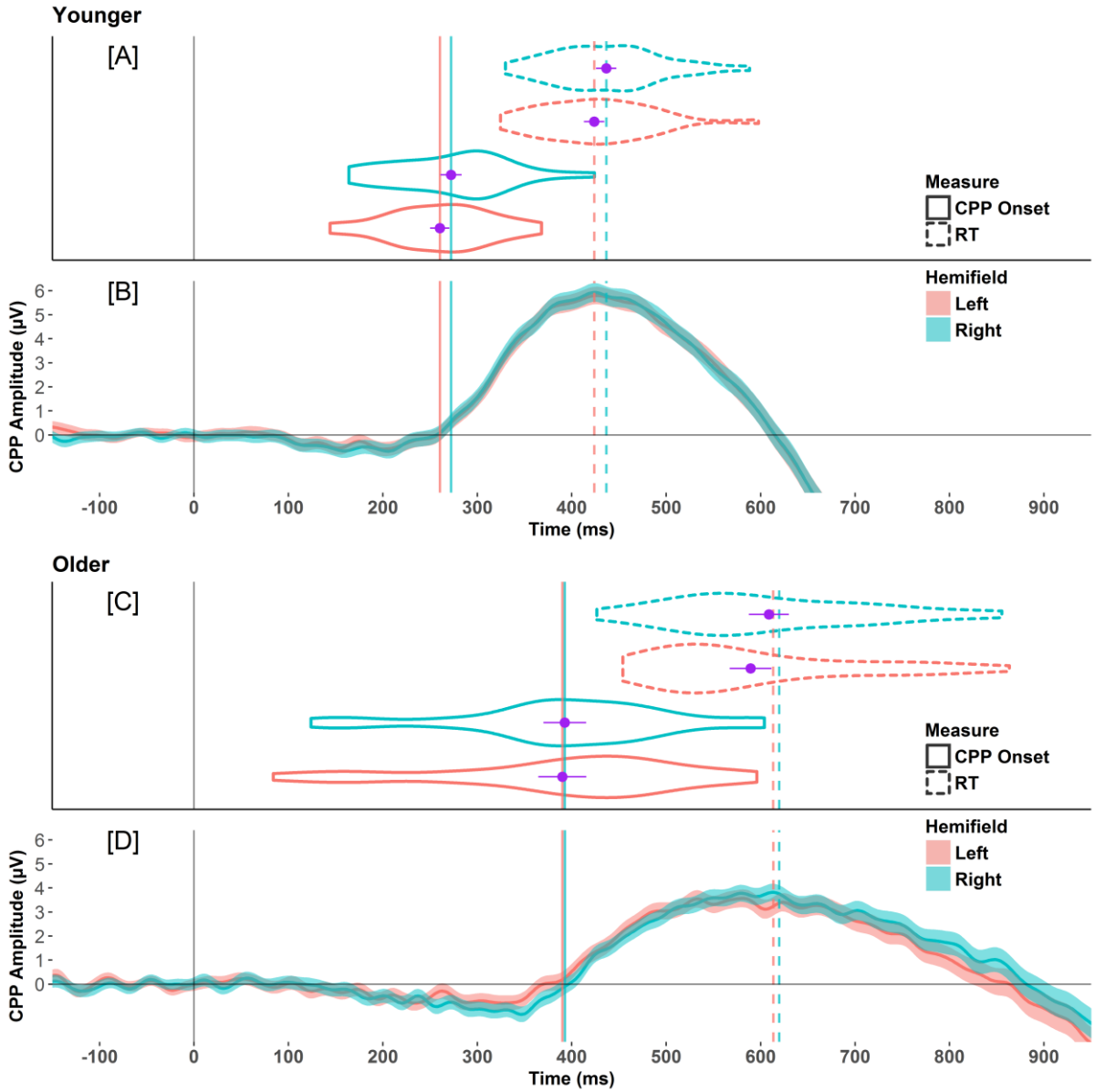

Figure 2.2. RT distributions and CPP signals for younger [A, B] and older [C,D] participants. [A & C] Violin plots show conditional distributions for younger and older groups, respectively. Purple dot-and-whisker plots show mean and standard error, and vertical lines project the means down to panels [B & D]. Error ribbons represent 95% CI for mean amplitude. CPP-onset occurred significantly earlier in younger participants when compared to older participants (see panel [C]). Panel [B] illustrates that Younger participants have an earlier onset and significantly steeper CPP when compared to the CPP slope of older participants [D].

Table 2.1. Logistic Regression outlining ability for $N2_{(c)}$ peak latency, CPP onset, CPP slope and CPP amplitude to discriminate between older and younger groups.

	B	SE	Wald	*df*	*p*	Odds ratio
$N2_{(c)}$ peak latency	-3.18	1.24	6.58	1	.010	.042
CPP onset	-4.062	1.62	6.26	1	.012	.017
CPP slope	3.69	1.63	5.15	1	.023	39.93
CPP amplitude	1.10	.99	1.45	1	.23	2.99
Constant	-.59	.62	.91	1	.34	.56

Discussion

Consistent with previous reports showing slower reaction times and less accurate behavioural performance in older participants (Forstmann et al., 2011; Ratcliff, Hasegawa, Hasegawa, Smith, & Segraves, 2007; Ratcliff et al., 2003), older adults in the current study were slower and less accurate on the bilateral motion detection task. Of importance, these age-related behavioural differences were accompanied by significant differences in the attention orienting signals ($N2_{(c)}$) and the established electrophysiological marker of evidence accumulation, the CPP.

Longer time to peak $N2_{(c)}$ latencies were observed in older individuals, when compared with younger participants. Importantly, $N2_{(c)}$ latency was able to accurately discriminate between younger and older groups of participants. Previously, Loughnane et al. (2016) reported that earlier $N2_{(c)}$ peak latency predicted earlier CPP onset and resulted in faster RTs, thereby reflecting more efficient target selection. Our $N2_{(c)}$ latency results together with the slowed RTs noted in older participants, are consistent with this account and suggest that inefficient target selection is a contributing factor to the inefficient processing of information observed in older healthy adults. Furthermore, this work is consistent with investigations of the N2pc, a signal that shows many of the same characteristics as the $N2_{(c)}$, with slowing in N2pc peak latencies observed in older participants (Cespón, Galdo‐Álvarez, & Díaz, 2013; Lorenzo-Lopez, Amenedo, & Cadaveira, 2008). The culmination of these results suggest that healthy aging results in significant slowing in target detection and the allocation of visuospatial attention.

With respect to our CPP results, we found evidence of slower CPP onset latency and a shallower CPP gradient in older adults, suggesting slowed integration of sensory evidence in these participants. Importantly, both CPP onset and CPP slope were able to discriminate between younger and older participants. These results are consistent with the slower RTs observed in older participants compared to younger participants. It is also consistent with previous work that has found that faster RTs are predicted by earlier onset of the CPP latency (Kelly & O'Connell, 2013; Loughnane et al., 2016; Twomey et al., 2015) and work detailing slowed P300 latencies in older adults (Anderer, Saletu, Semlitsch, & Pascual-Marqui, 2003; Miller, Bashore, Farwell, & Donchin, 1987).

It has been proposed that all age-related cognitive deficits are the result of a generalised reduction in processing speed, which subserves other cognitive operations (Anderer et al., 2003; Miller et al., 1987). Although we do not suggest that perceptual decision-making and processing speed are synonymous, we believe it a reasonable assertion that poor evidence accumulation in older participants would detrimentally impact the ability to perform tasks quickly and efficiently. Processing speed decrements are such an integral aspect of the aging process that it has been the focus of cognitive training techniques aimed at enhancing cognitive performance of older adults (Birren & Fisher, 1995; Salthouse, 1996). For example, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study investigated the impact of speed of processing training (amongst other training programs) on cognitive abilities and driving capability (Ball, Berch, Helmers, & Jobe, 2002; Rebok et al., 2014; Tennstedt & Unverzagt, 2013). The processing speed training aimed to improve a participant's ability to identify and locate visual information quickly in increasingly demanding visual displays (Ball et al., 2010), a set of training paradigms that likely incorporates perceptual decision-making skills. The speed-of processing training had positive results, with improved visual awareness, as measured by the Useful Field of View task (Edwards et al., 2002; Edwards et al., 2005) and better on-road driving safety evident following the intervention (Ball, Berch, Helmers, Jobe, et al., 2002; Willis et al., 2006). The knowledge that perceptual decision-making and more specifically, evidence accumulation is slowed with age in the current task, highlights specific processes that could be better targeted by neuro-rehabilitation protocols in ageing. Moreover, the CPP affords a neural metric that could be

harnessed to longitudinally measure the efficacy and utility of the impact of pre-existing intervention strategies on older adults' ability to accumulate evidence.

With respect to CPP amplitude, older participants exhibited smaller CPP amplitudes than younger participants. Though contradictory to the predictions of sequential sampling models which suggest that older individuals have a higher boundary criterion and require more information to be processed before making a decision (Roenker et al., 2003), these results are consistent with the P300 literature where smaller amplitudes have repeatedly been reported in older, compared to younger participants (Ratcliff et al., 2001; Ratcliff, Thapar, Gomez, et al., 2004; Ratcliff et al., 2003; Ratcliff, Thapar, & McKoon, 2004; Ratcliff et al., 2006; Starns & Ratcliff, 2010; Thapar et al., 2003). We note that this consistency of results occurred despite differences in signal alignment - P300 is traditionally a stimulus-aligned average, whereas the CPP is a response-aligned signal. The smaller amplitudes of P300 signals in aging populations are thought to reflect less efficient information processing (Ashford et al., 2011; Bourisly, 2016; Kuba et al., 2012; Polich, 1996; Rossini et al., 2007; van Dinteren et al., 2014; Walhovd et al., 2008) and the current results support this assertion, with older participants having slower RTs and reduced accuracy compared to younger participants. Importantly, CPP amplitude did not discriminate between older and younger adults over and above other perceptual decision-making metrics, such as $N2_{(c)}$ latency, CPP onset and CPP slope. These other neural metrics may therefore have utility when investigating cognitive change with age.

Finally, to our knowledge, this is the first investigation of the $N2_{(c)}$ / $N2_{(i)}$ in an aging sample and the first to harness these signals as a means of investigating hemifield differences between younger and older participants. Behavioural results indicate that the entire sample reacted faster for left hemifield targets, with no significant difference between younger and older participants. Further, there was evidence of reduced $N2_{(c)}$ latencies for left hemifield targets, across all participants, irrespective of group. These results are inconsistent with past accounts of changes in spatial bias as a function of age. In healthy young adults, the spatial attention literature consistently reports a subtle processing advantage for visuospatial information presented in the left hemifield, a phenomenon known as "pseudoneglect"

(Brooks, Sala, & Darling, 2014; Jewell & McCourt, 2000; Newman et al., 2017; Voyer, Voyer, & Tramonte, 2012). Previous reports note that in the later decades of life, there is an attenuation, elimination, or in some cases a reversal of this spatial bias, resulting in right spatial bias (Barrett & Craver-Lemley, 2008; Benwell, Thut, Grant, & Harvey, 2014; Brooks et al., 2014; Failla, Sheppard, & Bradshaw, 2003; Fujii, Fukatsu, Yamadori, & Kimura, 1995; Hatin, Sykes Tottenham, & Oriet, 2012; Jewell & McCourt, 2000; Schmitz & Peigneux, 2011). Here, we did not find any robust evidence in either the behavioural or electrophysiology measures of a rightward shift of attention in older participants. One potential explanation for this is task difficulty. Here, both groups searched for targets defined as instances where 90% of the dots moved coherently, a task that could be considered relatively simple, given previous literature has used considerably lower coherence levels (25%-70%; Loughnane et al., 2016; Newman et al., 2016). This study was part of a larger project investigating perceptual decision-making in neurological patients and therefore the low task difficulty was a conscious manipulation. It may however have reduced our ability to detect any subtle shifts in spatial bias. We therefore cannot rule out the potential for a shift in spatial attention if the difficulty level of the task was increased (coherence level was decreased).

In summary, our findings confirm previous results of slowed behavioural responses in older, compared to younger healthy participants. Further, age-related differences in attention orienting and evidence accumulation adversely impacted older adults performance on this bilateral motion detection task. These results support previous work highlighting an information processing decrement in older participants. We suggest that impaired target selection and attention orienting, as measured by the $N2_{(C)}$; and slowed evidence accumulation, as indexed by CPP onset and slope, could be better targeted by training techniques aimed at improving speed of information processing in older adults. Further, we contend that these perceptual decision-making metrics have utility as measurement of improvement in aging intervention projects.

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CHAPTER THREE: ELECTROPHYSIOLOGY REVEALS EVIDENCE FOR IPSILESIONAL ADAPTATION IN RIGHT HEMISPHERE SPATIAL NEGLECT

CHAPTER THREE

Declaration for Thesis Chapter Three

Declaration by candidate

In the case of Chapter Three, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution (%)
Literature review, hypothesis conception and analysis design, recruitment and testing of participants, data processing, inferential data analysis, and manuscript write-up.	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of Contribution	Extent of contribution (%) for student co-authors only
Dr. Gerard Loughnane	Data processing and inferential data analysis.	
Dr. Daniel Newman	Data processing and inferential data analysis.	
Dr. Méadhbh Brosnan	Critical reviews of manuscript.	
Dr. Trevor Chong	Imaging consult.	
Dr. Renerus Stolwyk	Study design	
Dr. Peter New	Study design and recruitment.	
Dr. Redmond O'Connell	Data analytics and critical reviews of manuscript.	
Prof. Mark Bellgrove	Study design, critical reviews of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

Candidate's Signature:	[redacted]	Date: 19/10/17
Main Supervisor's Signature	[redacted]	Date: 19/10/17

Preamble to Chapter Three

The previous chapter employed a perceptual decision-making framework to investigate the impact of natural aging on attention orienting and evidence accumulation. As previously mentioned, this comparison between younger and older neurologically healthy adults was a necessary first step to understand the impact of age on perceptual decision-making. In Chapter Three, we employ the same strategy with the aim of investigating the underlying mechanisms in neglect participants. These neglect results are then qualitatively compared to that of older neurologically healthy adults. This sample of older neurologically healthy adults is the same group that has previously been presented in Chapter Two.

Although the behavioural phenotype of neglect is well documented, little is known about the underlying mechanisms causing aberrant spatial attention in these patients. Current diagnostic assessments for neglect involve behavioural observations and clinical assessments that remain heavily reliant on paper and pencil tests. One caveat of current assessments is that they are unable to differentiate between various potential underlying mechanisms (arousal, attention, sensory and motor components).

In this chapter, we investigate the underlying neural mechanisms in right hemisphere stroke patients with neglect, focusing particularly on attention orienting signals (N2 and sub-components) and evidence accumulation (CPP) processes. To achieve this, we analysed the integrity of these signals in four groups of participants: (1) neurologically healthy participants; (2) neglect participants; (3) severe neglect participants and (4) no neglect. In neglect participants, there was evidence of dysfunctional attention orienting for left hemifield targets (right hemisphere $N2_{(c)}$) but evidence of compensation from the left hemisphere in the form of the $N2_{(i)}$. Importantly, this compensation was not evident in severe neglect participants. Here, we present a proof-of-concept study that this perceptual decision-making framework can have utility in investigating the underlying mechanisms in stroke. We highlight potential future research studies, which should aim to investigate the potential of translating this approach to clinical settings to improve diagnostic processes and the application of rehabilitation strategies.

Note: Please see **Appendix 4** for supplemental material related to this chapter.

Abstract

Neglect is a common neurological syndrome post-stroke and it is clinically defined as the inability to detect, respond to, and orient towards stimuli on the side contralateral to cerebral damage. It is more severe following right hemisphere stroke, resulting in left inattention. Current diagnostic assessment tools for neglect involve behavioural observations and clinical assessments that remain heavily reliant on pen and paper tests. One caveat of current assessments is that they are unable to differentiate between potential underlying mechanisms (arousal, attention, sensory and motor components). Here, we leveraged recent advancements in perceptual decision-making paradigms to investigate the underlying neural mechanisms in right hemisphere stroke patients, focusing particularly on attention orienting signals ($N2_{(c)}$/$N2_{(i)}$) and evidence accumulation (CPP) processes. Neurologically healthy participants (*N*=27) and stroke participants (*N*=7) completed a bilateral motion detection task with simultaneous electroencephalography (EEG) and eye tracking. In neurologically healthy participants, there was no significant spatial bias in behavioural performance. Analyses of single trial data revealed that right hemisphere $N2_{(c)}$ and the central CPP signals significantly impacted RT, with larger $N2_{(c)}$ amplitude and steeper CPP slope associated with faster RTs. Stroke participants were categorised into three groups based on trial counts and behavioural results: (1) neglect (*n*=3), (2) severe neglect (*n*=2), and (3) no neglect (*n*=2). In neglect participants, there was evidence of dysfunctional attention orienting for left hemifield targets (right hemisphere $N2_{(c)}$) but evidence of compensation from the left hemisphere in the form of the $N2_{(i)}$. Importantly, this compensation was not evident in severe neglect participants. Evidence accumulation, as measured by the CPP, was found to be important for sound behavioural performance in neurologically healthy participants, neglect participants and no neglect participants, with greater CPP slope related to faster RTs in both hemifields. Here, we provide proof-of-concept evidence that a perceptual decision-making framework shows promise for investigating the underlying mechanisms in stroke. We highlight potential future research studies, which should aim to investigate translating this approach to clinical settings to improve diagnostic processes and the application of rehabilitation strategies.

Neglect is a common and disabling neurological syndrome clinically defined as the inability to detect, respond to, and orient towards stimuli on the side contralateral to cerebral damage (Heilman & Valenstein, 1979; Parton, Mahotra, & Husain, 2004). It is more severe and enduring following stroke to the right hemisphere (resulting in inattention to the left side of space), compared to the left hemisphere, with damage generally affecting the territories supplied by the middle cerebral artery (Ringman, Saver, Woolson, Clarke, & Adams, 2004; Swan, 2001). The prevalence of neglect varies widely from 10%-85% (Azouvi et al., 2002; Bowen, McKenna, & Tallis, 1999), with some estimates postulating that anywhere between three and five million patients suffer from neglect post-stroke each year (Appelros, Karlsson, Seiger, & Nydevik, 2002; Azouvi et al., 2002; Chen, Hreha, Fortis, Goedert, & Barrett, 2012; Halligan, Marshall, & Wade, 1989; Stone, Halligan, & Greenwood, 1993; Stone et al., 1991; Zoccolotti et al., 1989). Although many of these individuals recover, approximately one-third of patients manifest a chronic form of neglect, with a substantial proportion exhibiting clear deficits more than six months post-stroke (Karnath, Rennig, Johannsen, & Rorden, 2011; Rengachary, He, Shulman, & Corbetta, 2011). The presence of on-going neglect is a significant issue as neglect is associated with poor functional outcomes (Jehkonen, Laihosalo, & Kettunen, 2006; Ween, Alexander, D'Esposito, & Roberts, 1996), including longer hospital stays (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001), slower and attenuated recovery rates (Gillen, Tennen, & McKee, 2005), reduced ability to complete activities required for daily living (Di Monaco et al., 2011; Katz, Hartman-Maeir, Ring, & Soroker, 1999), and worse functional improvement during rehabilitation (Paolucci et al., 2000).

Neglect is by no means a homogeneous nostological entity, and it has been suggested that it may in fact represent a set of disorders (Driver, 1994). As Mesulam (1994) highlighted “depending on the personal tastes, preference, and creativity of the investigator, neglect behaviour has been divided into a number of components” (p. 173). Common distinctions within the disorder are often made by subdividing neglect based on different underlying mechanisms, modalities, regions of space, and spatial coordinates (Bartolomeo, 2014). At a mechanistic level, neglect may be categorised as sensory (inattention) or motor (intention) neglect. Inattentional neglect refers to the deficit in awareness of contralesional stimuli, however it can be more precisely clarified by the regions of space affected (personal, peri- or extra-personal) or by the

modality affected. The most compelling manifestations of neglect affect vision; perhaps as this modality is most entangled with activities of daily living. However, it must be noted that inattentional neglect can involve other sensory modalities including touch (tactile neglect), audition, and olfaction (Jacobs, Brozzoli, & Farne, 2012), with combinations of more than one modality often present. In contrast to inattentional neglect, intentional neglect is the underutilisation of one side of the body that cannot be explained by awareness deficits or physical defects in strength, reflexes or sensibility (Heilman, Valenstein, & Watson, 1994; Laplane & Degos, 1983). Intentional neglect may be categorised by a failure to move (akinesia), slowness in initiation of contralesional movement (hypokinesia), insufficient amplitude of contralesional movement (hypometria), impersistence in moving or maintaining posture and reduced spatial exploration (Heilman et al., 1994; Làdavas, 1994). It is important to note that the dichotomy between inattentional and intentional components of neglect is not absolute and it likely represents a gross oversimplification of the underlying contributory mechanisms. A more realistic hypothesis is that the systems interact in a dynamic circuit, with sensory information informing the spatio-temporal coordinates required for motion, and subsequent alterations of sensory targets are made to match or anticipate the needs of the motor system (Adair, Na, Schwartz, & Heilman, 1998). That being said, it has been suggested that patients with differing neglect subtypes respond differentially to specific rehabilitation strategies (Adair et al., 1998; Làdavas, 1994) and it is possible to dissociate between neglect *predominately* determined by perceptual factors and neglect *primarily* influenced by premotor factors.

Regardless of the neglect subtype, diagnosis currently involves behavioural observations and clinical assessments that remain heavily reliant on pen and paper assessment tools used. Atleast 28 standardised and 34 non-standardised behavioural and functional neglect assessment tools are currently available for diagnostic purposes (Menon & Korner-Bitensky, 2005). Yet, no single test has sufficient sensitivity to enable a reliable diagnosis on its own (Azouvi et al., 2002; Halligan et al., 1989) and as such, it is recommended that more than one behavioural test be used in clinical settings (Karnath et al., 2011). A further caveat of current neglect assessment tools is the inability to detect subtypes of neglect or differentiate between various mechanisms of spatial neglect, such as arousal, attention, sensory and motoric aspects

of the deficit (Buxbuam et al., 2004; Chen et al., 2012). Menon-Nair, Korner-Bitensky, and Ogourtsova (2007) report that in some settings, neglect assessments are not employed in any form. Chen et al. (2012) suggests that this lack of assessment may potentially be due to perceived obstacles in the application of the assessments themselves. Overall, the current state of assessment tools likely contribute to the inconsistency of diagnosis and the low detections rates of neglect within medical settings (Edwards et al., 2006). This is concerning given patients may carry persistent deficits which subsequently impair function yet remain untreated. The lack of a single sensitive assessment tool also hampers efforts to appropriately apply therapeutic interventions for neglect. Current neglect assessment tools are problematic to the extent that the Australian National Stroke Foundation's Clinical Guidelines (2010) have recently highlighted the need for further development of sensitive, reliable and objective tests of spatial neglect that will enable accurate diagnoses and help to enhance targeted treatment.

Historically, neglect has been viewed as a disorder of selective attention, in part because primary sensory processing is often intact (Driver & Mattingley, 1998), and adopting attentional cueing strategies can transiently reduce neglect in some patients (Riddoch & Humphreys, 1983). Traditional neuropsychological accounts of neglect posit that the allocation of attention in space is governed by competitive interactions between the cerebral hemispheres (Kinsbourne, 1977, 1993, 1994), which are disrupted in neglect. In neurologically healthy individuals, the processing of spatial information preferentially activates the right hemisphere resulting in a contralateral orienting bias that dictates faster and more accurate processing of stimuli presented in left space – a phenomenon known as pseudoneglect (Bowers & Heilman, 1980; Kinsbourne, 1993; Nicholls, Bradshaw, & Mattingley, 1999). However, in the case of right hemisphere lesions and spatial neglect, the right hemisphere dominance is thought to be lost, thus unmasking the orienting bias of the left hemisphere, and driving a pathological bias of attention away from left space and toward the right (Kinsbourne, 1993). It is important to note that although the spatial asymmetries seen in disordered and neurologically healthy populations are generally opposite in direction (left-neglect vs. the right bias observed in pseudoneglect), the factors influencing the distribution of attention in space appear to be largely continuous. In addition to the lateralised spatial deficits observed in neglect, theorists are now

incorporating the impact of non-spatial functions, namely sustain attention, arousal, and alertness; on spatial attention into the contemporary accounts of neglect (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta, Kincade, & Shulman, 2003; Corbetta & Shulman, 2011). This addition has been made as a result of evidence highlighting the profound impairments of non-spatial attention that occur following right hemisphere damage (Bartolomeo, 2014; Bellgrove, Eramudugolla, Newman, Vance, & Mattingley, 2013; Robertson, Tegnér, Tham, Lo, & Nimmo-smith, 1995).

The intertwined nature of sustained attention, arousal and spatial attention is a fundamental component of the prominent model of neglect posited by Corbetta and Shulman (Corbetta et al., 2005; Corbetta et al., 2003; Corbetta & Shulman, 2011). Neuroimaging studies have suggested that two largely separate and discrete attentional networks exist, a bilateral dorsal frontoparietal attention network (DAN) and a right lateralised ventral frontoparietal attention network (VAN; Corbetta & Shulman, 2002; He et al., 2007; Shulman et al., 2009; Vandenberghe & Gillebert, 2009). The bilateral DANs connect the superior parietal lobes and intraparietal sulci, with the dorsal frontal lobes and frontal eye fields and are involved in goal-directed attentional selection and the facilitation of space exploration contralaterally (Ting et al., 2011). Intuitively, it would be damage to this system, particularly the right DAN that would result in neglect; however, Corbetta and colleagues (Corbetta et al., 2005; Corbetta et al., 2003; Corbetta & Shulman, 2002, 2011) instead posit that neglect results from damage to the right lateralised VAN. The right lateralised VAN system is associated with the maintenance of arousal, vigilance, and stimulus-driven, bottom-up attentional selection (Corbetta et al., 2005; Corbetta et al., 2003; Corbetta & Shulman, 2002, 2011) and includes the right tempero-parietal junction and right ventral frontal cortex. The right VAN has been conceptualised as analogous to a circuit breaker, as it is thought to send interrupting signals to the DANs in order to modulate ongoing selection (Chang et al., 2013). This prominent theory is supported by reports that the tempo-parietal junction (TPJ; Azouvi et al., 2002; Mort et al., 2003; Robbins, 1994; Vallar & Perani, 1986) and underlying white matter, such as the superior longitudinal fasciculus (SLF; Bird et al., 2006; Doricchi & Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005) are among the most commonly affected regions in neglect patients. The consequence of damage to the VAN is thought to be a general reduction in arousal, which therefore results in abnormal VAN-DAN interactions. The theory postulates

that an interhemispheric imbalance between DAN networks results, whereby the left hemisphere becomes hyperactive, whereas the right becomes hypoactive. This pattern of activation results in an extreme inverse of pseudoneglect, whereby a rightward bias of attention results, ultimately manifesting as neglect of left space.

Despite decades of research and the development of novel theories, the exact neural mechanisms contributing to the overt behavioural phenotype of neglect remains unclear. The general lack of consensus is likely due to several factors, including the heterogeneous nature of the syndrome, differences in lesion location and symptomatology between patients, and the possibility that several independent deficits, most likely interacting with each other, may contribute to this complex syndrome (Bartolomeo, 2014). One technique that could further the current understanding of neglect is electroencephalography (EEG). Compared to the abundance of MRI/fMRI studies in neglect, relatively few have harnessed the potential of EEG, with only few qualitative EEG (Colson, Demeurisse, Hublet, & Slachmuylder, 2001; Demeurisse, Hublet, & Paternot, 1998; Watson, Andriola, & Heilman, 1977) and event related potential (ERP) studies (Angelelli, De Luca, & Spinelli, 1996; Deouell, Bentin, & Giard, 1998; Deouell, Bentin, & Soroker, 2000; Di Russo, Aprile, Spitoni, & Spinelli, 2008; Pitzalis, Spinelli, & Zoccolotti, 1997; Saevarsson, Kristjansson, Bach, & Heinrich, 2012; Spinelli, Angelelli, De Luca, & Burr, 1996; Spinelli, Burr, & Morrone, 1994; Vallar, Sandroni, Rusconi, & Barbieri, 1991; Verleger, Heide, Butt, Wascher, & Kompf, 1996; Watson, Miller, & Heilman, 1977). This is in spite of the fact that EEG is a highly advantageous method for examining specific cognitive subsystems (Luck, Woodman, & Vogel, 2000).

Here, we suggest that recent advancements in the perceptual decision-making literature could be leveraged to provide valuable insights into the underlying mechanisms in neglect. Perceptual decision-making encompasses multiple neural processing stages from representing, selecting and accumulating sensory information to preparing and executing actions (Gold & Shadlen, 2007; Sternberg, 1969). A range of novel behavioural/EEG paradigms have recently been developed allowing for distinct neural signals that can be associated with discrete stages of perceptual decision-making (Kelly & O'Connell, 2013; Loughnane et al., 2016; Newman et al., 2016; Newman, Loughnane, Kelly, Connell, & Bellgrove, 2017; O'Connell, Dockree,

& Kelly, 2012). Although spatial attention and perceptual decision-making have not historically been co-examined, it is clear that a breakdown in any stage of the perceptual decision-making process could affect the ability to orient in space, suggesting this approach may contribute significantly to the current understanding of neglect. In recent years, this approach has been successfully harnessed to investigate spatial bias in healthy participants (Loughnane et al., 2016; Newman et al., 2016; Newman et al., 2017; Newman, O'Connell, & Bellgrove, 2013).

Perceptual decision-making paradigms generally involve monitoring continuously presented stimuli for gradual changes in appearance, be it variations in contrast or periods of coherent motion amongst periods of random motion (Britten, Shadlen, Newsome, & Movshon, 1992; Kelly & O'Connell, 2013; Kelly & O'Connell, 2015; Newsome, Britten, & Movshon, 1989; O'Connell et al., 2012; Shadlen, Britten, Newsome, & Movshon, 1996). The continuity of stimulus presentation has important implications for electrophysiological analyses, as it eliminates sensory-evoked deflections in the EEG signal, thereby allowing for the "parallel tracking of freely-evolving sensory evidence, decision variables and motor preparation signals" (Kelly & O'Connell, 2015, p. 32). Two noteworthy neural signals able to be extracted using this approach are the N2 and central parietal positivity (CPP). The N2 is a signal representative of early target selection and spatial attention orienting (Burra & Kerzel, 2013; Eimer & Mazza, 2005; Loughnane et al., 2016; Robitaille & Jolicoeur, 2006). When attention is oriented to the left hemifield, an N2 contralateral component ($N2_{(c)}$) is evident in the right hemisphere and a later N2 ipsilesional component ($N2_{(i)}$) is evident in the left hemisphere (Loughnane et al., 2016). The inverse pattern is observed when attention is oriented to the right hemifield. Loughnane and colleagues (2016) note that the N2 signals share many of the key characteristics of the N2pc component, such as "polarity, topography, latency, contralateral dominance and contingency on task relevance..." (p.498). However, unlike the N2pc which relies on cross-condition subtractions (e.g., target-present versus target-absent trials), the N2 components are able to be measured using a hemispheric-specific method. Given this, the novel N2 signal presents a unique opportunity to investigate differences in spatial orienting ability between hemifields (Kiss, Van Velzen, & Eimer, 2008; Woodman & Luck, 1999), a prospect that is unrivalled in neglect patients. The second intriguing component is the CPP, a signal able to track perceptual evidence accumulation

independent of sensory or motor requirements (Kelly & O'Connell, 2013; O'Connell et al., 2012). The CPP commences soon after target onset, increasing steadily over time as sensory evidence is accumulated, before reaching a fixed threshold at which the perceptual decision is made (O'Connell et al., 2012). Importantly, the CPP demonstrates similar evidence-dependent build-up dynamics regardless of response format (button press versus counting), modality (visual versus audition), or target features (upward or downward motion, pitch changes, intensity changes versus dot-motion detection; Kelly & O'Connell, 2013; O'Connell et al., 2012). This result highlights two key aspects of the CPP: (1) this signal is able to index information processing independent of motor requirements and (2) it is supramodal in nature. Importantly, the dynamics of the N2 and CPP are able to predict the timing and accuracy of subsequent perceptual reports (Kelly & O'Connell, 2013; Loughnane et al., 2016; Newman et al., 2017; O'Connell et al., 2012).

The N2 and CPP, in combination with a novel bilateral dot motion detection paradigm, have recently been leveraged to trace the temporal evolution of spatial biases in the context of investigating individual differences on spatial asymmetries (Newman et al, 2017). Ultimately, the development of a single paradigm that enables distinct neural processes to be measured with temporal specificity (Kelly & O'Connell, 2013; Loughnane et al., 2016; Newman et al., 2017; O'Connell et al., 2012), presents a unique opportunity to further our understanding of the individual neural mechanisms underpinning aberrant spatial attention.

Here, we leveraged the recent advancements in perceptual decision-making paradigms to investigate the underlying neural mechanisms in right hemisphere stroke patients with neglect, focusing particularly on hemispheric-specific attention orienting signals (N2 and sub-components) and evidence accumulation (CPP) processes.

Method

Ethical approval was obtained from the Monash Health and Monash University Human Research Ethics Committee prior to the commencement of the study. The experimental protocol was approved and carried out in accordance with the approved guidelines. All participants were volunteers naive to the experimental hypotheses being tested and each provided written informed consent.

Participants

Neurologically Healthy Participants

Data were collected from 27 neurologically healthy participants aged 57 to 90 years (17 female; *M*=73.29 years, *SD*= 7.11). All participants were right-handed, as determined by a handedness inventory (Nicholls, Thomas, Loetscher, & Grimshaw, 2013), had normal or corrected to normal vision, had no history of neurological or psychiatric disorder, had no head injury resulting in loss of consciousness and were not medicated with steroids, tranquilizers or any other medication that would affect arousal levels. Participants were screened for cognitive impairment using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and all participants received a score > 26 (education adjusted), suggesting there was no presence of significant cognitive impairment. The sample of neurologically healthy participants presented here the same sample of participants presented in Chapter Two.

Stroke Participants

Twenty-three patients with right middle cerebral artery involvement were recruited from sub-acute rehabilitation settings and the community, and enrolled in Stage 1: Spatial Inattention Screening (see Figure 3.1 for stroke participant recruitment and retention). Inclusion criteria included a diagnosis of stroke based on neurological examination and brain imaging, right-handedness, proficiency in English, and sufficient cognitive function to complete the study. Exclusion criteria included epilepsy, seizures, and personal history of unexplained fainting or sensitivity to flickering light, significant head injuries, and any history of psychiatric or neurological illness. Participants were contacted post-discharge and invited to participate in Stage 2: Assessment of Perceptual Decision-making. Of the original 23 participants, fourteen were excluded from Stage 2; five participants declined to participate; six were unable to comprehend task instructions; one participant developed post-stroke epilepsy; one participant's stroke classification was re-classified to right posterior cerebral artery with hemianopia; and one participant was unable to be tested using EEG (see Supplemental Materials Table S3.1, Table S3.2 and Table S3.3 for excluded participant's demographics, imaging summaries and screening results, respectively). Therefore, nine participants attempted Stage 2:

Assessment of Perceptual Decision-making. Of these nine, two participants completed the task using portable EEG in their homes. Of note, there was no eye tracking available to ensure task compliance in this testing environment. Further, abnormal drift was established within the EEG signal and subsequently these participants were removed from further analyses. The final sample of participants (N=7) were aged 58-71 years at time of screening (M = 64.14 years, SD = 4.49). Participant characteristics and demographics were collected from medical records (see Table 3.1). In addition, stroke specific information including the National Institute of Health Stroke Scale (NIHSS; Brott et al., 1989) and the Functional Independence Measure (FIM; Keith, Granger, Hamilton, & Sherwin, 1987) were obtained where possible. The NIHSS is a systematic assessment tool that provides a quantitative measure stroke-related neurological deficit (0 = no measurable deficit, 1-4 = minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-42 = severe stroke; Brott et al., 1989). The FIM (Keith et al., 1987) is an 18-item scale used to measure patient disability, with lower scores representing higher levels of disability (see Supplemental Materials for scale specifics). Imaging reports were used to confirm the presence of right middle cerebral artery involvement as documented in participant medical records (see Table 3.2). CT and MRI scans were reviewed by authors M.O and T.C. (a consultant neurologist), who delineated lesions and mapped each onto a lesion map using MRIcron (see Figure 3.2; Rorden, Karnath, & Bonilha, 2007b). Visual field assessments were not conducted as part of this study but any visual field deficits documented by medical teams during rehabilitation admissions were noted. None of the nine participants included in Stage 2 had medical records indicating a visual field deficit. Participant medication varied at the time of testing, but included hypolidaemic agents, anti-hypertensives, anti-coagulants/anti-thrombotic, and beta-adrenergic blocking agents.

