Neuropsychological Deficits of Visuospatial Attention: Subtypes, Clinical Utility, and Underlying Mechanisms



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To my Dad,
for teaching me to love learning.

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Abstract:

Visuospatial neglect is a common neuropsychological syndrome characterised by consistently lateralised spatial attentional deficits. The purpose of this thesis is to investigate patterns of heterogeneity within visuospatial neglect, to determine this syndrome's underlying mechanisms, and to investigate the practical utility of considering this heterogeneity within clinical settings.

Chapter Two presents a critical analysis of common neglect assessment methods and investigates the utility of neglect severity metrics which can be extracted from neuropsychological measures. Chapter Three analyses behavioural heterogeneity in neglect dyslexia to investigate the relationship between reading-related and domain-general neglect impairments. Chapter Four presents three case studies characterising representation-level neglect dyslexia in order to evaluate existing models of spatial attention. Chapter Five presents a detailed, lesion-mapping analysis of visuospatial neglect deficits aiming to determine whether right neglect is anatomically homologous to left-lateralised neglect. Finally, Chapter Six analyses the relationship between the occurrence of acute neglect and poor long term recovery outcomes to determine whether the specific behavioural phenotype of acute neglect impairment acts as a useful prognostic indicator.

The findings of these data chapters are then cumulatively discussed to extend fundamental understanding of the neglect syndrome, establish a novel conceptualisation of representation-level neglect dyslexia, evaluate current neglect-related clinical practices, and clarify the recovery outcome of stroke survivors exhibiting acute neglect impairment.

1 Chapter One: General Introduction

1.1 Introduction

Visuospatial neglect is a common neuropsychological syndrome characterised by consistently lateralised spatial attentional deficits (Parton et al., 2004). In traditional broad definitions of the syndrome, patients present with unimpaired visual processing but are unable to respond or attend to stimuli presented on one side of their environment (Heilman and Valenstein, 1987). More recently, research has suggested that instead of being a unitary deficit, visuospatial neglect is better characterised as a heterogenous syndrome composed of a cluster of district, but interrelated spatial-attentional impairments (Cubelli et al., 1991; Hillis and Caramazza, 1995). The overall purpose of this thesis is to investigate patterns of heterogeneity within neglect, to determine specific underlying mechanisms, and to investigate the practical utility of considering this heterogeneity within clinical settings. In furthering understanding of mechanisms, underpinning neuroanatomy and clinically relevant links to every day behaviours and longer term outcomes, the work presents advances across the translational spectrum.

1.2 Visuospatial Neglect and Behaviour

Importantly, visuospatial neglect is not a vision problem (Corbetta and Shulman, 2011). Stroke survivors with lesions impacting early visual processing areas (e.g. V1) commonly exhibit lateralised visual deficits, such as hemianopia or quadrantanopia (Huber, 1992; Ishiai et al., 1987; Zhang et al., 2006). Patients with hemianopia commit consistently lateralized visual errors similar to those seen in patients exhibiting unilateral visuospatial neglect (Huber, 1992; Ishiai et al., 1987; Zhang et al., 2006), but these errors can be attributed to impaired vision or complete blindness in one visual field while patients with visuospatial neglect have intact early visual processing. Patients with hemianopia or visual field deficits very quickly learn to compensate for these impairments by saccading into the impaired visual field while patients with visuospatial neglect cannot compensate for their perceptual deficits, as they are unaware that their neglected

space exists (Ishiai et al., 1987; Zihl, 1995). Visuospatial neglect and visual field deficits represent doubly dissociated cognitive impairments which can occur independently of one another and are related to distinct patterns of cortical damage (Beschin Facchin, 2016; Cassidy et al., 1999; Halligan et al., 1990). Visuospatial neglect can also be dissociated from visual extinction, an attentional deficit in which patients fail to perceive contralesional stimuli when stimuli are simultaneously presented in the ipsilesional and contralesional visual field (Beume et al., 2020; Vossel et al., 2011). Unlike patients with neglect alone, visual extinction patients are able to orient, interact and perceive items in their contra-lesional field without errors when presented in isolation (Vossel et al., 2011).

Previous investigations have provided strong evidence that visuospatial neglect involves a core attentional deficit (Bonato et al., 2013; Corbetta and Shulman, 2011; de Schotten et al., 2011). First, the severity of visuospatial neglect has consistently been found to be modulated by attentional factors. Patients with neglect exhibit a more severe impairment when completing dense compared to diffuse object cancellation tasks (Husain and Kennard, 1997; Trojano et al., 2009). Similarly, reducing exposure time has been found to exacerbate visuospatial biases in patients with neglect (Bonato et al., 2013; Russell et al., 2004; Russell et al., 2013). Non-spatial phasic alerting has also been found to improve neglect patients' spatial biases (George et al., 2008; Thimm et al., 2006; Thimm et al., 2009). Finally, visuospatial neglect most commonly results from damage to cortical areas which are traditionally associated with spatial attention (Chechlacz et al., 2012; Hillis, 2005; Mort et al., 2003).

This evidence has given rise to a well-accepted conceptualisation of visuospatial neglect as a consequence of damage to right-hemisphere attentional areas (Buxbaum et al., 2004; Parton et al., 2004). In this model, the right hemisphere is thought to be attentionally dominant and responsible for distributing attention across contralateral and ipsilateral hemispace while the left hemisphere only attends to contralateral hemispace (He et al., 2007; de Schotten et al., 2011; Urbanski et al., 2008). When the right hemisphere attentional areas are damaged, the left visual field is thought to no longer be attended to, resulting in visuospatial neglect (Corbetta and Shulman, 2011; de Schotten et al., 2011; Weintraub Mesulam, 1987). This imbalance is thought to

result in abnormal, spatially-biased attentional weightings within the salience maps computed for visual stimuli (Pisella and Mattingley, 2004). This bias, in turn, causes patients to over-attend to stimuli presented within the attended hemifield and to fail to spontaneously direct attention away from these over-attended features to additional stimuli present within the neglected hemifield. This conceptualisation of visuospatial neglect outlines the basic attentional aspects of the syndrome. However, visuospatial neglect is not a unitary syndrome but instead involves a heterogenous cluster of interrelated spatial-attentional deficits.

1.3 Heterogeneity within the Neglect Syndrome

Previous research has demonstrated that visuospatial neglect can impact multiple, distinct spatial reference frames (Baylis et al., 2004; Demeyere and Gillebert, 2019; Hillis Caramazza, 1995). Visuospatial neglect is most commonly characterised as a deficit which occurs within an egocentric (body-centred) frame of reference (Parton et al., 2004). However, patients exhibiting deficits within allocentric (object-centred) reference frames have also been identified (Baylis et al., 2004; Chatterjee, 1994; Demeyere and Gillebert, 2019; Driver and Halligan, 1991). These impairments can be reliably distinguished by standard neuropsychological assessments such as the Oxford Cognitive Screen's Cancellation Task. In this task, participants are asked to search through a spatially-distributed matrix of heart line drawings. Participants are instructed to mark all complete (target) heart while ignoring distractors (hearts with gaps on the left or right) (Demeyere et al., 2015). Patients with egocentric neglect fail to identify targets within the neglected visual field while patients with allocentric neglect commit consistently lateralised false positive errors. These consistent false positives suggest that a subset of patients are failing to perceive lateralised portions of individual objects, regardless of where these objects are presented in egocentric space. Allocentric neglect occurs frequently within the acute stroke population, with studies estimating between 24% and 32% incidence (Bickerton et al., 2011; Demeyere and Gillebert, 2019).

Previous theories have asserted that allocentric neglect is best understood as a consequence of egocentric neglect rather than an independent condition. For example, Driver and Pouget (2000) proposed that allocentric neglect can be explained in terms of "relative" domain-

general unilateral visuospatial neglect. In this model, egocentric neglect is described as a gradient of attention slanting from full attention within the non-neglected hemifield to complete inattention in the contralesional field (Driver and Pouget, 2000). Driver and Pouget (2000) argue that regardless of where a patient sets their retinal position in this gradient, the relative non-neglected space be more attended to than the relative neglected space, resulting in apparent object-centred neglect biases. A direct prediction of this model is that allocentric neglect should only be found in patients who also exhibit egocentric neglect, but previous research has found that this is not the case. Bickerton et al. (2011) conducted standardised egocentric and allocentric neglect neuropsychological assessments in a cohort of 115 acute stroke survivors and which identified 17 patients with pure egocentric and 19 patients with pure allocentric neglect deficits. Of the 18 patients in this study who were found to exhibit both egocentric and allocentric neglect, 2 patients exhibited these deficits co-occurring in opposite lateralisations (e.g. left egocentric neglect with right allocentric neglect) (Bickerton et al., 2011). Similar results have been identified in a number of subsequent group and case studies of neglect (Costello and Warrington, 1987; Moore and Demeyere, 2017). These results cannot be accounted for by considering allocentric neglect as a side-effect of egocentric neglect. The current literature provides strong evidence that egocentric and allocentric neglect represent independent cognitive impairments. These conditions have reliably been found to be behaviourally doubly dissociated, to follow different recovery trajectories, and to be associated with distinct neural correlates (Bickerton et al., 2011; Costello and Warrington, 1987; Cubelli et al., 1991; Demeyere and Gillebert, 2019).

It should be noted that as well as occurring in distinct reference frames, visuospatial neglect can selectively impact different areas of space. Some previous investigations have distinguished between neglect impacting perception within near (personal) space and far (extra-personal) space). Personal and extra-personal neglect have been demonstrated to be doubly dissociated behavioural impairments and to be associated with distinct neural correlates (Committeri et al., 2007, 2018; Ten Brink et al., 2019). Neglect can also impact additional sensory modalities. A subset of patients have been found to exhibit auditory neglect, a condition in which patients are unable to perceive auditory stimuli presented from a specific side of space (Bellmann et al., 2001;

Guilbert et al., 2016; Gutschalk and Dykstra, 2015). Cases of motor neglect, or an underutilisation of one side of the body in the absence of any physical deficits, have also been documented (Laplane and Degos, 1983; Punt and Riddoch, 2006; Triggs et al., 1994). These non-visuospatial neglect subtypes can occur independently of classic, visuospatial neglect deficits and provide insight into how spatial information is employed throughout multi-modal sensory processing. This thesis will primarily focus on visuospatial neglect impairments.

1.4 Three-Tier Theory of Visuospatial Neglect

This section presents the main theoretical framework which will be employed and evaluated within this thesis. First, Hillis and Caramazza's (1995) model of reference frames in neglect is presented and critically analysed in the context of existing literature. Next, a novel strategy for testing the predictions of this model is described. Overall, this section provides the theoretical framework and underlying justification for the neglect dyslexia studies presented throughout this thesis.

Hillis and Caramazza (1995) propose a multi-tiered model of visuospatial neglect in which patients can exhibit impairment within three distinct reference frames: retinocentric, stimulus-centred, or representation-level (Figure 1.1). In retinocentric (egocentric) neglect, patients exhibit perceptual deficits which are mediated by each stimulus' location within egocentric space (Beschin et al., 2014; Hillis and Caramazza, 1995). A second type of visuospatial neglect is characterized by a stimulus-centred (allocentric) error pattern in which the location of perceptual deficits are unaffected by egocentric location but are instead modulated by viewer-independent, stimulus-centred spatial-attentional biases (e.g. allocentric visuospatial neglect). Finally, a subset of patients can exhibit neglect deficit occurring at the level of internally stored spatial representation. In this form of neglect, patients commit errors which occur with respect to stored representations of orientation-canonical stimuli, rather than visually presented stimuli. For clarity, these three levels of neglect will be referred to as egocentric, allocentric, and representation-level neglect respectively throughout this thesis. This model is best demonstrated by examining different behavioural patterns within patients exhibiting neglect dyslexia.

Neglect dyslexia is a form of acquired dyslexia characterised by consistently lateralised omission, addition, and substitution when reading (Moore and Demeyere, 2017; Riddoch, 1990; Vallar et al., 2010). Neglect dyslexia is generally classified as a peripheral reading deficit, resulting from damage to domain-general spatial perceptual mechanisms rather than reading-specific processes (Ellis et al., 1987; Ellis and Young, 2013; Riddoch, 1990; Shallice, 1988). Previous research has strongly suggested that neglect dyslexia is a highly heterogenous condition with different patients exhibiting distinct patterns of reading impairment. Patient's exhibiting egocentric neglect dyslexia commit consistently lateralised full-word omission errors when reading spatially presented passages of text (Hillis and Caramazza, 1995; Vallar et al., 2010) (Figure 1.1). For example, the neglect dyslexic patient JOD, a patient with left, egocentric neglect dyslexia, was found to read words presented in the right hemifield with significantly greater accuracy than individual words presented in centrally or in the left hemifield (Hillis and Caramazza, 1995). This pattern of neglect dyslexia can be explained by visuospatial neglect impairment which occurs within a viewer-centred (egocentric) reference frame. This impairment corresponds to the first level of egocentric visuospatial neglect impairment proposed by Hillis and Caramazza (1995).

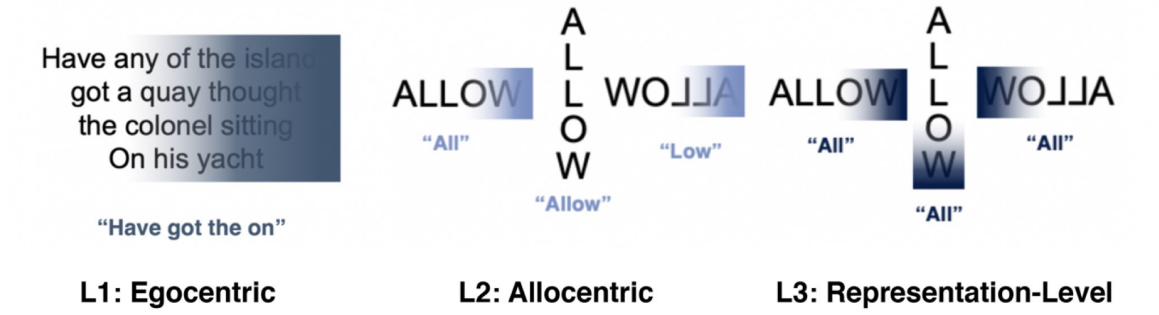


Figure 1.1: The three levels of visuospatial neglect impairment as proposed by Hillis and Caramazza (1995).

Conversely, patients exhibiting allocentric neglect dyslexia commit consistently lateralised letter omission, addition, and substitution errors when reading individual words (Hillis and Caramazza, 1995). For example, a patient with left allocentric neglect dyslexia might read "impartial" as "partial", "smart" as "outsmart", or "tested" as "bested" while a patient with right neglect dyslexia might read the same words as "impart", "smartly", and "testing" (Vallar et al., 2010). Ellis et al.

(1987) conducted a case study involving patient VB, a stroke survivor with left neglect dyslexia. When asked to read individual words, VB was found to reliably misread letters presented on the left side of words (e.g. RIVER read as “Liver”, YELLOW read as “Pillow”) (Ellis et al., 1987). VB also misread the initial digits in number strings. However, VB was unimpaired when asked to read words which were printed vertically. Similarly, patient SP (Young et al., 1991) was found to commit similar frequencies of left allocentric neglect dyslexia errors when reading in both the left and right visual field, suggesting that the spatial bias seen in this form of neglect dyslexia can operate independently of egocentric spatial coordinates. This impairment pattern is characteristic of allocentric neglect dyslexia.

Finally, L3 neglect dyslexia or “representation-level neglect dyslexia”, is characterised by reading errors which impact letters in a specific location within individual words, regardless of how these words are presented in space (Hillis and Caramazza, 1995) (Figure 1.1). These reading errors occur with respect to stored, orientation-canonical spatial representations of words, rather than how these stimuli are visually presented. For example, Caramazza and Hillis (1990) identified patient NG, a patient exhibiting right representation-level neglect dyslexia following extensive lesions to the left parietal white matter and left anterior basal ganglia. When reading horizontally presented words, NG was found to commit left neglect dyslexia reading errors which affected the terminal (right-lateralised) letters of these words. Strikingly, NG also misread the terminal letters when left-right spatial biases were controlled for by presenting words vertically. Most notably, NG continued to commit reading errors affecting the terminal (originally right-lateralized) letters even when words were mirror-reflected so that these letters were presented in the left side of egocentric space (Caramazza and Hillis, 1990). These findings demonstrated that NG’s reading impairment was unaffected by topographical stimulus transformations, implying that her neglect dyslexia was caused by a deficit at a level of processing where grapheme information is represented within a representation-level coordinate system. This impairment pattern is known as representation-level neglect dyslexia.