Materials

Stage 1: Spatial Inattention Screening

As part of Stage 1: Spatial Inattention Screening, stroke participants completed four spatial attention screening tasks to assess perceptual neglect. The Greyscales task (Nicholls et al., 1999), Landmark task (Bellgrove et al., 2005; Fink et al., 2000; Marshall & Halligan, 1995), Bells cancellation (Gauthier, Dehaut, &

Joanette, 1989) and a computerised extinction task (Bender, 1952) were administered. Further information regarding the screening measures can be found in the Supplemental Materials. The results of the spatial inattention screening for the final sample revealed three participants (AA, CC, DD) who demonstrated neglect symptomatology on at least two spatial attention tasks, two participants who had neglect on one task (EE, JJ) and two participants who did not present with neglect (FF, KK; see Table 3.3 for results summary).

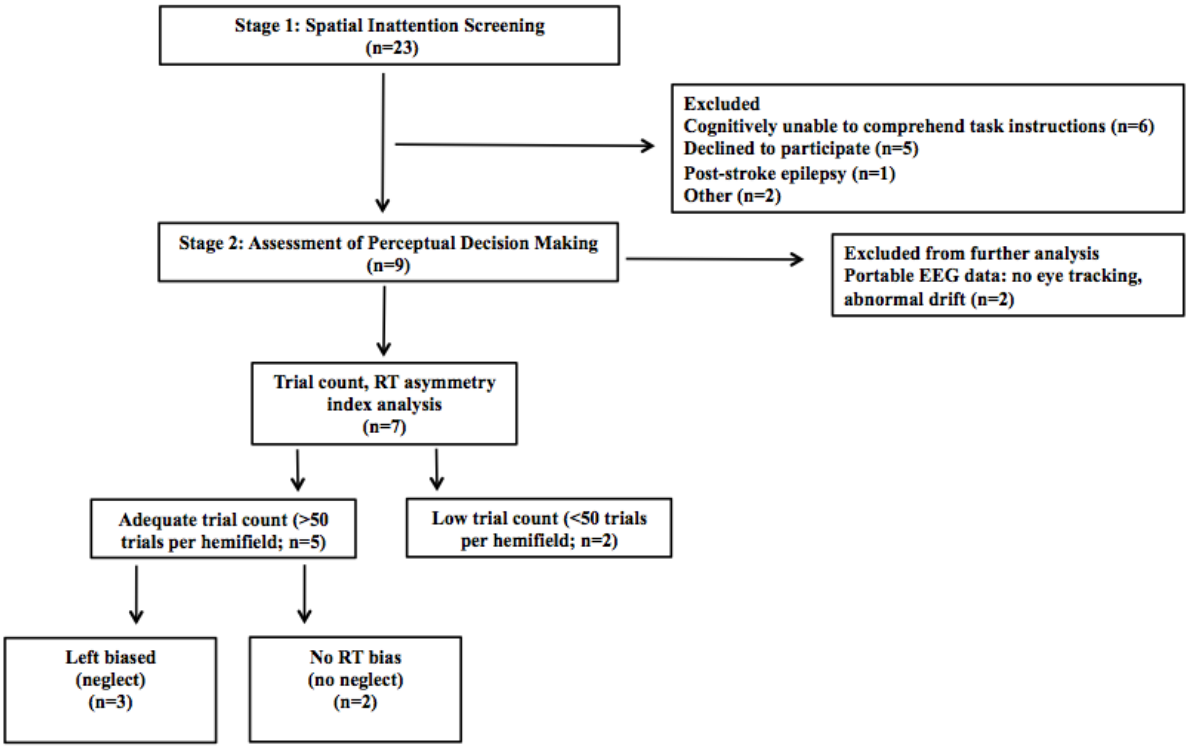

Figure 3.1. Consort flow chart for stroke participants screening, retention and classification**.**

Table 3.1. Stroke participant demographics and stroke specific data

Participant	Sex	Age at screening	Years of Education	Stroke Type	NIHSS on admission	Oxford classification	FIM admission	FIM discharge	Left spatial inattention noted in medical records	Time since stroke at Stage 1	Time since stroke at Stage 2
AA	M	69	3	R) MCA	13– moderate	PACI	69	110	Yes	3wks	3mnths
CC	F	63	15	R) MCA	22 - severe	LACI	75	118	Not noted	3wks	2.5mnths
DD	F	63	15	R) MCA/ACA	6 - moderate	PACI	-	-	Yes	1yr, 7mnths	1yr, 8mnths
EE	M	61	9	Bilateral MCA	4 - minor	PACI	62	-	Yes	3wks	6mnths
FF	M	71	10	R) MCA	3 - minor	PACI	70	108	Yes	1yr, 6mnths	2yr, 6mnths
JJ	M	64	12	R) MCA	2 - minor	PACI	66	110	Yes	1yr, 10mnths	2yr, 2mnths
KK	F	58	10	R) MCA	-	PACI	-	-	Not noted	7yr 7mnths	7yr, 7mnths

Note: R) MCA denotes right hemisphere middle cerebral artery involvement; R) ACA denotes right anterior cerebral artery damage; NHISS= National Institute of Health Stroke Scale; FIM=Functional Independence Measure, wks = weeks; mnths = months; yr = year.

Table 3.2. Imaging summaries for stroke participants in enrolled in Stage 2: Behavioural/EEG protocol.

Participant	Imaging findings
AA	**CT -** revealed infarction involving the right lentiform nucleus, external capsule and caudate nucleus measuring approximately 2.5 x 4.1 x 3.9 (lateral lenticulostriate distribution).
CC	**CT -** There is loss of grey-white matter differentiation in the right frontal lobe. Right insular ribbon sign. Hyperdense right MCA noted in the Sylvian fissure. Thrombus is noted within the distal right M1 with poor opacification of the subcortical MCA. **MRI** - There is an area of encephalomalacia and gliosis involving the right MCA territory, including the frontoparietal junction and the insular cortex.
DD	**CT –** revealed cerebral infarction within the medial and lateral aspects of the right frontal lobe, the posterior right temporal lobe and the right parietal lobe superiorly. Small bilateral cerebral hemisphere infarcts are also demonstrated. **MRI -** evidence of an old right anterior cerebral artery infarct, which has undergone previous haemorrhagic transformation, involving the parasagittal frontal lobe. There is also evidence of an old right occipito-parietal infarct, which demonstrated minor haemorrhagic transformation. An old right frontal infarct is also present in the middle cerebral artery territory. A small focus on subependymal diffusion restriction is present in the singular gyrus medial to the body of the right lateral ventricle. There is evidence of small bilateral cerebellar infarcts.
EE	**CT -** There is loss of grey-white matter differentiation in the bilateral frontal and left temporal lobes, consistent with acute bilateral MCA territory infarction. No acute intra- or extra-axial haemorrhage, mass lesion or collection.
FF	**CT -** Extensive area of encephalomalacia involving the right parieto-occipital lobe consistent with an area of chronic infarction. Further focal area of encephalomalacia involving the right corona radiata consistent with a further of chronic infarction. No intra-axial or extra-axial haemorrhage.
JJ	**CT** - Loss of grey-white matter differentiation is present in the right frontal lobe. Increased attenuation is present along the inferior to branch within the sylvian fissure, however no associated grey-white matter abnormality is identified in this vascular territory. Increased MTT with associated decreased CBF is present in a large region of the right MCA territory with associated reduced CBV in the right frontal lobe correlating to the area of grey-white matter abnormality, and further volume reduction in the territory associated with the dense M2 segment seen on unenhanced imaging. Previous right PCA territory infarct is unchanged from previous imaging.
KK	**CT** - Low density changes involving the right insula, frontal and parietal regions are evident, suggestive of a very early right MCA infarct. Decreased blood volume is noted in the right frontotemporal region associated with an increased mean transit time in the same region confirming a right MCA territory infarct. A filling defect is noted in the distal M1 and M2 segment of the right MCA associated with poor enhancement of the right cortical vessels, suggestive of a thrombus +/- embolus in the M1 segment. **Follow-up CT** - Extensive infarction is demonstrated in a right middle cerebral artery territory mostly bearing any underlying basil ganglia. MRA images show some evidence of flow within right middle cerebral artery branches but the signal remains reduced in the right M1 segment consistent with incomplete recanalisation following right middle cerebral artery embolus. **MRI** - Old left cerebellar hemisphere and large right MCA territory infarcts. Associated ex vacuo dilatation of the right lateral ventricle. Hypoplastic A1 segment of left ACA noted. No major intracranial vessels occlusion or significant stenosis. Cervical vertebral and carotid arteries are patent, with no evidence of dissection.

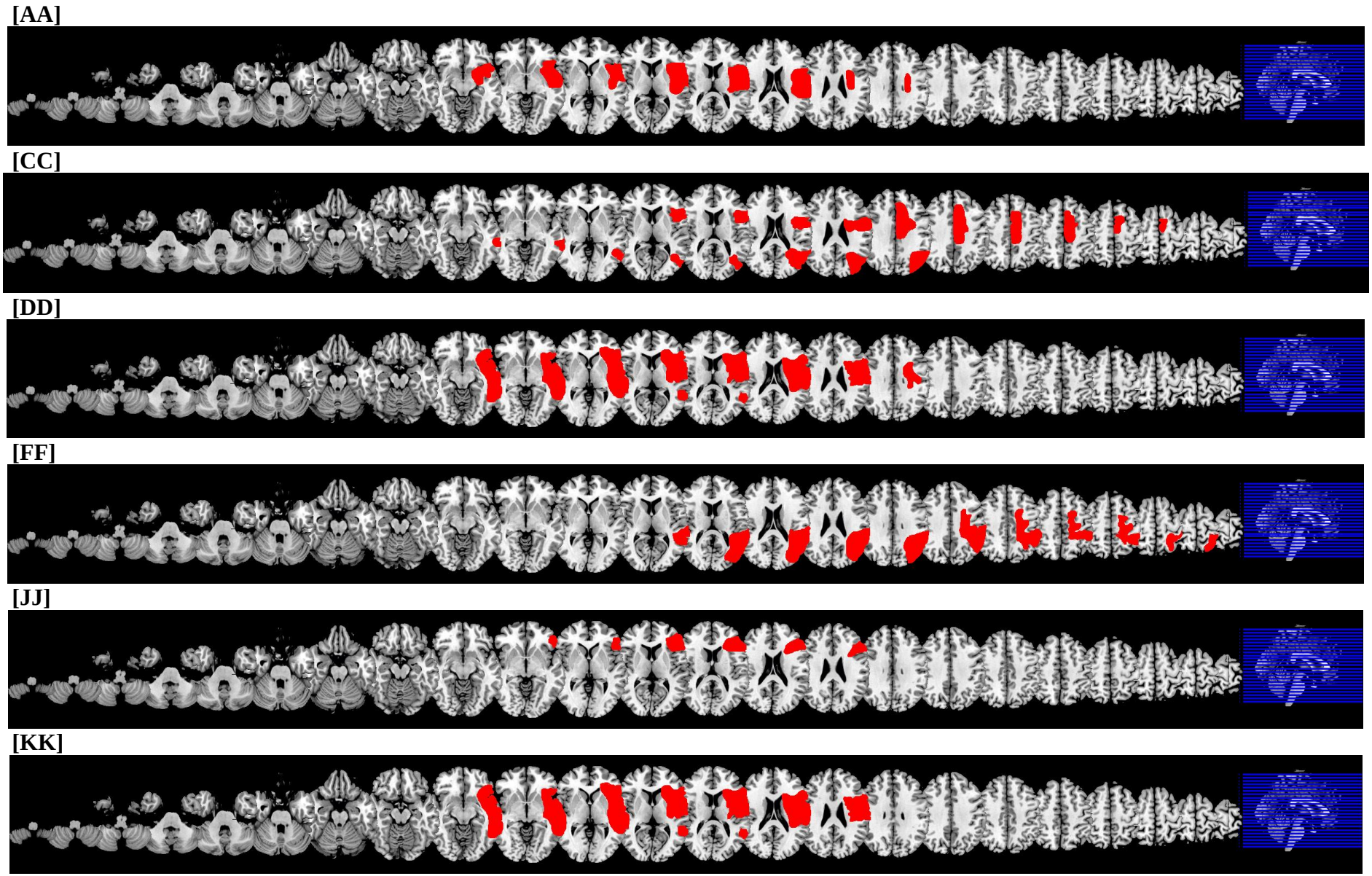

Figure 3.2. Participant's lesion maps. CT and MRI scans were reviewed by M.O. and T.C (consultant neurologist), who delineated lesion boundaries. Note there is no lesion map for EE as lesions could not be delineated of CT with precision. Lesion regions were then mapped using MRIcron (C Rorden et al., 2007b) ch2bet.nii template and multislice views were created using axial slices, z= 14,20,26,32,38,44,50,56,62,68,74,80,86,92,98,104,110,116,122,128,134,140,146. All lesions have been flipped to the right hemisphere. Sagittal slices for visualization are provided on the far right.

*Table **3.**3.* Results from spatial inattention screening tasks in stroke participants.

Participant	Greyscales		Landmark		Bells Cancellation		Extinction				
	Number correct	Left selected	Spatial index	Spatial bias	Targets found (/35)	CoC Index	Total correct (/36)	Left correct (/8)	Right correct (/8)	Bilateral correct (/16)	Nil target correct (/4)
AA	34 (47.2%)	**4 (5.6%)**	**1**	**Right**	29	-0.008	35	8	8	15	4
CC	36 (50.0%)	**0 (0.0%)**	**0.2**	**Right**	17	**0.314**	36	8	8	16	4
DD	33 (45.8%)	**7 (9.7%)**	**0.6**	**Right**	31	-0.040	36	8	8	16	4
EE	44 (61.1%)	28 (38.9%)	**0.6**	**Right**	32	0.027	36	8	8	16	4
FF	36 (50%)	24 (33.3%)	-0.4	Left	35	0.00	35	8	8	15	4
JJ	37 (51.4%)	**1 (1.4%)**	-0.2	Left	29	0.021	**13**	**1**	**8**	**0**	**4**
KK	60 (83.3%)	46 (63.9%)	-0.2	Left	28	0.021	36	8	8	16	4

Note: Results bolded indicate results indicative of left spatial inattention.

Stage 2: Assessment of Perceptual Decision-making

Neurologically healthy participants (*N*=27) and stroke participants meeting inclusion criteria (*N*=7) completed a bilateral variant of the random dot motion task (Britten et al., 1992; Loughnane et al., 2016; Newsome et al., 1989; Shadlen et al., 1996). The use of a bilateral measure allowed for subtle spatial asymmetries to be investigated. Participants were seated in a dimly lit sound-attenuated room, supported by a chin rest, at a viewing distance of 57 cm. The paradigm was run on a 32-bit windows XP machine using MATLAB (MathWorks) and the Psychophysics Toolbox extensions (Brainard, 1997; Cornelissen, Peters, & Palmer, 2002; Pelli, 1997) and stimuli were displayed on a 21-inch CRT monitor (85Hz, 1024 x 768 resolution). Before beginning the task, participants read on-screen instructions and an experimenter subsequently explained the task verbally to ensure adequate comprehension. Participants were required to fixate centrally and were discouraged from blinking or moving during each trial. Eye tracking was used to ensure fixation. If a fixation break occurred during a trial (either a blink or a gaze deviation >4° left or right of centre, detected via EyeLink1000, SR Research Ltd), the task halted (stationary dots), and text (dark grey, RGB: 109) appeared at fixation for 200ms reminding participants to "keep [their] eye on the spot". Once fixation returned to the central fixation dot, the trial restarted. Participants monitored two peripheral circular patches (one in each of the lower quadrants) of 150 moving dots. Participants were required to identify targets, defined by a seamless transition from random motion to coherent motion in an upward or downward direction (see Figure 3.3). Once a target was detected, participants made a speeded button press with their right index finger (dominant hand). The responding hand was kept constant across trials. Stroke participants completed between 5 and 20 blocks of the task, with each block consisting of 24 trials (resulting in a total of between 120 and 480 trials per participant). The discrepancy in block numbers between stroke participants was due to participant fatigue and competing medical needs. There was a large difference in patient's ability to attend and therefore each participant completed a different number of blocks. Neurologically healthy participants completed 8-9 blocks, with each block consisting of 24 trials (total trial no. = 192-216 trials). The number of blocks completed varied based on participant fatigue. A short break (15-60 seconds)

interleaved each block of trials. Each trial consisted of a period of random motion (initiated on fixation and lasting 1800ms, 2800ms or 3800ms) followed by a coherent motion target (90% of the dots moved coherently), which ceased following a response or after 3000ms. Targets (coherent motion) only appeared in one of the two patches on any given trial. The 12 possible trial types (each a combination of one of the 3 periods of random motion, 2 target locations, and 2 coherent motion directions) occurred in a pseudorandom order with the constraint that each different trial type arose twice every 24 trials. The parameters used in this version of the paradigm can be found in the Supplemental Materials.

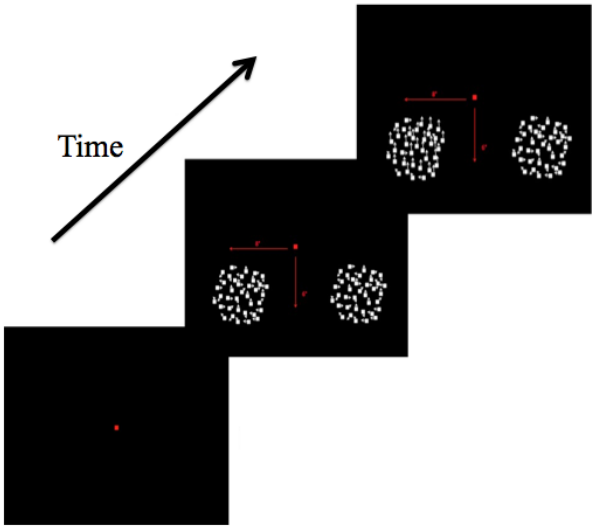

Figure 3.3. Schematic of a single trial. The screen remained blank (apart from the fixation dot) until the trial was manually started by the examiner, at which point two peripheral patches of randomly moving dots appeared. Participants monitored these patches for instances of coherent motions (either upward or downward). Participants responded to motion targets via a speeded button press. Coherent motion only occurred in one of the two patches per trial. The pre-target random motion lasted either 1800ms, 2800ms or 3800ms, chosen pseudorandomly on a trial-by-trial basis.

Analysis

EEG Acquisition and Preprocessing

EEG was simultaneously acquired from 64 scalp electrodes using a Brain Products BrainAmp DC system digitized at 500Hz. All data were processed using a combination of custom scripts and EEGLAB[64] (Delorme & Makeig, 2004) routines

implemented in MATLAB (MathWorks). A 35Hz low-pass filter was applied offline using 4th order Butterworth filters, noisy channels were interpolated (spherical spline) and the data were re-referenced to the average reference. All signals were subjected to a current source density transformation using the CSD Toolbox for Matlab (Kayser & Tenke, 2006). Epochs were then extracted from the continuous data from -1000ms to 1880ms around target onset, and baselined with respect to -100ms to 0ms before target onset.

Data exclusion

Trials were excluded from analysis if: (a) RTs were < 150ms (pre-emptive responses) or >1800ms (responses after coherent motion offset); (b) RTs were beyond 3 sd from the mean (measured across trials for each individual participant); (c) EEG from any channel exceeded +/- 100μV during the interval from -100ms before target onset to 100ms after RT for the ERP analysis; and (d) if central fixation was broken by blinking or eye movement >4° from centre, during the interval between 100ms before target onset and 100ms after response for the ERP analysis.

EEG Data Extraction

The $N2_{(c)}$ and $N2_{(i)}$ components were measured contralaterally and ipsilaterally to the target location, respectively, at electrodes P7 and P8 (Loughnane et al., 2016), whereas the CPP was measured at peak electrodes CPz (Kelly & O'Connell, 2013; Loughnane et al., 2016; O'Connell, Dockree, & Kelly, 2012). The $N2_{(c)}$, $N2_{(i)}$ and CPP signals were aggregated to average waveforms as a function of target hemifield for each participant, as per Newman et al. (2017). N2-latency was identified as the time-point with the most negative amplitude value in the stimulus-locked waveform between 150-400ms for the $N2_{(c)}$ and $N2_{(i)}$, whereas N2-amplitude was measured as the mean amplitude inside a 100ms window centred on the stimulus-locked grand average peak ($N2_{(c)}$: 266ms; $N2_{(i)}$: 340ms; Loughnane et al., 2016). CPP build-up rate was defined as the slope of a straight line fitted to the response-locked waveform (Kelly & O'Connell, 2013; Loughnane et al., 2016; O'Connell et al., 2012) with the time window defined individually for each participant as the 100ms prior to the maximum CPP amplitude pre-response. Onset latency of the CPP was measured by performing running sample-point-by-sample-point t-tests against zero across each

participant's stimulus-locked CPP waveforms. CPP-onset was defined as the first point at which the amplitude reached significance at the 0.05 level for 25 or more consecutive points (Foxe & Simpson, 2002; Kelly, Gomez-Ramirez, & Foxe, 2008; Loughnane et al., 2016).

Inferential Analysis

Inferential statistics were calculated using a combination of custom Matlab scripts. First, valid trials counts were calculated for both healthy and stroke participants. Participants were then categorised as having either adequate trials counts (>90 trials per hemifield) or poor trial counts (<90 trials per hemifield). Next, the percentage of correct valid trials ("hits") for left and right trials were calculated for all participants and compared using a chi-square statistic, and RT asymmetry index to assess spatial bias for each participant. The RT asymmetry (Newman et al., 2017; Thut, Nietzel, Brandt, & Pascual-Leone, 2006) was derived from RT (ms) using the following formula:

$$\text{RT asymmetry index} = \frac{\text{(left target RT)} - \text{(right target RT)}}{\text{(mean left and right target RT)}}$$

This index gives positive values when RTs are faster for right, relative to the left, targets (rightward spatial bias) and negative values when the opposite is true (leftward bias). If no asymmetry exists in the RT then the index gives a zero value. A one-sample t-test was then used to establish if there was a statistical difference between RT-asymmetry and zero.

Based on the above analyses, stroke participants were categorised into one of three groups: good trial counts and RT asymmetry (left neglect; AA, CC, DD); poor trial counts with a trend for left spatial inattention (FF, JJ); and good trial counts and no RT asymmetry (no neglect; EE, KK). Neurologically healthy participants comprised a fourth group.

For those participants with adequate trial counts: neurologically healthy participants, good trials counts with neglect and good trial counts without neglect, a series of linear mixed effects-models were then fit to single trial data to investigate the predictive value of each factor ($N2_{(c)}$, $N2_{(i)}$, CPP slope) on the dependent variable

(RT). The linear mixed models were run with participant as a random intercept, for left and right hemifield targets separately.

Results

Neurologically Healthy Participants

Behavioural Results

Calculation of trial counts indicated that all neurologically healthy participants had adequate trial counts for RT analyses, with at least 90 valid trials per hemifield (see Supplemental Materials Table S3.4). Further, there was no significant difference in the hit-rate analyses, suggesting that the accuracy of these participants was equivalent across left and right targets (see Supplemental Materials Table S3.4). RT asymmetries were individually calculated (see Supplemental Materials Table S3.5) and although there was some individual variability in spatial bias, a one-sample t-test determined that RT-asymmetry within the neurologically healthy group was not significantly differently from zero (i.e., there was no significant bias) (p=. 18). This suggested that neurologically healthy participants had comparable RTs for left and right targets, with no significant bias evident.

EEG Results

$N2_{(c)}$

Visual analyses of the waveforms revealed largely comparable right and left hemisphere $N2_{(c)}$ (see Figure 3.4). The linear mixed models on single trial data included a fixed effect of $N2_{(c)}$ on RT and random intercepts for participants. For left hemifield targets, the significant fixed effect showed that greater right hemisphere $N2_{(c)}$ amplitude was related to faster RTs in the left hemifield, b = 0.70 (95% CI = 0.44 to 0.96), $t(1849) = 5.21$, $p < .001$. In contrast, the fixed effect of left hemisphere $N2_{(c)}$ amplitude on right hemifield RT was not significant, b = 0.27 (95% CI = -.004 to 0.53), $t(1841) = 1.93$, $p = .054$, although there was a trend in such a direction.

N2(i)

Visual analyses of the waveforms revealed an $N2_{(i)}$ that was reduced in amplitude compared to the $N2_{(c)}$, but comparable for left and right hemifield targets (see Figure 3.4). The linear mixed models on single trial data included a fixed effect of $N2_{(i)}$ on RT and random intercepts for participants. For left hemifield targets, the fixed effect of left hemisphere $N2_{(i)}$ amplitude on RT was not significant, b = -.007 (95% CI = -.25 to 0.25), $t(1849) = -0.053$, p = .0.96. Similarly, the fixed effect of right hemisphere $N2_{(i)}$ amplitude on right hemifield RTs was not significant, b = 0.21 (95% CI = -.083 to .51), $t(1841) = 1.41$, p = .16.

CPP slope

Visual analyses of the waveforms revealed comparable CPP onset and slope between left and right hemifield targets (see Figure 3.5). The linear mixed model on single trial data included a fixed effect of CPP slope on RT and random intercepts for participants. For left hemifield targets, the significant fixed effect showed that greater CPP slope was related to faster RTs in the left hemifield, b = -101.28 (95% CI = -143.07 to -59.50), $t(1849) = -4.75$, $p < .001$. For right hemifield targets, the significant fixed effect showed that greater CPP slope was related to faster RTs in the right hemifield b = -143.36 (95% CI = -186.02 to -100.70), $t(1841) = -6.59$, $p < .001$.

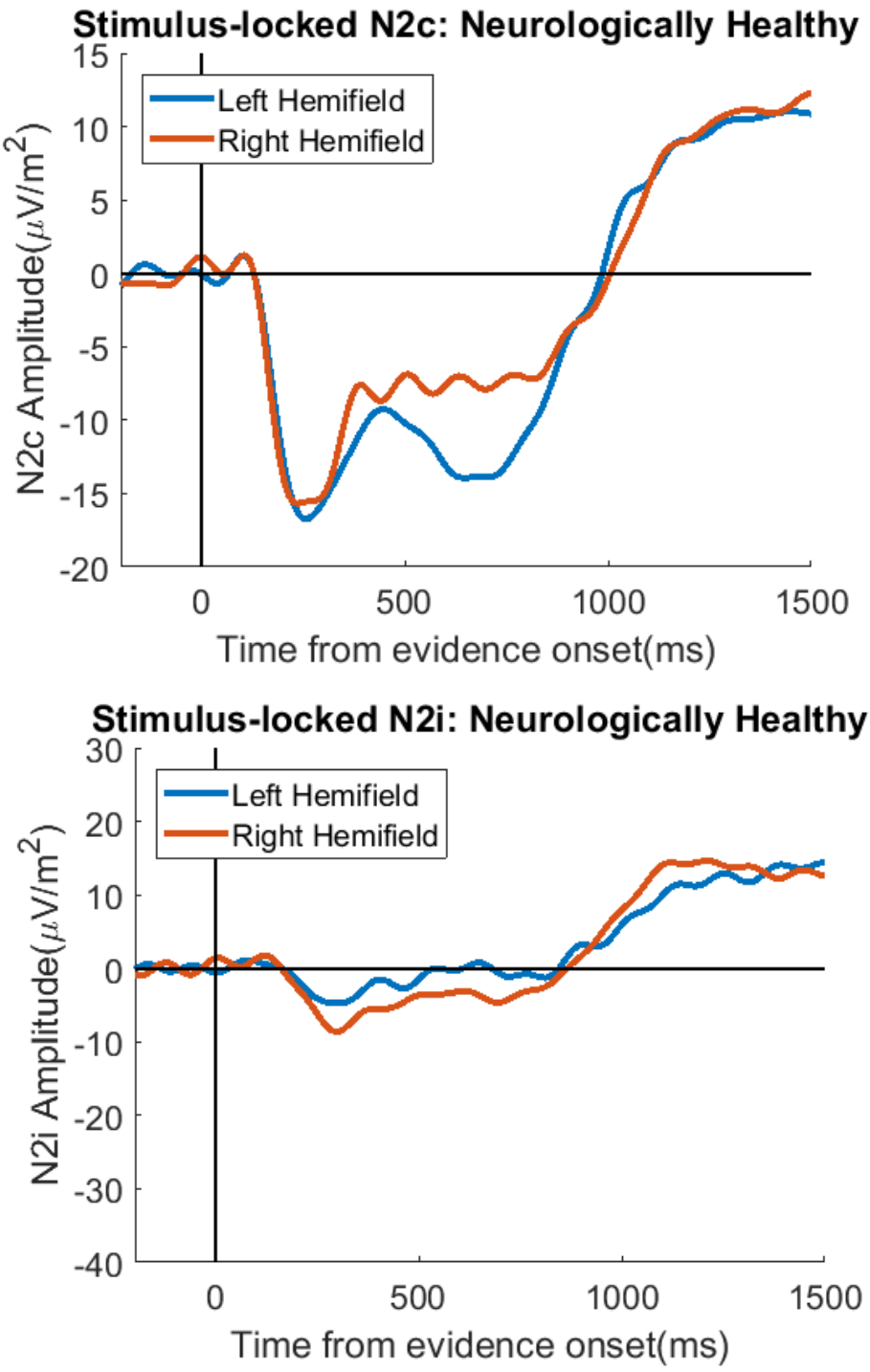

Figure 3.4. $N2_{(c)}$ and $N2_{(i)}$ waveforms for left hemifield targets and right hemifield targets in neurologically healthy participants. Visual analyses of the waveforms revealed largely comparable right and left hemisphere $N2_{(c)}$. The $N2_{(i)}$ was reduced in amplitude compared to the $N2_{(c)}$, but comparable for left and right hemifield targets.

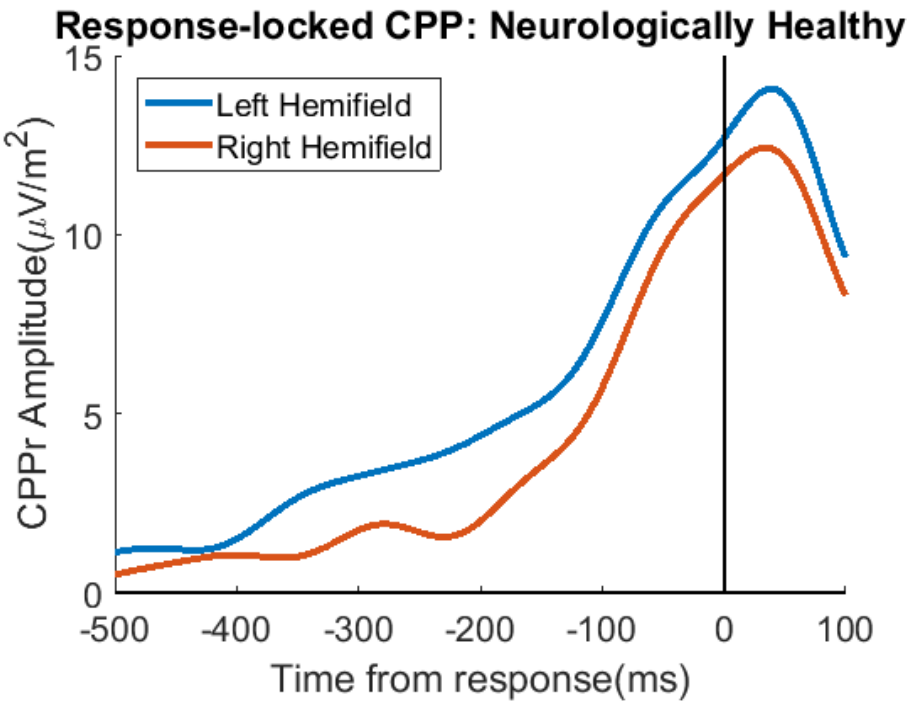

Figure 3.5. CPP waveforms for left hemifield targets and right hemifield targets in neurologically healthy participants. Visual analyses of the waveforms revealed comparable CPP onset and slope between left and right hemifield targets.

Stroke Participants

Behavioural Results

Calculation of trial counts indicated that five participants (AA, CC, DD, EE, and KK) had trial counts appropriate for RT analyses, with at least 90 valid trials per hemifield (see Table 3.4 and Figure 3.6). In contrast, FF and JJ had inadequate trial counts, with trial counts ranging from 5 to 45 per hemifield (see Table 3.4 and Figure 3.7). This low trial count suggests that these two participants found the task more difficult and had a more severe form of neglect. RT asymmetries for the high trial count participants, indicated that three participants (AA, CC and DD) had significantly slower RTs for left targets compared to right targets ($p<.05$; see Table 3.5), while two participants (EE and KK) did not demonstrate a significant RT asymmetry. For participants with a low trial count, one had significantly faster RTs for left targets (FF; $p=.001$) while for the other (JJ), there was a trend of faster RTs for left targets although this wasn't statistically significant ($p=0.058$; see Table 3.5).

Based on the above, neglect participants were separated into three groups for further analyses: (1) neglect; (2) severe neglect; and (3) no neglect.

*Table **3.4**.* Valid trial numbers, percentage of correct trials for left and right trials and hit-rate analysis (chi-square comparison) for stroke participants.

Participant	Total Valid Trials	Valid Left Trials	% of left trials correct	Valid Right Trials	% of right trials correct	Chi-square *p* value
AA	256	112	100%	144	100%	$p=1$
CC	219	108	98.87%	111	99.44%	$p=0.96$
DD	281	133	99.39%	148	99.42%	$p=0.99$
EE	255	125	100%	130	100%	$p=1$
FF	63	18	54.35%	45	98.19%	$p=0.058$
JJ	33	5	42.86%	28	95.24%	$p=0.048$
KK	260	126	100%	134	100%	$p=1$

*Table **3.5***. RT asymmetry index for stroke participants and within sample t-tests comparing left and right hemifield RTs.

Participant	RT asymmetry	Bias	Within sample p value
AA	0.11	Right biased	$p<0.001$
CC	0.15	Right biased	$p<0.001$
DD	0.08	Right biased	$p=0.003$
EE	0.05	Right biased	$p=0.075$
FF	0.43	Right biased	$p=0.001$
JJ	0.19	No significant bias	$p=0.717$
KK	-0.02	No significant bias	$p=0.287$

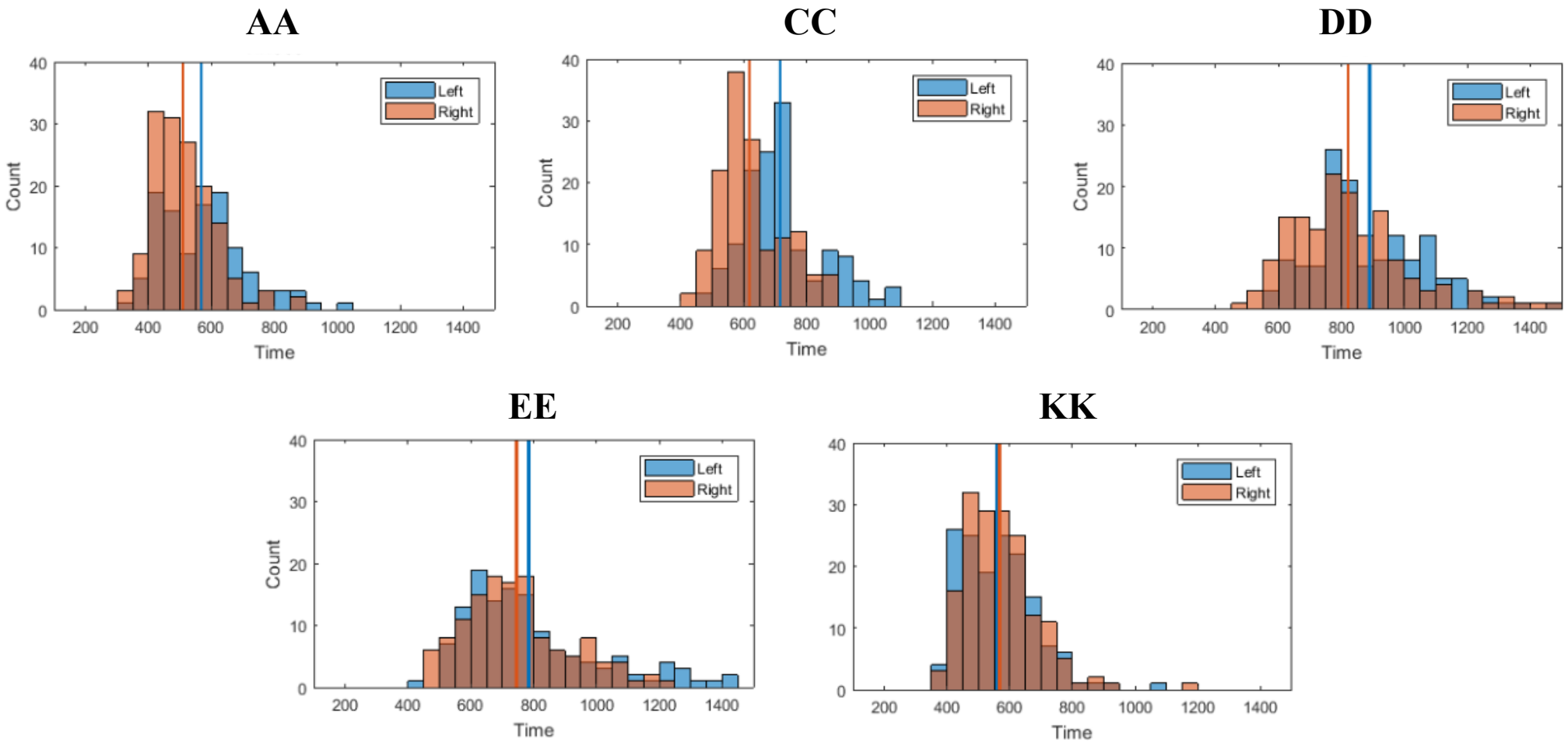

Figure 3.6. Behavioural RTs and associated RTs for left and right hemifield target in participants with high trial counts. Blue histogram bars represent left hemifield targets, whereas orange histogram bars represent right hemifield targets. Vertical lines represent mean RTs for left hemifield targets (blue) and right hemifield targets (orange). Five participants were categorised as having good trial counts (> 50 trials per hemifield). AA = 112 left, 114 right; CC = 109 left, 111 right; DD = 113 left, 148 right; EE = 125 left, 130 right; KK = 126 left, 124 right.

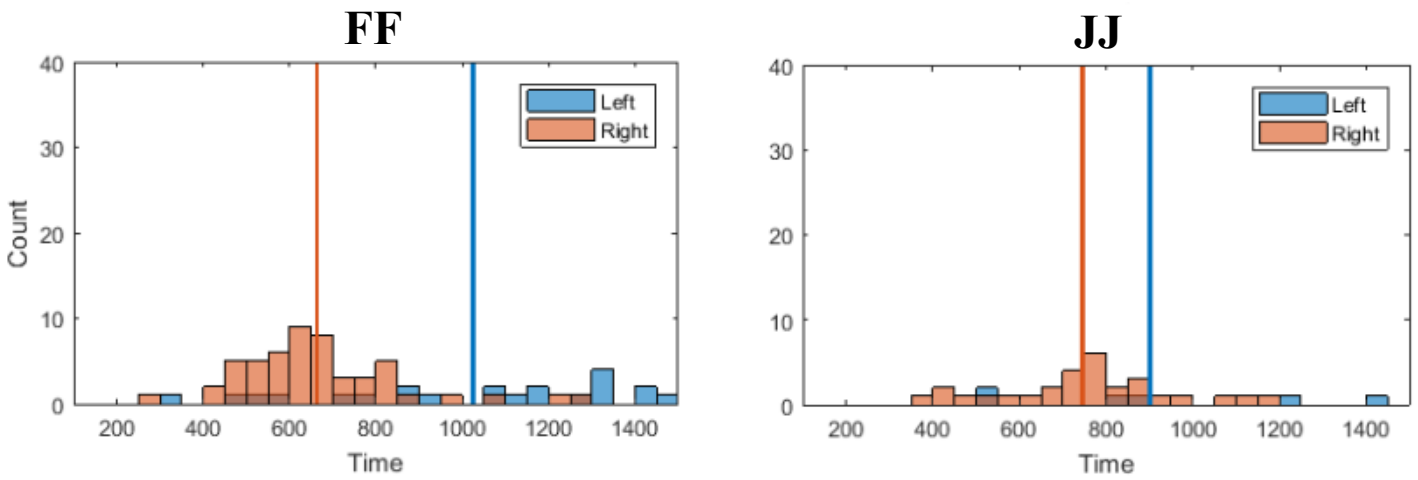

Figure 3.7. Behavioural RTs and associated RTs for left and right hemifield targets in participants severe neglect. Blue histogram bars represent left hemifield targets, whereas orange histogram bars represent right hemifield targets. Vertical lines represent mean RT for left hemifield targets (blue) and right hemifield targets (orange). FF and JJ were categorised as having poor trial counts, with trial numbers <50 per hemifield. FF = 18 left, 45 right; KK= 5 left, 28 right.

EEG Results

Neglect Participants

$N2_{(c)}$

Visual inspection of the waveforms revealed a strong left hemisphere $N2_{(c)}$ for right hemifield targets but a reduced right hemisphere $N2_{(c)}$ for left hemifield targets in participants with good trial counts and neglect (AA, CC, DD; see Figure 3.8). The linear mixed models on single trial data included a fixed effect of $N2_{(c)}$ on RT and random intercepts for participants. The fixed effect of right hemisphere $N2_{(c)}$ amplitude on left hemifield RTs was not significant, b = 0.28 (95% CI = -.43 to 1.00), $t(276)$ = .78, p =.43. For right hemifield targets, the significant fixed effect of $N2_{(c)}$ amplitude on RT showed that greater left hemisphere $N2_{(c)}$ amplitude was related to faster RTs in the right hemifield, b = 1.13 (95% CI = 0.44 to 1.82), $t(285)$ = 3.23, p = .001.

$N2_{(i)}$

Visual inspection of the waveforms revealed a pronounced $N2_{(i)}$ in the left hemisphere for left hemifield targets (see Figure 3.8). This pattern was not evident in the right hemisphere $N2_{(i)}$ for right hemifield targets. The linear mixed models on single trial data included a fixed effect of $N2_{(i)}$ on RT and random intercepts for participants. For left hemifield targets, the fixed effect was significant, such that greater left hemisphere $N2_{(i)}$ was related to faster RTs, b = 1.36 (95% CI = .59 to 2.12), $t(276)$ = 3.51, p <.001. For right hemifield targets, the fixed effect of right hemisphere $N2_{(i)}$ amplitude on right hemifield RT was not significant, b = -.088 (95% CI = -.75 to .57), $t(285)$ = -.26, p = .79.

CPP

Visual inspection of the waveforms for revealed largely similar CPP slopes in left and right hemifields (see Figure 3.9). Linear mixed models on single trial data for a fixed effect of CPP and random intercepts for participants revealed that greater CPP slope was related to RTs for both hemifields. For left hemifield targets, b = -233.64 (95% CI = -347.06 to -120.22), $t(276)$ = -4.05, p < .001. For right hemifield targets, b = -132.32 (95% CI = -222.54 to -42.09), $t(285)$ = -2.88, p = .004.

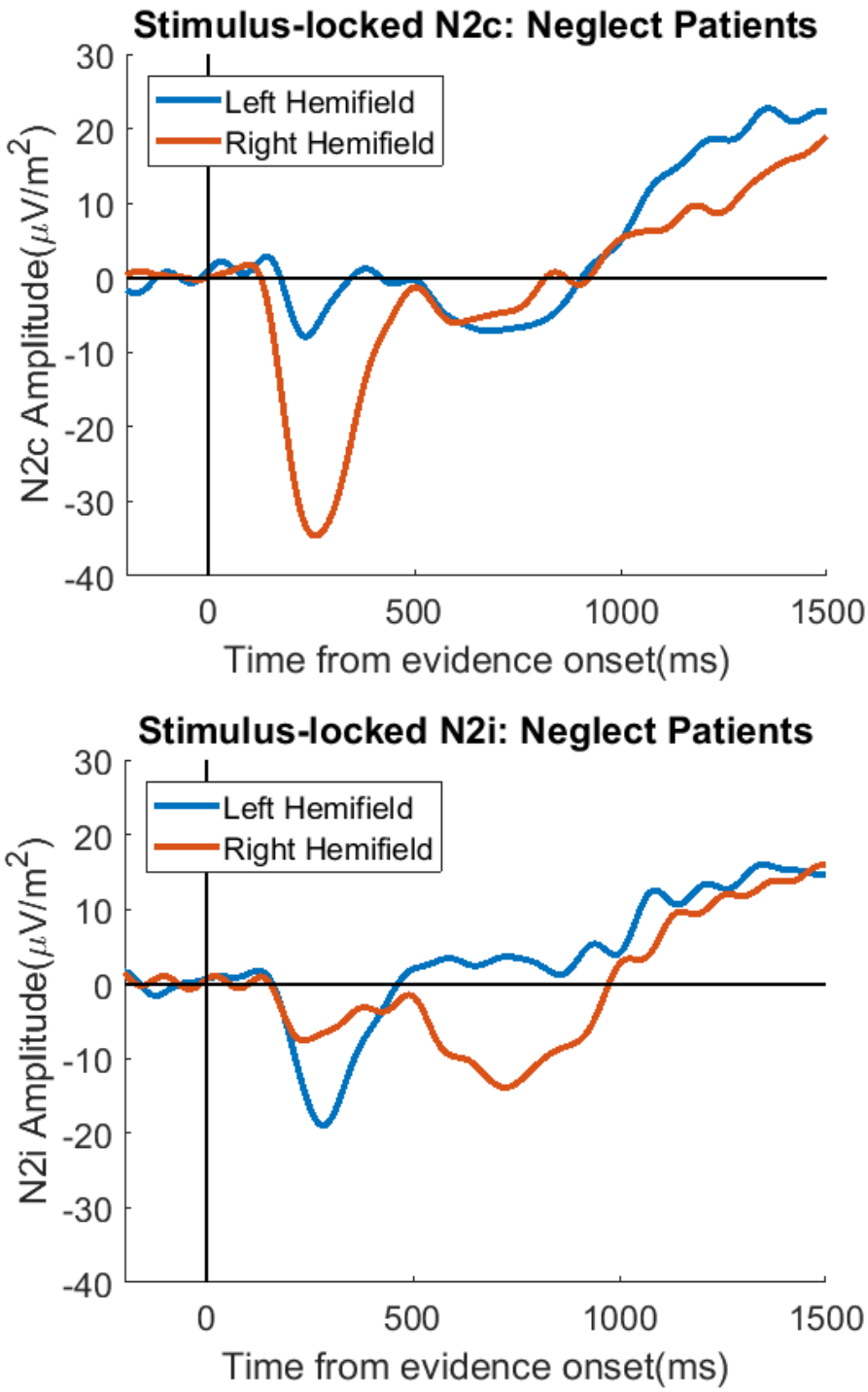

Figure 3.8. $N2_{(c)/(i)}$ waveforms for left and right hemifield targets in three participants with good trial counts and RT asymmetry indicating neglect. A strong left hemisphere $N2_{(c)}$ was evident for right hemifield targets but there was a reduced right hemisphere $N2_{(c)}$ for left hemifield targets. With respect to the $N2_{(i)}$, a pronounced left hemisphere $N2_{(i)}$ was evident for left but not right hemifield targets.

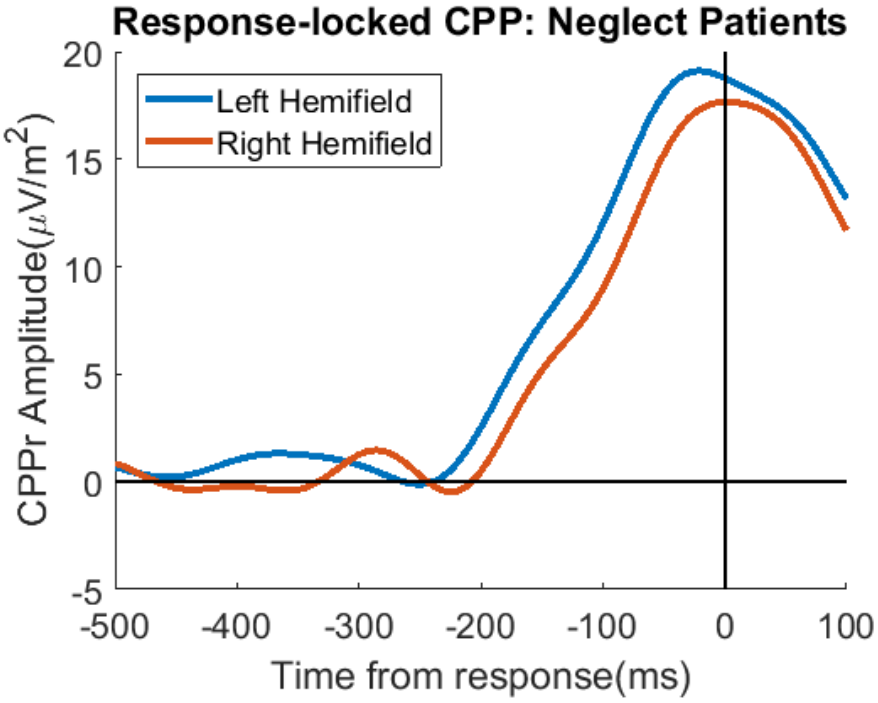

Figure 3.9. CPP waveforms for left hemifield targets and right hemifield targets in three participants with good trial counts and RT asymmetry indicating neglect. CPP slope was largely comparable for both left and right hemifield targets and greater CPP slope was related to faster RTs in both hemifields.

Severe Neglect Participants

Visual inspection of the waveforms revealed a similar pattern of dysfunction in the $N2_{(c)}$ observed in severe neglect participants (FF, JJ). There was a reduced right hemisphere $N2_{(c)}$ for left hemifield targets but an intact left hemisphere $N2_{(c)}$ for right hemifield targets (see Figure 3.10). However, unlike those participants with good trial counts, there was no evidence of a pronounced left hemisphere $N2_{(i)}$ for left hemifield targets (see Figure 3.10). The $N2_{(i)}$ for both left and right hemifield were comparable. With respect to the CPP, there was a significant reduction in the CPP for left targets with almost no discernable CPP evidence (see Figure 3.11).

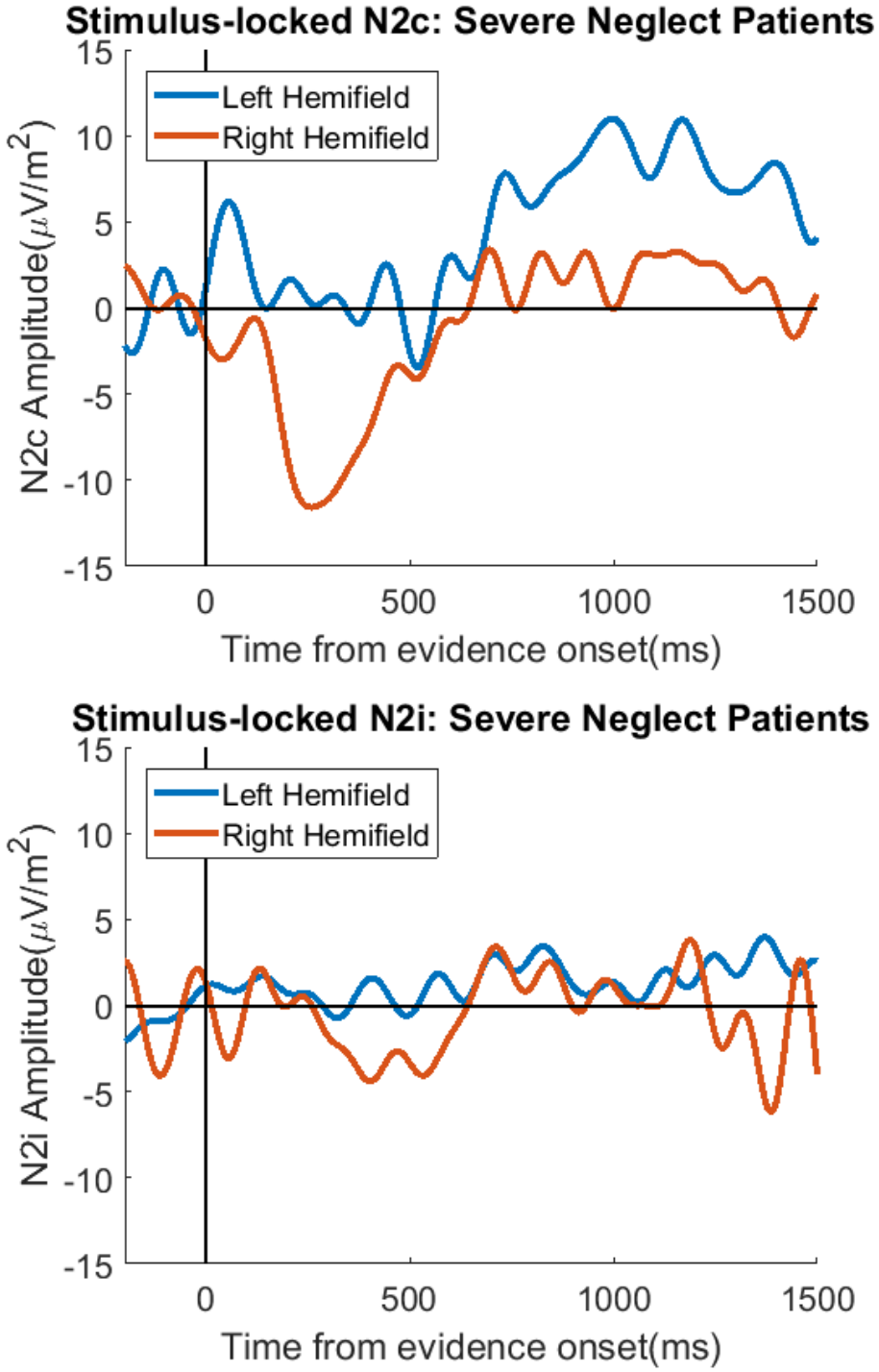

Figure 3.10. $N2_{(c)}$ and $N2_{(i)}$ waveforms for left and right hemifield targets in two participants with low trial counts and patterns of left inattention. Like those participants with good trial counts and neglect symptoms, there was reduced right hemisphere $N2_{(c)}$ for left hemifield targets. However, unlike those participants, there was no significant left hemisphere $N2_{(i)}$ in these participants.

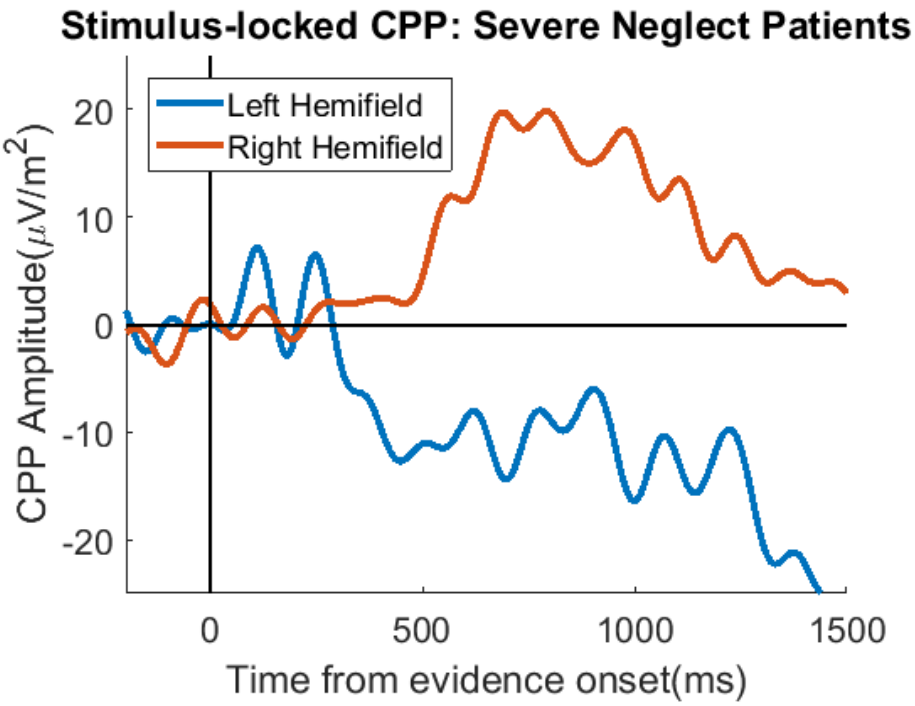

Figure 3.11. CPP waveforms for left and right hemifield targets in two participants with low trial counts and patterns of left inattention. In these two participants, there was a significant reduction in the CPP trace for left targets with no discernable CPP. *Note*: In these participants, response-locked signals were not able to be determined given these participants did not respond to a sufficient number of trials.

Non-Neglect Participants

Visual inspection of the waveforms revealed no discernible differences between left and right hemifield targets in the $N2_{(c)}$, $N2_{(i)}$ or CPP in patients without neglect (EE, KK; see Figure 3.12 and 3.13).

$N2_{(c)}$

The linear mixed models on single trial data included a fixed effect of $N2_{(c)}$ on RT and random intercepts for participants. The fixed effect of both right hemisphere $N2_{(c)}$ amplitude on left hemifield RTs, and left hemisphere $N2_{(c)}$ amplitude on right hemifield RTs were not significant, b = -.81 (95% CI = -1.84 to .23), $t(191) = -1.53$, p=.12 and b = .41 (95% CI = -.41 to 1.23), $t(201) = .98$, p = .33, respectively.

$N2_{(i)}$

The linear mixed models on single trial data included a fixed effect of $N2_{(i)}$ on RT and random intercepts for participants. The fixed effect of both left hemisphere $N2_{(i)}$ amplitude on left hemifield RTs, and right hemisphere $N2_{(i)}$ amplitude on right hemifield RTs were not significant, b = .14 (95% CI = -.87 to 1.15), $t(191) = .27$, p=.78 and b = .19 (95% CI = -.061 to .99), $t(201) = .48$, p = .63, respectively.

CPP

The linear mixed models on single trial data included a fixed effect of CPP on RT and random intercepts for participants. The models revealed that the CPP slope was related to both left and right hemifield RTs. For left hemifield targets, greater CPP slope was related to faster RTs, b = -124.57 (95% CI = -248.09 to -1.05), $t(191) = -1.99$, p = .048. For right hemifield targets, greater CPP slope was related to faster RTs, b = -150.79 (95% CI = -274.39 to -27.19), $t(201) = -2.41$, p = .017.

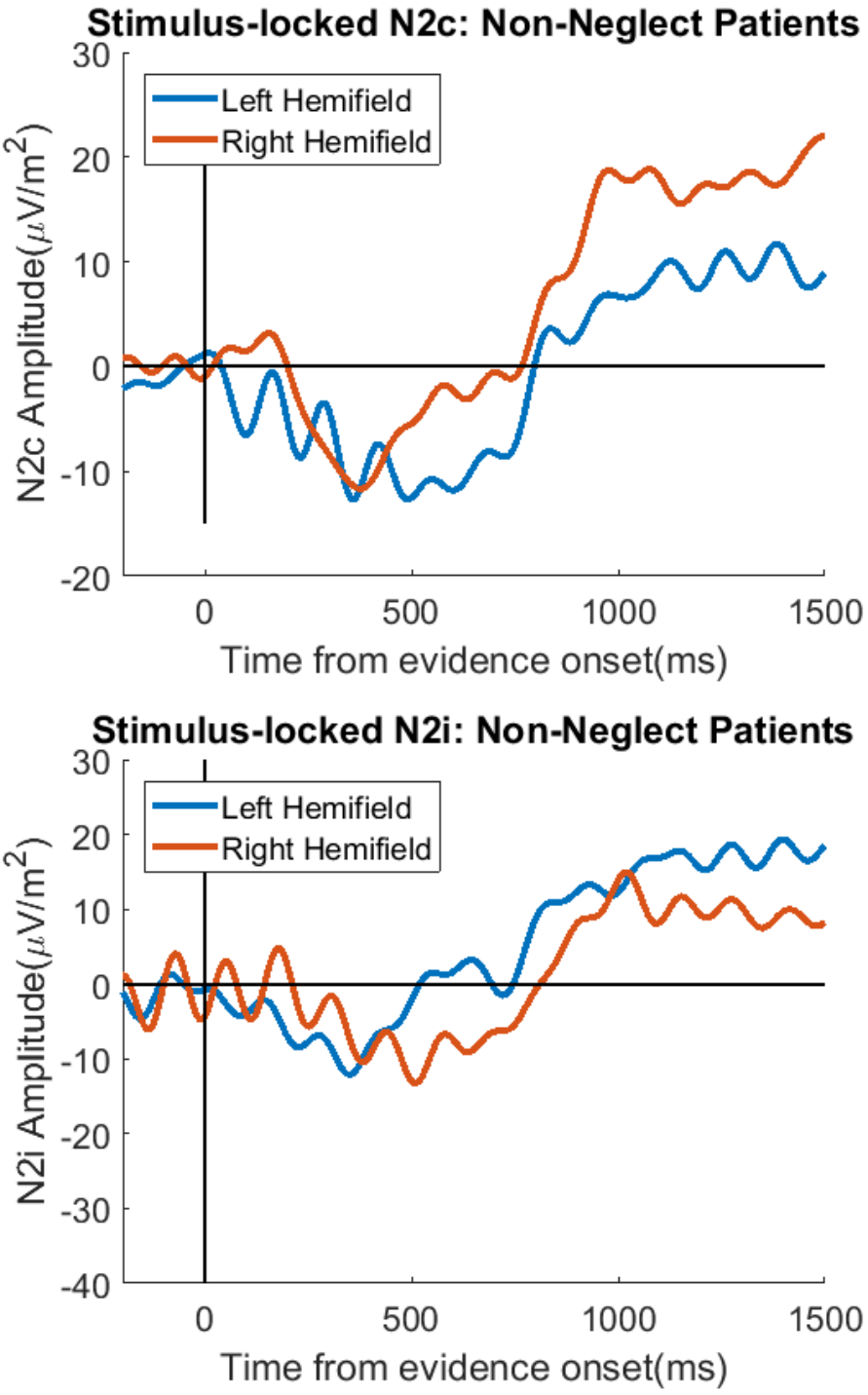

Figure 3.12. $N2_{(c)}$ and $N2_{(i)}$ waveforms for left hemifield targets and right hemifield targets in two participants with good trial counts but no RT asymmetry (no neglect). A discernible $N2_{(c)}$ was evident for both left and right hemifield targets and the $N2_{(i)}$ for both left and right hemifield targets was comparable.

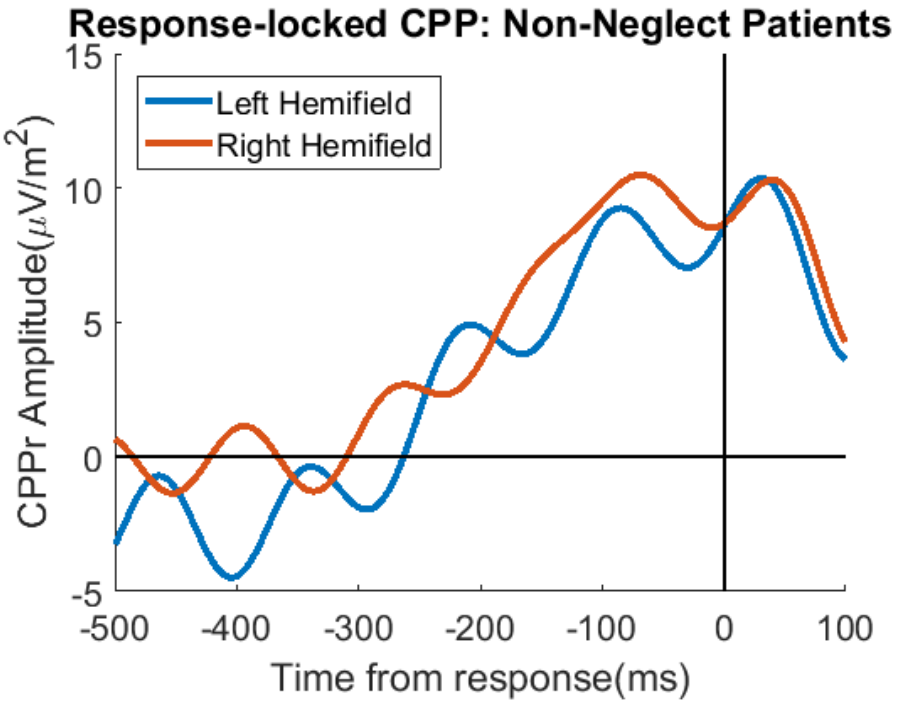

Figure 3.13. CPP waveforms for left hemifield targets and right hemifield targets in two participants with good trial counts but no RT asymmetry (no neglect). In these two participants, CPP slope (evidence accumulation rate) was comparable between hemifields.

Discussion

Neglect is a common and disabling neurological syndrome and despite the detrimental impact neglect has on functional outcomes post-stroke, little is known about the underlying mechanisms. Here, we leveraged recent advances in the perceptual decision-making literature. Uniquely, our EEG method allowed us to observe the temporal dynamics of information processing underpinning perceptual decisions and investigate these in right hemisphere stroke patients with and without neglect, and neurologically healthy controls. Here, we focused on two components, the $N2_{(c)}/N2_{(i)}$ indexing attention orienting and the CPP, a signal known to measure evidence accumulation over time (CPP).

Neurologically Healthy Participants

In the neurologically healthy participants, there was variability in behavioural spatial asymmetries with some participants exhibiting a leftward bias, some showing no bias and others a right bias. This is consistent with previous work that has highlighted the impact of individual differences on visuospatial biases (Bellgrove et al., 2008; Bellgrove et al., 2007; Bellgrove et al., 2005; Bellgrove et al., 2009; Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015; Marshall, Bergmann, & Jensen, 2015; Newman, O'Connell, Nathan, & Bellgrove, 2012; Thiebaut de Schotten et al., 2011; Tomer et al., 2013; Zozulinsky et al., 2014). There was, however, no significant RT-asymmetry at the group level suggesting that overall these neurologically healthy participants did not display a bias to either left or right hemifield targets. Although this result is consistent with aging accounts of spatial asymmetry, which document significant changes in spatial bias across the lifespan, we must note that in Chapter 2 we did not find any significant differences in RT asymmetry between younger and older neurologically healthy adults. Therefore the following discussion must be considered within this context. Traditionally, there is a propensity for a left spatial bias, referred to as 'pseudoneglect' in younger adults (Bowers & Heilman, 1980), a phenomenon that is analogous in concept, but opposite in direction to that observed in neglect (Bartolomeo, 2014; Manly, Dobler, Dodds, & George, 2005). However, later in life there is an attenuation, elimination, or in some cases a reversal of this spatial bias, resulting in right spatial bias (Barrett & Craver-Lemley, 2008; Benwell, Thut, Grant, & Harvey, 2014; Brooks, Sala, & Darling, 2014; Failla, Sheppard, & Bradshaw, 2003; Fujii, Fukatsu, Yamadori, & Kimura, 1995; Hatin, Sykes Tottenham, & Oriet, 2012; Jewell & McCourt, 2000; Schmitz & Peigneux, 2011). To understand why these shifts in spatial bias occur, models of cognitive aging have

been applied to the phenomenon of pseudoneglect. For example, the Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002) model posits that with age, individuals begin to recruit supplementary and contralateral brain regions to compensate for neural degeneration, which subsequently leads to a decrease in functional lateralisation (Cabeza et al., 1997). Support for this model stems from imaging studies reporting that younger subjects recruit lateralised cortical regions during memory tasks, whereas older adults exhibit bi-hemispheric activation (Backman et al., 1997; Cabeza, 2002; Cabeza et al., 2004; Dixit, Gerton, Kohn, Meyer-Lindenberg, & Berman, 2000; Dolcos, Rice, & Cabeza, 2002; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Madden et al., 1999; Nielson, Langenecker, & Garavan, 2002; Reuter-Lorenz et al., 2000; Stebbins et al., 2002). Benwell and colleagues (2014) note that although a reduction in the brain's lateralisation during the later years of life could account for symmetrical spatial attention, it does not explain why the left hemisphere can become *more* dominant than the right, thereby causing a rightward bias (Brooks et al., 2014). One model that does predict a rightward bias in aged participants is the right hemi-aging model, a model which suggests a faster and more severe deterioration of the right hemisphere compared to the left (Brown & Jaffe, 1975). This perspective originated from work documenting increased dysfunction on visuospatial tasks primarily mediated by the right hemisphere, compared to relatively intact verbal skills associated with the left hemisphere (Goldstein & Shelly, 1981). Although there has been inconsistent evidence for this theory across cognitive domains (Elias & Kinsbourne, 1974; Nebes, Madden, & Berg, 1983; Park et al., 2002; Schear & Nebes, 1980), a recent examination of changes in performance on selective attention tasks, processing of hierarchical visual stimuli and attentional control have provided evidence of disproportionate right hemisphere impairment in older individuals (Chokron, Helft, & Perez, 2013; Lux, Marshall, Thimm, & Fink, 2008; Nagamatsu, Carolan, Liu-Ambrose, & Handy, 2011). Other explanations for pseudoneglect include changes to the callosum and degradation in the brain's overall level of alertness. The latter is interesting given evidence that both tonic and chronic levels of arousal/alertness can modulate spatial bias in both healthy (Bellgrove, Dockree, Aimola, & Robertson, 2004; Dodds, Muller, & Manly, 2008; Dufour, Touzalin, & Candas, 2006; Fimm, Willmes, & Spijkers, 2006; Manly et al., 2005; Matthias et al., 2010; Newman et al., 2013) and clinical patients (Bartolomeo & Chokron, 2002; Lazar et al., 2002; Robertson et al., 1997; Robertson, Mattingley, Rorden, & Driver, 1998), likely due to right lateralised underpinnings of the alertness systems (Bartolomeo, 2007, 2014; Posner & Petersen, 1990). Again, given we did not find any significant difference between RT asymmetries between younger healthy

participants and older neurologically healthy adults in Chapter 2, we are unable to confirm or dispute these claims.

Our results indicate that for left hemifield targets, the right hemisphere $N2_{(c)}$ does significantly influence behavioural performance with larger $N2_{(c)}$ amplitude associated with faster RTs, which is consistent with previous work in young healthy participants (Loughnane et al., 2016). Further, the CPP impacted behavioural performance with significantly steeper slopes related to faster RTs in both left and right hemifield targets. Again, this result is consistent with previous work noting the impact of the evidence accumulation processes on behaviour (Kelly & O'Connell, 2013; O'Connell et al., 2012). Further in line with past research, the $N2_{(i)}$ did not significantly impact behaviour in either the left or right hemifields in older neurologically healthy participants, suggesting that the ipsilateral components do not contribute significantly to perceptual decision-making in this population, a finding that is consistent with studies focused on younger participants (Loughnane et al., 2016). In the neurologically healthy sample, we did find deviations from past research in the form of the left hemisphere $N2_{(c)}$. Previously, left hemisphere $N2_{(c)}$ has been shown to predict RT in the right hemifield (Loughnane et al., 2016), however, in this sample, the left hemisphere $N2_{(c)}$ had no significant impact on right hemifield RTs. Task difficulty in combination with the natural shift in spatial bias towards to midline in these participants may be one potential explanation for this discrepancy. In the current task, coherent motion was defined at 90%, such that 90% of the randomly moving dots started to move coherently at target onset. This is a relatively easy task considering other healthy studies have generally employed considerably lower coherence levels (25%-70%; Loughnane et al., 2016; Newman et al., 2016; Newman et al., 2017). This low difficulty level coupled with the natural shift in spatial bias observed in older participants may have reduced the need for older neurologically healthy adults to actively orient attention to the right hemifield in this case. The reasoning behind a 90% coherence level was to ensure that stroke participants would be able to complete the task, however, in future one potential option is to use a staircase method to control for task difficulty (Harty et al., 2014). This method allows for accuracy to be kept constant across participants by altering the percentage of coherently moving dots between blocks.

Stroke Participants

The stroke patients were separated into three sub-groups: (1) neglect; (2) severe neglect; and (3) no neglect. The need to separate these participants into multiple groups reflects the heterogeneity that is quintessential in neglect.

In neglect patients, there was evidence of dysfunctional attention orienting in the right hemisphere for left hemifield targets. Yet, despite this dysfunction these participants were able to respond to left hemifield targets, albeit with slower responses for left hemifield targets compared to right hemifield targets. In younger healthy participants (Loughnane et al., 2016) and in our neurologically healthy older participants, the $N2_{(i)}$ does not influence RT. However, in these neglect patients, there was evidence of a pronounced $N2_{(i)}$ signal sourced from the left hemisphere that significantly impacted behavioural performance within the left hemifield. We suggest that this represents compensation from the left hemisphere to help overcome damage from the right hemisphere. Of note, this potential compensation and adaptation from the left hemisphere $N2_{(i)}$ was not evident in severe neglect participants. We suggest that the lack of left hemisphere compensation may have contributed to the inability for these participants to respond to a large number of trials. Intriguingly, neither the $N2_{(c)}$ nor the $N2_{(i)}$ were predictive of RTs in non-neglect participants. We would suggest that this result might be due to lesion location in these participants, particularly in EE. EE experienced loss of grey-white matter differentiation consistent with a bilateral middle cerebral artery stroke. It is likely that this pattern of infarct affected the integrity of both hemispheric signals ($N2_{(c)}$/$N2_{(i)}$). The results suggest that the $N2_{(i)}$ may provide compensation in some stroke participants, suggesting that this signal may be of interest in future studies. Further longitudinal research is required to map this metric over time and to investigate the utility of using the $N2_{(i)}$ as a marker of recovery.