Notably, this theorised representation-level neglect impairment is not analogous to cases of “representational neglect” which have been documented in previous investigations. For example,

Bisiach and Luzzatti (1978) conducted a seminal case study on unilateral representational neglect in which they asked two left egocentric neglect patients to imagine viewing Milan's Piazza del Duomo once from a position directly across from the square's cathedral and again from the opposite side of the square. In this task, these patients reliably failed to identify features present within the egocentric left side of the imagined space. Similar impairment patterns have been documented on a range of imagined environment tasks (Beschin et al., 1997; Boccia et al., 2018; Rode et al., 2004). This "representational neglect" has key differences from a deficit within Hillis and Caramazza's (1995) theorised representation-level reference frame. First, the specific area neglected within Bisiach and Luzzatti's (1978) study was found to change based on imagined point of view. This orientation-sensitivity demonstrates that patients made neglect errors with respect to their imagined egocentric viewpoint, not with respect to an orientation-canonical representation of the square. By definition, representation-level neglect deficits should be orientation-insensitive and should selectively impact stored, orientation-canonical representations of stimuli. Therefore, the neglect impairment documented by Bisiach and Luzzatti (1978) is best characterised as egocentric-level neglect impacting imagined stimuli rather than a representation-level neglect deficit.

Distinct patterns of behavioural impairment in neglect dyslexia have provided support for the three-tier model of visuospatial neglect proposed by Hillis and Caramazza (1995). However, this model is theorised to apply to all forms of spatial-perceptual processes, not just those involving reading. Impairment within any level of this model is thought to result in impairment to processing all spatially presented stimuli, regardless of their semantic content (Caramazza and Hillis, 1990; Haywood and Coltheart, 2000; Hillis and Caramazza, 1995). This conceptualisation is well accepted, but it is not yet clear if this conclusion is not strongly supported by the existing data. Strong support for the existence of a representational neglect reference frame would be provided if patients exhibiting representational neglect deficits in non-word stimuli were successfully identified. Several previous investigations have attempted to document this error pattern, but methodological limitations with these studies preclude valid conclusions based on the data provided. First, Cubelli and Speri (2001) attempted to document representational errors within

a sample of eight left neglect patients. In this study, patients were shown a series of chimerical pictures of objects and animals in various rotations and were asked to the two components of the stimuli. When pictures were rotated 90 degrees to the right, participants reported both object components with equivalent accuracy. However, when stimuli were rotated 90 degrees leftwards, patients omitted the left half of the stimulus more often than the right half. This error pattern was taken as evidence of mental rotation and "normalisation" and therefore evidence of object-centred neglect for non-orthographic stimuli (Cubelli and Speri, 2001). However, there are several critical issues with this conclusion.

First, by definition, object-centred neglect errors should only impact stimuli for which patients have a stored, orientation-canonical representation (Caramazza and Hillis, 1990; Haywood and Coltheart, 2000; Hillis and Caramazza, 1995). It is unclear why any participant would be expected to have a stored spatially-specific of the highly non-naturalistic stimuli employed in this investigation. Second, participants in this investigation were found to commit errors primarily impacting the canonical left side of stimuli within the upright condition, but primarily the right canonical side of images within the inverted condition. This means that participants were found to make omission errors with regard to egocentric space, not with regard to an object-centred frame of reference. This error pattern is characteristic of an egocentric neglect pattern, not a representational one. Given these limitations coupled with the small sample size within this investigation, the results of this study do not provide strong evidence in support of the claim that representational errors can impact non-orthographic stimuli.

Similarly, Driver et al. (1994) aimed to document evidence of representational neglect errors within non-orthographic stimuli. This experiment employed a novel equilateral triangle gap-detection test in which the location of gaps relative to a biased principal axis was varied while maintaining the same egocentric location. For example, each trial consisted of a line of triangles presented along a diagonal axis. Participants were asked to identify gaps within the central triangle, whilst ignoring information from the surrounding triangles creating an illusory axis. This investigation included three patients with left-sided neglect, who were found to miss more gaps on the left of the illusory axis than on the right. This finding was taken as evidence of axis-based

neglect, which is analogous to Hillis and Caramazza's (1995) proposed representational reference frame neglect. Like Cubelli and Speri's (2001) investigation, this study employs stimuli for which participants would not be expected to have stored, orientation canonical representations, precluding conclusions pertaining to the occurrence of representational neglect errors.

A subsequent study conducted by Savazzi et al. (2009) attempted to control for this issue by inducing specific "canonical" representation of line bisection stimuli, and identified a single patient exhibiting bisection bias reversal within reflected stimuli. In this study, 14 patients with left neglect were asked to learn a new, orientation canonical stimulus. This stimulus was a single line stimuli ending with a square on one side and a circle shape on the other. Participants were first asked to bisect 20 of these canonical stimuli. This exposure was posited to lead participants to form a stored representation of this stimuli. The participants then bisected a series of 75 horizonal, 15 mirror-reversed, and 10 vertical representations of this canonical stimulus. Participants were asked to draw the original, canonical stimuli after every 20 trials to ensure that they had learned the stimulus. Three patients exhibited a significant reduction or reversal of bisection error when bisecting mirror-reversed versus canonical stimuli. This error pattern is interpreted as being characteristic of representational neglect within non-orthographic stimuli. However, this study is not without methodological limitations.

First, a large body of literature has strongly suggested that line bisection does not represent a valid method for assessing the severity of visuospatial neglect (Ferber and Karnath, 2001; Sperber and Karnath, 2016). Sperber and Karnath (2016) assessed a cohort of 180 right hemisphere stroke patients on three standard neglect tests (line bisection, cancellation, and figure copying) which employed factor analysis to determine whether impairment on each of these metrics was indicative of the same underlying deficit. Factorial analysis concluded that the bisection task was represented by different factors than the cancellation/copying tests, suggesting that these measures are assessing different underlying cognitive impairments. The authors conclude that line bisection does not represent a valid method for assessing visuospatial neglect in stroke (Sperber and Karnath, 2016). Additional research has suggested that performance on bisection tests could be confounded by co-morbid motor and cognitive impairments which are unrelated to spatial at-

tention. For example, a patient with impaired fine motor function may not be able to reliably bisect lines at the point they perceive to be the middle of the line due to poor pen control. similarly, a patient with a visual field deficit may appear impaired on a bisection task because they are unable to see a portion of the line. It is not clear how this investigation accounted for these potential confounding comorbidities. Additionally, it is not clear whether asking patient to bisect 20 copies of a specific line is sufficient to induce a orientation-specific internal representation of that stimuli. Considered cumulatively, these methodological weaknesses imply that the study conducted by Savazzi et al. (2009) does not provide convincing evidence that representational neglect errors can impact non-orthographic stimuli.