The development of analyses that can be applied at a single subject level is a significant advancement. Across all groups who were able to be analysed at a single trial level (neglect participants and non-neglect participants), the CPP, a signal of evidence accumulation predicted behavioural performance. In these stroke participants, steeper CPP slope, which reflects faster evidence accumulation, was related to faster RTs. This is consistent with both the sample of neurologically healthy older participants tested here and previous work in younger healthy adults (Kelly & O'Connell, 2013; O'Connell et al., 2012). This suggests that these neglect patients are able to accumulate information adequately and

that this process it is not grossly dysfunctional in these participants. It is however likely that slowed evidence accumulation, as evidenced by more gradual CPP slope, may be contributing to the slowed RT for left targets observed in these participants. In severe neglect participants, visual examination of the CPP revealed a significantly reduced CPP for left hemifield targets. This accords with the behavioural results, given these participants did not respond to a large number of left hemifield targets. FF had a total of eighteen valid left trials and JJ responded to five valid left trials.

Overall, the CPP results support assertions from the perceptual decision-making literature that evidence accumulation is key to sound perceptual decisions (Kelly & O'Connell, 2013; Kelly & O'Connell, 2015; Newman et al., 2017; O'Connell et al., 2012).

Conclusion and future research

In summary, here we present preliminary evidence outlining the utility of using a perceptual decision-making framework to investigate the underlying mechanisms driving neglect behaviour following right hemisphere stroke. This work is significant as a major limitation of current clinical tests for neglect is that they are unable to distinguish potential contributing mechanisms, such arousal, attention, sensory and motoric aspects of the deficit. Here, we have demonstrated that individual perceptual decision-making can be dissociated in neglect patients. In this case, we have focused on the attention orienting and evidence accumulation components, both of which are components that could contribute to the development of neglect. This work presents a proof-of-concept that this approach can provide valuable information to the understanding of contributing mechanisms. As acknowledged by the Australian National Stroke Foundation Clinical Guidelines (National Stroke Foundation, 2010), there is an imperative for the development of sensitive, reliable and objective tests of spatial neglect that will underpin enhanced targeting of treatments. Currently, there is no gold standard for neglect and there is no clear evidence for preferentially using one rehabilitation strategy over another (Loetscher & Lincoln, 2013). This ineffectiveness likely stems from the inability to pair patients with the most appropriate rehabilitation technique. Given this, increased understanding of the underlying mechanisms of neglect, particularly at an individual subject level, may have great clinical potential, as it may better inform both diagnostic procedures and the application of rehabilitation strategies. If the point of dysfunction can be accurately identified in individual neglect patients, we may be better equipped to apply the most appropriate rehabilitation strategy. For example, patients with

arousal deficits could best be ameliorated by phasic alerting (Robertson et al., 1998) or stimulants (Luvizutto, Bazan, Braga, Resende, & El Dib, 2013); attention deficits may be best treated using self-alerting or sustained attention training (Robertson et al., 1995); spatial orienting deficits could be most effectively targeted using prism adaptation or visual scanning training (Priftis, Passarini, Pilosio, Meneghello, & Pitteri, 2013); visuomotor feedback training (Harvey, Hood, North, & Robertson, 2003) may be most appropriate for those with perceptual deficits; and limb activation therapy (Priftis et al., 2013) may be the best treatment approach for those patients with neglect due to motor deficits.

It should be noted that there are limitations to the current research. Firstly, there were a number of stroke participants that were unable to participate in Stage 2 due to cognitive difficulties and comprehension deficits. This is an important caveat to this work as it likely means that the perceptual decision–making framework and the accompanying paradigm is not going to be of use in all stroke patients. Secondly, there are limits to the utility of this approach in patients with visual field deficits. In participants with visual difficulties, this approach is likely to result in false positives (neglect where no neglect truly exists). Caution should be taken when applying this framework to those with visual field defects as they will likely be unable to *visually* perceive the left hemifield targets. Thirdly, in this sample participants were able to complete variable numbers of trials due to fatigue and competing medical needs. As the analysis was completed on a trial-by-trial basis, we do not believe that this significantly confounded results, it cannot be denied that those participants with more trials will have more stable results. Finally, we note that we do not currently have information about how performance on the behavioural task maps on to traditional screening methods. Given screening measures were only completed during sub-acute rehabilitations stays, we were unable to accurately assess how these results mapped onto behavioural RT results. Based on the above, future research should aim to include measures of other processes that could potentially be contributing to neglect behaviour. For example, it would be beneficial to include pre-target α-band (8 –14 Hz) activity, a measure of spatial attention bias (Thut et al., 2006) as this may be another contributing factor. Sauseng et al. (2005) documented a decrease in α-band activity contralateral to the attended target location and this has been interpreted as enhanced cortical excitability that facilitates future visual processing to the attended position (Thut et al., 2006). Further, it would also be beneficial to include motoric metrics and assess their influence on neglect behaviour, such as the lateralised readiness potential (LRP). The LRP is a negative potential that commences prior to a motor response

and its onset is generally interpreted as the time at which the brain began preparing to make a motor response (Smulders & Miller, 2013). Finally, the addition of pupillometry would allow for the influence of small modulations in arousal to be tracked and measured. The addition of these metrics would further enhance our understanding of the underlying component deficits in neglect. The investigation of how these deficits maps onto lesion location would also be beneficial. We also suggest that future research aim to use voxel-based lesion-symptom mapping (Molenberghs, Sale, & Mattingley, 2012; Chris Rorden, Karnath, & Bonilha, 2007a) to investigate the origins, at a lesion level, of these distinct deficits. Of note, in instances where future research is conducted longitudinally, we would suggest that spatial inattention screening measures (cancellation, extinction, landmark and greyscales) are used at multiple time-points. This inclusion would allow for an assessment of whether spontaneous recovery contributes to performance changes between stages.

Finally, research should further investigate perceptual decision-making metrics in a larger group of stroke participants. We believe that with further research this approach could have significant clinical utility within medical settings, particularly as it pertains to diagnosis. Importantly, these signals can be investigated using low-density electrode arrays (approximately 3-5 electrodes) making them appropriate for acute and sub-acute rehabilitation wards. From a practical and logistic perspective, further work should focus on utilising portable technologies, such as EEG and eye tracking, as this method would be of most use within clinical settings where flexibility is required for complex patients.

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CHAPTER FOUR: THE EFFECT OF BLUE ENRICHED LIGHT ON ALERTNESS AND VISUOSPATIAL ATTENTION ASYMMETRY

CHAPTER FOUR

Declaration for Thesis Chapter Four

Declaration by candidate
In the case of Chapter Four, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution (%)
Literature review, study design, participant testing.	5%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of Contribution	Extent of contribution (%) for student co-authors only
Dr Daniel Newman	Literature review, study design, testing of participants, analysis, manuscript preparation.	70%
Prof. Steven Lockley	Study design, critical reviews of manuscript	
Dr. Gerard Loughnane	Critical reviews of manuscript	
Ms. Ana Carina Martins	Recruitment and testing of participants	5%
Mr. Rafael Abe	Recruitment and testing of participants	5%
Mr. Marco Zoratti	Recruitment and testing of participants	5%
Dr. Simon Kelly	Paradigm programming	
Prof. Shantha Rajaratnam	Critical reviews of manuscript.	
Dr. Redmond O'Connell	Critical reviews of manuscript.	
Prof. Mark Bellgrove	Study design, critical reviews of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

Candidate's Signature:	[redacted]	Date: 19/10/17
Main Supervisor's Signature	[redacted]	Date: 19/10/17

Preamble to Chapter Four

The two previous chapters have investigated the impact natural aging and brain injury (damage to the right middle cerebral artery) have on target selection, attention orienting and evidence accumulation. The impact of aberrant spatial attention, particularly following stroke is debilitating and neglect is associated with poor functional outcomes (Chen Sea et al., 1993; Ween et al., 1996). Despite this, there is a distinct lack of effective rehabilitation strategies for neglect. Here, we suggest that the acute alerting effect of short-wavelength light could be harnessed as a non-invasive treatment option. Light has an alerting effect on the brain, mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) that are maximally sensitive to blue light (~480nm; Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Berson, 2003; Berson, Dunn, & Takao, 2002; González & Aston-Jones, 2006; Gooley, Lu, Chou, Scammell, & Saper, 2001; Perrin et al., 2004; Schmidt et al., 2011; Vandewalle et al., 2006; Vandewalle et al., 2013; Vandewalle, Gais, et al., 2007; Vandewalle et al., 2009; Vandewalle, Schmidt, et al., 2007; Zaidi et al., 2007)

In this chapter, we investigate if exposure to blue-enriched light could activate right-hemisphere attention networks, thus enhancing attention to left space in healthy individuals. Investigation of the utility of this approach in healthy participants is a natural first-step before investigating any potential effect in clinical populations. In previous chapters we have used a two patch version of the perceptual decision making paradigm as it was a more feasible task for the older adults and stroke patients being studied. Here, using a four patch version of the perceptual decision-making paradigm, the results showed that exposure to higher, relative to lower, intensity blue-enriched light enhanced response-times for stimuli in the left, but not right, visual hemifield. This processing benefit was mediated by a specific effect of light intensity on right-hemisphere parieto-occipital α-power. These behavioural and neurophysiological effects were sustained over task duration (~36 minutes). These data provide convincing evidence for a direct modulatory influence of alertness on the physiological substrates of spatial attention, using a non-invasive, non-pharmacological manipulation of alertness, which lasts post light exposure.

It is important to note that Chapter Four is a previously published paper to which the candidate made a contribution. The inclusion of this chapter is of relevance as it provides a narrative of the scientific basis that underpins work conducted by the candidate in Chapter Five, where this blue light intervention was trialled in a clinical population. We do not expect

Chapter 4 to constitute a substantial portion of the thesis and it is purely included for cohesion.

Note: Please see **Appendix 5** for supplemental material related to this chapter and referred to in the paper below.

SCIENTIFIC REPORTS

OPEN

Ocular exposure to blue-enriched light has an asymmetric influence on neural activity and spatial attention

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Brain networks subserving alertness in humans interact with those for spatial attention orienting. We employed blue-enriched light to directly manipulate alertness in healthy volunteers. We show for the first time that prior exposure to higher, relative to lower, intensities of blue-enriched light speeds response times to left, but not right, hemifield visual stimuli, via an asymmetric effect on right-hemisphere parieto-occipital α-power. Our data give rise to the tantalising possibility of light-based interventions for right hemisphere disorders of spatial attention.

The mechanisms for alertness in humans interact with those for spatial attention orienting in an intriguing fashion[1,2]. For example, the debilitating inattention of left space observed in patients suffering from unilateral spatial neglect subsequent to right-hemisphere damage can be temporarily overcome by phasic alerting tones[3]. Sleep deprivation in healthy participants causes relative left hemifield inattention in the visual domain[4], while a pronounced auditory inattention to left space occurs during drowsy periods prior to sleep onset[5]. Brain imaging work in both neglect patients and neurologically healthy participants suggests that the distribution of attention between the hemifields is balanced by competitive activation between the hemispheres, specifically within a bilaterally represented dorsal network for spatial attention orienting[1,6,7]. Current models propose that this bilateral orienting network interacts with the right-hemisphere-lateralised ventral network subserving non-spatial processes such as alertness[1,2] which may be preferentially innervated by the locus-coeruleus/noradrenergic (LC-NA) system[1,8,9].

Despite demonstrations that manipulations of alertness can transiently shift spatial attention bias, neuroscience has thus far failed to identify non-invasive methods of manipulating alertness that lead to an enduring improvement in attention to left space. One promising avenue for manipulating alertness is offered by recent photobiology studies of light. Although it is recognised that light exerts powerful alerting effects on brain and behaviour, its mechanism of action has only recently been studied. Specifically, recent research has identified a set of intrinsically photosensitive retinal ganglion cells (ipRGCs) which are maximally sensitive to short wavelength (blue) light (~480 nm) and which mediate a light induced alerting signal to the human brain, in a dose dependent manner[10–12]. Since (a) rodent work suggests that the alerting effects of light on the brain are achieved in part via inputs from the suprachiasmatic nucleus to the LC-NA arousal system[13,14], and (b) human brain imaging shows that light exposure activates key areas of right-hemisphere attention networks[15,16], we asked if light-induced manipulations of alertness could be harnessed to activate right-hemisphere attention networks and thus improve the direction of attention to left space.

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We hypothesized that pre-exposure to higher, relative to lower, intensities of blue-enriched light, would promote attention to the left visual hemifield, indicative of enhanced activation of right hemisphere attention networks. Neurologically healthy subjects participated in an electrophysiological study of visuospatial attention subsequent to 1 hour exposure of either low (50 lux), medium (350 lux) or high (1400 lux) intensity blue-enriched light. The effect of light on attention-related brain activity was measured via hemisphere-specific parieto-occipital α-power (8–13 Hz), a robust EEG marker of spatial attention[17] which is also sensitive to blue light exposure[18]. Our application of multi-level statistical modelling[19] allowed us to simultaneously model behaviour as a function of both categorical experimental conditions and pre-target neural activity, thus fully capitalizing on the richness of the single-trial EEG data.

This study yielded a number of novel and exciting findings. Light exposure enhanced response times for visual stimuli in the left, but not the right, hemifield, with a parametric speeding of left hemifield responses caused by increasing the intensity of the light. This effect did not diminish over the duration of the ~36 min attention task demonstrating that prior light exposure had an enduring impact on attention for left hemifield stimuli. This processing benefit for left hemifield stimuli was mediated by an effect of increasing light intensity on right-hemisphere parieto-occipital α-power. Our data provide the most convincing evidence yet for a direct modulatory influence of alertness on the physiological substrates of spatial attention, using a non-invasive, non-pharmacological manipulation of alertness which lasts post light exposure.

Results

Subsequent to a 1 hour exposure to low (50 lux), medium (350 lux) or high (1400 lux) intensity blue-enriched fluorescent light (henceforth the "Light" manipulation), neurologically healthy participants performed a ~36 minute variant of the random dot motion task[20–22] which involved monitoring four bilaterally distributed dot kinematograms. On each trial, after a variable delay, one of the kinematograms underwent a transition from incoherent to coherent motion (upward or downward direction) which participants were instructed to report via a speeded right-hand button press. Participants were not required to indicate either the direction or location of coherent motion. Testing occurred in the evening after ~14 hours of wakefulness. Testing an independent sample ($N = 80$) using a similar random dot paradigm between 9:30 am and 3:00 pm with no light manipulation showed that under normal daytime alertness healthy participants responded faster to coherent motion targets in the left than right hemifield [$t(79) = -3.06$, $p = 0.003$; see supplemental information for details]. The effect of prior light exposure on cortical spatial attention networks was measured via hemisphere-specific parieto-occipital α-power (8–13 Hz) recorded during the 500 ms prior to coherent motion onset[17]. We used maximum likelihood ratio tests for the fixed effects of light intensity, target hemifield and hemisphere on single trial measures of α-power and response-time (RT) (see Methods for details).

Higher light intensity speeds target detection, specifically to left-hemifield targets. Although the main effect of Target hemifield [$\chi^2(1) = 1.21$, $p = 0.272$] was not significant, there was a main effect of Light [$\chi^2(2) = 9.95$, $p = 0.006$] on RT which was modified by a significant Light × Target hemifield interaction [$\chi^2(2) = 6.81$, $p = 0.033$]. Separate tests for each Target-hemifield showed no impact of Light on RTs for right-hemifield targets [all $ps > 0.926$], while left-hemifield RTs were significantly faster after high intensity Light ($M = 490$ ms, $SE = 1.65$) than after both medium ($M = 497$ ms, $ES = 1.77$) [$b = -6.83$, $SE = 2.15$, $t = -3.17$, $p = 0.004$] and low intensity ($M = 499$ ms, $SE = 1.76$) [$b = -8.35$, $SE = 2.14$, $t = -3.90$, $p < 0.001$] Light exposure (Fig. 1A). The difference between low and medium intensity was not significant [$b = -1.53$, $SE = 2.15$, $t = -0.71$, $p = 0.758$]. A lack of any significant Target-hemifield × Vertical Visual Field [$\chi^2(1) = 1.11$, $p = 0.292$], Light × Vertical Visual Field [$\chi^2(2) = 0.82$, $p = 0.662$] or Target-hemifield × Vertical Visual Field × Light [$\chi^2(2) = 0.31$, $p = 0.856$] interactions, indicated that the effect of Light on left-hemifield RTs was consistent regardless of whether the target appeared in the upper or lower visual field.

We next sought to determine whether the influence of the Light manipulation persisted as a function of time-on-task (trial number). The lack of any Light × Target-hemifield × Time-on-task [$\chi^2(2) = 2.89$, $p = 0.236$] or Light × Time-on-task interactions for left-hemifield RTs specifically [$\chi^2(1) = 1.88$, $p = 0.389$], indicated that the effect of Light on left-hemifield RTs persisted over the duration of the task. There was however a significant Target-hemifield × Time-on-task interaction [$\chi^2(2) = 9.41$, $p = 0.002$] whereby responses were slower for right than left-hemifield targets at the beginning of the task but this advantage waned with time (see Supplemental Fig. 1). This latter observation is consistent with previous reports of a rightward shift in spatial attention bias with time-on-task[4,23–25].

Light intensity asymmetrically modulates α-power over right-hemisphere regions that are sensitive to spatial attention orienting. Prior work has shown that night-time exposure to blue light increases α-power in waking EEG[12,18,26]. The current data support this observation since higher intensity Light increased pre-target (mean −500 ms to target onset) α-power pooled from all parieto-occipital electrodes (see Supplementary Results). Given Light had an asymmetric effect on behaviour (Fig. 1A), and since hemispheric asymmetry in posterior α-power is an established EEG correlate of the distribution of attention in space[17], we asked whether higher intensities of Light differentially influenced α-band activity within each hemisphere. To this end we measured α-band activity over each hemisphere during the 500 ms interval immediately prior to coherent motion onsets. A scalp plot of the cumulative change in α-power across Light conditions (i.e. the sum of the change in grand average α-power between conditions [(High-Low) + (High-Medium) + (Medium-Low)]) shows that Light influenced parieto-occipital α-power over right-hemisphere electrodes more than over left electrodes (Fig. 1C). To explore this effect further, single-trial α-power measures were pooled from the four lateral parieto-occipital electrodes within each hemisphere that exhibited the strongest desynchronisation in response to covert shifts in attention towards left versus right-hemifield targets (see Experimental Methods). Light had a

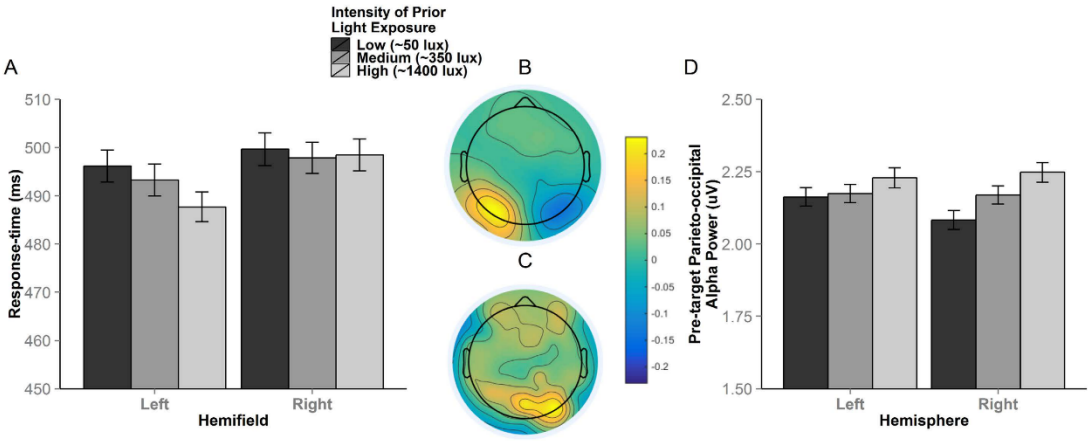

Figure 1. The intensity of blue-enriched light influenced response-times to targets in the left, but not right, visual hemifield (**A**). The difference in grand average post-target α-desynchronisation for left versus right-hemifield targets shows that lateral parieto-occipital electrodes were most sensitive to covert shifts in attention towards each hemifield (**B**). Increased intensity of blue-enriched light increases α-power over the right hemisphere more than left hemisphere electrodes (**C**,**D**). Note that the electrodes exhibiting strongest modulation by light in (**C**) are the same electrodes that were most sensitive to shifts in spatial attention (**B**). Error bars represent 95% CIs.

significant effect on α-power [$\chi^2(2) = 9.80$, $p = 0.007$] that was modified by a significant Light × Hemisphere interaction [$\chi^2(2) = 17.0$, $p < 0.001$; see Fig. 1D] while there was no main effect of Hemisphere [$\chi^2(1) = 0.89$, $p = 0.891$].

Follow-up contrasts showed that the Light × Hemisphere interaction was driven by a greater effect of Light on right-hemisphere than on left-hemisphere α-power (Fig. 1C,D). The effect of Light on the right-hemisphere scaled significantly in a step-wise fashion [high versus low, $b = 0.07$, $SE = 0.007$, $t = 9.55$, $p < 0.0001$; high versus medium, $b = 0.03$, $SE = 0.007$, $t = 3.57$, $p = 0.001$; medium vs low, $b = 0.04$, $SE = 0.007$, $t = 5.97$, $p < 0.0001$]. In contrast, there was no difference between medium and low Light on left-hemisphere α-power [$b = 0.01$, $SE = 0.007$, $t = 1.66$, $p = 0.220$], while the other two contrasts were significant but of smaller effect size [high versus low, $b = 0.03$, $SE = 0.007$, $t = 4.33$, $p < 0.001$; high versus medium, $b = 0.02$, $SE = 0.007$, $t = 2.66$, $p = 0.021$]. A main effect of Time-on-task [$\chi^2(1) = 99.07$, $p < 0.0001$] indicated α-power tended to increase over time, in line with previous findings[25,27,28]. However, there were neither Light × Time-on-task [$\chi^2(2) = 1.42$, $p = 0.491$] nor Lig ht × Hemisphere × Time-on-task interactions [$\chi^2(2) = 0.97$, $p = 0.615$], indicating that the specific effect of Light on right hemisphere α-power persisted throughout the task.

Higher light intensity suppresses the effect of α-power on forthcoming RTs. It is commonly assumed that posterior α-band activity scales inversely with cortical excitability[29–33]. This view is supported by studies showing an inverse relationship between pre-stimulus α-power and perceptual performance, such that higher α-power is associated with slower RTs and diminished accuracy[20,34–40]. As shown above (Fig. 1D), however, exposure to higher intensity blue-enriched light actually *increased* α-power while simultaneously *improving* RTs. In a further analysis we examined the possibility that blue-enriched light exposure modifies the relationship between α-power and behavioural performance. Single-trial α-power measures were pooled from the same posterior left- and right-hemisphere electrodes used above, and entered into a model predicting RT over and above the Light × Target-hemifield effect. In line with previous studies[20,34,35], greater α-power was generally associated with slower forthcoming RTs [$\chi^2(1) = 4.89$, $p < 0.027$]. Crucially, this relationship was modified by a Light intensity × α-power interaction [$\chi^2(2) = 35.14$, $p < 0.0001$]. Follow-up contrasts revealed that higher intensity Light suppressed the relationship between α-power and forthcoming RTs (see Fig. 2). This suppression effect scaled with light intensity [high versus medium $b = -2.21$, $SE = 0.82$, $t = -2.70$, $p = 0.019$; medium vs low $b = -2.80$, $SE = 0.86$, $t = -3.26$, $p = 0.003$; high vs low b = −5.02, $SE = 0.85$, $t = -5.9.$, $p < 0.001$]. No other interactions reached significance, and there were no substantive differences in results when α-power measures were used from the left or right hemisphere separately instead of pooling across hemisphere.

Right hemisphere α-power mediates the causal effect of light intensity on left-hemifield RTs. We next sought to test whether the causal effect of Light intensity on left-hemifield RTs (Fig. 1A) was mediated by light's influence on right-hemisphere α-power (Fig. 1D). Only low (~50 lux) versus high (~1400 lux) Light conditions were used as mediation analysis necessitates binary categorical predictors. Path parameters for the mediation model were calculated from the fixed effects of Light and α-power using the same linear multilevel modelling technique as above. A Sobel test[41] demonstrated that the effect of Light intensity on left-hemifield RTs was partially mediated by parieto-occipital α-power pooled from right-hemisphere (*Indirect effect* = 0.35, *se* = 0.16, $p = 0.03$). Inspection of path parameters from the significant mediation model (Fig. 3) show that path *c'*

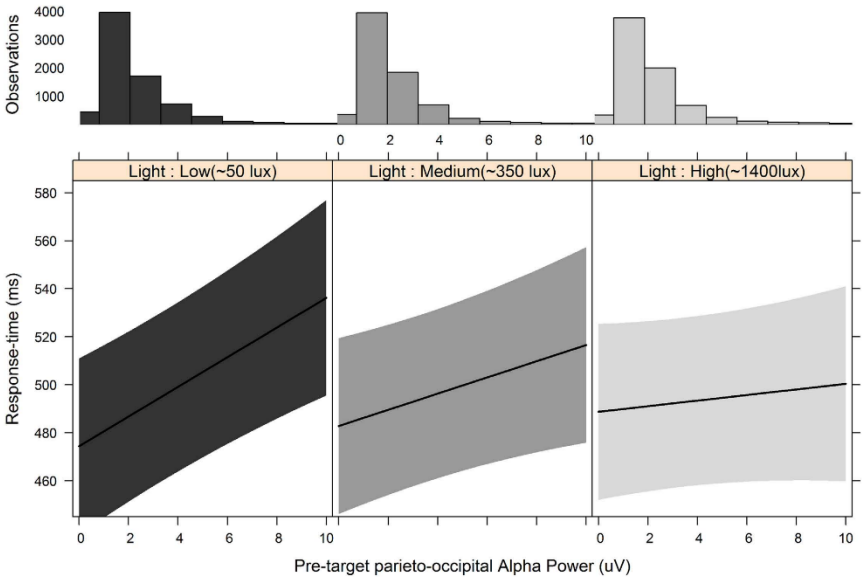

Figure 2. Although greater parieto-occipital α (8–13 Hz) power preceding target onset was associated with slower response times, exposure to higher intensity blue-enriched light weakened this relationship. Inserted histograms show that the distribution of observations as a function of pre-target α-power does not change across light conditions. Error bars represent 95% CIs.

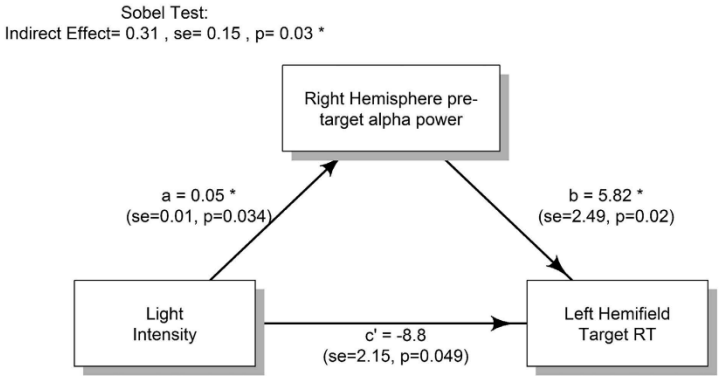

Figure 3. Sobel tests revealed that pre-target α-power pooled from right hemisphere parieto-occipital channels mediates the causal influence between increasing light intensity and faster RTs for left-hemifield targets. The mediation model shows that path *c'* is opposite in sign to paths *a* and *b* suggesting an 'inconsistent mediation' effect in line with higher Light intensity both increasing α-power (Fig. 1D) while also suppressing its slowing effect on forthcoming RTs.

is opposite in sign to paths *a* and *b*, indicating an 'inconsistent mediation' effect[42]. This accords with our observations above that higher Light intensity increases α-power (Fig. 2) while also suppressing its relationship with forthcoming RTs (Fig. 3).

In summary, we showed that greater α-power is associated with slower forthcoming RTs in line with previous studies[20,34,35], however exposure to relatively higher intensities of blue-enriched light simultaneously increases α-power over parieto-occipital regions and improves behavioural performance for left-hemifield targets. This effect is driven in part by increasing light intensity exerting a suppressive effect on the relationship between α-power and behavioural performance, thereby facilitating faster RTs for left-hemifield targets.

Discussion

Although it is well established that light exerts a powerful alerting influence on the human brain, its specific influence on the physiological substrates of spatial attention has not been explored. Here we show for the first time

that pre-exposure to high intensity blue-enriched light can speed detection specifically for left-hemifield visual targets. This left-hemifield enhancement is driven by an enduring effect of exposure to light on right-hemisphere parieto-occipital α-power. Our results provide the most compelling evidence yet that a direct manipulation of non-spatial alertness can modulate activity within spatial attention brain networks. That these effects were achieved by manipulating the intensity of blue-enriched light, a non-pharmacological, reversible and safe stimulant, prompts consideration of future research into whether light exposure may have therapeutic benefit for disorders of spatial attention.

There are a number of novel aspects to the data reported herein. First, since previous studies of spatial attention have reported decreased α-power in the hemisphere contralateral to an attended target location, we might have expected that the light-induced enhancement of left-hemifield performance would have been coupled with a corresponding decrease in right-hemisphere α-power. Instead, however, we observed a light-induced *increase* in right-hemisphere α-power. To understand these seemingly counterintuitive findings, we tested a model by which reaction time could be predicted by the intensity of blue-enriched light, pre-target α-power and their interaction. Whereas at lower light intensity we observed the stereotypical relationship between increasing α-power and slower response times, higher light intensities weakened this effect of α-power on forthcoming response times.

So what biological process might underpin this light-induced suppression of the relationship between α-power and response times that is typically seen during tasks of spatial attention? Previous work at the intersection of circadian neuroscience and photobiology has shown that waking α-power measured at rest, which appears to be strongly modulated by the circadian system[43], is increased during exposure to monochromatic blue light at night[12,18,26]. Lockley *et al.* hypothesized that the alerting effect of light during the night-time may be achieved by α-modulation reflecting 'inhibition of the circadian drive for sleep'[26]. Since the participants in our study were tested in the evening after ~14 hours of wakefulness, it is possible that higher intensity blue-enriched light invoked such a mechanism, and this separate source of α-modulation merged on the scalp with the signal produced by α-generators for spatial attention. Specifically, we hypothesise that night-time exposure to higher intensities of blue-enriched light disrupts the slowing influence of α-power on forthcoming response times, by introducing greater α-modulation related to inhibition of the circadian drive for sleep. That this effect is maximal for right-hemisphere parieto-occipital α-power may explain the enhancement of attention to the left hemifield. Although previous studies of circadian and blue light modulation of resting α-power split the α-band into low and high α[12,18,26,44], here the impact of blue-enriched light on spatial-attention related α-power was invariant across the 8–13 Hz range, consistent with literature on the relationship between spatial attention and α-power[17,39]. Nevertheless, future studies may benefit from explicitly contrasting the impact of exposure to blue-enriched light on both resting and active task scenarios as well as testing the generalisation of results reported herein to daytime light exposure.

Studies involving day-time fMRI[16] and night-time PET[15] have previously demonstrated that blue light disproportionately activates key right-hemisphere regions related to attention, but this is the first demonstration that these asymmetric activation patterns translate to asymmetric behavioural changes. Current models for spatial attention suggest that the distribution of attention between the hemifields is balanced by competitive activation between the hemispheres, specifically within a bilaterally represented dorsal network for spatial attention orienting[1,6,7,45], that is in turn influenced by the right-hemisphere-lateralized ventral network subserving non-spatial processes including alertness[1,2,46–51]. This account can explain many asymmetric features of visuo-spatial attention including pseudoneglect during normal daytime alertness, reductions in responsiveness to items in left space under conditions of lower alertness, and left unilateral spatial neglect which is most common after right-hemisphere damage[1]. The non-visual effects of light on the brain are achieved in part via inputs from the suprachiasmatic nucleus to the locus-coeruleus (LC)[13,14,52]. It is therefore possible that higher intensity blue-enriched light preferentially activates right-hemisphere attention networks through the LC/noradrenergic (LC-NA) system[1,8,53], thus leading to the asymmetric behaviour-brain effects observed herein. These observations, along with the recent findings that blue light exposure improves alertness in patients with traumatic brain injuries[54], offer the tantalizing, though speculative, possibility that light might be harnessed as a tool to promote attention to left space in disorders involving right-hemisphere dysfunction and leftward inattention such as unilateral spatial neglect[1,3] and ADHD[55,56]. This must be confirmed by future research.

Methods

Participants. Data were collected from 24 (14 female) healthy right-handed volunteers, aged 19 to 25 (M = 22.6 years), reporting normal or corrected to normal vision, no history of neurological or psychiatric disorder and no head injury resulting in loss of consciousness. Ethics was obtained from the Monash University Human Research Ethics Committee (MUHREC) prior to testing. The experimental protocol was approved by MUHREC and carried out in accordance with the approved guidelines. Informed consent was obtained from all participants prior to testing.

Light intensity manipulation. Each participant was exposed to three different blue-enriched white light intensities (low: 50 lux; medium: 350 lux; high: 1400 lux - at eye level, vertical plane) across separate sessions in a counterbalanced order (72 testing sessions in total). Participants were seated in front of two identical light boxes (Philips EnergyLight HF3305, Philips Lighting, Eindhoven, The Netherlands) fitted with blue-enriched white lamps (17000 K, PL-L ActiViva, Philips Lighting, Eindhoven, The Netherlands)[57]. One light box was placed on a table at eye level 60 cm from the eyes. The other was positioned on the floor in front of the participant 45° degrees below eye level but pointing towards the eyes at a 110 cm distance. Light intensity (lux) was manipulated by placing the appropriate neutral density filter 'stop' over the source to modify the intensity (lux) of all wavelengths of light equally without altering the spectrum. Lux at eye level was verified via a lux meter (Testo 540). The only variable that differed between light conditions was the strength of the neutral density filter used.

Each participant maintained a regular sleep-wake cycle (~11:00 pm – ~7:00 am) for 7 days, with compliance confirmed both verbally and via wrist actigraphy (Actiwatch 2; Philips Respironics, Bend, Oregon, USA). Participants were instructed to avoid afternoon caffeine consumption and to maintain consistent consumption across all 7 days. On nights 5, 6 and 7 participants visited the laboratory at Monash University from 8:15 pm to 10:15 pm. Sessions comprised 10 minutes dark adaptation (complete blackout goggles), followed by 1 hour exposure to one of three light intensities (administered in a counterbalanced order). Subjective sleepiness was assessed directly before and after light exposure with the Karolinska Sleepiness Scale (KSS)[58]. Immediately following light exposure and KSS rating, participants performed the behavioural task for ~36 minutes while EEG was recorded.

Participants were not made aware of the light intensity manipulation during testing. To evaluate their perceptions of the light conditions, they completed a questionnaire directly after their third session, which asked them to judge during which of the sessions the light intensity was (a) the brightest, (b) the least bright and (c) of medium brightness. Participants then stated their confidence in these judgments, by reporting "to what extent [they] were aware each night that the light's brightness was different to that of the other nights", on a scale from 1 to 10 (1 - "not aware at all"; 5 - "somewhat aware, but not sure of the change"; 10 - "very aware/certain of the change"). To account for the possibility that participants were aware of the light intensity manipulation, participants' judgments and confidence ratings were examined. Although 50% of participants correctly judged the order of light intensity exposure, there was no relationship between participants' accuracy in these judgements and their confidence that they were correct [incorrect *mean confidence* = 6.25, $SD = 2.93$, $n = 12$; correct *mean confidence* = 7.67, $SD = 2.5$, $n = 12$. Robust t-test alternatives were used since confidence distributions were not normal[59] - bootstrapped Yuen-Welch test with 20% trimmed means and windsorized variances: $t = 1.62$, $p = 0.083$; Bayesian t-test analogue: posterior mean confidence difference = 1.49, 95% HDI = −0.94 to 3.91]. Nor was there any effect of judgment accuracy or Light intensity on change in KSS subjective sleepiness scores after light exposure [Light intensity $\chi^2(2) = 0.75$, $p = 0.688$; Judgment Accuracy $\chi^2(2) = 0.29$, $p = 0.590$; Light intensity × Judgment Accuracy $\chi^2(2) = 1.23$, $p = 0.539$]. Our finding that accuracy in judging light intensity bore no relationship to subjective sleepiness ratings as a function of light intensity, together with an absence of a relationship between accuracy and confidence, suggest the absence of any expectancy effects or demand characteristics[60].

Behavioural paradigm. Participants were seated in a darkened room, 56 cm from a 21 inch CRT (85 Hz, 1024 × 768 resolution) to perform a novel variant of the random dot motion (RDM) task[20–22] where they fixated centrally and monitored 4 peripheral patches (one in each quadrant) of 150 moving dots for targets defined by a seamless transition from random motion to coherent motion in an upward or downward direction (see Fig. 4). Upon detecting a target, participants made a speeded button press with their right index finger. Since response hand was held constant across the three repeated-measures levels of Light, response hand cannot have influenced the key effects of Light on RT and α-power observed herein. Stimuli appeared white (RGB: 221) against a black background. The fixation mark was a central 5 × 5 pixel square. The circular dot patches were of 8 degrees diameter with the centre of each patch situated 6 degrees below or above and 10 degrees to the left or right of the central fixation point (see Fig. 4). During random motion, 150 dots per patch (each dot 6 × 6 pixels) were placed at random and independent positions within each of the patches at a rate of 21.25 frames/s. During coherent motion targets, 60% of these dots were randomly selected on each frame to be displaced by a fixed distance of 0.282 degrees in either a downward or upward direction on the following frame, resulting in a motion speed of 6 degrees/s. The four dot patches and fixation mark remained on screen throughout the entire task, however dot motion paused (i.e. all dots became stationary) between trials. When dot motion was paused, stationary dots were set slightly darker (RGB: 181) to account for the absence of the 21.25 frames/s flicker. The motivation behind using relatively high dot coherence (60%) was to ensure fast RTs with relatively low variability to enable detection of subtle processing differences between left and right hemifield targets.

Participants completed 336 trials containing no fixation breaks during each session. Each trial consisted of a period of random motion (initiated on fixation and lasting 1.8, 2.8 or 3.8 s) followed by a coherent motion target (terminated directly after a response or after 1 s). Targets only appeared once within one of the 4 patches/quadrants on any given trial. If a fixation break occurred during a trial (either a blink or a gaze deviation >4 degrees from centre, detected via EyeLink1000, SR Research Ltd), the task paused (stationary dots), and text (dark grey, RGB: 109) appeared at fixation for 200 ms reminding participants to "keep [their] eye on the spot", before the trial restarted. The 24 possible trial types (each a combination of one of the 3 periods of random motion, 4 target locations, and 2 coherent motion directions), occurred in a pseudorandom order with the constraint that each different trial type arose twice every 48 trials. Following the coherent motion target, all dots paused and remained stationary on the screen for 100 ms before a "blink now" message (RGB: 109; 200 ms) appeared at fixation. Stationary dots then remained onscreen for a further 400 ms fixation period before the next trial began. The paradigm was run on a 32-bit windows XP machine using MATLAB (MathWorks) and the Psychophysics Toolbox extensions[61–63]. Paradigm scripts can be found online.

Data processing. Data were processed using a combination of custom scripts and EEGLAB[64] routines implemented in MATLAB (MathWorks). All processing scripts used for the current study can be found online (https://github.com/DanielPNewman/BlueEnrichedLightRepo). Continuous EEG was acquired from 65 scalp electrodes using a Brain Products BrainAmp DC system digitized at 500 Hz. A 35 Hz low-pass filter was applied offline using 4 th order Butterworth filters, noisy channels were interpolated (spherical spline) and the data were re-referenced to the average reference. Epochs were then extracted from the continuous data from −700 ms to 1200 ms around target onset, and baselined with respect to −100 to 0 ms before target onset. Power in the α-band was calculated following the methods by Thut and colleagues[17]. Each epoch was band-pass filtered to α range (8–13 Hz), rectified (converted to absolute values) and trimmed to exclude the 200 msec at the beginning and end of the epoch in

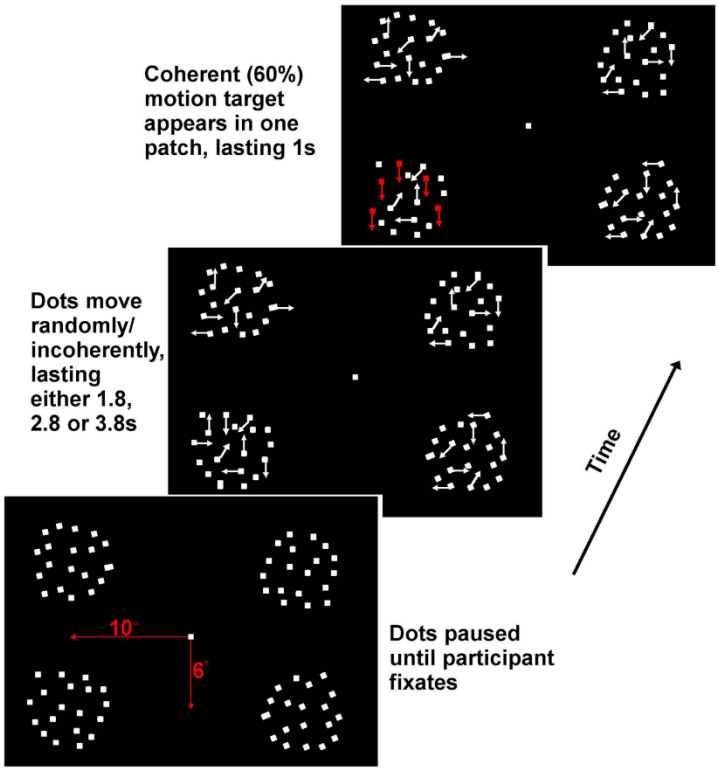

Figure 4. Schematic of a single trial. Participants fixated on the central dot and monitored the peripheral patches of randomly moving dots for instances of coherent motion (either upward or downward). Participants responded to motion targets via a speeded button press. Coherent motion targets only occurred in one of the four patches, once per trial. The pre-target random motion lasted either 1.8, 2.8 or 3.8 s, chosen randomly on a trial-by-trial basis.

order to eliminate filter warm-up artefacts. Data were then smoothed by averaging inside a moving window of 100 ms, moving forward in 50 ms increments.

Electrode selection for pre-target α analysis as a function of hemisphere. Since short-wavelength light has been shown to modulate α-power at rest[18] and pre-target parieto-occipital α-power is a robust marker of attentional deployment between the hemifields[17], the current study focused on parieto-occipital α-power measured during the interval immediately prior to coherent motion onsets (mean −500 ms to target onset). The difference in grand average α-desynchronisation elicited by left- versus right-hemifield targets indicated that lateral parieto-occipital electrodes were the most sensitive to covert shifts in attention towards each hemifield (see Fig. 1B), in line with previous work[17,25,40,65–69]. Post-target α-desynchronisation was used to select individualized parieto-occipital electrodes for α-power analysis, ensuring α was measured from electrodes most sensitive to spatial orienting. Since light exposure asymmetrically influenced the RT measure of spatial attention orienting (Fig. 1A), individualized electrodes were chosen on a per-session basis. This approach focuses on the parieto-occipital regions while permitting some variation in electrode selection between sessions to account for: (a) subtle individual differences in cap fit, scalp morphology, and cortical folding between participants, and (b) subtle differences in spatial attention processing related to the light manipulation. Four electrodes per hemisphere with maximal difference in mean post-target (50–600 ms) α-desynchronisation for contralateral versus ipsilateral targets (calculated from average post-target α waveforms for each session) were selected from the 16 lateral parieto-occipital electrodes (left hemisphere P1, P3, P5, P7, PO3, PO7 PO9, O1; right-hemisphere P2, P4, P6, P8, PO4, PO8, PO10, O2).

Inferential analysis. Inferential statistics were calculated using a combination of custom scripts and packages in R. All R scripts and data for reproduction of results can be found online (https://github.com/DanielPNewman/BlueEnrichedLightRepo). Target detection accuracy was at ceiling (mean = 97.4%). We used multilevel linear modelling and maximum likelihood ratio tests via the *lme4* package[70] to test for fixed effects of light intensity, target-hemifield and hemisphere on single trial measures of RT and α-power data. Follow-up contrasts were performed as appropriate using the *multcomp* package[71]. This multilevel approach was preferred over classic ANOVA methods as it accommodated dependent data due to repeated measures[19] and allowed random intercepts

to account for the nesting of each cerebral hemisphere (for α-power measurements) inside participants who were nested inside different Light Condition Orders (6 possible orders administered in a counterbalanced manner). To identify the final random effect structure we first followed the criteria of Barr *et al.*[72,73] by fitting a maximal model including by-subjects random slopes of each fixed effect and crossed factors of Light Intensity (low, medium, high), Incoherent Motion Period (1.8, 2.8, 3.8 seconds), Motion Direction (upward, downward), Target Location (1 of 4 quadrants) and Trial Number (1 to 336). This maximal random effects structure failed to converge, however, showing the maximal model was over-parameterized[74,75]. Therefore, we identified a parsimonious[74] random effect structure using an iterative procedure[76] which employed likelihood ratio tests to compare models without each particular random effect to the model including the random effect, and retained only the random effects which both improved the model fit and did not lead to failure to converge. This lead to the inclusion of by-subjects random slopes of Hemifield and pre-target alpha power, but the exclusion of random slopes of Light, when modelling RT, and the exclusion of random slopes for Light and Hemisphere when modelling pre-target alpha power. Fixed effect plots were created using the *Effects* and *ggplot2* packages[77,78].

As described above, all completed trials were uncontaminated by eye blinks or fixation breaks. Trials were excluded from analysis if: (a) RTs were <200 ms (pre-emptive responses) or >1000 ms (responses after coherent motion offset); (b) broad-band (0–35 Hz) EEG from any channel exceeded $+/-100\,\mu V$ during the interval from -500 ms to 0 ms before target onset for pre-target α analysis, or during the interval from -100 ms before target onset to 100 ms after RT for the α desynchronisation analysis which was used to select electrodes most sensitive to covert shifts in attention (see below). The distribution of single trial α-power measures had strong positive skew so they were log transformed to normality for any analysis in which α-power was the criterion/dependent variable. RT data did not require transformation. Outlying data points (greater than 3 standard deviations from the participants' conditional mean) were removed from single trial RT and α-power measures prior to inferential analysis.

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Author Contributions
The experiment was conceived by D.P.N. and designed by D.P.N., S.W.L., A.C.P.M., R.A., M.H.O.N., M.T.R.Z. and M.A.B. The attention task was programed by S.P.K. with amendments made by G.M.L. and D.P.N. Data collection was performed by D.P.N., A.C.P.M., R.A., M.T.R.Z. and M.H.O.N. Data analyses was conducted by D.P.N. D.P.N., S.W.L., G.M.L., A.C.P.M., M.H.O.N., S.W., R.G.O.C. and M.A.B. wrote the manuscript.

Additional Information
Data availability: Analysis scripts and paradigm code (https://github.com/DanielPNewman/BlueEnrichedLightRepo) as well as the raw data (https://dx.doi.org/10.4225/03/574CEA1FAFB69) are open access and available under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 International License.

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CHAPTER FIVE: TESTING THE EFFICACY OF SHORT WAVELENGTH LIGHT FOR IMPROVING SPATIAL ATTENTION AFTER RIGHT HEMISPHERE STROKE

CHAPTER FIVE

Declaration for Thesis Chapter Five

Declaration by candidate

In the case of Chapter Five, the nature and extent of my contribution to the work was the following:

Nature of Contribution	**Extent of contribution (%)**
Literature review, hypothesis conception and analysis design, recruitment and testing of participants, data processing, inferential data analysis, and manuscript write-up.	85%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of Contribution**	**Extent of contribution (%) for student co-authors only**
Dr. Daniel Newman	Study design, critical reviews of manuscript	
Dr. Gerard Loughnane	Data analysis and critical reviews of manuscript	
Dr. Rene Stolwyk	Critical reviews of manuscript.	
Prof. Shantha Rajartnam	Study design and critical reviews of manuscript.	
Dr. Trevor Chong	Imaging consultation and critical reviews of manuscript.	
Dr. Peter New	Critical reviews of manuscript.	
Dr. Redmond O'Connell	Critical reviews of manuscript.	
Prof. Mark Bellgrove	Study design, critical reviews of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

Candidate's Signature:	[redacted]	Date: 19/10/17
Main Supervisor's Signature	[redacted]	Date: 19/10/17

Preamble to Chapter Five

In the previous chapter, Newman et al. (2016) investigated if exposure to blue-enriched light could activate right-hemisphere attention networks, thus enhancing attention to left space in healthy individuals. The results of Chapter Four showed that exposure to higher, relative to lower, intensity blue-enriched light enhanced response-times for stimuli in the left, but not right, visual hemifield. This processing benefit was mediated by a specific effect of light intensity on right-hemisphere parieto-occipital α-power. These behavioural and neurophysiological effects were sustained over task duration (~36 minutes). These data provide convincing evidence for a direct modulatory influence of alertness on the physiological substrates of spatial attention, using a non-invasive, non-pharmacological manipulation of alertness, which lasts post light exposure. This investigation suggested that this approach had utility as a potential rehabilitation strategy for neglect patients.

In this chapter, we investigate the utility of short-wavelength light as a means of remediating spatial bias using a single-case repeated measures in four stroke patients with right middle cerebral artery involvement and neglect. Participants completed a five-session protocol involving a baseline session (no light intervention), two sessions of active control (low intensity blue-enriched white light; 50 lux) and two sessions of the active intervention (high intensity blue-enriched white light; 1400 lux). The light intervention (1 hour) occurred prior to the completion of a bilateral motion detection paradigm (total ~ 1,200 trials per participant), with the primary outcome measure being a reaction time (RT) asymmetry index. Results indicated that there was no significant effect of blue-enriched white light on spatial inattention in this sample. We discuss the limitations of this particular study but given the paucity of evidence for current rehabilitation strategies in neglect, we ultimately advocate for further investigation of novel rehabilitation strategies in this population.

Note: Please see **Appendix 6** for supplemental material related to this chapter and referred to in the paper below

Abstract

Hemispatial neglect is a disabling neurological syndrome that most commonly arises from stroke affecting the right hemisphere. Neglect is defined by a pathological inattention for the contralesional hemifield and a bias of attention towards the ipsilesional hemifield. There is no current consensus regarding the "gold standard" for the rehabilitation of neglect, and overall the evidence-base of neglect rehabilitation is weak. Exposure to light - particularly that enriched for the blue spectrum (459-483nm) - has been shown to activate key right-hemisphere attention networks and to enhance attention-related functions, such as vigilance and spatial attention. This study employed a within-participants design to examine the effects of blue-enriched white light on spatial inattention in four stroke patients with right middle cerebral artery involvement and neglect. Participants completed a five session protocol involving a baseline session (no light intervention), two sessions of active control (low intensity blue-enriched white light; 50 lux) and two sessions of the active intervention (high intensity blue-enriched white light; 1400 lux). The one hour light intervention occurred prior to the completion of a bilateral motion detection paradigm (total ~ 1,200 trials per participant), with the primary outcome measure being a reaction time (RT) asymmetry index. Visual analyses and planned Tau-U analyses did not reveal any significant effect of blue-enriched white light on spatial inattention in this sample. Limitations of this study include individual differences (sleep, mood) that are common in stroke populations, the age of the current sample and a small sample size. This is the first study to investigate the utility of blue-enriched white light to remediate pathological biases of spatial attention after right hemisphere stroke. We advocate for the further investigation of novel rehabilitation strategies for neglect.

Neglect is a common and disabling neurological syndrome clinically defined as the inability to detect, respond to, and orient towards stimuli on the side contralateral to cerebral damage (Heilman & Valenstein, 1979; Parton, Mahotra, & Husain, 2004). It is more severe and enduring following stroke to the right hemisphere (resulting in inattention to the left side of space), compared to the left hemisphere, with damage generally affecting the territories supplied by the middle cerebral artery (Ringman, Saver, Woolson, Clarke, & Adams, 2004; Swan, 2001).

The incidence of neglect reported within stroke populations varies widely, from 10%-82%, with some estimates postulating that anywhere between three and five million patients worldwide suffer from neglect post-stroke each year (Appelros, Karlsson, Seiger, & Nydevik, 2002; Chen, Hreha, Fortis, Goedert, & Barrett, 2012). Although the majority of these individuals recover, approximately one-third of patients manifest a chronic form of neglect, with a substantial proportion exhibiting clear deficits more than six months post-stroke (Karnath, Rennig, Johannsen, & Rorden, 2011; Rengachary, He, Shulman, & Corbetta, 2011). This is important for stroke rehabilitation given that neglect is associated with poor functional outcomes (Ween, Alexander, D'Esposito, & Roberts, 1996), including longer hospital stays (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001), slower and attenuated recovery rates (Gillen, Tennen, & McKee, 2005), reduced ability to complete activities required for daily living (Di Monaco et al., 2011; Katz, Hartman-Maeir, Ring, & Soroker, 1999), and worse function improvement during rehabilitation (Paolucci et al., 2000).

A variety of rehabilitation strategies have been developed to alleviate, reduce or remediate chronic neglect symptoms (Luaute, Halligan, Rode, Rossetti, & Boisson, 2006; Maxton, Dineen, Padamsey, & Munshi, 2013; Tsai et al., 2013). Techniques that have previously been trialled include visual scanning training (Kerkhoff & Schenk, 2012; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002), sustained attention training (Robertson, Tegnér, Tham, Lo, & Nimmo-smith, 1995), sensory stimulation (Kerkhoff et al., 2012; Utz, Keller, Kardinal, & Kerkhoff, 2011), prism adaptation (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Ladavas, Bonifazi, Catena, & Serino, 2011; Serino, Barbiani, Rinaldesi, & Ladavas, 2009), pharmacological treatments (Danckert & Ferber, 2006; Dodds, Muller, & Manly, 2009; Gorgoraptis et al., 2012; Lucas et al., 2013; Malhotra, Parton, Greenwood, & Husain, 2006; van der Kemp, Dorresteijn, Ten Brink, Nijboer, & Visser-Meily, 2017), and brain stimulation (Brighina et al., 2003; Oliveri et al., 2001; Song et al., 2009; Sparing et al., 2009).

One promising approach for remediating pathological spatial biases is through

modulations of the arousal system (Van Vleet & DeGutis, 2013). The inter-linked nature of spatial and non-spatial functions, such as alertness and arousal, are fundamental to the contemporary model of neglect posited by Corbetta and Shulman (2002). Corbetta and colleagues (2011) postulate that neglect results from damage to the right lateralised ventral attention network (VAN), a system that is associated with the maintenance of arousal, vigilance, and stimulus-driven, attentional selection (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta, Kincade, & Shulman, 2003; Corbetta & Shulman, 2002, 2011). The consequence of damage to the VAN is thought to be a general reduction in arousal, which subsequently causes an imbalance of the bilateral dorsal attention network, such that the left hemisphere becomes hyperactive, and the right hemisphere becomes hypoactive. This dysfunctional pattern of activation results in a shift of attention rightwards, ultimately manifesting as neglect of left space. This theory is supported by the work of Robertson, Mattingley, Rorden, and Driver (1998) who reported that the presentation of loud and unexpected tones phasically alerted the brain and significantly ameliorated (or in some cases reversed) neglect on subsequent trials during a lateralised temporal order judgment task. Furthermore, pharmacological treatments that increase arousal, namely bromocriptine and methylphenidate, have been shown to temporarily reduce neglect symptomology (Hurford, Stringer, & Jann, 1998). However, despite the multitude of attempts to find an effective rehabilitation strategy, a recent Cochrane review on neglect rehabilitation concluded that there was no clear evidence for preferentially using one rehabilitation strategy over another (Bowen, Hazelton, Pollock, & Lincoln, 2013). Further, according to the Australian Clinical Guidelines for Stroke Management (National Stroke Foundation, 2010), no treatment protocol has received a grade higher than a C indicating that the "body of evidence provides some support for recommendation(s) but care should be taken in its application" (p.4). Given these limitations, there is an imperative to identify novel treatment options that are practical and effective. Here we tested the hypothesis that ocular-light exposure may provide a non-invasive, non-pharmacological mode of ameliorating pathological biases of spatial attention in neglect patients.

Light not only provides visual information but it also modulates many non-visual functions, including alertness and performance on cognitive tasks (Berson, 2003; Viola, James, Schlangen, & Dijk, 2008). A non-rod, non-cone photoreceptor system is thought to mediate the non-visual effects of light, using a subset of intrinsically photosensitive retinal ganglion cells (ipRGCs) that are maximally sensitive to blue light (459-483nm; Brainard et al., 2001; Chellappa et al., 2012; Vandewalle et al., 2011). These cells are present at low

densities throughout the entire retina and utilise the photopigment melanopsin to influence the non-visual effects of light (Ferlazzo et al., 2014; Lucas et al., 2014). A series of PET and MRI studies have examined light-induced modulations of brain activity in healthy participants during non-visual cognitive tasks, such as auditory 2-back and oddball tasks (Lehrl et al., 2007; Perrin et al., 2004; Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007). These studies have demonstrated increased activation in regions associated with a large occipito-parietal attention network, such as the right intraparietal sulcus (Perrin, 2004). Further, light exposure has been found to activate key areas of right-hemisphere attention networks (Perrin et al., 2004; Vandewalle et al., 2006). It has been suggested that the alerting effect of light is transmitted indirectly via a multisynaptic pathway from the suprachiasmatic nucleus, via the dorsomedial hypothalamus, to the locus coeruleus, from which widespread projections of norepinephrine to the cerebral cortex regulate arousal and alertness (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Vandewalle, Maquet, & Dijk, 2009). The alerting effect of light varies as a function of wavelength, with blue light (480nm) more effective in promoting improvements on a vigilance task than green light (550nm; Lockley et al., 2006). In addition, exposure to blue light resulted in increased activation in areas including the left hippocampus, left thalamus and right amygdala when compared to green light; and the left middle frontal gyrus, left thalamus and bilateral brainstem when compared to violet light (Vandewalle, Schmidt, et al., 2007).

Convergent evidence thus suggests that blue-light exposure can positively influence the alerting system of the brain and may therefore be an effective treatment for disorders of alertness. This has recently been investigated in a traumatic brain injury population, using a randomised, placebo-controlled trial assessing the efficacy of a 45 minute/day home-based blue light (465nm) treatment to combat fatigue (Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2014). Compared to yellow (574nm) or no light treatment, blue-light exposure resulted in significantly less subjectively reported fatigue and daytime sleepiness.

Newman and colleagues (2016) recently investigated the effect of blue-enriched light on spatial attention in healthy individuals, using a bilateral perceptual decision-making paradigm and simultaneous electroencephalography (EEG). Previous work with this task has demonstrated that healthy adults are faster to detect targets in the left, compared with right, hemifield targets (i.e., the task elicits pseudoneglect; Newman et al., 2014; Newman, Loughnane, Kelly, Connell, & Bellgrove, 2017). Using a dose-response within-subjects method, exposure to one hour of high intensity blue-enriched light (~1400 lux) pre-task was found to speed detection of left, but not right, hemifield targets. Newman et al (2016)

reported that the reduced response times for left-hemifield targets was driven by an enduring effect of the light exposure on right-hemisphere parieto-occipital α-power, a robust measure of spatial attention (Thut, Nietzel, Brandt, & Pascual-Leone, 2006). Further, this effect did not diminish over the duration of the ~36 minute task demonstrating that prior light exposure can have an enduring impact on attention for the left hemifield. These results suggest the possibility of using of blue-enriched light to overcome the persistent and aberrant right spatial bias in neglect patients.

In this study, we conducted the first reported use of blue-enriched white light in stroke patients with right hemisphere neglect. It was hypothesized that our bilateral perceptual decision-making paradigm would elicit a right spatial bias at baseline in neglect patients. Secondly, it was hypothesized that exposure to high, relative to lower, intensity blue-enriched white light would shift this pathological right bias seen at baseline in a leftward direction.

Method

Ethical approval was obtained from the Monash Health and Monash University Human Research Ethics Committee prior to the commencement of the study. The experimental protocol was approved and carried out in accordance with the approved guidelines. All participants were volunteers naive to the experimental hypothesis being tested and each provided written informed consent.

Participants

Four stroke patients with right middle cerebral artery involvement and neglect were recruited from sub-acute rehabilitation settings (AA, BB, and CC) and the community (DD). Inclusion criteria included a diagnosis of stroke based on neurological examination and brain imaging, notation of left spatial inattention in sub-acute rehabilitation medical notes, the presence of neglect on screening measures, right handedness, proficiency in English, and sufficient cognitive function to complete the study. Exclusion criteria included epilepsy, seizures, and personal history of unexplained fainting or sensitivity to flickering light, significant head injuries, or any history of psychiatric or neurological illness.

At the time of testing, all participants were aged 62-69 years, years of education varied (range = 8-15 years), as did time since injury (range = 6 months 22 days – 18 months 22 days). The National Institute of Health Stroke Scale (NIHSS; (Brott et al., 1989) was

completed on admission to the rehabilitation setting for three participants (AA, BB, and CC) and was retrospectively completed based on medical records for DD (Williams, Yilmaz, & Lopez-Yunez, 2000). The NIHSS is a systematic assessment tool that provides a quantitative measure stroke-related neurological deficit (0= no measurable deficit, 1-4 = minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-42= severe stroke; Brott et al., 1989). The Functional Independence Measure (FIM; Keith, Granger, Hamilton & Sherwin, 1987) is an 18-item scale used to measure patient disability, with lower scores representing higher levels of disability and higher scores representing more functional independence (see Supplemental Material). Participant characteristics and demographics were collected from participants and medical records (see Table 5.1). Imaging confirmed the presence of right middle cerebral artery involvement (see Table 5.2 for imaging summaries). MRI and CT brain imaging were reviewed by a neurologist (T.C.), who delineated the lesion and it was subsequently mapped onto a lesion map using MRICron (see Figure 5.1; Rorden, Karnath, & Bonilha, 2007). Participant medication varied at the time of testing, but included hypolidaemic agents, anti-hypertensives, anti-coagulants/anti-thrombotic, and beta-adrenergic blocking agents (for complete list see Supplemental Material, Table S5.1). Of note, AA and DD were taking prescribed anti-depressants (SSRI) and BB was being treated with a narcotic analgesic. At the time of study participation, no participant had a diagnosis of a primary sleep disorder. Prior to study involvement, the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) were used to evaluate the nature of participant's daytime sleepiness (Johns, 1991) and subjective sleep quality (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). Two participants (BB, DD) endorsed items indicative of excessive daytime sleepiness on the ESS (score > 9), while AA and CC had normal levels of daytime sleepiness. One participant (DD) reported poor sleep quality (PSQI > 5; Buysse et al., 1989).

Screening Measures

Prior to testing, participants were screened for the presence of neglect using four spatial attention screening tasks - Greyscales task (Nicholls, Bradshaw, & Mattingley, 1999), Landmark task (Bellgrove et al., 2005; Fink et al., 2000; Marshall & Halligan, 1995), Bells cancellation (Gauthier, Dehaut, & Joanette, 1989) and a computerised extinction task (Bender, 1952). The screening measures indicated that each of the four stroke patients presented with spatial inattention for left space on the Greyscales and Landmark tasks (see Table 5.3).

Further information regarding the screening measures can be found in Supplementary Information.

Study design

The study used a within-participants design. Session order was pseudo-randomised across participants, such that participants either completed the sessions as BLHHL or BHLLH, where B was a baseline session with no light intervention, L was a low intensity blue enriched white light intervention and H was a high intensity blue enriched white light intervention. The low intensity blue enriched white light was used as an active control condition to safeguard against a placebo effect. Each phase comprised a single session, lasting approximately two hours.

Materials

Outcome measure

A bilateral perceptual decision-making paradigm, which is a novel variant of the random dot motion (RDM) task (Loughnane et al., 2016), was used to measure spatial inattention. Participants were required to fixate centrally and were discouraged from blinking or moving during each trial. Participants monitored two peripheral circular patches (one in each of the lower quadrants) of 150 moving dots.

Participants were required to detect targets, defined by a seamless transition from random motion to coherent motion in either an upward or downward direction in one hemifield (see Figure 5.2). Once a target was detected, participants made a speeded button press with their right index finger (regardless of motion direction). The responding hand was kept constant across trials. For all participants, this was their dominant and unaffected hand. Before beginning the task, participants read on-screen instructions and the experimenter also explained the task verbally to ensure adequate comprehension. To assess spatial bias, an index of visuospatial attention asymmetry was calculated. The RT asymmetry (Newman et al., 2017; Thut et al., 2006) was derived from RT (ms) using the following formula:

$$\text{RT asymmetry index} = \frac{\text{(left target RT)} - \text{(right target RT)}}{\text{(mean left and right target RT)}}$$

This index gives positive values when reaction-times are faster for right, relative to the left, targets (rightward spatial bias) and negative values when the opposite is true (leftward bias). If no asymmetry exists in the RT then the index gives a zero value.

Participants completed 10 blocks of the task (~28 minutes), with each block consisting of 24 trials (resulting in a total of 240 per session; 960 trials across the four intervention sessions). The two patch version of the random dot motion task has been shown to have good test-retest reliability (Newman, 2014). A short break (~15 seconds) interleaved each block of trials. Each trial consisted of a period of random motion (initiated on fixation and lasting 1800ms, 2800ms or 3800ms) followed by a coherent motion target (90% of the dots moved coherently), which ceased following a response or after 3000ms. Pilot testing with single participants demonstrated that 90% coherence was appropriate for stroke patients in sub-acute and rehabilitation settings. Targets (coherent motion) only appeared in one of the two patches on any given trial. The 12 possible trial types (each a combination of one of the 3 periods of random motion, 2 target locations, and 2 coherent motion directions) occurred in a pseudorandom order with the constraint that each different trial type arose twice every 24 trials. The paradigm was run on a 32-bit windows 7 laptop using MATLAB (MathWorks) and the Psychophysics Toolbox extensions (Brainard, 1997; Cornelissen, Peters, & Palmer, 2002; Pelli, 1997). The parameters used in this version of the bilateral perceptual decision-making paradigm can be found in the Supplemental Information.

Intervention materials

Each participant was exposed to two different blue-enriched white light intensities (low: 50 lux; high: 1400 lux – measured at eye level, vertical plane) across separate intervention sessions in a pseudo-randomised counterbalanced order (AA and CC completed BLHHL; BB and DDB completed BHLLH). During light sessions, participants were seated in front of two identical light boxes (Philips EnergyLight HF3305, Philips Lighting, Eindhoven, The Netherlands) fitted with high colour temperature, blue-enriched white lamps (17000K, PL-L ActiViva, Philips Lighting, Eindhoven, The Netherlands; Brainard et al., 2015). During the light intervention, participants were permitted to read books or magazines but were informed that their activity had to be consistent across all four testing session. All participants decided to read across all sessions and given the within-subject design, no further control was necessary.

One light box was placed at eye level 60cm from the eyes, while the other was positioned on the floor in front of the participant 45° degrees below eye level but pointing towards the eyes at a distance of 110cm (Newman et al., 2016). Light intensity (photopic lux) was manipulated by placing the appropriate neutral density filter 'stop' over the source to modify the intensity (lux) of all wavelengths of light equally without altering the spectrum. Photopic lux at eye level was verified via a lux meter (Testo 540; Newman et al., 2016). The only variable that differed between light conditions was the strength of the neutral density filter used. The timing of the sessions was individualised to commence eight hours after waking from sleep, to allow sleep pressure to increase through the waking day but avoid the wake maintenance zone (a period of reduced sleep propensity that occurs for a short period of time prior to the onset of melatonin secretion; Shekleton et al., 2013). To determine waking time, participants completed an adapted version of the National Sleep Foundation sleep diary (retrieved from https://sleepfoundation.org) to track sleep patterns (see Supplemental Materials, Table S5.2). Participants also wore a Philips Actiwatch 2 (http://www.usa.philips.com) to monitor participant's sleep/wake cycles, movement and light exposure. The actiwatch was worn on the wrist and recorded both activity and phototropic light data in 30-seconds epochs.

Procedure

For one week prior to the first session participants completed the adapted National Sleep Foundation sleep diary and wore the Philips Actiwatch 2 while completing their day-to-day activities in their home. This data were collected by the research team prior to the first session and was subsequently used to establish the individualized start time of the intervention sessions.

All sessions were conducted in the participant's home, in a dimly lit (<1 lux) room that was kept constant between each testing session. Participants completed five sessions, one baseline session and four light intervention sessions, across a five-week period. The baseline sessions were conducted prior to the intervention sessions, during which participants completed 240 trials of the bilateral perceptual decision-making paradigm without any light intervention. The subsequent light intervention sessions all comprised ten minutes of dark adaptation (complete blackout goggles), followed by exposure to one hour (Newman et al., 2016) of the two light intensities (administered in a counterbalanced order; BLHHL for AA and CC; BHLLH for BB and DD). Subjective sleepiness was assessed directly before and

after light exposure with the Karolinska Sleepiness Scale (KSS; Åkerstedt & Gillberg, 1990). Immediately following light exposure and KSS rating, participants performed the behavioural task for approximately 28 minutes. Note that there was no light exposure during performance of the task. A Dell Latitude E6440 laptop (15.12 inch x 10.16 inch screen, 60Hz, 1920 x 1080 resolution) was used for task completion and participants were seated at a viewing distance of 60cm. Participants were instructed to avoid afternoon caffeine consumption on the testing days and to maintain consistent consumption across all seven days.

Participants were not made aware of the light intensity manipulation during the study. To evaluate their perceptions of the light conditions, they completed a questionnaire following the final light intervention session, which asked them to judge during which of the sessions the light intensity was: (a) the brightest; (b) the least bright; and (c) of medium brightness. Participants then stated their confidence in these judgments, by reporting "to what extent [they] were aware each night that the light's brightness was different to that of the other nights", on a scale from 1 to 10 (1 - "not aware at all"; 5 - "somewhat aware, but not sure of the change"; 10 - "very aware/certain of the change"). All four participants reported that they were not aware of any changes in light intensity across the four sessions. There were no instances of adverse events as a result of the intervention and participants did not report any discomfort associated with the light intervention.

Table 5.1. Participant demographics and stroke data

Participant	Sex	Age at screening	Stroke Type	NIHSS on admission	Oxford classification	FIM admission	FIM discharge
1 - AA	M	69	R) MCA	13– moderate	PACI	69	110
2 - BB	F	62	R) MCA	8 – moderate	PACI	41	42
3 - CC	F	64	R) MCA	22 - severe	PACI	75	118
4 -DD	F	63	R) ACA & R) MCA	6 - moderate	PACI	64	110

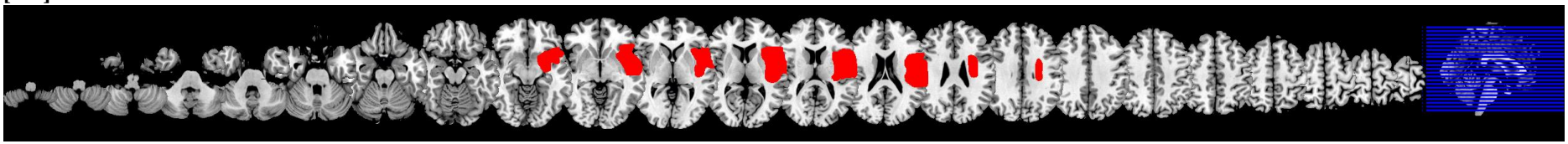
Note: R) MCA denotes right hemisphere middle cerebral artery involvement; R) ACA denotes right anterior cerebral artery damage;

NHISS= National Institute of Health Stroke Scale; FIM=Functional Independence Measure.

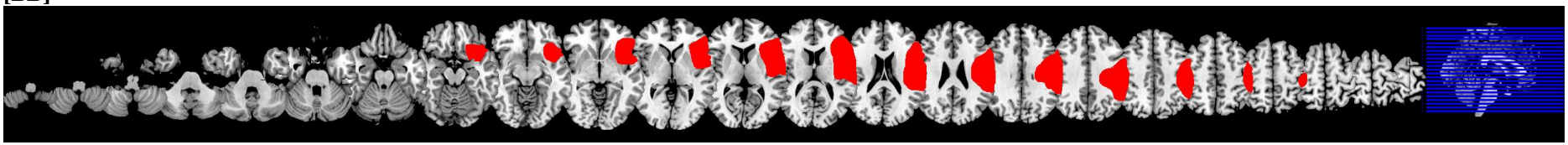
Table 5.2. Participant's imaging summaries

Participant	Imaging findings
1 - AA	**CT** - infarction involving right lentiform nucleus, external capsule and caudate nucleus measuring 2.5 x 4.1 x 3.9 (lateral lenticulostriate distribution).
2 - BB	**CT** - large area of right frontal and parietal cortical low attenuation with associated diffuse right cerebral sulcal effacement and 2 mm of midline shift to the left. Appearances compatible with acute right MCA territory infarction with associated moderate positive mass effect. Within the frontal low attenuation region, there is a punctate 1mm focus of high attenuation, which likely represents acute petechial haemorrhage.
3 - CC	**CT** - There is loss of grey-white matter differentiation in the right frontal lobe. Right insular ribbon sign. Hyperdense right MCA noted in the Sylvian fissure. Thrombus is noted within the distal right M1 with poor opacification of the subcortical MCA. **MRI** - There is an area of encephalomalacia and gliosis involving the right MCA territory, including the frontoparietal junction and the insular cortex.
4 - DD	**CT** – revealed cerebral infarction within the medial and lateral aspects of the right frontal lobe, the posterior right temporal lobe and the right parietal lobe superiorly. Small bilateral cerebral hemisphere infarcts are also demonstrated. **MRI** - There is also evidence of an old right occipito-parietal infarct, which demonstrated minor haemorrhagic transformation. An old right frontal infarct is also present in the middle cerebral artery territory. A small focus on subependymal diffusion restriction is present in the singular gyrus medial to the body of the right lateral ventricle. There is evidence of small bilateral cerebellar infarcts.