If the three-tier model of visuospatial neglect can be applied across all forms of spatial perception, impairment within any single reference frame should not be content specific. In other words, impairment within one reference frame should result in impairment across all stimuli processed within that reference frame, regardless of the content of these stimuli. This prediction can be critically evaluated by comparing the relationship between domain-general visuospatial neglect and neglect dyslexia. The double dissociation is the gold-standard neuropsychological approach for determining whether or not two cognitive deficits represent independent impairments (Fama Sullivan, 2014). If deficits A and B are related to the exact same underlying mechanism, there should be no cases of either deficit occurring independently, only cases of them in conjunction (no dissociation). If A and B are singly dissociated, condition A can occur without condition B, but condition B would never occur in the absence of condition A. For example, reading and cortical blindness are singly dissociated. All patients with cortical blindness are unable to read, but not all patients with reading impairments are cortically blind. Single dissociations illustrate that process A is necessary for process B, but that these processes are not entirely identical. In double dissociations, conditions A and B may co-occur, but both conditions can also occur independently (e.g. egocentric and allocentric neglect). Based on the theory put forward by Hillis and Caramazza (1995), neglect dyslexia reading impairments should not be able to be doubly dissociated from their respective reference frame of domain-general visuospatial neglect. This prediction is supported when considering data from patients exhibiting egocentric visuospatial neglect and

egocentric neglect dyslexia. Previous research has strongly suggested that egocentric neglect dyslexia is a consequence of severe domain-general neglect impairment rather than an independent cognitive impairment. While not all patients with egocentric visuospatial neglect exhibit egocentric neglect dyslexia (Lee et al., 2009; Moore and Demeyere, 2017; Vallar et al., 2010), previous research has not identified any patients exhibiting egocentric neglect dyslexia in the absence of domain-general egocentric neglect. For example, Beschin et al. (2014) investigated reading impairment in a cohort of stroke survivors with clear symptoms of egocentric neglect. This study found that 70% of these patients reliably omitted words on the left side of passages of prose (egocentric neglect dyslexia). Egocentric neglect dyslexia patients were found to have significantly more severe neglect than those without this reading impairment, but were found to have similar underlying lesion patterns (Beschin et al., 2014). This evidence is in line with the predictions made by Hillis and Caramazza (1995).

However, this theory is not as clearly supported by considering patients with stimulus- and word- centred neglect dyslexia. Previous studies have identified cases of neglect dyslexia which appears to occur independently of domain-general visuospatial deficits. Friedman and Nachman-Katz (2004) identified a case of developmental allocentric neglect dyslexia in a 10-year-old boy with no history of neurological abnormalities or signs of spatial-attentional impairments. Strikingly, Cubelli et al. (1991) and Costello and Warrington (1987) report cases of left lateralised allocentric neglect dyslexia within a patient with right egocentric visuospatial neglect. While these case studies provide preliminary evidence that not all cases of neglect dyslexia can be neatly explained as direct side-effects of domain general visuospatial neglect, these studies are not without limitations. First, these studies have consistently failed to distinguish between allocentric and representation-level patterns of neglect dyslexia. Allocentric and representation-level neglect dyslexia error patters cannot be distinguished by considering data from reading horizontal words alone, and these previous investigations have failed to include the topographical manipulations needed to tell these two conditions apart. Additionally, these investigations did not explicitly test for domain-general allocentric neglect, meaning that the relationship between word-level reading errors and visuospatial neglect remains unclear. For these reasons, additional research is needed

to evaluate whether the relationship between allocentric and representation-level neglect dyslexia aligns with the predictions made by Hillis and Caramazza (1995). It is important to determine whether allocentric and representation-level neglect dyslexia can be dissociated from domain-general visuospatial neglect. Exploring this avenue of research provides an useful method for determining whether the Three-Tier model of neglect proposed by Hillis and Caramazza (1995) does, in fact, represent a valid framework for interpreting distinct patterns of visuospatial neglect.

1.5 The Neuroanatomy of Visuospatial Neglect

The underlying neuroanatomy of visuospatial neglect is not yet well understood. Visuospatial neglect is most commonly characterised as a left-lateralised spatial attentional deficit which occurs following damage to right hemisphere temporo-parietal areas (Chechlacz et al., 2012; Parton et al., 2004). However, visuospatial neglect is a highly heterogenous condition which can occur following both left or right hemisphere damage. For example, Stone et al. (1993) assessed a continuous cohort of 171 acute stroke patients and identified some form of visuospatial neglect impairment in 82% of right hemisphere and 65% of left hemisphere patients. More recently, Demeyere and Gillebert (2019) conducted a study including 366 acute stroke survivors which identified significant left-lateralised neglect in 65% and right-lateralised neglect in 35% of patients. Subsequent lesion mapping studies have reliably identified both right- and left- hemisphere neural correlates associated with visuospatial neglect (Beume et al., 2017; Chechlacz et al., 2012; Suchan and Karnath, 2011). In order to understand the complexity of the syndrome, this heterogeneity in terms of lateralisation needs be taken into account when investigating the neural correlates of the neglect syndrome.

Previous studies have primarily focused on identifying the neural correlates of left egocentric neglect in patients with right hemisphere damage. Left neglect is generally associated with damage to right hemisphere temporo-parietal regions, mainly the temporoparietal junction and right superior temporal gyrus (Chechlacz et al., 2010; Chechlacz et al., 2012; Hillis, 2005; Karnath et al., 2004; Molenberghs et al., 2012; Mort et al., 2003; Vossel et al., 2011). However, a wide range of lesion patterns have been implicated in left-lateralised neglect. A series of studies has

suggested that damage to the right angular gyrus and parahippocampal region (Mort et al., 2003) or the white matter tracts connecting these areas are critically implicated in neglect (Bird, 2006). Karnath et al., (2002) found that damage to subcortical structures including the right putamen, pulvinar, and caudate nucleus was associated with left egocentric neglect impairment. In addition, visuospatial neglect has also been found in a number of patients with damage confined to the cerebellum (Hildebrandt et al., 2002; Kim et al., 2008; Silveri, 2001). This heterogeneity in results has led to the hypothesis that visuospatial neglect represents a disconnection syndrome (Bartolomeo et al., 2007) and this claim has been supported by studies linking left visuospatial neglect to damage to the right superior longitudinal (He et al., 2007; de Schotten et al., 2008), inferior longitudinal (Bird, 2006), and inferior fronto-occipital fasciculi (Urbanski et al., 2008). However, a portion of this disagreement may also be reconciled by treating visuospatial neglect as a heterogenous syndrome rather than a unitary behavioural deficit.

Previous lesion mapping investigations which have considered egocentric and allocentric neglect as independent constructs have consistently identified distinct neural correlates associated with each of these deficits (Chechlacz et al., 2010; Chechlacz et al., 2012; Medina et al., 2008, 2008; Ptak et al., 2012). Medina et al. (2008) found that left egocentric neglect was associated with hypoperfusion within right hemisphere dorsal stream areas (e.g. the supramarginal gyrus) while allocentric impairment was associated with damage to areas of the ventral visual processing stream (e.g. the posterior inferior temporal gyrus). Similarly, Hillis et al. (2005) found that damage to the right superior temporal gyrus was implicated in allocentric neglect while damage to the right angular gyrus was predictive of egocentric neglect impairment. Chechlacz et al. (2010) conducted an anatomical likelihood estimate meta-analysis of 1306 neglect patients from 32 different lesion-symptom mapping studies which concluded that egocentric symptoms are associated with damage to the perisylvian network (e.g. pre- and postcentral, supramarginal, and superior temporal gyri) while allocentric symptoms are associated with more posterior lesions impacting the angular, middle temporal, and middle occipital gyri. These findings support the characterisation of neglect as a cluster of distinct impairments rather than a unitary syndrome. However, these investigations focused exclusively on patients with left neglect following right hemisphere damage.

Few previous studies have investigated the neural correlates of visuospatial neglect following left hemisphere lesions. Suchan and Karnath (2011) conducted a lesion-symptom mapping analysis investigating the neural correlates of right egocentric neglect following left hemisphere lesions. This investigation identified 11 patients with right egocentric neglect and found that this impairment was most strongly associated with damage to voxels within the left superior and middle temporal gyri, inferior parietal lobule, and insular cortex (Suchan and Karnath, 2011). Similarly, Beume et al. (2017) found that damage to the superior and middle temporal gyrus, temporal pole, frontal operculum, and insula were the strongest predictors of right egocentric impairment within a cohort of 121 left hemisphere patients (21 with neglect). Additional studies have aimed to investigate the neural correlates of right egocentric neglect following left-hemisphere lesions, but these studies have employed categorical lesion comparisons (e.g. vascular territory, stroke severity) instead of more detailed voxel-wise analyses (Beis et al., 2004; Maeshima et al., 1992; Ogden, 1985; Ringman et al., 2004). Notably, no previous study has investigated the neural correlates of right allocentric neglect. Suchan and Karnath (2011) propose that right egocentric neglect occurs following damage to left hemisphere homologs to right-hemisphere spatial orienting areas. According to this theory, representation of spatial orienting in left hemisphere areas is thought to be a subdominant remnant of more primitive neural structure in humans. However, it is not yet clear whether this is an accurate characterisation of right neglect. Previous research has suggested that at least a portion of right-lateralised egocentric neglect cases occur following right hemisphere lesions (Agrell et al., 1997; Kim et al., 1999; Kwon et al., 2012; Weintraub and Mesulam, 1987; Williamson et al., 2018). For example, Kim et al. (1999) assessed 30 consecutive right hemisphere stroke survivors on a line bisection task and identified 5 patients exhibiting ipsilesional (right) egocentric neglect deficits. This ipsilesional neglect could not be explained as a compensatory strategy, as these patients did not initially present with contralesional neglect impairment.