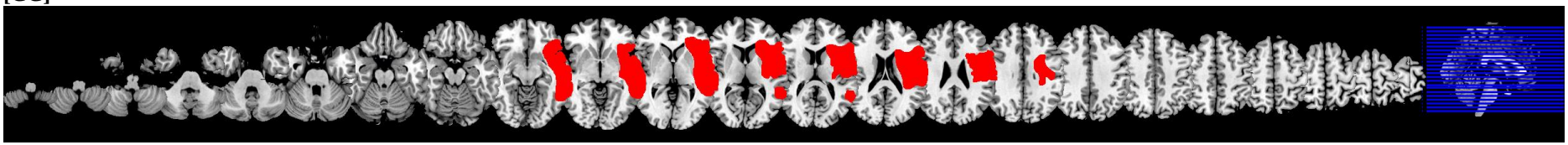
[AA]



[BB]



[CC]



[DD]

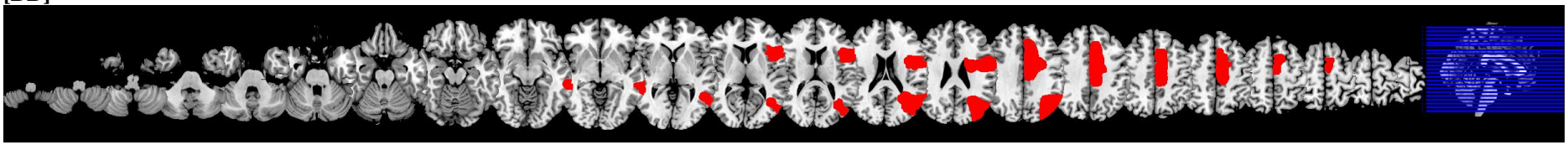


Figure 5.1. Participant's lesion maps. MRI and CT scans were reviewed by a neurologist (T.C.) who delineated lesion boundaries. Lesion regions were then mapped using MRIcron (Rorden et al., 2007) ch2bet.nii template and multislice views were created using axial slices, z= 14,20,26,32,38,44,50,56,62,68,74,80,86,92,98,104,110,116,122,128,134,140,146. All lesions have been flipped to the right hemisphere. A sagittal slices for visualization are provided on the far right.

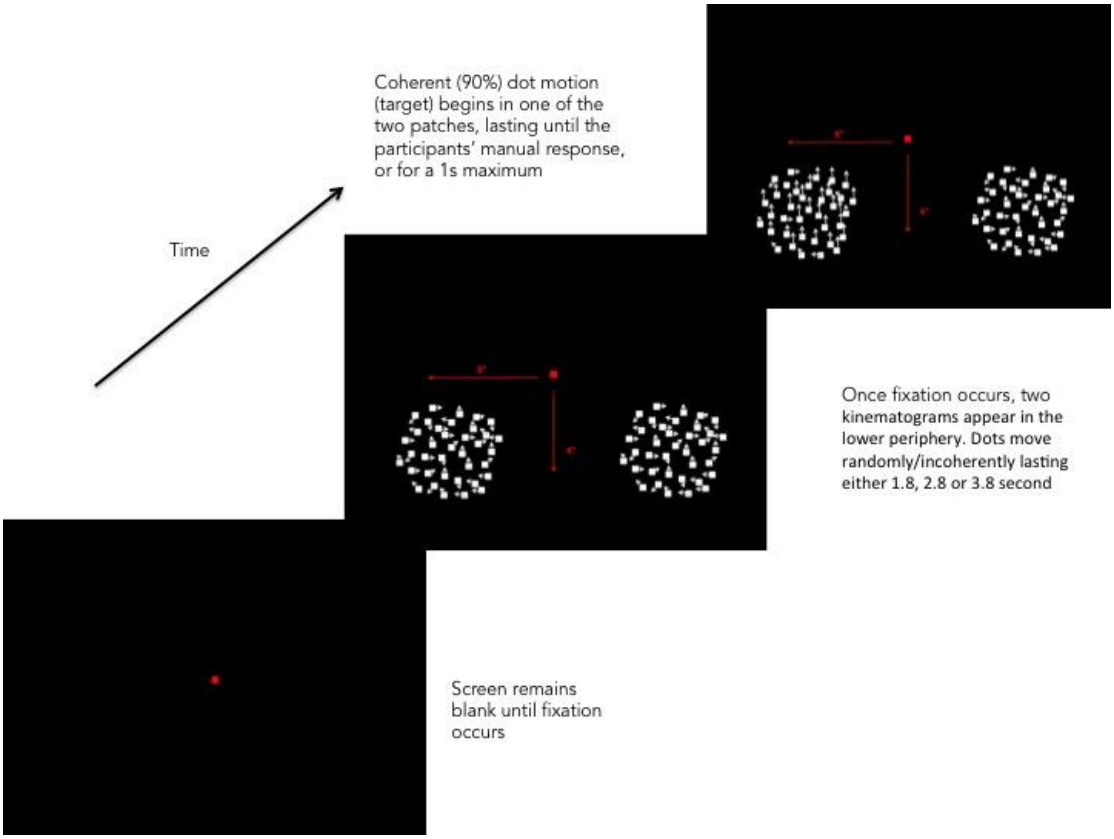


*Figure 5.2***.** Schematic of a single trial. The screen remained blank (apart from the fixation dot) until the trial was manually started by the examiner, at which point two peripheral patches of randomly moving dots appeared. Participants monitored these patches for instances of coherent motions (either upward or downward). Participants responded to motion targets via a speeded button press. Coherent motion only occurred in one of the two patches per trial. The pre-target random motion lasted either 1800ms, 2800ms or 3800ms, chosen psuedorandomly on a trial-by-trial basis.

Results

First, one sample t-tests were conducted on Session 1 (baseline) RT asymmetry data (10 RT asymmetry indices, one derived for each of the 10 blocks within the session) to ensure spatial bias was evident on the task prior to the light intervention. All participants displayed an RT asymmetry significantly different from 0, with a right bias evident such that RTs for right hemifield targets were significantly faster than RTs for left hemifield targets (see Table 5.4).

The impact of the high intensity light condition on participant's self-reported levels of sleepiness was analysed by visually assessing changes in KSS ratings following the presentation of high light intensities (see Supplemental Material, Figure S5.1). The effect was variable across participants and at times, within participants.

AA reported improvement in alertness during the first high intensity light session but a decrease in alertness during the following high light session. BB and CC's subjective levels of alertness did not alter following the high light condition. DD reported becoming less alert following both high light interventions.

Visual inspections were conducted according to the method recommended by Lane and Gast (2014) for single subject analysis, which includes within and between-condition analyses. In terms of within-condition analysis, RT asymmetries were variable within each block and in all participants, as determined by the application of the stability envelope to trend lines. Visual analyses were subsequently conducted to investigate whether there was a trend in participants' spatial bias during each session.

An RT asymmetry index was calculated for each block within each of the four intervention sessions (10 RT asymmetry indices per block; 40 in total per participant across four intervention testing sessions). Progression through the baseline and intervention sessions were displayed graphically and quantified in GraphPad Prism (version 7 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com). Linear regressions were used to assess whether the slope within each session differed significantly from 0.00 (see Figure 5.3). For AA, CC, and DD statistical analyses revealed that slopes of trend lines did not significantly differ from 0.00 (see Supplemental Materials, Table S5.3 for non-significant results), suggesting that there was no consistent pattern of RT asymmetry within each session for these participants. For BB, the slope line trend for the first high intensity light session (Session 2) was significantly different from 0.00, $F(1,8) = 5.921$, $p=0.040$ with a regression equation of RT asymmetry = 0.010*blocks x -0.046, suggesting that for this block participant BB became progressively more right biased (increased left neglect), a pattern potentially reflective of a time-on-task effect (Newman, O'Connell, & Bellgrove, 2013). There was no significant difference from zero between the slope of BB's other trend lines. Reflecting an inconsistency of RT asymmetries within these subsequent sessions.

With respect to between-condition analyses, visual inspection of the data (Figure 5.3) revealed no significant or consistent improvement in spatial bias (an RT asymmetry closer to 0.00) as a result of the treatment intervention (high intensity light). Planned comparisons were conducted using Tau-U, to statistically investigate differences in RT asymmetry between sessions. Tau-U is a nonparametric technique measuring data non-overlap between two conditions (Parker, Vannest, Davis, &

Sauber, 2011). Tau-U calculations were performed via the website: http://www.singlecaseresearch.org/calculators/tau-u (Vannest, Parker, & Gonen, 2011). It should be noted that statistical significance obtained via Tau-U is based on the assumption that the data are not autocorelated: There was no evidence of baseline trend in any participant (see Table 5.5) and therefore no baseline corrections were made to subsequent comparisons. Following Gast and Spriggs' (2009) assertion, only adjacent conditions were directly compared. For AA and CC, the following comparisons were made: B to L1, L1 to H1, H1 to L2 and L2 to H2. For BB and DD the following comparisons were made: B to H1, H1 to L1, L1 to L2 and L2 to H2. As seen in Table 5.5, for AA, CC and DD, there was no significant changes between any adjacent conditions, indicating that there was no significant effect of high intensity light exposure on RT asymmetry. For BB, there was a significant difference between baseline RT asymmetry and the first session of high intensity light (Session 2), Tau-U = -0.62, p=0.019. Visually, this effect was maintained across subsequent light intervention conditions and statistically there were no other significant differences between subsequent adjacent conditions, suggesting the RT asymmetries during the intervention sessions were comparable.

Table 5.3. Results from spatial inattention screening tasks conducted prior to intervention.

Participant	Greyscales		Landmark		Bells Cancellation		Extinction				
	Number correct	Left selected	Spatial index	Spatial bias	Targets found (/35)	CoC Index	Total correct (/36)	Left correct (/8)	Right correct (/8)	Bilateral correct (/16)	No target presented correct (/4)
1 - AA	34 (47.2%)	4 (5.6%)	1	Right	29	-0.008	35	8	8	15	4
2 - BB	35 (48.6%)	1 (1.4%)	0.6	Right	24	0.191	24	8	6	6	4
3 - CC	36 (50.0%)	0 (0.0%)	0.2	Right	17	0.314	36	8	8	16	4
4 - DD	33 (45.8%)	7 (9.7%)	0.6	Right	31	-0.040	36	8	8	16	4

Table 5.4. Results of one sample t-test testing each participant's Session 1 (baseline) RT asymmetry.

AA	RT asymmetry (M=0.045, SD=.047) was rightward biased, a statistically significant mean difference of 0.045, 95% CI [0.012, 0.079], $t(9) = 3.076$, p=0.013, d=0.973.
BB	RT asymmetry (M=0.179, SD=.068) was rightward biased, a statistically significant mean difference of 0.179, 95% CI [0.131, 0.228], $t(9) = 8.339$, p<0.001, d=2.637.
CC	RT asymmetry (M=0.093, SD=.042) was rightward biased, a statistically significant mean difference of 0.093, 95% CI [0.063, 0.123], $t(9) = 7.070$, p<0.001, *d=2.236*.
DD	RT asymmetry (M=0.915, SD=.074) was rightward biased, a statistically significant mean difference of 0.092, 95% CI [0.039, 0.144], $t(9) = 3.917$, p=0.004, d=1.238.

Discussion

It is well recognized that light has an alerting effect on the brain and can enhance non-visual functions, including alertness and cognitive performance (Berson, 2003; Brainard & Hanifin, 2005; Viola et al., 2008). Here we sought to capitalise on the observation that light, in particular blue or blue-enriched white light, can act as a non-pharmacological stimulant in remediating pathological biases of spatial attention arising from right hemisphere damage. Although all patients displayed rightward spatial bias (i.e., hemispatial neglect) on baseline testing, we observed no evidence that exposure to blue-enriched white light could shift this pathological spatial bias leftward. Consistent with our first hypothesis, our novel variant of the bilateral random dot motion task was able to elicit a right spatial bias at baseline, with all participants demonstrating slower RTs for left hemifield targets compared to right hemifield targets. Evidence that these patients continue to experience a significant left neglect following their return home demonstrates the need for further efforts at developing sensitive screening tools for neglect and highlights the need for a continued effort in developing accessible and efficacious rehabilitation techniques.

*Table 5.5***.** Tau-U results for planned comparisons for participants on RT Asymmetry on adjacent conditions.

Participant	Baseline Trend Contrast Tau (p value)	B v L1	B v H1	L1 v H1	H1 v L1	H1 v H2	L1 v L2	H2 vL2	L2 v H2
AA	-0.29 (*p*= 0.25)	-0.06		0.16		.02		0.06	
BB	-0.02 (*p*= 0.93)		-0.62*		-0.44		0.28		-0.40
CC	-0.11 (*p*= 0.65)	0.12		-0.14		0.22		-0.64	
DD	0.16 (*p*= 0.53)		0.12		0.48		-0.28		-0.44

* Significance at $p<0.05$

B: Baseline; L1: Low intensity light session 1; L2: Low intensity light session 2; H1: High intensity light session 1; H2: High intensity light session 2.

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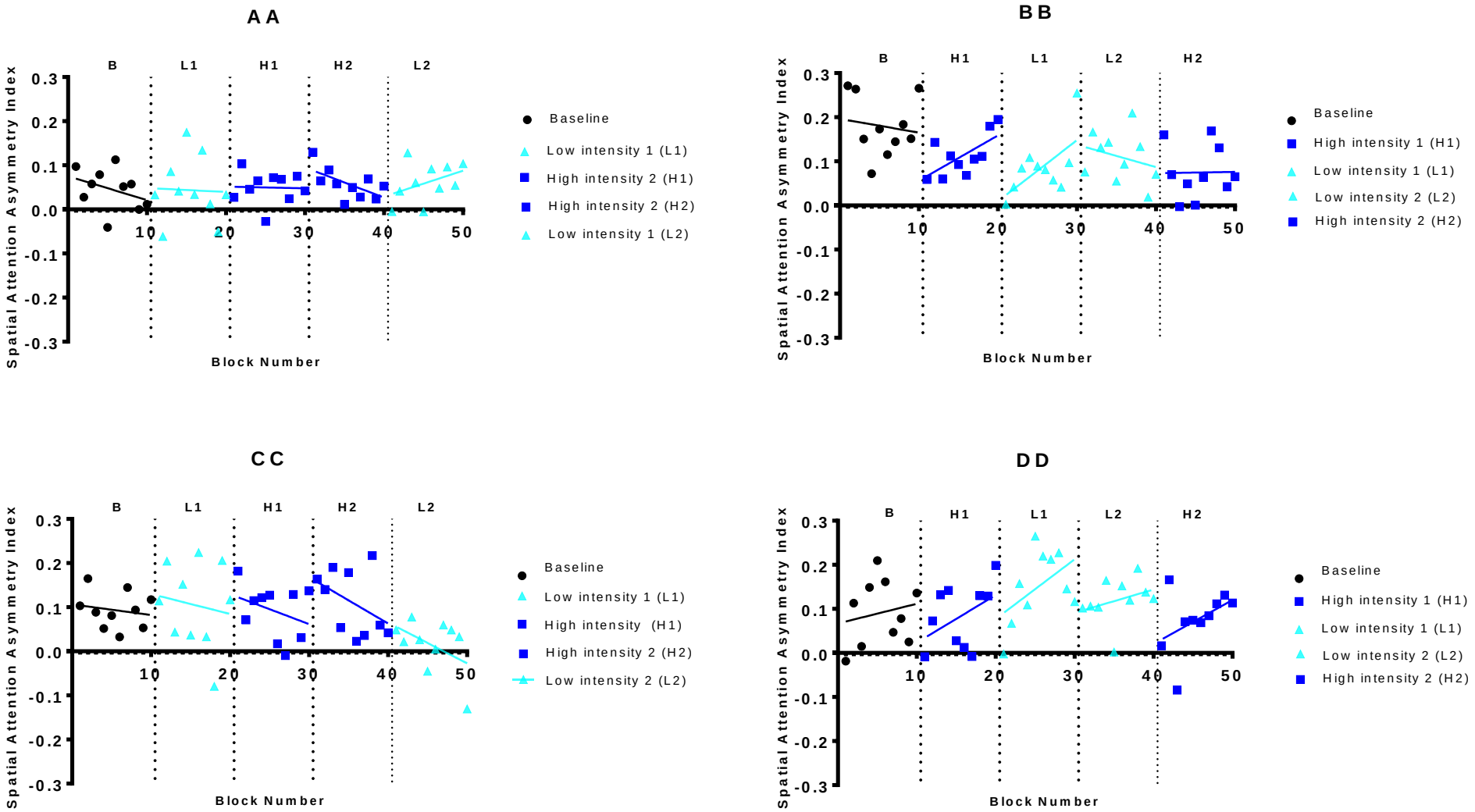

Figure 5.3. A graphical representation of RT asymmetries across the five sessions (baseline, low intensity, high intensity) for each participant. Positive RT asymmetries represent a right spatial bias (left neglect) and negative RT asymmetries represent a left spatial bias.

Contrary to our second hypothesis, we did not observe any systematic reduction in rightward spatial bias (rightward RT asymmetry) following the presentation of high intensity blue-enriched white light. The light intensity we selected for the high intensity condition is well within the range expected to elicit alerting effects in healthy volunteers (Zeitzer, Dijk, Kronauer, Brown, & Czeisler, 2000). For AA, CC and DD, visual and statistical analysis did not reveal any significant effect of low or high intensity blue-enriched white light on spatial bias. Overall, the RT asymmetries within each session for each participants were highly variable. This mitigated the ability to observe a systematic trend within sessions. In the case of BB, there was a reduction in right spatial bias when comparing performances during the baseline session (no light) to the first session of high intensity blue-enriched white light, however, it is important to note that there was no significant differences between subsequent low intensity and high intensity sessions. Therefore, this change should be interpreted with caution as the presence of a placebo effect or alternatively the presence of spontaneous improvement (Corbetta et al., 2005) cannot be discounted.

One potential explanation for why high intensity blue-enriched white light did not have the hypothesised effect on spatial bias within this set of patients is the age of our sample. Daneault et al. (2014) have previously reported that the older brain is less responsive to light than those of younger participants and support is now growing that aging differently affects a range of the non-visual functions of light (Daneault, Dumont, Massé, Vandewalle, & Carrier, 2016; Daneault et al., 2014; Revell & Skene, 2010). This possibility is perhaps best demonstrated by the lack of a consistent impact of high intensity blue light on the KSS ratings taken pre and post-light intervention in this sample. In small mammal studies, aging is associated with a decrease in the number of ipRGCs at a cellular level, which subsequently impacts the activation of ipRGC targets (Lupi, Semo, & Foster, 2012; Semo, Lupi, Peirson, Butler, & Foster, 2003; Semo, Peirson, et al., 2003). In addition, there are significant aging-associated changes in structures that are important for facilitating the non-visual effects of light, such as the suprachiasmatic nucleus, pulvinar, dorsomedial thalamus, insula, amygdala, frontal operculum (Daneault et al., 2016; Daneault et al., 2014; Gibson, Williams, & Kriegsfeld, 2009; Hofman & Swaab, 2006). Additionally, aging is associated with a yellowing of the lens, which leads to a reduced light transmission (Kessel, Lundeman, Herbst, Andersen, & Larsen, 2010). Nevertheless, studies using older adults have previously reported positive effects of blue light on prefrontal and

thalamic brain regions involved in alertness and cognition (Vandewalle et al., 2013). Despite these potential influencing factors, we believed it reasonable to assert that the arousal deficit would be greater in middle cerebral artery stroke patients than in healthy aging adults and therefore we felt it was reasonable to investigate the impact of light therapy despite these issues.

There are also a number of potential confounding variables that are inherent to the early recovery stage of neglect. Firstly, many patients post-stroke experience a disruption to their sleep wake-cycle and increased fatigue throughout the day that could be detrimental to the effect of blue-enriched white light on alertness (Stein, Harvey, Winstein, Zorowitz, & Wittenberg, 2014). Sleep disruptions can be the result of primary damage to brain tissues associated with the modulation of attention and sleep-wake patterns or an undiagnosed primary sleep disorder; or alternatively sleep disturbances can arise via secondary causes, such as depression (van der Werf, van den Broek, Anten, & Bleijenberg, 2001). These are important considerations within this sample given BB and DD reported excessive daytime sleepiness, DD reported poor sleep quality overall, and AA and DD had a diagnosis of depression requiring anti-depressant medication. The various medications used by the current sample are important to note, particularly the use of narcotic analgesics by BB, given the potential for this medication to induce drowsiness (Onen, Onen, Courpron, & Dubray, 2005) which could itself promote rightward spatial bias.

Although the current study yielded a null result we cannot discount the possibility that a larger trial with further optimised light protocols might yield evidence in favour of our hypothesis. We would suggest future studies investigate the impact of prolonged light therapy (i.e. one hour daily sessions over a month) on spatial inattention. Importantly, we contend that this result should not dissuade others from trialling novel interventions. This is particularly so, since all patients displayed significant rightward spatial bias at baseline on our experimental tasks, indicative of residual dysfunction. Moreover, the continued lack of consensus regarding the most effective therapeutic approach most likely reflects the heterogeneity of neglect and encourages the appropriate targeting of interventions to cognitive deficit. Riestra and Barrett (2013) have previously noted that given clinical heterogeneity "it is unlikely that a single form of intervention will prevail as the sole rehabilitation treatment" for neglect. Given the current set of potential neglect rehabilitation methods do not have a strong scientific basis and are variable in their efficacy, it is imperative that innovative approaches continue to be developed and evaluated.

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CHAPTER SIX: GENERAL DISCUSSION

Summary and implications of findings

Neglect is a common and disabling neurological syndrome clinically defined as the inability to detect, respond to, and orient towards stimuli on the side contralateral to cerebral damage (Heilman & Valenstein, 1979; Parton et al., 2004). Although many individuals recover, approximately one-third of patients manifest a chronic form of neglect, with a substantial proportion exhibiting clear deficits more than six months post-stroke. The presence of on-going neglect is significant as the disorder is associated with poor functional outcomes (Chen Sea et al., 1993; Ween et al., 1996), including longer stays in hospital (Cherney et al., 2001), slower and attenuated recovery rates (Gillen et al., 2005), reduced ability to complete activities required for daily living (Di Monaco et al., 2011; Katz et al., 1999), and greater functional deterioration following the end of rehabilitation (Paolucci et al., 2000). Yet despite decades of research the disorder is not well understood and this has subsequently hampered attempts to develop efficacious rehabilitation strategies.

This thesis had three core aims: (1) to investigate how perceptual decision-making and specifically the neural correlates associated with attention orienting and evidence accumulation are affected by aging; (2) to investigate the role of attention orienting and evidence accumulation in producing the archetypal left hemifield inattention in patients with neglect symptomatology following stroke; and (3) to investigate the utility of ocular blue-enriched light exposure, a non-pharmacological manipulation of alertness, to remediate the pathological bias of spatial attention to left space observed in neglect patients.

As such, **Chapter Two** presented work investigating perceptual decision-making processes - attention orienting ($N2_{(c)}$/ $N2_{(i)}$) and evidence accumulation metrics (CPP) in healthy aging. To our knowledge, this is the first study to use a bilateral motion detection paradigm in a healthy aging population as a means of investigating perceptual decision-making processes and subtle differences in spatial biases. There was evidence of significant group differences regardless of target hemifield, with older participants exhibiting slower peak $N2_{(c)}$ latency, later CPP onset, reduced CPP amplitude and a more gradual CPP slope overall. Importantly, it was $N2_{(c)}$ latency, CPP onset and CPP slope that were able to accurately discriminate between younger and older participants. These results suggested that declines in efficiency of attention orienting and evidence accumulation adversely impacted older adults performance on this

bilateral motion detection task. Further, these results supported previous work highlighting an information processing decrement in older participants. We suggest that impaired target selection and attention orienting, as measured by the $N2_{(c)}$; and slowed evidence accumulation, as indexed by CPP onset and slope, could be targeted by training techniques aimed at improving cognitive processes in older adults. Further, we propose that these perceptual decision-making metrics potentially have utility as a means of measuring improvement in aging intervention projects.

Next, we applied the perceptual decision-making framework to an investigation of spatial asymmetry in neglect patients. This study represented a proof-of-concept study demonstrating the ability to implement a perceptual decision-making framework in a neglect population. **Chapter 3** demonstrated that this approach can have utility to isolating and measuring ERPs related to attention orienting and evidence accumulation. Chapter **Three** indicated that there was dysfunctional attention orienting for left hemifield targets (aberrant right hemisphere $N2_{(c)}$) but evidence of compensation from the left hemisphere in the form of a pronounced $N2_{(i)}$ in neglect patients. Importantly, this compensation was not evident in patients with a more severe form of the disorder. Evidence accumulation, as measured by the CPP, was found to be important for sound behavioural performance in neurologically healthy participants, neglect participants and stroke participants without neglect, such that greater CPP slope was related to faster RTs in both hemifields. This is the first study to use a perceptual decision-making framework and EEG to investigate the underlying mechanisms in neglect. The unique contribution of this study is twofold. Firstly, we demonstrated that this approach provides insightful information about the neurophysiological processes that contribute to deviant spatial attention evident in neglect. Of note, this approach can be applied at the single subject level, which from a diagnostic perspective is an important consideration if this approach is to be of future clinical utility. Secondly, we have isolated and identified ipsilesional compensation in a sub-group of neglect patients. Given this compensation was not evident in patients with more severe spatial bias, we suggest that this ipsilesional component ($N2_{(i)}$) may be of use to track neglect recovery longitudinally. Further, with additional work clarifying the role of this component in a larger set of patients, it is possible that this neural process may itself be a good target for future rehabilitation in neglect patients.

Chapter Four outlined work previously published by Newman et al. (2016), a project to which the candidate made a contribution. In this work, we investigated the impact of blue-enriched light on alertness and spatial attention in healthy volunteers. Results showed that

exposure to higher, relative to lower, intensity blue-enriched light enhanced response-times for left hemifield targets but not right hemifield targets. The increased processing speed observed was mediated by a specific effect of light intensity on right-hemisphere parieto-occipital α-power. Of note, the behavioural and neurophysiological effects were sustained over task duration (~36 minutes). These results suggested that this approach might be an effective non-pharmacological rehabilitation strategy for patients with disordered spatial inattention, such as that observed in neglect. Therefore, this work was integral in providing the experimental foundation for the work completed in **Chapter Five.**

In the last experimental chapter, we investigated the effects of blue-enriched white light on spatial inattention in four stroke patients with right middle cerebral artery involvement and neglect. To our knowledge, this was the first investigation of light as a method of altering spatial biases in stroke patients. Although we did not find support for an effect of blue-enriched white light on spatial inattention in these patients, we advocate for further investigations of novel treatment approaches, as current rehabilitation strategies continue to be plagued by short treatment effects and non-compliance by patients due to discomfort.

Overall, this thesis provides novel contributions to the understanding of neglect and the fields of spatial attention and perceptual decision-making more broadly. For the first time, we have demonstrated that there is utility in applying a perceptual decision-making framework to a neglect population. The results of this thesis demonstrated that neglect has been decomposed into its component electrophysiological signatures. These same neural signatures have also been isolated and related to behaviour in healthy aging, furthering the current understanding on how perceptual decision-making is altered as a function of age. As each of the experimental chapters above include their own discussion section, this discussion chapter will focus its attention on highlighting the limitations to the current work before focusing on future research ideas arising from the experimental chapters.

Limitations

Firstly, we must acknowledge the small sample sizes in the clinical population work (**Chapter Three** and **Chapter Five**) presented within this thesis. Although neglect is prevalent in the acute stages post stroke (Appelros et al., 2002; Chen et al., 2012) spontaneous recovery occurs with approximately 60-90% of patients within 3-12 months of the onset (Karnath et al.,

2011; Swan, 2001). Given the nature of the current perceptual decision-making task and the use of EEG, it was impractical to complete this during an acute hospital admission. A number of factors contribute to this. Firstly, a number of stroke patients experience delirium, an acute confusional state, post-stroke (Caeiro, Ferro, Albuquerque, & Figueira, 2004) making research inappropriate at that point in time. For those individuals who are able to complete neuropsychological examinations, a sizeable proportion exhibit cognitive difficulties, with Nys et al. (2007) reporting that 55% of stroke participants exhibit cognitive impairment in at least one domain within three weeks of the initial neurological event. Of note, 39.1% demonstrate difficulties with executive functioning (Nys et al., 2007). The task used in this thesis is rather abstract and qualitatively patients reported that it is difficult to grasp. The task required an adequate level of cognitive function to allow participants to understand and retain task instructions. The cognitive impairment noted above is particularly pertinent in neglect research as there is high comorbidity between neglect and cognitive impairment post-stroke. Linden et al. (2005) reported that 15% of their stroke sample presented with visual neglect and these patients were twice as likely to have cognitive impairments when compared to those participants who did not have neglect. We note that in our sample, six out of the fourteen participants excluded (42%) from participating in Stage 2: Assessment of Perceptual Decision-Making were unable to comprehend task instructions. Other common post-stroke symptoms, such as seizures, also prevent participation (Myint, Staufenberg, & Sabanathan, 2006). It is estimated that 11.5% of stroke patients are at risk of developing post-stroke seizures within five years of an initial neurological event (Burn et al., 1997). Our exclusion of stroke patients with a history of epilepsy, seizures or a personal history of unexplained fainting or sensitivity to flickering light was a conscious safety precaution given the flickering nature of the current perceptual decision-making paradigm.

It is important to note that these recruitment and testing difficulties are reflected in other neglect work and as such, case study and single case approaches are common in the neglect literature. For example, Wang et al. (2015) recently utilised a case study approach following two patients through a three week protocol investigating mirror neuron therapy. Similarly, O'Shea and colleagues (2017) investigated the efficacy of prism adaptation in combination with anodal transcranial direct current stimulation (tDCS) in three male patients with chronic neglect. In those studies that continue to utilise a group approach to investigating neglect behaviour,

samples sizes are generally small. For example, Bonato, Saj, and Vuilleumier (2016) investigated the processing of time-ordered events in a group of eight neglect patients, with a further six non-neglect control patients. Furthermore, Saj et al. (2013) employed a group of seven right hemisphere patients with neglect to examine the effect of right-deviating prisms. Although the limited sample size used here is important to note, the ability to analyse our clinical data at a single trial level is an important caveat to note when discussing sample sizes. Indeed, we contend that the ability to individualise this approach and apply it to single participants is a significant strength within clinical populations.

Secondly, only right-handed participants were included in the experimental investigations presented in this thesis and thus the results outlined can only be generalised to the right-handed population. We note that the vast majority of the population are right-handed, with 90% of individuals characterised as right-hand dominant (Sun & Walsh, 2006) and therefore these results can be extended to the majority. The restriction of the sample to right-handed participants in these experimental studies was a conscious decision given the lateralisation of function is more variable in left-handed individuals (Badzakova-Trajkov, Haberling, Roberts, & Corballis, 2010; Sommer, Ramsey, Mandl, & Kahn, 2002; Steinmetz, Volkmann, Jäncke, & Freund, 1991; Szaflarski et al., 2002). Although the inclusion of left handed participants may have contributed unwanted confounding variables to these initial investigations, future work may wish to investigate whether the patterns of function and dysfunction are reflected in left-handed or ambidextrous individuals. Finally, we must acknowledge that the current perceptual decision-making framework used here is isolating and measuring relatively small basic neurophysiological processes. We do not currently possess experimental data that outlines how these metrics ($N2_{(c/i)}$, CPP) link with broader functional measures of day-to-day performance. Although this is a caveat in the extrapolation of current results, we believe that a basic understanding of the dysfunctional mechanisms in neglect is vital prior to extending this work into a functional framework. Further, we note that the utilisation a perceptual decision-making framework will not be possible in all stroke participants. For example, for participants with visual defects, such as hemianopia, the task will have limited utility, as their inability to visually perceive the left side targets will cause biased RT asymmetries for reasons beyond neglect symptomatology. As such, it will therefore be important for visual field testing to exclude this potential confound prior to its further. The task will also be limited when participants have

limited capacity for comprehending task instructions. This is an aspect of the task that will also need to be investigated in future studies. It would be beneficial to develop both written and verbal instructions for participants with varying deficits in comprehension. These limitations have important implications for the implementation of this research and therefore we would suggest that the above are key areas for future research.

Future Directions

Linking white matter changes in natural aging with perceptual-decision making metrics.

In **Chapter Two**, we outlined the neural mechanisms altered as a result of natural aging. Specifically, we found evidence for later peak $N2_{(c)}$ latency and CPP onset, a more gradual CPP slope, indicating slower evidence accumulation, and smaller CPP amplitudes. We suggested that the slowed behavioural performance and slowed evidence accumulation reflected the generalised reduction in processing speed theorised to underpin cognitive decline in healthy aging (Birren & Fisher, 1995; Kail & Salthouse, 1994; Salthouse, 1996). We suggest that future work investigate how the decrements in these perceptual decision-making processes link with white matter changes in older individuals.

White matter pathways of the brain allow for the transmission of information across the cortex and supports the successful completion of cognitive operations (Mesulam, 1998, 2000). White matter changes have long been associated with a decline in mental processing speed (Turken et al., 2008; Ylikoski et al., 1993) and individual differences in processing speed are thought to be the result of structural variations in the organisation of the white matter tracts (Turken et al., 2008). The speed at which the white matter structures transmit information across long-myelinated axons is related to their thickness and degree of myelination (Gutiérrez, Boison, Heinemann, & Stoffel, 1995; Tolhurst & Lewis, 1992; Waxman, 1980). Engel, Fries, and Singer (2001) note that efficient communication and coordination between network nodes relies upon the temporal accuracy, which in turn is reliant on the structural properties of the white matter fibre bundles responsible for signal transmission. In the context of the current aging results, it is important to note that white matter changes are particularly common in elderly individuals, with the prevalence ranging from 50%-98% (de Leeuw et al., 2001; Launer et al., 2006; Liao et al.,

1996; Longstreth et al., 1996). We would suggest that future research investigate the link between perceptual decision-making metrics, such as the $N2_{(c)}$ and CPP, and the white matter changes that occur in the later decades of life, using mixed-methods (Huster, Debener, Eichele, & Herrmann, 2012). The combination of the rich temporally specific EEG data and the spatially specific functional magnetic resonance imaging and diffusion tensor imaging data, has the potential to enrich our understanding of the aging brain and further elucidate how structural and functional changes interact with the perceptual decision-making framework.

Extending the perceptual decision-making paradigm in right-hemisphere patients.

In **Chapter Three,** we presented a proof-of-concept study outlining the utility of using a perceptual decision-framework to isolate distinct processes in neglect patients. We suggest that the next step in this work is to extend this protocol in a larger group of stroke patients and include measures of other processes that could potentially be contributing to neglect behaviour, such as pre-target α-band (8 –14 Hz) activity, a measure of spatial attention bias (Thut et al., 2006) and the lateralised readiness potential (Smulders & Miller, 2013) to measure motoric components that may impact neglect behaviour. Finally, the addition of pupillometry would allow for the influence of small modulations in arousal to be tracked and measured. The addition of these metrics would further enhance our understanding of the underlying component deficits in neglect. We would suggest that these discrete neurophysiological signatures then be mapped to discrete lesion locations using voxel-based lesion-symptom mapping (Meyer et al., 2016; Molenberghs et al., 2012).Within this larger study, it would be necessary to develop cut-off criteria for behavioral results and ERP patterns in order to ensure the clinical viability of this approach. Further, noting that there are limitations to the implementation of this approach in stroke populations, we suggest that this larger study collect information regarding the percentage of patients where this approach is able to be utilized (i.e. those that do not present with visual field deficits or cognitive difficulties that limit comprehension). This will be important in determining the viability of using this approach in clinical settings in the future.

Beyond neurophysiological and imaging investigations, there is also an imperative to further our understanding of how deficits found within the perceptual decision-making framework impact participants' everyday experience, thus bridging the aforementioned gap in the current work. Future work should aim to include a range of functional measures to

supplement EEG and imaging. Such functional measures may include the Rivermead Mobility Index (Antonucci, Aprile, & Paolucci, 2002; Forlander & Bohannon, 1999), a mobility scale; the Modified Rankin Scale (Bonita & Beaglehole, 1988), a measure of global disability; the Barthel index (Mahoney & Barthel, 1965), a measure of disability/activities of daily living; Berg Balance assessment (Berg, Maki, Williams, Holliday, & Wood-Dauphinee, 1992; Berg, Wood-Dauphinee, & Gayton, 1989), a simple well-established balance assessment; the Mini-Mental Examination (Folstein, Folstein, & McHugh, 1975) or the Montreal Cognitive Assessment (Nasreddine et al., 2005), both cognitive screening measures; the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), a mood screen; and the Stroke self-efficacy questionnaire (Jones, Partridge, & Reid, 2008), which includes questions about the patient's confidence in their ability to complete tasks. With the addition of such functional measures, future research will not only further our understanding of the physiological (EEG/pupillometric) metrics and anatomical (voxel-based lesion-symptom mapping) correlates of information processing disturbances experienced by neglect patients but it will allow for an increased understanding of how these disturbances affect every-day life.