Patients with ipsilesional neglect were found to have damage to right hemisphere fronto-subcortical circuits, suggesting that the right hemisphere may play a role in maintaining attention to ipsilesional hemispace. This finding is in line with a theory proposing that the right hemisphere

plays a role in distributing attention across both the right and left visual fields while the left hemisphere solely attends to contralesional hemispace (Corbetta and Shulman, 2011; de Schotten et al., 2011; Weintraub and Mesulam, 1987). However, it is not yet clear what implications this finding has concerning the overall anatomy of right egocentric neglect.

Previous research investigating either right or left visuospatial neglect has systematically excluded patients exhibiting ipsilesional deficits and has only analysed the implicated anatomy within a single hemisphere. Given that at least some cases of neglect have been found to ipsilesional, it is important to account for this heterogeneity by considering the full brain in lesion symptom mapping analyses.

1.6 Voxel-Lesion Symptom Mapping and Visuospatial Neglect

Voxel-Lesion Symptom Mapping (VLSM) is one of the most common techniques used to elucidate the neural correlates of neuropsychological disorders. In VLSM, binarized patient imaging data is analysed to investigate the statistical relationship between damage to each individual voxel within the brain and behavioural impairment (Bates et al., 2003). VLSM groups patients according to whether the each individual voxel is spared or damaged then compares the average behavioural scores across these groups. Voxels that, when damaged, result in significantly stronger impairment compared to when they are intact are assumed to be critically involved in the behaviour in question.

VLSM provides an effective methodology for identifying the necessary neural correlates supporting human cognitive functions (Bates et al., 2003). However, the inferential power of VLSM is often greatly limited by the quality of data considered. Ideally, VLSM analyses should aim to include high-quality neuroimaging and behavioural data from large, representative samples of patients with acute brain injury (de Haan and Karnath, 2018). Unfortunately, it is often impossible to obtain high-quality imaging for acute stage patients as many have contra-indications for MR or are simply not able to lie still for MRI scanning (Hand, 2005; Singer et al., 2004). In addition, the higher costs of MRI scanning contribute to CT brain imaging still being the standard clinical pathway in most clinical settings (Khan et al., 2013). With respect to timing, neuropsychological studies often

require lengthy testing and stroke survivors are often not recruited to partake in research until the later stages of recovery. During this recruitment delay, cortical re-organisation and recovery may occur, weakening the relationship between lesion damage and behaviour (de Haan and Karnath, 2018; Green, 2003; Grefkes and Ward, 2014). Previous research has strongly suggested that VLSM analyses which do not include both acute neuroimaging and acute behavioural data may not be able to precisely identify neural correlates (de Haan and Karnath, 2018; Karnath and Rennig, 2017). Additionally, many VLSM studies include only small patient samples, restricted to patients exhibiting only specific stroke types or locations, or very specific, often milder impairments linked to smaller stroke damage. This frequent reliance on non-representative samples greatly limits the generalisability of many VLSM studies' findings. Given these common limitations, new avenues for improving the interpretation of VLSM results are needed.

Within the UK, NICE Clinical Stroke Guidelines (Dworzynski et al., 2013; Swain et al., 2008) require that each suspected stroke patient within the UK completes diagnostic CT scans and bedside cognitive assessment within the acute stage of stroke recovery. This routinely collected clinical data offers a potentially invaluable resource for investigating the neural correlates of human cognitive functions, but the feasibility of using this routine clinical data for lesion-symptom mapping analyses has not yet been established. Acute clinical CT scans are low-resolution and often do not clearly show the full extent of the stroke damage due to the presence of tissue which has been irreversibly damaged, but has not yet been replaced by cerebrospinal fluid (Khan et al., 2013; Urbach et al., 2000). This development of lesions over time may lead to underestimations of the extent of lesion damage based on acute CT imaging alone, which is generally cited as grounds for avoiding CT data in VLSM analyses.

Moore and Demeyere (preprint DOI: 10.1101/2021.02.17.21251846, see also Appendix I) conducted a large-scale, multi-domain lesion mapping study in order to establish the feasibility of employing routinely collected clinical imaging data to investigate the neural correlates of higher-order cognitive functions. In this investigation, a consecutive cohort of 573 acute stroke survivors completed the Oxford Cognitive Screen (OCS) and routine CT or MR stroke imaging. VLSM analysis was then conducted to identify the neuroanatomy significantly associated with impairment

within the OCS' 12 subtests assessing functions across five distinct cognitive domains (language, memory, number, attention, and praxis). As a whole, the anatomical correlates identified in this investigation agree well with those documented in past literature. Language functions were most strongly associated with damage to left hemisphere frontal/temporal areas (Dronkers et al., 2004; Hickok, 2000, 2009). Visual field deficits were reliably associated with damage to posterior occipital areas including the intracalcarine sulcus and left visuospatial neglect was most strongly associated with damage to the right temporo-parietal region (Hinds et al., 2009; Mort et al., 2003; Parton et al., 2004; Reitsma, 2015). The cognitive impairments which were not found to be associated with significant clusters of localised voxels (e.g. praxis, executive function) are generally thought to represent distributed functions rather than strictly localised cognitive abilities (Hoeren et al., 2014; Hua et al., 2014; Schumacher et al., 2019; Varjačić et al., 2018; Weiss et al., 2016). This finding is not unexpected as VLSM is designed to identify localised neural correlates and is less appropriate for identifying the underlying mechanisms of diffuse functions or disconnection syndromes (Gajardo-Vidal et al., 2018).

This investigation demonstrates the validity of using routinely collected clinical neuroimaging data for lesion-symptom mapping analysis with standardised cognitive screening data. The lesion mapping investigations conducted within this thesis will aim to employ routinely collected clinical imaging and standardised cognitive assessment data to investigate the neural correlates of visuospatial neglect subtypes.

1.7 Detecting and Diagnosing Visuospatial Neglect

It is well established that visuospatial neglect is a common consequence of stroke. However, exact prevalence estimates have varied dramatically between 13% and 81% (Buxbaum et al., 2004; Demeyere and Gillebert, 2019; Lee et al., 2008; Parton et al., 2004). Bowen et al. (1999) suggest that at least a portion of this variance can be explained by varying inclusion criteria, but also results from the exact methods used to detect this behavioural impairment.

Line bisection tasks are commonly used as neuropsychological measures of visual neglect impairment (Schenkenberg et al., 1980; Sperber and Karnath, 2016). In these tests, patients

are presented with a series of horizontal lines and are asked to mark the centre of each line. In theory, participants with neglect fail to perceive portions of lines within the neglected side of space, resulting in consistent, spatially-lateralized response biases (Schenkenberg et al., 1980). Line bisection tasks are commonly employed, but several recent studies have strongly suggested that these tasks are not an effective method for detecting neglect impairment. Line bisection has been found to exhibit poor neglect sensitivity, missing 40% of cases of clear unilateral spatial neglect (Ferber and Karnath, 2001). Sperber and Karnath (2016) compared the performance of 180 stroke patients on cancellation and line bisection measures. Factor analysis revelated that line bisection and cancellation tasks were supported by two distinct factors, strongly suggesting that these tests are not assessing the same underlying cognitive function. Additionally, spatial biases in line bisection tasks may arise from causes other than neglect such as hemianopia, optic ataxia, or the handedness of participants, suggesting that line bisection-based assessments may similarly lack specificity (Barton Black, 1998; Kerkhoff and Bucher, 2008; Sampaio and Chokron, 1992; Scarisbrick et al., 1987). Considered cumulatively, the existing literature suggests that line bisection tasks are not a valid method for detecting or quantifying the severity of visuospatial neglect impairment.