Future Treatment Opportunities in Neglect.

As noted in **Chapter Five**, we did not find any evidence of improved spatial attention following four one-hour sessions of ocular blue-enriched white light. Despite the null result, we cannot discount the possibility that a larger trial with a more extensive light protocol may have the desired effect of ameliorating spatial bias in neglect patients. If future studies wish to investigate the use of light therapy in this population, we suggest that intervention be implemented over a prolonged period of time. For example, the presentation of light for a one-hour session daily over a period of a month may reveal a different result.

Another potential avenue for future work is to combine known rehabilitation strategies to optimise recovery potential. This approach has recently been utilised by Allman et al. (2016) who examined the ability of anodal tDCS to boost the effects of motor training and therefore improve rehabilitation outcomes in stroke patients. The authors reported that those patients who received tDCS in combination with motor training demonstrated persistent improvement for at least three months post-intervention. Importantly, this sustained improvement was not evident in those patients who received sham stimulation. O'Shea et al. (2017) has recently applied a similar

approach to neglect patients, combining anodal tDCS and prism adaptation training. The authors hypothesised that a single one-off stimulation session could enhance the consolidation of the behavioural therapy. Results indicated that for the three neglect participants included, 20 minutes of combined stimulation and prism adaptation could produce persistent changes in neglect symptoms, with the improvement lasting between 18 and 46 days. Again, there was no improvement noted when behavioural adaptation occurred without concurrent stimulation. Thus, this work suggests that tDCS may have utility in enhancing the impact of other therapies.

Beyond Neglect

Neglect is just one disorder where there is evidence of aberrant spatial attention. Similarly to neglect patients, children with Attention-Deficit Hyperactivity Disorder and Developmental Dyslexia (DD) have disordered spatial attention, with a lack of pseudoneglect also documented in these populations (Bellgrove et al., 2005; Facoetti et al., 2003; Malone, Couitis, et al., 1994; Malone, Kershner, & Swanson, 1994; Sheppard, Bradshaw, Mattingley, & Lee, 1999). In DD, it has been established that children have a reduced ability to process information presented in the left hemifield (Hari, Valta, & Uutela, 1999; Ruffino et al., 2010), not dissimilar to the pattern observed in neglect. This left hemifield dysfunction is coupled with ineffective suppression of stimuli in the right hemifield (Hari et al., 1999; Ruffino et al., 2010). The combination of the aforementioned difficulties results in a mini-neglect on spatial tasks (Facoetti et al., 2003; Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000; Facoetti et al., 2006; Hari & Renvall, 2001; Rayner, Murphy, Henderson, & Pollatsek, 1989), that is also evident when DD children perform word-reading tasks (Eden, Stein, Wood, & Wood, 1994; Facoetti & Turatto, 2000; Friedmann, Kerbel, & Shvimer, 2010; Illingworth & Bishop, 2009; Valdois et al., 2003). It has been suggested that the strength of the right-sided advantage seen in dyslexia is potentially sub-type and severity specific. For example, Stenneken, van Eimeren, Keller, Jacobs, and Kerkhoff (2008) suggest that stronger deviations in visuospatial attention occur in DD children that demonstrate more severe deficits in reading ability. To date, however, the impact of subtype or severity on the allocation of attentional resources has not been investigated in DD. We suggest that the bilateral perceptual decision-making paradigm employed in this thesis could provide clarity to understanding what drives the spatial asymmetry in these children and this information could potentially be harnessed as a target of intervention strategies.

Conclusions

This thesis has investigated the impact of natural aging and neurological damage on visuospatial attentional asymmetry. The findings presented provide new insights into how aging impacts the perceptual decision-making processes and highlights the utility of this framework to provide useful insights into how distinct processes change with age. Additionally, this thesis has presented innovative findings in the realm of neglect. We have demonstrated that perceptual decision-making paradigms with simultaneous EEG can have great utility in investigating the underlying neural dysfunction responsible for the behavioural phenotype in neglect. Further, we have isolated a metric, the $N2_{(i)}$, that demonstrates evidence of ipsilesional compensation in neglect patients. These results are significant as they not only provide an opportunity to track recovery of time by following changes in the $N2_{(i)}$ longitudinally but it also presents the tantalising possibility of targeting this process in future rehabilitation protocols. Finally, we investigated the utility of using ocular blue-enriched white light as a means of improving spatial attention in neglect patients. The work conducted herein paves the way for a future series of studies to shed further light on the neurophysiology of spatial attention, both within stroke and neglect participants, and in other populations where spatial inattention is a contributing symptom.

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Appendix 1

Stolwyk, O'Neill et al. (2014)

Stolwyk, R. J., **O'Neill, M. H.**, McKay, A. J. D., & Wong, D. K. (2014). Are Cognitive Screening Tools Sensitive and Specific Enough for Use After Stroke? *Stroke*, *45*(10), 3129.

Topical Review

Section Editors: Amanda Thrift, PhD, and Barbara G. Vickrey, MD, MPH

Are Cognitive Screening Tools Sensitive and Specific Enough for Use After Stroke?

A Systematic Literature Review

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It is estimated that up to three quarters of acute and subacute stroke survivors exhibit cognitive impairment, with many experiencing ongoing problems.[1,2] Cognitive impairment can significantly compromise functional recovery, quality of life, and social engagement after stroke.[2-4] Encouragingly early detection and rehabilitation can improve functional recovery of stroke-related impairments.[5] Unfortunately, however, a significant amount of cognitive dysfunction is not detected by health professionals in acute and subacute settings.[6]

Comprehensive neuropsychological assessment using reliable and valid tools to measure multiple cognitive domains is considered the gold standard method of detecting and characterizing cognitive dysfunction after stroke. However, neuropsychological assessments are often considered too expensive and lengthy to be routinely administered to patients with stroke. In an attempt to improve detection of cognitive impairments, while managing expense, many national stroke clinical management guidelines now recommend the use of screening measures to detect cognitive impairment.[7-9] If cognitive difficulties are detected during this screening process, comprehensive assessment and intervention is then recommended. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are 2 screening tools that are regularly used in clinical practice. Although these tests are commonly used to detect cognitive impairment in dementia settings, neither was specifically designed for use after stroke. The profile of cognitive impairment after stroke is heterogeneous, and focal impairments such as dysphasia, dyspraxia, unilateral inattention, and agnosia are often observed. Therefore, we cannot assume that reliability and validity of cognitive screening tools found in other clinical populations will be comparable in stroke.

It is acknowledged that numerous reliability and validity indices are important to consider when evaluating neuropsychological measures. However, when considering the use of cognitive screening measures, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are particularly important to ensure patients with cognitive impairment are not missed, and patients without cognitive impairment do not undergo comprehensive neuropsychological evaluation unnecessarily. Several studies have investigated the sensitivity and specificity of cognitive screening tools within stroke populations. However, a range of different methodologies have been used, and results seem to vary considerably across studies. Thus, the aims of this review were (1) to systematically review the sensitivity, specificity, PPV, and NPV of a range of cognitive screening tools used in stroke and (2) to critically evaluate methodologies used within these studies. It is intended that findings from this review will inform clinicians regarding suitability of these screening tools for clinical use and direct best practice for future research in this field.

Methods

Search Strategy

This systematic literature review was conducted and reported in line with the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Articles were identified through MedLine, PsychInfo, Scopus, PubMed, and CINAHL databases. Keywords included stroke, cerebrovasc*, cognit*, screen*, sensitivity, and specificity. Common screening measure names were also used. See Figure I in the online-only Data Supplement for an example of key words and search strategy. The search was limited to studies of adult humans published in English. The electronic search was conducted on December 27, 2013. Reference lists of articles included in this review and other relevant publications were also used to identify any studies overlooked in the electronic search.

Study Selection

Articles were included in this review if they met 3 key criteria: (1) male or female participants aged ≥18 years; (2) confirmed ischemic or hemorrhagic stroke, and (3) analysis of the sensitivity and specificity of a cognitive screening measure compared with a gold standard neuropsychological assessment. If >1 clinical population was included

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in a study (eg, transient ischemic attack and stroke), stroke-specific data must have been available. Cognitive screening measures were included if they were designed to screen for cognitive impairment or had been used for that purpose and typically took <30 minutes to administer. Gold standard neuropsychological assessments were included if they used multiple domain-specific neuropsychological assessments with established reliability and validity.[10] Some studies identified during the literature search investigated screening tools that aim to detect just 1 cognitive domain, such as dysphasia or dyspraxia. However, understandably these studies typically only included 1 cognitive domain within their gold standard assessment and thus did not meet our eligibility criteria.

In line with PRISMA guidelines, 2 authors (R.J.S. and M.H.O.) separately reviewed results from the electronic search and identified potentially relevant titles and abstracts. If the abstract suggested the article met the inclusion criteria, the full-text article was obtained and evaluated. Full-text articles were then compared across authors, and contrasting/ambiguous studies were discussed to determine whether they met criteria for inclusion. Articles that met the inclusion criteria were included for subsequent data extraction.

Data Extraction

The following data were extracted from each article: author, year, title, participant data (sample size, age, sex, education), stroke data (mechanism, location, hemisphere, severity), recruitment procedures (inclusion/exclusion criteria, participant attrition), cognitive screening measure used, domains and tests included in gold standard cognitive assessment, time poststroke of screening and gold standard cognitive assessments, and sensitivity, specificity, PPV, and NPV results. In some studies, multiple sets of sensitivity, specificity, PPV, and NPV data were presented at different screening measure cut points. To limit the amount of data presented, the cut point that resulted in the most favorable sensitivity and specificity results was selected. This was based on commonly used criteria of sensitivity >80% and specificity >60%.[11,12]

Results

Search Results

Electronic and additional searching returned 13 201 records; duplicate ones were removed. Sixty-six records remained following title and abstract screening. A further 50 records were excluded during full-text review for the following reasons: review articles (n=2), combined transient ischemic attack/stroke data (n=3), full neuropsychological battery used instead of screening tool (n=4), screening measure did not meet inclusion criteria (n=3), not written in English (n=2), no sensitivity and specificity data (n=6), nonstroke samples used (n=11), and gold standard neuropsychological battery did not meet inclusion criteria (n=19). Sixteen articles were found to meet our inclusion criteria and were retained for analysis. See Figure II in the online-only Data Supplement for a summary of the above.

Study Participants

Summary of study descriptions and evaluations is presented in Tables I and II in the online-only Data Supplement. All studies adequately reported sample size; however, few justified the sample size used or reported whether assumptions for statistical analyses were met. Based on key references within this field,[13,14] it seems that many studies did not use sufficient sample sizes, particularly those that used samples of ≤50 people.[15–18] This may have contributed to the large confidence intervals of sensitivity and specificity results noted across studies.

With regard to demographic variables, all studies provided adequate information regarding age and sex. Four studies failed to include education information.[11,15,16,19] Most study samples appeared representative of stroke populations. However, most studies excluded nonnative language speakers. With regard to stroke variables, most studies reported key information such as stroke mechanism (12 of 16), location (12 of 16), and severity (11 of 16). Stroke mechanism and lesion location variables across studies appeared generally representative of stroke populations. However, most studies excluded people with severe stroke. Only 2 studies provided adequate statistical analysis of whether the final study sample used for analysis was representative of the wider patient group within their clinical setting.[20,21] There was significant heterogeneity across studies regarding time since stroke, with mean/median times ranging from 6 days[17] to 29 months[18] across studies. Two studies failed to report this information,[15,22] and others provided only limited information.

Sensitivity and Specificity Methodology

All studies calculated sensitivity and specificity using receiver operative characteristics curve analysis. Only 9 of 16 studies calculated PPV or NPV data. Gold standard assessments used to classify the cognitive status of participants differed across studies. Cognitive domains such as language, visual/space perception, attention, memory, and executive functions were generally well represented. However, cognitive functions such as calculic function, praxis, and mental speed were less well represented, included in ≤4 of the 16 studies. Most studies used age- and education-based normative data to interpret gold standard test performances, using a criterion ranging from fifth to tenth percentile as an indicator of impaired performance. However, studies differed regarding whether impairment on single or multiple cognitive domains was required to classify participants as impaired on gold standard assessments. Furthermore, some studies did not use psychometric criteria at all, instead relying on clinician opinion taken from neuropsychological reports.[11,15,20] To reliably and validly assess sensitivity and specificity, it was expected that screening and gold standard assessments would be conducted within a short period of each other. Unfortunately, 5 studies did not sufficiently report this information,[16,18,20,23,24] and 3 reported the mean time interval between assessments as >10 days.[11,15,25] Only 6 studies stratified sensitivity or specificity results according to demographic or stroke variables.[20,22,23,25–27]

Sensitivity and Specificity Results

As seen in Table, the MMSE and MoCA were the most commonly studied screening measures. With regard to the MMSE, 11 studies investigated the sensitivity and specificity of the measure, with just 3 reporting sensitivity and specificity at or above commonly regarded acceptable levels (sensitivity >80% and specificity >60%).[23,25,27] All 3 studies obtained these levels using cut points of either 26/30 or 27/30. Bour et al[25] achieved acceptable sensitivity and specificity levels only when the gold standard assessment impairment criterion was increased to ≥2 cognitive domains. Of the 3 studies that reported adequate sensitivity and specificity, PPVs were generally >80%; however, NPVs were less impressive, ranging from 65% to 73% across studies.

Table. Results From Included Studies

Study	Screening Measure	Screening Measure Cut Point	SE, % (CI)	SP, % (CI)	PPV, % (CI)	NPV, % (CI)
Agrell et al[20]	MMSE	23/24	56	80		
Blake et al[11]	MMSE	<24	62	88		
Boosman et al[26]	BNI	Age <55, <47	80 (49–94)	39 (20–61)	61	93
		Age >55, <41	92 (67–99)*	84 (58–96)*	92	96
Bour et al[25]	MMSE	27/28 ≥1 impaired gold standard domain	72	71	93	
		27/28 ≥2 impaired gold standard domains	80*	70*	86	
		26/27 ≥4 impaired gold standard domains	82*	75*	72	
Cartoni et al[15]	MEAMS	≥3 failed subtests	52 (32–71)	100 (29–100)		
		≥5 failed subtests	26 (11–46)	100 (29–100)		
Cumming et al[27]	MMSE	26/27†	82*	76*	86	70
	MoCA	23/24	92*	67*	84	82
Godefroy et al[23]	MMSE	≤26	80*	77*	88	65
	MoCA	≤23	88*	71*	86	73
	$MMSE_{adj}$	≤27	89*	61*	83	73
	$MoCA_{adj}$ (adjusted scores created using control group to account for age and education)	≤23	84*	81*	90	71
Grace et al[22]	MMSE	<27	81	45		
	Modified MMSE	<86	94	50		
Green et al[28]	RBANS	83/84	84*	90*	98	53
Morris et al[12]	ACE-R	82	80	40	87	28
	MMSE	27	80	20	84	16
Nøkleby et al[16]	Cognistat	8/9	81 (68–93)*	67 (22–96)*		
	SINS	2/3	71 (57–85)	67 (22–96)		
	CDT	9/10	63 (49–78)	67 (22–96)		
Nys et al[17]	MMSE	<27	96	40		
Salvadori et al[21]	MoCA	21	91*	76*	80	89
Schweizer et al[18]	MMSE	<27				
	MoCA	<26	Domain-specific data provided. No global sensitivity/specificity data; MMSE: sensitivity=0 for all cognitive domains, specificity=1.00 for all cognitive domains; MoCA: sensitivity ranged from 40 to 100 across domains; specificity ranged from 54 to 70 across domains			
Srikanth et al[24]	MMSE-S	≤23	14 (4–32)	100 (92–100)	100 (40–100)	63 (50–74)
Wong et al[19]	MoCA	2–4 wk 17/18	75 (43–95)	95 (87–99)	75 (41–95)	95 (87–99)
		1 y 21/22	100 (74–100)*	75 (63–85)*	41 (24–61)	100 (93–100)
	MMSE	2–4 wk 23/24	75 (43–95)	90 (80–96)	60 (32–84)	95 (86–99)
		1 y 23/24	58 (28–85)	84 (73–92)	39 (17–64)	92 (82–97)

ACE-R indicates Addenbrooke Cognitive Examination, Revised; AUC, area under the receiver operating curve; BNI, Barrow Neurological Institute (screen for higher cerebral functions); CDT, clock drawing task; CI, confidence interval; MEAMS, Middlesex Elderly Assessment of Mental State; MMSE, Mini-Mental State Examination; MMSE-S, MMSE-Standardized; MoCA, Montreal Cognitive Assessment; NPV, negative predictive value; PPV, positive predictive value; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SE, sensitivity; SINS, Screening Instrument for Neuropsychological Impairments in Stroke; and SP, specificity.

*Results reach traditionally acceptable levels of 80% SE and 60% SP.

†Improved AUC for MMSE noted when *z* score criterion increased to −1.5.

Five studies investigated the sensitivity and specificity of the MoCA. Three of these reported adequate sensitivity and specificity[21,23,27]; 1 further study reported adequate sensitivity and specificity at 1 year poststroke, but not 2 to 4 weeks poststroke,[19] and the final study reported adequate sensitivity and specificity for only 2 of the 13 gold standard tests included (naming and verbal learning).[18] Acceptable sensitivity and specificity were found at different MoCA cut points across the studies, ranging from 21 to 26. Of the 4 studies that reported adequate sensitivity and specificity, only 2 studies also reported PPVs and NPVs >80%.[21,27]

Four studies directly compared the MMSE and MoCA. Using area under the receiver operating curve scores, 2 studies reported no significant differences between the MMSE and MoCA,[23,27] whereas another reported higher MoCA area under the receiver operating curve scores compared with the MMSE at 1 year poststroke only.[19] The final study reported superior sensitivity of the MoCA compared with the MMSE.[18] The general trend noted across these 4 studies was of somewhat better sensitivity and slightly poorer specificity of MoCA compared with the MMSE.

The sensitivity and specificity of other screening measures have been investigated in only a single study that met our inclusion criteria. Both the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Cognistat demonstrated typically accepted sensitivity and specificity levels; however, NPV was only 53% for the RBANS, and no PPV or NPV data were presented for the Cognistat.[16,28] The Barrow Neurological Institute (BNI) screen for higher cerebral functions returned acceptable sensitivity, specificity, PPV, and NPV levels in people aged >55 years but not <55 years.[26] The Middlesex Elderly Assessment of Mental State (MEAMS), Addenbrooke Cognitive Examination, Revised (ACE-R), Screening Instrument for Neuropsychological Impairments in Stroke (SINS), and Clock Drawing Test all failed to achieve adequate levels of sensitivity and specificity.[12,15,16]

In addition to providing total scores, some cognitive screening measures also provided domain-specific subscores. Four studies included in this review examined the sensitivity and specificity of these subscores to detect domain-specific cognitive impairment assessed using gold standard measures.[12,15,16,28] This information is presented in Table III in the online-only Data Supplement. Three of the 5 subscores from the RBANS achieved acceptable sensitivity and specificity levels (immediate memory, language, visuospatial) with the other 2 subtests only just under acceptable thresholds (delayed memory, attention).[28] Results from the Cognistat, MEAMS, ACE-R, and SINS were less impressive. The Cognistat and MEAMS both achieved acceptable results for their naming subscores; however, all other subscores did not reach acceptable levels.[15,16] No subscores from ACE-R or SINS reached acceptable levels.[12,16] Although memory, language, and visuospatial domains were regularly assessed, attention, processing speed, praxis, and executive function were seldom examined.

Few studies specifically investigated whether methodological factors or patient variables impacted on sensitivity and specificity results. Qualitatively there was no consistent evidence to suggest time poststroke significantly affected sensitivity and specificity results. Although Wong et al[19] reported acceptable MoCA sensitivity and specificity at 1 year but not 2 to 4 weeks after stroke, other studies reported favorable MoCA, Cognistat, RBANS, and BNI sensitivity and specificity ranging from 1 week to 1 year poststroke. With regard to time interval between screening and gold standard assessments, almost all studies that reported favorable sensitivity and specificity of the MoCA, Cognistat, RBANS, and BNI used mean assessment time intervals within ≈1 week. Studies varied regarding their criteria for impairment on gold standard assessment. Those who used a multiple cognitive domain criterion were more likely to report adequate sensitivity and specificity compared with those who used a single-domain criterion. A minority of studies stratified sensitivity and specificity results according to demographic and stroke variables. One study reported better sensitivity and specificity results in older stroke participants.[26] Lesion hemisphere effects were equivocal. One study reported no effect,[25] whereas others reported better results in right hemisphere[20,27] or left hemisphere groups.[22] No studies specifically investigated the impact of premorbid cognitive function, stroke severity or mechanism, or cultural factors on screening measure performance. Few studies directly compared screening measure performance across different gold standard cognitive domains. The MoCA was shown to be relatively more sensitive to naming and verbal learning difficulties compared with other cognitive domains in 1 study,[18] whereas performance was higher for language and visuospatial impairments in another.[19]

Discussion

Sixteen articles that investigated the sensitivity and specificity of cognitive screening tools in stroke met our inclusion criteria. Eleven of these studies investigated the MMSE, and most reported inadequate sensitivity and specificity. MoCA results were somewhat better, with 3 of 5 studies reporting consistent acceptable sensitivity and specificity results. It is not clear why the MoCA performed better than the MMSE. However, possible reasons include the fact the MoCA contains items assessing executive functions, which are often affected by stroke and the total score of MoCA can be adjusted for education level, albeit crudely. Interestingly, 2 relatively more recently developed measures, the RBANS and Cognistat, demonstrated traditionally acceptable levels of sensitivity and specificity. There is also some preliminary support for the use of BNI within older stroke populations. Furthermore, analysis of RBANS subscores highlighted promising sensitivity and specificity results to detect a range of focal cognitive difficulties, including memory, language, and visuospatial difficulties. However, it is noted that the RBANS, Cognistat, and BNI were only investigated in 1 study that met our eligibility criteria, and further research confirming these initial findings is warranted.

The above findings provide some preliminary support for the use of the MoCA, BNI, Cognistat, and RBANS as screening measures for stroke. However, these findings should be considered in the context of some key methodological issues. First, of the 7 studies that reported adequate sensitivity and specificity of MoCA, BNI, Cognistat, and RBANS, 3 either failed to report PPVs and NPVs[16] or reported NPVs <80% (indicating

≥20% false-negative rates).[23,28] Second, adequate sensitivity and specificity of the MoCA were found at different cut points, making recommendations for clinical practice difficult. Third, most studies did not include calculation, praxis, and speed of information processing within gold standard assessments. Thus, capacity for screening measures to detect these cognitive difficulties remains unknown, which is problematic considering that impairments of calculic, praxis, and mental speed functions are not uncommon after stroke and can significantly impact functional recovery.[1] Fourth, most studies that reported adequate sensitivity and specificity used a criterion of multiple cognitive impairments (≥2 domains) within their gold standard assessments. Studies have shown higher screening measure sensitivity for multiple-domain versus single-domain cognitive impairments.[25,29] Thus sensitivity results from studies that used multiple-domain impairment as a gold standard criterion may have been lower if a single-domain criterion was used (although equally specificity results may have been higher). Finally, few studies stratified sensitivity and specificity results according to demographic and stroke variables. This can be problematic for several reasons. For example, many screening measures do not account for age, education, or premorbid intelligence. Thus, it is possible that sensitivity of these screening measures for young and highly intelligent people may be limited, and specificity may be limited in older people and those with lower premorbid intelligence. Furthermore, people with severe stroke and those from culturally and linguistically diverse backgrounds were often excluded from studies altogether. Additional research is required within these groups before use of these screening measures is warranted. See Figure for recommendations for future research.

With regard to more general methodological issues, significant heterogeneity and poor reporting regarding time interval between screening and gold standard assessments and time of assessment since stroke were noted across studies. Unless long-term predictive validity is a specific research aim, we recommend screening and gold standard assessments be conducted as time-congruent as possible. Cognitive function can change significantly during the course of stroke recovery, and results from early screening cannot be assumed to be an accurate picture of longer-term cognitive function. Thus, we recommend further research investigating the potential impact of time since stroke on the sensitivity and specificity of screening measures. On another note, although it is important to report PPV and NPV data, we acknowledge these values vary according to prevalence of impairment in the population. Thus, direct comparison of these values across studies is not valid. Importantly, however, PPVs and NPVs can be calculated based on sensitivity, specificity, and prevalence data.[30] Thus, clinicians and researchers alike may choose to use data presented in this review to estimate PPV and NPV across a range of stroke populations where prevalence data are known. Finally, few studies have investigated which specific cognitive domains are more or less likely to be detected by these screening measures. Further research is warranted.

- ✓ Adequate sample size used with clear justification.
- ✓ Comprehensive documentation and analysis of patient recruitment and attrition.
- ✓ Report key demographic (age, sex, education) and stroke (mechanism, lesion location, severity) variables.
- ✓ SE and SP investigated in severe stroke and CALD groups.
- ✓ Comprehensive gold standard assessment including (mental speed, attention, visual/space perception, praxis, language, calculation, verbal/visual memory, executive functions).
- ✓ Screening and gold standard assessment conducted concurrently and time of assessment post-stroke documented.
- ✓ SE and SP stratified according to key demographic and stroke variables.
- ✓ Confidence Interval data included for SE and SP data.
- ✓ PPV and NPV data included.

Figure. Recommended methodological considerations for future studies. CALD indicates culturally and linguistically diverse; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; and SP, specificity.

Many researchers have previously suggested that 80% sensitivity and 60% specificity of cognitive screening measures is considered adequate for clinical practice. However, the significant negative impact of cognitive impairment in stroke survivors has been consistently demonstrated.[2-4] As such, 20% nondetection of patients with cognitive impairment seems unacceptable for clinical practice. Further research is required to more comprehensively examine existing screening measures that show initial promise (MoCA, Cognistat, RBANS, BNI) addressing previous methodological weaknesses noted above. Further development of more appropriate stroke-specific screening measures may be warranted if future research does not generate positive results. Furthermore, it is important to evaluate how current recommended guidelines (cognitive screening followed by comprehensive assessment) are being implemented in clinical practice. There is evidence to suggest good adherence to cognitive screening protocols, but limited provision of further comprehensive assessment when indicated by screening results.[31] Further research exploring potential modifications to screening processes is also warranted. For example, benefits of including patient, close other, or clinician reports of cognitive difficulties, in conjunction with screening measures, to improve detection of cognitive difficulties could be explored. Addition of items not included in current screening measures, but often affected by stroke such as calculation, praxis, and mental speed, should also be considered. It would be particularly helpful for these cognitive measures to be incorporated as standard measures within stroke trials to ensure ongoing comprehensive investigation of their utility across research and clinical settings. Although beyond the scope of this review, it is also important to consider cognitive screening in other cerebrovascular disorders. For example, some screening protocols have been specifically developed for small-vessel disease and have demonstrated encouraging results.[32] This may be because of the relatively more homogeneous neuropathology and associated cognitive profile seen in this population, compared with the relatively more heterogeneous cognitive profile across the stroke population, which seems to present as a challenge for some existing screening measures to accommodate.

In conclusion, a limited number of studies have adequately investigated the sensitivity and specificity of cognitive screening measures after stroke. Although most studies do not support the MMSE for clinical use, the MoCA, Cognistat,

RBANS, and BNI show some initial promise. However, further research addressing key methodological considerations and further discussion regarding what is considered acceptable sensitivity and specificity for clinical practice is required before use of these screening measures can be fully supported.

Disclosures

None.

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KEY WORDS: cognition ■ neuropsychology ■ sensitivity and specificity ■ stroke

Appendix 2

Corbetta and Shulman's theory of attention concept map

This concept map details Corbetta and Shulman's (2008, 2011) theory of attention, as it pertains to spatial orienting. This theory is extremely popular within neglect research as it helps explain why many patients show robust recovering despite permanent brain injury. Such recovery is thought to be due to reactivation of the structurally intact DAN. The far left of this concept map details the functional and anatomical correlates of spatial orienting, as it is thought to exist in a healthy individual. The model proposes the existence of a right lateralised Ventral Alerting Network (VAN) and a bilateral Dorsal Orienting Attention Network (DAN). A simplistic explanation of this model is that the VAN regulates the inter-hemispheric rivalry between the left and right DANs. A balanced interaction between the DANs results in equal activation of both hemispheres and a visual search of space that is equal for both side of space. This is what is seen in healthy individuals. However in neglect, reductions in alertness, due to lesions to the VAN (specifically TPJ), are thought to impact the DANs ability to exhibit goal-directed spatial orienting. Decreased interaction between alertness and spatial attention networks is thought to result in an imbalance favoring the left hemisphere, this in turn results in a rightward spatial bias. The right side of the map details the evidence for dysfunction of the VAN in neglect.

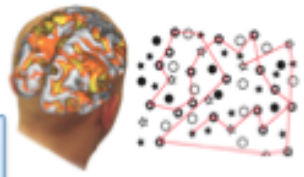
Abbreviations:
AC – anterior cingulate
DAN – Dorsal Orienting Attention Network
FEF – frontal eye fields
IPs – intraparietal sulcus
IFG – inferior frontal gyrus
LC – locus coeruleus
MCA – middle cerebral artery
NE – norepinephrine
PreCS – precentral sulcus
SFS – superior frontal sulcus
TPJ – tempoparietal junction
VAN – Ventral Attention Network
VFC – ventral frontal cortex

Spatial Orienting - Dorsal and Ventral Attention Theory

AC

L) FEF
Respond to symbolic cues by shifting attention voluntarily to stimuli in ipsilateral space → **contributes to eye movement**

R) FEF
Similar to L) FEF but dorsal regions (SFS & PreCS) code for both contralateral & ipsilateral space



If the VAN & DAN are functioning, there is equal activation in both hemispheres → equal visual orienting & search

Stimulus-response selection

L) IPs
Integration & functional linkage of top-down & bottom-up signals are mediated by feedback projections btw IPs & sensory areas

R) IPs
Ventral sector of R) IPs, exhibits some lateralization – coding for both contralateral & ipsilateral regions. Due to stronger ipsilateral connections btw R) TPJ & IPs

R) IFG
Involved in more lasting adjustments to sensory events

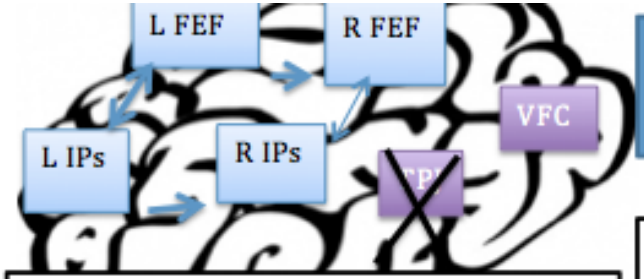
R) VFC
Target detection
Task control
Error detection
Response inhibition

R)TPJ
Non-spatial alerting signals

Top-down control

Stimulus-driven control

Primary Visual Cortex



Damage to TPJ (VAN) → imbalance of DAN networks with left>right, leading to a shift in attention with a rightward bias

VAN > DAN damage implicated in Neglect

Spatial deficits (DAN regulated) are dynamic & plastic → Can be modified by phasically increasing alertness (using auditory tones)

Lateralisation of VAN to R) Hemisphere:

Due to a slight asymmetric (right>left) arousal input from the brainstem LC/NE system (a higher concentration of NE terminals in right pulvinar).

Suggests spatial deficits are mediated by parts of the brain (VAN), that still function, albeit abnormally.

VAN lesions have the ability to alter the physiology of the structurally undamaged DAN, leading to spatial deficits.

Dysfunction of Spatial Orienting in Hemispatial Neglect

Spatial symptoms - bias in spatial attention & salience mapping

Non-Spatial symptoms - deficits in arousal, re-orienting, detection, & vigilance

Lesions of the DAN

Lesions of the VAN

However, neglect is most common following R) MCA stroke.

Lesion mapping has identified the TPJ as the region most commonly implicated in neglect

DAN – 1) Stimulus Selection function: represents stimulus saliency, encodes and maintains cognitive expectations about visual information, applies expectations to incoming stimuli. 2) Response selection functioning: IPs subdivisions have been linked to planning a response by hand or eye movements.

VAN – mediates alertness + sensory-driven reorienting. Acts as a circuit breaker – interrupting selective processing in DAN when relevant stimuli are detected.
Most importantly it **regulates the interhemispheric rivalry of L) & R) DANs. This competition btw DANs is key to efficient control of spatial orienting attention**

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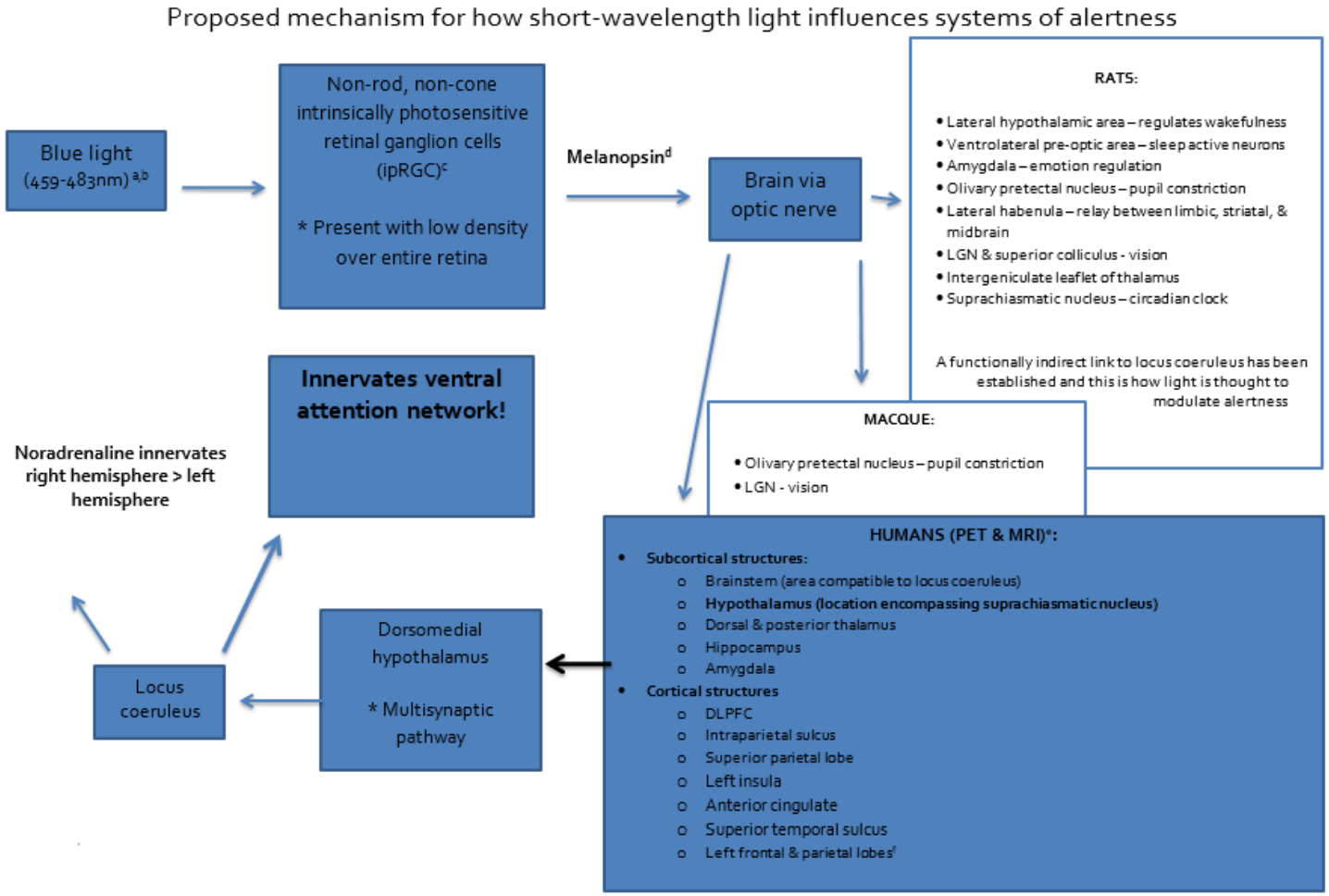
Appendix 3

Proposed mechanisms of how light influences systems of alertness



a – the non-visual system is maximal for blue light (~480nm; Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Berson, 2003; Berson, Dunn, & Takao, 2002; González & Aston-Jones, 2006; Gooley, Lu, Chou, Scammell, & Saper, 2001; Perrin et al., 2004; Schmidt, Chen, & Hattar, 2011; Vandewalle et al., 2006; Vandewalle et al., 2013; Vandewalle, Gais, et al., 2007; Vandewalle, Maquet, & Dijk, 2009; Vandewalle, Schmidt, et al., 2007; Zaidi et al., 2007), which is at odds with the classic photoreceptor system that is most sensitive to green light (~550nm; Vandewalle, Gais, et al., 2007).

b – blue light (~480nm) is more effective in sustaining performance than green light (~550nm) in a simple vigilance task (Lockley et al., 2006). Blue light enhances brain activation > green or violet light during 2-back working memory task, with modulations in locus coeruleus of brainstem, thalamus and insula (Vandewalle, Schmidt, et al., 2007).

c – evidence for this system comes from experiments with blind participants, who have no rod or cone system but exhibit both short-term and long-term non-visual effects of light (Gooley et al., 2012; Vandewalle et al., 2013).

d – melanopsin is expressed in the human inner retina (Provencio et al., 2000). The response of ipRGC is sluggish compared to cones, which respond to light immediately (Vandewalle, Schmidt, et al., 2007). ipRGC require higher light intensities and however unlike cones, the non-visual effect of light is maintained after light exposure ceases. This suggests that these cells account for increased integration time, higher response thresholds and slower response dynamics.

e – modulations seen during light exposure continued following the cessation of light exposure. Longer durations and higher intensities triggered longer lasting modulations in task-related responses. These experiments were based on non-visual cognitive tasks (Perrin et al., 2004; Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007) .

f – the tasks in these experiments involved working memory and therefore these areas are activated. The distribution of activation is likely to be task-dependent (Vandewalle et al., 2009).

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Appendix 4

Supplemental Material for Chapter 3

"Electrophysiology reveals evidence for ipsilesional adaptation in right hemisphere spatial neglect"

*Table S3.1.*Participant demographics and stroke data of stroke participants not included in Stage 2: Assessment of Perceptual Decision-making

Participant	Sex	Age at screening	Years of Education	Stroke Type	NIHSS on admission	Oxford classification	FIM admission	FIM discharge
BB	F	62	8	R) MCA	8 -moderate	PACI	41	42
LL	F	58	9	R) MCA	12 - moderate	PACI	45	-
MM	F	84	9	R) MCA	14 - moderate	PACI	22	-
NN	F	67	-	R) MCA	18 – moderate/severe	PACI	60	107
OO	M	87	16	R) MCA	-	PACI	74	108
PP	M	79	-	R) MCA	-	PACI	57	104
QQ	F	83	10	R) MCA	9 - moderate	PACI	95	104
RR	F	61	15	R) MCA	-	PACI	45	102
SS	F	75	9	R) MCA	-	PACI	41	MBI (0)
TT	F	79	10	R)MCA & bilateral frontal	7 - moderate	PACI	85	117
UU	M	88	7	R) MCA	9 - moderate	PACI	52	47
VV	F	84	7	R) MCA	4 - moderate	PACI	37	MBI (42)

Table S3.2. Participant's imaging summaries for stroke participants not included in Stage 2: Assessment of Perceptual Decision-making

Participant	Imaging findings
BB	**CT -** Large area of right frontal and parietal cortical low attenuation with associated diffuse right cerebral sulcal effacement and 2 mm of midline shift to the left. Appearances compatible with acute right MCA territory infarction with associated moderate positive mass effect. No evidence of uncal or transtentorial herniation. Within the frontal low attenuation region, there is a punctate 1mm focus of high attenuation, which likely represents acute petechial haemorrhage. No acute intracranial haemorrhage elsewhere. There is asymmetric prominence of the right temporal horn suggestive of early entrapment. Normal remaining ventricular calibre. Left cortical and cerebellar grey-white matter differentiation is preserved. Basal cisterns are capacious. Conclusion: Acute large right MCA territory infarction with associated focus of petechial haemorrhage, moderate positive mass effect and probable early entrapment of the right temporal horn of the lateral ventricle.
LL	**CT -** There is loss of grey-white differentiation in the right frontal lobe and right insula cortex, consistent with an acute right MCA territory infarct. The right MCA appears mildly hyperdense. **MRI -** The diffusion-weighted series shows a large area of acute infarction in the right middle cerebral artery, measuring approximately 87 x 61 x 70 mm (AP x TV x SI), for an estimated volume of approximately 190 mL; ASPECTS score 3/10. The extent of the lesion appears greater than that of the clearly hypodense region seen at CT. A few small satellite lesions are noted in the right parietal lobe, posterior to the main lesion. Two tiny cortical infarcts are seen in the medial aspect of the right superior frontal gyrus.
MM	**CT -** perfusion showed M1 filling defect MCA with largely matched defect involving entire R)MCA with some evidence of collateralisation resulting in some sparing of cortex. Loss of insula ribbon with early loss of caudate head and putamen. CT post thrombolysis established R)MCA + R)post frontal ACA
NN	**CT -** There is subtle hypodensity in the right posterior frontal and parietal lobes with loss of grey-white differentiation, consistent with acute infarction. There is prolonged mean transit time in the superior right MCA territory associated with matched cerebral blood flow and volume defects, consistent with acute infarction.
OO	**MRI -** The diffusion weighted series shows approximately 20 small foci of abnormal signal involving cortex and white matter of the right hemisphere, as well as the right lentiform nucleus. Lesions lie at the expected margins of the right middle cerebral artery territory. T2-weighted images show extensive patchy T2 hyperintensity in the subcortical white matter of both hemispheres, consistent with underlying chronic small vessel ischaemic change. There is relatively mild involvement of the brainstem, while the cerebellum appears spared.
PP	**CT -** Area of low attenuation with loss of grey-white matter differentiation in the R)MCA. Mild positive mass effect with local sulcal effacement with a subacute infarct. No evidence of haemorrhagic transformation.
QQ	**CT -** Apparent focus of low attenuation of the L)cerebellar white matter probably from the hardening artifact through the posterior fossa. No corresponding grey matter low attenuation. No evidence of acute supratentorial infarct. Periventricular and subcortical white matter low attenuation consistent with mild chronic vessel disease.
RR	**CT -** There is cortical low attenuation involving the anterior superior right temporal lobe, associated with a hyperdense distal right M1 segment. These findings are compatible with an acute infarction. **Follow-up CT -** There is interval extension of the previously identified right temporal lobe infarction, with areas of low attenuation now extending into the subcortical right frontal and parietal lobes as well as involving the right external capsule and lentiform nucleus. No evidence of haemorrhagic transformation. There is mild increasing effacement of the right lateral ventricle, with no evidence of midline shift.

SS	**CT -** extensive R)MCA territory with acute and subacute mild hypertensity of R)lentiform nucleus/external capsule up to 21mm possibly representing a small volume of haemorrhagic transformation. There is a 3mm right to left midline shift.
TT	**CT –** Hypo-attenuation in the right frontal lobe, with corresponding prolonged MTT and reduced CBV in the same area, consistent with established infarction. Large extra-axial, heavily calcified mass overlying the left frontoparietal region likely represents a meningioma. This measures 5.5 x 5.5 cm and there is adjacent hyperostosis. There is mild surrounding vasogenic oedema with effacement of the adjacent **left** lateral ventricle and associated displacement of the choroid plexus. There is no evidence of hydrocephalus. **MRI -** A large, well-defined and extra axial mass is demonstrated in the left frontoparietal region containing areas of low signal intensity consistent with the a calcified meningioma. It measures 64 x 44 x 47 mm. There is no surrounding CSF cleft and mass effect on the underlying parenchyma. Surrounding T2 FLAIR hyperintensity is consistent with the oedema. There is effacement of the trigone of left ventricle. Diffusion restriction is demonstrated in the bilateral frontal, right insula, parietal and occipital cortex with corresponding hypo intensity in keeping with ischaemic infarct. Moderate grade punctate FLAIR hyperintense foci in the cerebral hemispheres in keeping with microvascular ischemia. There is stenosis of A1 segment of left ACA.
UU	**CT -** There is loss of cortical grey-white matter differentiation in the posterior aspect of the right insular cortex and right temporal lobe, compatible with acute ischaemia. This is associated with localised sulcal effacement in the right temporal lobe. Sulcal prominence, basal cisterns and ventricular size are age-appropriate. Mastoid air cells and paranasal sinuses are well aerated. No calvarial fracture. Conclusion: Acute right MCA territory infarct involving the right insular cortex and right temporal lobe.
VV	**CT -** There is no evidence of acute infarction. There is no evidence of intracranial haemorrhage or other explanation for the clinical findings. There is no major arterial stenosis or occlusion. Penumbral maps demonstrate normal perfusion.

Table S3.3. Results from spatial inattention screening tasks for participants not included in Stage 2: Assessment of Perceptual Decision-making

Participant	Greyscales		Landmark		Bells Cancellation		Extinction				
	Number correct	Left selected	Spatial index	Spatial bias	Targets found (/35)	CoC Index	Total correct (/36)	Left correct(/8)	Right correct(/8)	Bilateral correct (/16)	Nil target correct (/4)
BB	35 (48.6%)	1 (1.4%)	0.6	Right	24	0.191	24	8	6	6	4
GG	36 (50%)	16 (22.2%)	-1	Left	32	0.042	36	8	8	16	4
LL	37 (51.4%)	17 (23.6%)	0.8	Right	26	0.258	36	8	8	16	4
MM	33 (45.8%)	5 (6.9%)	1	Right	3	0.906	18	3	7	4	4
NN	33 (45.8%)	19 (26.4%)	1	Right	34	0.013	34	8	8	14	4
OO	36 (50.0%)	20 (27.8%)	0.2	Right	35	0	19	7	8	0	4
PP	36 (50.0%)	0 (0.0%)	0.4	Right	35	0	27	4	8	11	4
QQ	34 (47.2%)	6 (8.3%)	1	Right	29	0.004	36	8	8	16	4
RR	40 (55.6%)	16 (22.2%)	-1	Left	29	0.118	23	7	2	0	4
SS	37 (51.4%)	3 (4.2%)	-0.2	Left	15	0.615	19	6	8	1	4
TT	36 (50.0%)	0 (0.0%)	1	Right	24	-0.033	23	7	7	5	4
UU	35 (48.6%)	1 (1.4%)	0.8	Right	28	0.010	14	4	8	4	2
VV	34 (47.2%)	4 (5.6%)	1	Right	30	0.129	32	8	7	13	4

NIHSS

The National Institute of Health Stroke Scale (NIHSS; Brott et al., 1989) was completed on admission to the rehabilitation setting for those participants recruited from hospitals and was retrospectively completed based on medical records for community participants (Williams, Yilmaz, & Lopez-Yunez, 2000). The NIHSS is a systematic assessment tool that provides a quantitative measure stroke-related neurological deficit (0= no measurable deficit, 1-4 = minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-42 = severe stroke; Brott et al., 1989).

FIM

The Functional Independence Measure (FIM; Keith et al., 1987) is an 18-item scale used to measure patient disability, with lower scores representing higher levels of disability and higher scores representing more functional independence. The items are grouped into 2 subscales – motor (eating, grooming, bathing, dressing – upper body, dressing – lower body, toileting, bladder management, bowel management, transfers - bed/chair/wheelchair, transfers – toilet, transfer – bath/shower, walk/wheelchair, stairs) and cognition (comprehension, expression, social interaction, problem solving, memory). Each of the items is scored from (1) - Total assistance with helper to (7) - Complete independence with no helper,

Spatial Bias Screening Measures

Greyscales Task

The Greyscales task (Nicholls et al., 1999) requires participants to select from two horizontal stimuli, the horizontal bar which they perceive to be overall the darkest. The two bars presented change incrementally from white on one end to black on the other in 80 pixel increments and each stimulus pair is an exact left/right reversal of the other. Given this, if the lower stimulus is darker on the right, the upper stimulus will be darker on the left. Mattingley, Bradshaw, Nettleton, and Bradshaw (1994) report that patients with left neglect following right hemisphere damage display a strong bias on this task, such that they consistently report that the ‘darker’ bar that has darker edge on the right side. It is reported that abnormalities on this task often persist even after ‘recovery’ as measured on conventional tests of neglect (cancellation and

line bisection).

To complete the Greyscales task, participants were placed 50cm away from and with their midlines placed in the centre of the monitor. The task was untimed and participants were encouraged not to rush their decision. Subsequently, participants were able to respond either while the stimuli were present on the screen or following the trial. Participants indicated their response either by keyboard or verbally. A total of 72 experimental trials were completed. Based on the 72 experimental trials, each participant received a score out of 72 (number correct) and the number and percentage of trials where the participant chose the stimulus with the left side darker was also recorded. In the current study, a cut-off of < 25% left targets selected was used to indicate neglect.

Greyscales parameters

The parameters used for the Greyscales task were as follows: the vertical and horizontal midlines of the stimulus pairs are aligned with the centre of the display window (22cm x 16.5cm). The vertical distance between the upper and lower stimuli was 100 pixels (~3cm). The length of the stimuli was varied between 320 (~7cm), 400 (~8.75cm), 480 (~10.5cm), 560 (~12.25cm), 640 (~13.6cm) and 720 pixels (~15.7cm). Each stimulus was defined as thin black rectangle defined by a grey background and was 79 pixels (~1.5cm) high. The program presented different combinations of length, orientation (darker on the left or right) and stimulus choice in a pseudo-random order. Each pair of stimuli was exposed for 60,000 msec and the interstimulus interval was set at 1,500 msec. The difficulty level of trials was set at 200. This resulted in one of the stimuli being 200 pixels lighter, while the other stimuli was 200 pixels darker. Therefore, there was an overall difference of 400 pixels between the stimuli. The program randomly selected whether the upper or lower stimulus was manipulated to be darker or lighter.

Landmark Task

The Landmark task (Bellgrove et al., 2005) consists of 20 sheets of paper each containing a 20cm line that has been bisected. Participants are asked to verbally indicate which side of the line is shorter. Half of the lines (10 trials) are bisected in the centre, while the remaining 10 bisections are offset to either the left (5 trials) or right (5 trials). The degree to which each line is offset varied with 6 of 10 trials (3 trials per side) repositioned by 1mm, 2 (1 trials each side) offset by 2.5mm and the

remaining 2 (1 trial each side) moved by 5mm. Spatial bias is calculated using the formula: (L-R)/10, where L is the number of evenly bisected lines the participant believed to be bisected to the left (the left side is shorter) and R is the number of evenly by centered lines the participant believed to be bisected to the right (the right side is shorter). This calculation results in a score ranging from -1 to 1, where negative number indicate left spatial bias, positive numbers indicate right spatial bias and a score of zero indicates no spatial bias. In the current study, a positive value, indicate of left neglect was used to reflect neglect symptomatology. This is consistent with the work of Bellgrove et al (2005). **Bells Cancellation**

Bells cancellation (Gauthier, Dehaut, & Joanette, 1989) is an assessment tool used to gather qualitative and quantitative information regarding visual neglect in near extrapersonal space. The task consists of 35 bells and 40 distractor images presented on an A4 sheet of paper. The 35 bells are spread across seven columns, three on the left side of the A4 sheet (15 targets), one in the middle (5 targets) and three on the right (15 targets). Participants are asked to "circle with a pencil all the bells that you find of the sheet that will be placed in front of you. Participants were asked to inform the researcher when they felt they had circled all the bells. Participants were asked not to alter the orientation of the paper and refrain from moving their trunk. To assess neglect symptomatology, we calculated a Center of Cancellation (CoC) as suggested by C Rorden and Karnath (2010). The CoC allows for results on the Bells cancelation to be normalised, such that the mean horizontal position is converted so that all items are zero (baseline correction) and the scale of the horizontal axis is adjusted so that there is a range of two between the leftmost and rightmost target is 2. Using the CoC, individuals who identify all targets will score zero, individuals who only identify the left most item will receive a score near -1 and individuals who only identify the rightmost items will receive a score near +1. C Rorden and Karnath (2010) report than a CoC score greater than .081 on Bells Cancellation is indicative of left neglect following right hemisphere damage.

Extinction Task

Spatial extinction was assessed using a computerised version of a test based on the classical spatial extinction test by Bender (1952). In the original version of the test, the examiner briefly wiggles the left or right index finger or both while seated at 1 m distance from the patient. The patient then has to indicate if the experimenter

moved his right, left or both fingers. In our computerised version, participants were presented with either one white gabor patch to the left or the right of a central fixation point (16 unilateral conditions, 8 left/8 right), with two white gabor patches to the left and right of central fixation (16 bilateral conditions), or no gabor patches (4 catch trial). These trials were presented in a random order and participants were asked to respond verbally as to what they saw on the screen. The presence of neglect of extinction tasks is based on clinician judgment and in this case, failing to report left targets on more than one occasion while accurately reporting right targets was indicative of neglect behaviour. This is consistent with the instructions discussed by Azouvi et al (2002) when using manual extinction tasks to investigate spatial inattention.

Bilateral perceptual decision-making task parameters

Stimuli appeared white (RGB: 221) against a black background and a red (RGB) fixation mark was a 6×6 pixel square placed centrally. The circular dot patches were 6 degrees diameter with the centre of each patch situated 4 degrees below and 8 degrees to either the left or right of the central fixation point. During random motion, 150 dots per patch (each dot = 6x6 pixels) were placed at random and independent positions within each patch and moving at a flicker rate of 20.0 frames/s. During coherent motion targets, 90% of dots (135 total) were randomly selected and displaced in either a downward or upward direction on the following frame, resulting in a motion speed of 5 degrees/s. The fixation dot remained on screen throughout the entire task; however, the two peripheral patches were only present when the trial was initiated by the participant's fixation on the central point.

Table S3.4. Valid trial numbers, percentage of correct trials for left and right trials and hit-rate analysis (chi-square comparison) for neurologically healthy participants.

Participant	Total Valid Trials	Valid Left Trials	% of left trials correct	Valid Right Trials	% of right trials correct	Chi-square *p* value
999	170	69	100%	72	98.79%	*p*=.96
998	217	96	99.07%	99	100%	*p*=.96
996	223	106	100%	100	100%	*p*=1
995	184	94	100%	90	100%	*p*=1
994	222	103	100%	99	100%	*p*=1
993	191	95	100%	96	100%	*p*=1
990	181	87	100%	94	99.06%	*p*=.96
989	188	96	100%	92	100	*p*=1
988	169	83	100%	86	100%	*p*=1
987	199	99	100%	100	100%	*p*=1
986	199	102	100%	97	99.07%	*p*=.96
985	207	103	100%	104	100%	*p*=1
983	177	86	100%	91	100%	*p*=1
982	169	90	100%	79	100%	*p*=1
981	177	86	100%	91	100%	*p*=1
980	201	100	100%	101	100%	*p*=1
978	187	94	100%	93	100%	*p*=1

977	132	71	97.87%	61	97.87%	*p*=1
976	175	83	100%	87	99.02%	*p*=.96
975	149	69	98.78%	80	98.81%	*p*=.99
974	179	87	100%	92	100%	*p*=1
973	192	96	100%	96	99.03%	*p*=.96
972	169	81	100%	88	100%	*p*=1
971	191	96	100%	95	100%	*p*=1
970	178	90	100%	88	100%	*p*=1
969	182	91	100%	91	100%	*p*=1
968	181	89	100%	92	98.96%	*p*=.96

Table S3.5. RT asymmetry index with within sample t-tests for neurologically healthy participants.

Participant	RT asymmetry	Bias	Within sample p value
999	-0.020	No significant bias	*p*=.29
998	-0.067	Left bias	*p*=.019
996	-0.067	Left bias	*p*=.011
995	0.06	Right bias	*p*=.005
994	-0.005	No significant bias	*p*=.93
993	-.038	No significant bias	*p*=.29
990	-.031	No significant bias	*p*=.39
989	.059	Right bias	*p*=.02
988	.062	No significant bias	*p*=.091
987	.012	No significant bias	*p*=.68
986	-.049	No significant bias	*p*=.066
985	-0.46	Left bias	*p*=.028
983	-.026	No significant bias	*p*=34
982	.041	No significant bias	*p*=.18
981	.11	Right bias	*p*=.001
980	.067	Right bias	*p*=.012
978	-0.099	Left bias	*p*=.008
977	.078	Right bias	*p*=.009
976	-.12	No significant bias	*p*<.001
975	-.043	No significant bias	*p*=.17
974	-0.001	No significant bias	*p*=.94
973	.011	No significant bias	*p*=.54
972	-.021	No significant bias	*p*=.36
971	.028	No significant bias	*p*=.41
970	-.053	No significant bias	*p*=.11
969	-.075	Left bias	*p*=.023
968	-.046	No significant bias	*p*=.052

Appendix 5

Supplemental Material for Chapter 4

Newman et al (2016). ***Scientific Reports***

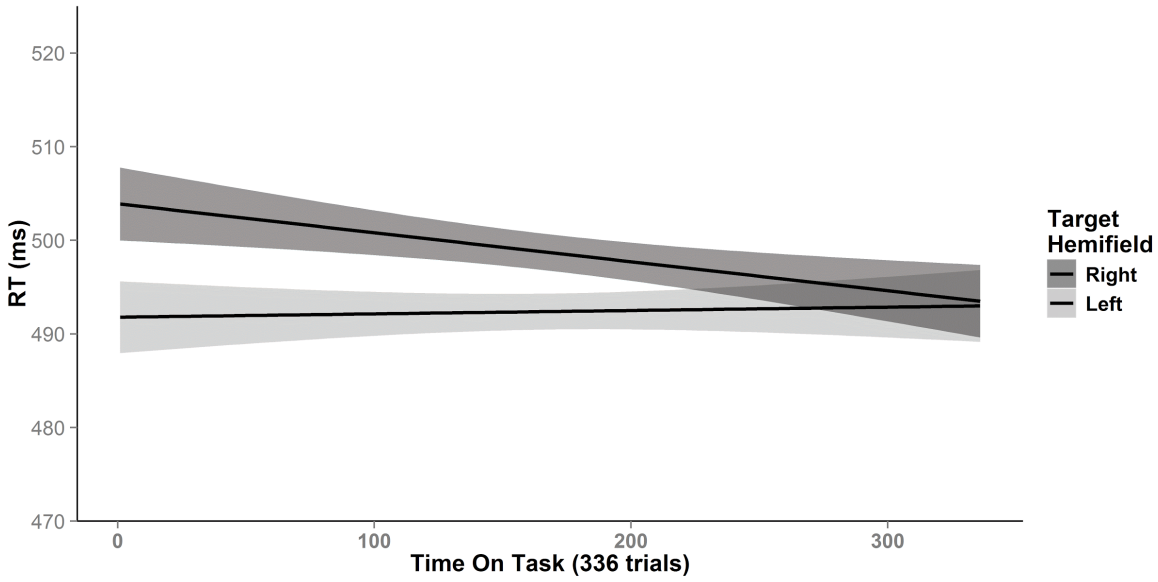

Figure S4.1. A left-hemifield RT advantage was present during the beginning of the task but became smaller with time-on-task and disappeared during the second half of the session. This is consistent with the rightward shift in spatial attention bias with time-on-task that has been reported previously[1–5].

The plot above depicts data from all three Light conditions since Light did not moderate the Hemifield × time-on-task effect. Simple effects of time-on-task on RTs from each Hemifield show that the Hemifield × Time-on-task interaction was driven by an improvement in right-hemifield RTs over time [b= -0.03, SE=0.009, t= -3.28, p=0.002] while the slowing of left-hemifield RTs over time was not significant [b= -0.009, SE=0.009, t= 1.01, p=0.525]. Note: Since time-on-task may be correlated with both practice effects (RTs may become faster over time as participants' skill on the task improves) and with declining alertness (RTs may become slower over time as alertness decreases), it could be the case that an overall practice effect tends to improve RT over time, but this effect is cancelled out for left hemifield targets only due to the asymmetric behavioural effect on spatial attention of declining alertness with time-on-task. As time-on-task is confounded with practice effects and alertness it is difficult to disentangle the

degree to which each of these influences RT as function of hemifield. This is why the direct manipulation of alertness via night-time exposure to blue-enriched light as presented in the current manuscript, is an important addition to the spatial attention/alertness literature.

Significant leftward RT bias under normal daytime alertness in an independent sample of healthy participants

An independent sample (*N*=80) of healthy participants completed a random dot paradigm similar to that reported in the main manuscript, with the following differences: (a) testing occurred between 9:30am and 3:00pm under normal daytime alertness levels; (b) there was no light manipulation; (c) only two lower visual-field dot patches were used, with the same characteristics as the lower visual-field patches in the main manuscript; (d) coherence set at 60%. A repeated-measures *t*-test on the mean participant-level reaction-times for left vs. right hemifield targets showed that under normal daytime alertness healthy participants responded faster to coherent motion targets in the left (*M*=571ms , *SE*=11) than right (*M*= 586, *SE*=12) hemifield [$t(79) = -3.06$, $p = 0.003$].

The effect of Light on α-power pooled from all parieto-occipital electrodes

Prior work shows that exposure to short-wavelength (blue) light increases α-power in waking EEG at rest[6–8]. The current data support this with a significant effect of Light exposure on α-power (mean -500ms to target onset) pooled from all parieto-occipital electrodes (Pz, P1, P2, P3, P4, P5, P6, P7, P8, POz, PO3, PO4, PO7, PO8, PO9, PO10, O1, O2, Oz). Since α-power was the criterion variable here, the pooled α measures were log transformed to a normal distribution and outliers removed leaving 22,355 observations for analysis. The main effect of Light across all parieto-occipital electrodes [$\chi^2(2) = 7.964$, $p = 0.0187$] was broken down with contrasts via glht() in the *multcomp* package[9] revealing that parieto-occipital α-power was significantly greater after high intensity light exposure than either low [$b = 0.04$, $SE = 0.006$, $t = 6.21$, $p < 0.001$] or medium intensity exposure [$b = 0.02$, $SE = 0.006$, $t = 3.90$, $p < 0.001$], and the increase in α-power between low and medium intensity light exposure was also [$b = 0.01$, $SE = 0.006$, $t = 2.35$, $p = 0.049$].

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Appendix 6

Supplemental Material for Chapter 5

"Testing the efficacy of short wavelength light for improving spatial attention after right hemisphere stroke"

FIM Scale items

The items are grouped into 2 subscales – motor (eating, grooming, bathing, dressing – upper body, dressing – lower body, toileting, bladder management, bowel management, transfers - bed/chair/wheelchair, transfers – toilet, transfer – bath/shower, walk/wheelchair, stairs) and cognition (comprehension, expression, social interaction, problem solving, memory). Each of the items is scored from (1) - Total assistance with helper to (7) - Complete independence with no helper,

Table S5.1. Participant medication at time of testing

Participant	Medication
1 - AA	Allopurinol (gout and hyperuricaemia – musculoskeletal system), Atorvastatin (hypolipidaemic agent – cardiovascular system), Citalopram Hydrobromide (anti-depressant - SSRI), Colchicine (gout and hyperuricaemia – musculoskeletal system), Perindopril (anti-hypertensive – musculoskeletal system), Warfarin (anticoagulant and antithrombotic – cardiovascular system)
2 - BB	Atenolol (beta-adrenergic blocking agent - cardiovascular), Atorvastatin (hypolipidaemic agent – cardiovascular system), Clexane (anticoagulant and antithrombotic – cardiovascular system), Fentanyl patch (narcotic – analgesic), Irbesartan (anti-hypertensive - cardiovascular), Moxonidine (anti-hypertensive - cardiovascular), Panadol (simple analgesic)
3 - CC	Apixaban ((anticoagulant and antithrombotic – cardiovascular system), Atorvastatin (hypolipidaemic agent – cardiovascular system), Candesartan (anti-hypertensive - cardiovascular), Metoprolol (beta-adrenergic blocking agent - cardiovascular)
4 - DD	Aropax (anti-depressant – SSRI), Atorvastain (hypolipidaemic agent – cardiovascular system), Eliquis (anticoagulant and antithrombotic – cardiovascular system)

Spatial Bias Screening Measures

Greyscales Task

The Greyscales task (Nicholls et al., 1999) requires participants to select from two horizontal stimuli, the horizontal bar which they perceive to be overall the darkest. The two bars presented change incrementally from white on one end to black on the other in 80 pixel increments and each stimulus pair is an exact left/right reversal of the other. Given this, if the lower stimulus is darker on the right, the upper stimulus will be darker on the left. Mattingley, Bradshaw, Nettleton, and Bradshaw (1994) report that patients with left neglect following right hemisphere damage display a strong bias on this task, such that they consistently report that the 'darker' bar that has darker edge on the right side. It is reported that abnormalities on this task often persist even after 'recovery' as measured on conventional tests of neglect (cancellation and line bisection).

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Greyscales parameters

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random order. Each pair of stimuli was exposed for 60,000 msec and the interstimulus interval was set at 1,500 msec. The difficulty level of trials was set at 200. This resulted in one of the stimuli being 200 pixels lighter, while the other stimuli was 200 pixels darker. Therefore, there was an overall difference of 400 pixels between the stimuli. The program randomly selected whether the upper or lower stimulus was manipulated to be darker or lighter.

Landmark Task

The Landmark task (Bellgrove et al., 2005) consists of 20 sheets of paper each containing a 20cm line that has been bisected. Participants are asked to verbally indicate which side of the line is shorter. Half of the lines (10 trials) are bisected in the centre, while the remaining 10 bisections are offset to either the left (5 trials) or right (5 trials). The degree to which each line is offset varied with 6 of 10 trials (3 trials per side) repositioned by 1mm, 2 (1 trials each side) offset by 2.5mm and the remaining 2 (1 trial each side) moved by 5mm. Spatial bias is calculated using the formula: (L-R)/10, where L is the number of evenly bisected lines the participant believed to be bisected to the left (the left side is shorter) and R is the number of evenly by centred lines the participant believed to be bisected to the right (the right side is shorter). This calculation results in a score ranging from -1 to 1, where negative number indicate left spatial bias, positive numbers indicate right spatial bias and a score of zero indicates no spatial bias. In the current study, a positive value, indicate of left neglect was used to reflect neglect symptomatology.

Bells Cancellation

Bells cancellation (Gauthier, Dehaut, & Joanette, 1989) is an assessment tool used to gather qualitative and quantitative information regarding visual neglect in near extrapersonal space. The task consists of 35 bells and 40 distractor images presented on an A4 sheet of paper. The 35 bells are spread across seven columns, three on the left side of the A4 sheet (15 targets), one in the middle (5 targets) and three on the right (15 targets). Participants are asked to “circle with a pencil all the bells that you find of the sheet that will be placed in front of you. Participants were asked to inform the researcher when they felt they had circled all the bells. Participants were asked not to alter the orientation of the paper and refrain from moving their trunk. To assess neglect symptomatology, we calculated a Center of Cancellation (CoC) as suggested by Rorden and Karnath (2010). The CoC allows for results on the Bells cancelation to

be normalised, such that the mean horizontal position is converted so that all items are zero (baseline correction) and the scale of the horizontal axis is adjusted so that there is a range of two between the leftmost and rightmost target is 2. Using the CoC, individuals who identify all targets will score zero, individuals who only identify the left most item will receive a score near -1 and individuals who only identify the rightmost items will receive a score near +1.

Extinction Task

Spatial extinction was assessed using a computerised version of a test based on the classical spatial extinction test by Bender (1952). In the original version of the test, the examiner briefly wiggles the left or right index finger or both while seated at 1 m distance from the patient. The patient then has to indicate if the experimenter moved his right, left or both fingers. In our computerised version, participants were presented with either one white gabor patch to the left or the right of a central fixation point (16 unilateral conditions, 8 left/8 right), with two white gabor patches to the left and right of central fixation (16 bilateral conditions), or no gabor patches (4 catch trial). These trails were presented in a random order and participants were asked to respond verbally as to what they saw on the screen.

Bilateral perceptual decision-making task parameters

Stimuli appeared white (RGB: 221) against a black background and a red (RGB) fixation mark was a 6×6 pixel square placed centrally. The circular dot patches were 6 degrees diameter with the centre of each patch situated 4 degrees below and 8 degrees to either the left or right of the central fixation point. During random motion, 150 dots per patch (each dot = 6x6 pixels) were placed at random and independent positions within each patch and moving at a flicker rate of 20.0 frames/s. During coherent motion targets, 90% of dots (135 total) were randomly selected and displaced in either a downward or upward direction on the following frame, resulting in a motion speed of 5 degrees/s. The fixation dot remained on screen throughout the entire task; however, the two peripheral patches were only present when the trial was initiated by the participant's fixation on the central point.

Table S5.2. National Sleep Foundation sleep diary exemplar that participants completed for the one week prior to Session One.

	Date	Bed Time	Time taken to fall asleep (minutes)	PRE-SLEEP Sleepiness (1-9)	Wake Time	*Office Use Sleep Duration (minutes)*	POST-SLEEP Sleepiness (1-9)	SLEEP QUALITY (1-6)	No. of Awakenings	Total Time Awake
E.g.	02 MAY 2012	2100	15 min	6	0700	*LEAVE BLANK*	2	3	3 times	30 min

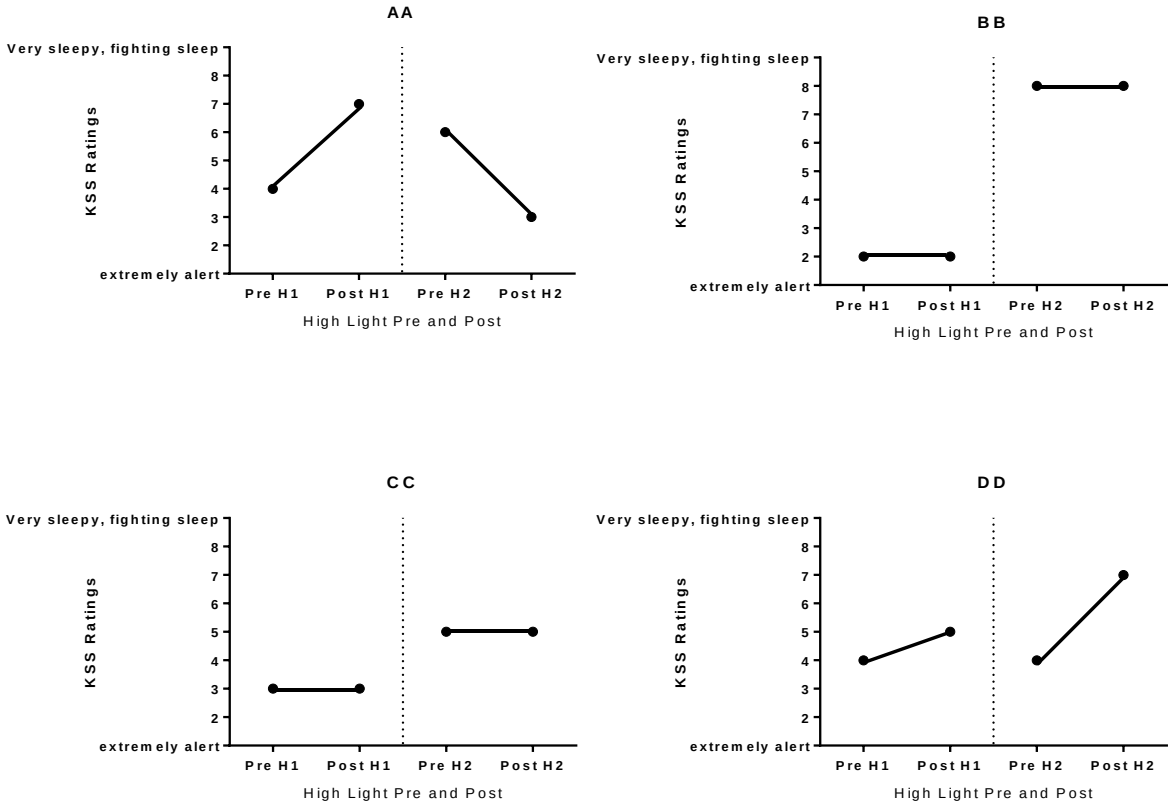

Figure S5.1. Karolinska Sleepiness Scale (KSS) ratings for each participant prior to and directly after the light intervention.

*Table S5.3.*Linear regression equations and significance testing on RT asymmetry within each individual session for each participant.

Participant	Session	Equation	P value	R^2
AA	Baseline	Y = -0.005*X + 0.075	0.319	0.124
	Low intensity 1	Y = -0.001*X + 0.057	0.920	0.00
	High intensity 1	Y = -0.0003*X + 0.059	0.930	0.001
	High intensity 2	Y = -0.007*X + 0.3	0.066	0.361
	Low intensity 2	Y = 0.006*X - 0.206	0.252	0.160
BB	Baseline	Y = -0.003*X + 0.196	0.701	0.019
	High intensity 1	Y = 0.010*X - 0.046	0.040*	0.428
	Low intensity 1	Y = 0.014*X - 0.267	0.056	0.385
	Low intensity 2	Y = -0.005*X + 0.290	0.455	0.072
	High intensity 2	Y = 0.0002*X + 0.062	0.968	0.0002
CC	Baseline	Y = -0.002*X + 0.106	0.628	0.031
	Low intensity 1	Y = -0.005*X + 0.175	0.696	0.020
	High intensity 1	Y = -0.007*X + 0.265	0.347	0.111
	High intensity 2	Y = -0.011*X + 0.483	0.218	0.183
	Low intensity 2	Y = -0.009*X + 0.436	0.182	0.211
DD	Baseline	Y = 0.004*X + 0.068	0.612	0.034
	High intensity 1	Y = 0.011*X - 0.085	0.196	0.199
	Low intensity 1	Y = 0.014*X - 0.194	0.143	0.248
	Low intensity 2	Y = 0.005*X - 0.067	0.377	0.099
	High intensity 2	Y = 0.010*X - 0.379	0.209	0.190