Fortunately, other neuropsychological tests have been demonstrated to act as more sensitive and specific neglect diagnostic tools. Cancellation tasks are widely considered the gold standard neuropsychological approach for detecting visual neglect related deficits (Ferber and Karnath, 2001; Hartman-Maeir and Katz, 1995). In these tasks, patients are presented with a search array of spatially presented target stimuli. Patients are then asked to search for and mark off target stimuli while ignoring irrelevant distractor stimuli. Ferber and Karnarth (2001) found that cancellation tasks were highly sensitive (94%) to egocentric neglect and acted as strong predictors of performance on other neuropsychological neglect measures such as figure copy tasks. Azouvi et al. (2006) compared the sensitivity of a battery of pen-and-paper neglect tests including cancellation, figure copy, clock drawing, line bisection, overlapping figures, and reading tests in a cohort of 395 subacute stroke survivors. This study found that cancellation task, specifically the Bell's Test, was found to act as the most sensitive neglect diagnostic tool (Azouvi et al., 2006).

Similar investigations have produced comparable results (Halligan et al., 1989; Alqahtani., 2015).

However, many versions of classic cancellation tasks have been proposed, and not all of these versions are equally sensitive to neglect. Mainly, not all cancellations tasks are able to detect and differentiate between egocentric and allocentric neglect impairment. For example, popular cancellation tasks including the Behavioural Inattention Task's Star Cancellation Task (Humphreys et al., 2012), Albert's Task (Albert, 1973), and Bells Test (Gauthier et al., 1989) do not include any allocentric neglect measures. However, several alternative cancellation tasks have been designed which are able to reliably detect allocentric impairment (Bickerton et al., 2011; Demeyere et al., 2015; Ota et al., 2001). These tasks employ stimuli designed to produce false positive responses in participants with allocentric neglect deficit. For example, the Birmingham Cognitive Screen's Apples Cancellation Task (Humphreys et al., 2012) includes a search matrix composed of complete, left-gap incomplete, and right-gap incomplete line drawings of apples. In this task, patients are instructed to mark all complete stimuli whilst ignoring all incomplete, distractor stimuli (Bickerton et al., 2011; Humphreys et al., 2012). Patients with egocentric neglect commit lateralised target omissions and patients with allocentric neglect commit consistently lateralised false positive errors (Humphreys et al., 2012). These alternative cancellation tasks have been found to be able to reliably differentiate between egocentric and allocentric neglect impairment (Bickerton et al., 2011; Chechlacz et al., 2010; Demeyere et al., 2015; Ota et al., 2001) and exhibit high sensitivity to neglect impairment versus more traditional neglect metrics (Bickerton et al., 2011; Demeyere et al., 2015).

While cancellation tasks have been found to be the most sensitive individual measure of neglect, previous research has suggested that neglect diagnoses should be made based on agreement across a range of neglect tests (Azouvi et al., 2006; Bailey et al., 2004; Halligan et al., 1989; Huygelier et al., 2020). Azouvi et al. (2006) assessed a cohort of 395 stroke survivors on six neuropsychological neglect tests and found that considering data from multiple tests was more sensitive to neglect impairment than any individual test alone. Similarly, Halligan et al. (1989) assessed a cohort of neglect patients on Albert's test, letter cancellation, Star cancellation, figure copying, line bisection, and drawing tests. Star cancellation task was found to be the single most

sensitive neglect measure. However, this investigation concluded that multiple neglect tests are more likely to detect this impairment than any single test due to the variable behavioural manifestation of neglect. Huygelier et al. (2020) found that comparing performance across multiple cancellation tasks can effectively reduce false-positive diagnoses due to non-spatial probabilistic error patterns. Taken together, the existing literature strongly suggests that administering multiple neuropsychological tests is the most effective way to diagnose visuospatial neglect impairment.

However, there is a clear disparity between these research-based neglect diagnosis recommendations and common clinical practice. In clinical settings, visuospatial neglect impairment is most commonly diagnosed using the National Institute of Health Stroke Scale's (NIHSS) inattention/extinction item (Goldstein et al., 1989; Kasner, 2006). The NIHSS is an observational post-stroke assessment method designed to evaluate functional and cognitive impairment (Goldstein et al., 1989). As of 2017, over 500,000 healthcare professionals had been certified to use the NIHSS and this assessment is considered the gold standard for studies involving stroke patients (Lyden, 2017). This assessment includes items covering common post-stroke impairments such as hemiplegia, facial numbness, aphasia, and visual neglect (Goldstein and Samsa, 1997; Kasner, 2006). The NIHSS provides a simple and time-efficient method for assessing the most common post-stroke patients with virtually any level of impairment severity and is used extensively by clinicians (Goldstein et al., 1989; Goldstein and Samsa, 1997; Kasner, 2006). Acute NIHSS total scores are strong predictors of overall recovery outcome, making this index particularly useful for predicting patient prognoses (Adams et al., 1999; Muir et al., 1996; Sato et al., 2008). The NIHSS has also been found to be more specific and sensitive post-stroke assessment method than other commonly used observation neurological screens, such as the Canadian Neurological Scale and the Middle Cerebral Artery Neurological Score, with a reported specificity of 90% and an overall accuracy of 83% to poor long-term outcome (Muir et al., 1996). However, it is not quite clear whether the NIHSS offers a suitably sensitive measure for detecting visual neglect.

Observational assessments, such as the NIHSS, rely predominantly on subjective impression of observed impairment levels rather than objective, standardised performance based measurements (Meyer and Lyden, 2009; Spilker et al., 1997). For example, a clinician completing an

observational assessment of visual perception might watch a patient and make note of whether they are struggling to attend to ward staff approaching from one side, or are directing their gaze to one side (Kasner, 2006). Previous research has provided evidence suggesting that observational post-stroke assessment methods may not be sufficiently sensitive to diagnose visual neglect (Bickerton et al., 2011; Meyer and Lyden, 2009; Parton et al., 2004; Puig-Pijoan et al., 2018). The severity of neglect varies drastically with some patients exhibiting a consistent inability to orient towards or attend to one side of space and others only demonstrating neglect when performing specific tasks (Bickerton et al., 2011; Hartman-Maeir and Katz, 1995; Muir et al., 1996). It is also unclear whether observational assessments are able to detect allocentric neglect deficits. This implies that while observational assessments may be sufficient for detecting the most severe occurrences of neglect, additional tools may be needed to detect less obvious cases.

Previous research has suggested that the NIHSS is substantially less sensitive to neglect impairment than common neuropsychological assessments. Puig-Pijoan et al. (2018) investigated the NIHSS' sensitivity to neglect in a group of 25 acute neglect patients who were diagnosed with neglect based on bisection, cancellation, and gap-detection tasks. The NIHSS inattention item as administered by trained medical professionals only detected 56% of these confirmed neglect cases (Puig-Pijoan et al., 2018). Gottesman et al. (2010) found that including simple cancellation tasks alongside the NIHSS significantly added to the the NIHSS' ability to predict lesion size and stroke severity. These studies have provided preliminary evidence that the NIHSS may not be sufficeintly sensitive to detecting neglect impairment, but additional research is needed to determine exactly why this method is comparatively insensitive. For example, the NIHSS's ability to detect allocentric neglect has not yet been investigated.

In an ideal world, clinicians would have the resources to conduct extensive neuropsychological neglect assessments for each stroke patient. Given that real-world time constraints (both in terms of clinician time, but also patient burden) as well as resource constraints make this ideal practice an unrealistic possibility, it is critical to determine the most sensitive, time-efficient method for detecting neglect in clinical settings.

1.8 Neglect Recovery and Functional Implications:

Visuospatial neglect is not only a deficit of significant theoretical importance, but is also a clinically relevant research topic. Stroke survivors who experience neglect often become unable to drive, read, or safely navigate through their environments. These functional deficits are often a key rehabilitation priority for patients, requiring a large amount of health system resources to adequately address (Cumming et al., 2013; Dworzynski et al., 2013). It is therefore critically important to understand the recovery trajectories of visuospatial neglect deficit, as this knowledge can help optimise current neglect rehabilitation practices. The neglect syndrome is represented by a highly heterogeneous group of symptoms and contains many subtypes (Bickerton et al., 2011; Li et al., 2014; Stone et al., 1993). It is not yet clear whether different subtypes of neglect follow similar recovery trajectories or whether neglect subtypes are differentially associated with poor long-term functional outcomes.

The occurrence of post-stroke cognitive impairments has been strongly associated with reduced quality of life throughout recovery (Jehkonen et al., 2000a; Katz et al., 1999; Langhammer et al., 2016; Nys et al., 2006). However, not all cognitive deficits appear to affect quality of life and functional outcome to the same extent. Previous research has demonstrated that patients who experience visuospatial neglect following stroke are significantly more likely to report higher levels of functional impairment and lower quality of life than patients without visuospatial neglect impairment (Cherney et al., 2001; Jehkonen et al., 2000a; Katz et al., 1999). This particularly robust effect has been documented across multiple different timepoints using a wide range of functional outcome measures. For example, Jehkonen et al. (2000a) found that performance on the Behavioural Inattention Test was the single best predictor (compared to hemianopia, age, and verbal memory) of poor functional outcome at 3, 6 and 12 month follow-up appointments (Jehkonen et al., 2000a). Cherney et al. (2001) determined that higher neglect severity was predictive of lower Functional Independence Measure scores at admission, discharge, and 3 month follow-up. Katz et al. (1999) found that acute neglect was associated with lower scores on various activities of daily living measurements as well as on standardised cognitive measures throughout the first five months following stroke. Similarly, Williams and Demeyere (2021) found that neglect impairment

was longitudinally associated with depression as reported by the Hospital Anxiety and Depression Scale (Williams and Demeyere, 2021). These findings demonstrate that the occurrence of visuospatial neglect acts as a significant predictor of functional outcome.

However, neglect is not a unitary syndrome. Following stroke, patients can exhibit left or right egocentric and/or allocentric neglect (Bickerton et al., 2011, 2011; Chechlacz et al., 2012; Chechlacz et al., 2012; Demeyere and Gillebert, 2017; Humphreys et al., 2013; Li et al., 2014; Ota et al., 2001). It is important to investigate whether different subtypes of neglect follow different recovery trajectories in order to better understand how neglect impacts patients to improve prediction of broad functional outcomes and to facilitate targeted rehabilitation programmes. For example, if all cases of a deficit are found to spontaneously recovery within the first week following stroke it is inefficient to expend health resources treating this condition, as these patients would recover without assistance. Alternatively, if a condition with a very low spontaneous recovery rate is identified, rehabilitation resources can be delegated to prioritise treating this condition, which would not be expected to recovery without significant intervention. If neglect syndrome recovery trajectories can be characterised and differentiated, this approach could be applied to help optimise neglect rehabilitation practices. Previous research has suggested that patients with egocentric and allocentric neglect may exhibit differing levels of functional impairment. Bickerton et al. (2011) found that patients with allocentric neglect scored significantly lower on the Barthel Index activities of daily life measurement (Quinn et al., 2011) compared to patients with egocentric neglect at a single, subacute timepoint. In this study, patients with both allocentric and egocentric neglect also reported significantly higher levels of depression on the Hospital Anxiety and Depression Scale than patients with either egocentric or allocentric neglect alone.

Similarly, although neglect is most commonly thought of as a left-lateralised impairment occurring following unilateral right-hemisphere damage, recent research has demonstrated that right-lateralised neglect impairments also frequently occur following stroke (Becker and Karnath, 2007; Beis et al., 2004; Demeyere and Gillebert, 2019; Lee et al., 2008; Stone et al., 1992). Patients with left and right neglect may exhibit differing levels of functional impairment. Ten Brink et al. (2017) investigated the relationship between neglect lateralisation and performance on

various cognitive and physical independence measures in a cohort of 335 acute stroke survivors. This study found that left-lateralised neglect impairment was more severe than right-lateralised neglect as assessed by both neuropsychological and observational measures. However, patients with right neglect exhibited lower scores on the Mini Mental State Examination (Folstein et al., 1983; Tombaugh and McIntyre, 1992) than patients without neglect (potentially through a co-occurring language deficit) and were more likely to exhibit impaired balance than patients with left neglect (Ten Brink et al., 2017). These findings suggest that the association between neglect and functional impairment may depend on the reference frame and lateralisation of neglect. However, these studies only employed data from a single timepoint acutely post stroke.

Previous research has suggested that some stroke-related deficits follow a proportional recovery rule in which the amount of improved function is proportional to the initial degree of function loss (Marchi et al., 2017; Smith et al., 2017). However, it is not yet clear whether egocentric and allocentric visuospatial neglect follow this proportional recovery pattern (Bonkhoff et al., 2019; Hope et al., 2019). If neglect impairments follow a proportional recovery rule, neglect cases which are initially more severe should be less likely to fully recover than less severe cases (Marchi et al., 2017; Smith et al., 2017). Conversely, if neglect does not follow a proportional recovery pattern, the initial severity of neglect would not be expected to differentiate between patients who do and do not recover over time. Similarly, it is important to investigate differences in rates of improvement over time across different neglect subtypes. For example, it is possible that patients with milder deficits improve gradually over time while patients with severe impairments do not experience any improvement. Alternatively, it is possible that all patients with neglect exhibit the same rate of change in severity over time, regardless of the severity of their initial deficits. It is therefore critically important to better characterise recovery trajectories in different neglect subtypes in order to identify the specific patients who are least likely to fully recover.

Stone et al. (1992) in a group of 68 patients with neglect, found that neglect following right hemisphere damage (N=34) was significantly slower to improve and less likely to fully recover than neglect following left hemisphere lesions (N=34) over the first six months following stroke. Demeyere and Gillebert (2019) found that of the 160 patients with follow up data 81% of egocen-

tric neglect (11 impaired at follow up versus 55 impaired at the acute stage) and 71% of allocentric neglect cases (10 chronic versus 39 acute) recovered within six months following stroke. Overall, a high proportion of visuospatial neglect cases were found to recover within the first six months following stroke (Demeyere and Gillebert, 2019; Stone et al., 1992), but this relationship may not be equivalently true for different neglect lateralisations and reference frames. However, these previous investigations into neglect recovery trajectories have not considered the interaction between neglect subtype and lateralisation when attempting to elucidate the predictive relationships between these acute factors and long-term neglect recovery outcomes. It is therefore critically important to disentangle how complex acute neglect behavioural phenotypes predict longer-term outcomes, both in terms of long-lasting neglect symptoms as well as broader functional outcomes related to activities of daily life and participation. This in turn, may help identify which specific patients are the most likely to benefit from targeted rehabilitation strategies.

Previous research has suggested that the exact method used to quantify variables of interest can potentially bias the conclusions of any one single study. This possibility is critically important to consider in the context of neglect recovery research. Given the diversity in methodologies previously employed, it is important to explicitly quantify how the specific inclusion criteria and outcome measures employed by each previous investigation into the relationship between acute neglect and long-term functional outcome have ultimately impacted the conclusions of each individual study. Conducting any research study inevitably involves choosing a specific analysis design from a multitude of possible methodologies. It is often unclear how these inherent, yet arbitrary methodological choices ultimately impact the final conclusions of any single study. It is plausible that the results of any one individual analysis can be drastically skewed, and therefore unrepresentative due to the specific combination of methodological choices made by the researchers. This possibility is critically important to consider within the context of any neurological research, including studies aiming to clarify the relationship between acute visuospatial neglect and poor long-term functional outcome. Planning research within patients with visuospatial neglect requires researchers to select specific combinations of potentially valid methodological choices. For example, some previous investigations of relationship between acute visual neglect

and poor functional outcome have included a sample restricted to only patients with right hemisphere damage (e.g. Jehkonen et al., (2000b)). Previous research has demonstrated that visual neglect commonly occurs following both right and left hemisphere lesions, but neglect following right damage is significantly more severe than neglect following left lesions. Therefore, including only right hemisphere patients in visuospatial neglect studies could potentially result in a sample which is biased towards more severe neglect cases and it is not yet clear whether these restricted samples are adequately representative of neglect within the full stroke population.

Similarly, previous studies have included samples of neglect patients recruited at different timepoints following stroke (Bickerton et al., 2011; Nys et al., 2006). Previous research has suggested that neglect follows a non-linear recovery trajectory throughout the first six months following stroke, with most spontaneous recovery occurring within the first ten days following stroke (Stone et al., 1992). This suggests that the "neglect" groups within more acute samples will include patients which will have recovered by later timepoints and would therefore not be included in the "neglect" groups of studies who recruit patients at a later timepoint. It remains unclear whether this difference in the specific patients included may significant influence the results of these studies. Finally, many studies investigating the relationship between neglect and functional outcome have exclusively included patients with egocentric neglect and have not included tests of allocentric neglect (Cherney et al., 2001; Jehkonen et al., 2000b; Nys et al., 2006; Stone et al., 1992). It therefore remains unclear whether studies which do not control for the potentially confounding impact of allocentric neglect impairment produce externally valid conclusions.

Given that research investigating the predictive relationship between neglect and poor functional outcome in stroke survivors inherently requires such a wide range of methodological choices, this topic of research is ideal for investigating the utility of multiverse analysis techniques within neurological patient research. Multiverse analysis evaluates the impact of arbitrary design choices on the conclusions of individual studies (Dragicevic et al., 2019; Steegen et al., 2016). In a multiverse analysis, a large number of potential datasets are generated by making each possible permutation of reasonable methodological choices within a single experiment. Each of these datasets are then independently analysed, and the cumulative results are used to evaluate the

overall robustness of the effect of interest. Critically, multiverse analysis clarifies which specific methodological choices may lead to significant effects. This increase in transparency can potentially help identify cases in which effects documented in neurological rehabilitation trials are simply due to the specific outcome measures employed or findings from drug trials cannot be generalised to wider patient populations. Research investigating the predictive relationship between the occurrence of visuospatial neglect and poor long-term functional outcome in stroke survivors provides an ideal context in which to investigate the utility of multiverse analysis within broader neurological research.

Finally, previous studies have focused on identifying domain-general functional impairment rather than specific behavioural patterns in patients exhibiting neglect. For example, investigations which have employed standardised questionnaires as outcome measures have identifying differences in aggregate scores rather than identifying specific behavioural patterns which may differ between patients with and without visuospatial neglect impairment (Bickerton et al., 2011; Cherney et al., 2001; Jehkonen et al., 2000a; Katz et al., 1999). It is critically important to identify specific functional impairments which distinguish patients with visuospatial neglect to help guide therapists and care workers toward the best approach for assisting participants with neglect deficits. First, developing a more thorough understanding of how neglect impacts behaviour offers an avenue for improving the efficiency of observational neglect assessments. Second, it is not yet well understood how quantitative neglect severity scores translate into qualitative behavioural impairments. Gaining a better understanding of how neglect severity scales with specific functional impairments can potentially help health professionals distinguish between patients who may be able to compensate for their attentional impairment, and those who will require assistance in daily tasks. Finally, establishing a detailed profile of specific behavioural impairments associated with egocentric/allocentric neglect is needed before tailored behaviour-based rehabilitation studies can be developed for these deficits.

1.9 General Aims and Objectives

Overall, the data and analyses presented within this thesis aimed to investigate the underlying mechanisms and clinical utility of behavioural heterogeneity within the visuospatial neglect syndrome. Each chapter includes an author's note including publication information and author contributions in line with standard CRediT reporting format (Brand et al., 2015).

Chapter Two presents a critical analysis of commonly employed neglect assessment methods and investigates the utility of neglect severity metrics which can be extracted from neuropsychological measures. The first section of this chapter (Chapter 2.1) has been published in the Journal of Neurology, Neurosurgery, and Neuropsychiatry (Moore et al., 2019).

Chapter Three analyses behavioural heterogeneity in neglect dyslexia to investigate the relationship between reading-related and domain-general neglect impairments. This analysis is published in the Journal of Clinical and Experimental Neuropsychology (Moore et al., 2020).

Chapter Four presents a series of three case studies aiming to characterise the properties of representation-level neglect dyslexia in order to critically evaluate Hillis and Caramazza's (1995) three-tier model of spatial attention. Sections one and two of this chapter are both published as single case studies in Cortex (Moore and Demeyere, 2018, 2020).

Chapter Five presents a detailed analysis of the neural correlates of various visuospatial neglect deficits and aims to determine whether right neglect is anatomically homologous to left-lateralised neglect. This project is currently under review at Neuropsychologia (pre-print DOI: 10.31234/osf.io/4kyf8).

Finally, Chapter Six analyses the relationship between the occurrence of acute neglect and poor long term functional outcome to determine whether the specific behavioural phenotype of acute neglect impairment can act as a prognostic indicator. Section one of this chapter is published in Neurorehabilitation and Neural Repair (Moore et al., In Press) (pre-print DOI: 10.1101/2021.03.29.21254555) while section two is published in the Journal of Neurology (Moore Demeyere, In Press) (Pre-Print DOI: 10.1101/2021.03.29.21254222).

These findings are then discussed in detail to fully analyse wider implications of each of individual finding to investigate patterns of heterogeneity within neglect, to determine this syndrome's

underlying mechanisms, and to investigate the practical utility of considering this heterogeneity within clinical settings.

2 Chapter 2.0: Quantifying Neglect Impairment

Author's Note:

In line with standard CRediT author roles (Brand et al., 2015), I was responsible for Formal Analysis, Data Curation, Writing - Original Draft, Writing - Review and Editing, and Visualising the material presented within Section One of this Chapter. The contents of this section is published in abbreviated form under the title "When Neglect is Neglected: The NIHSS observational assessment lacks sensitivity in identifying post-stroke unilateral neglect" in the Journal of Neurology, Neurosurgery, and Neuropsychiatry (Moore et al., 2019) (Appendix II).

Section Two represents a retrospective analysis of existing data in which I was responsible for Formal Analysis, Data Curation, Writing – Original Draft, Writing – Reviewing and Editing, and Visualising. This project is currently being prepared for publication.

2.0 General Introduction

This chapter will investigate methods for detecting and quantifying visuospatial neglect. The first section evaluates the diagnostic sensitivity of the National Institutes of Health Stroke Scale (NIHSS) as an observational assessment of neglect in acute stroke. This section investigates factors which modulate the probability of successfully detecting visual neglect, potential biases within these assessments, and these measures' sensitivity to different visual neglect subtypes within a sample of 428 acute stroke survivors. This study found that the NIHSS exhibits a low sensitivity to neglect (31.2%) compared to a standardised, quantitative neuropsychological neglect assessment.

The second section of this chapter elaborates on using neuropsychological cancellation tasks for quantifying visuospatial neglect impairment. This section explores novel neglect severity metrics that can be derived from a computerised version of the Hearts cancellation task, and descriptively compares different metrics in acute stroke survivors. Overall, this section demonstrates that centre of cancellation and allocentric proportional scoring metrics act as an effective method for detecting and quantifying the severity of neglect impairments on the OCS Cancellation Task.

Together, these two sections demonstrate the need for quantitative, neuropsychological neglect assessments and present novel neglect severity metrics which can be derived from these scores. These novel severity metrics are employed throughout the analyses presented within this thesis to further fundamental understanding of the neglect syndrome.

2.1 Chapter 2.1: Evaluating Observational Neglect Assessments

2.1.1 Introduction

In clinical settings, visual neglect is most commonly diagnosed using the National Institute of Health Stroke Scale (NIHSS), an observational assessment method designed to evaluate post-stroke functional and cognitive impairment (Goldstein and Samsa, 1997; Kasner, 2006). As of 2017, over 500,000 clinicians had been certified to use the NIHSS and this assessment is considered the gold standard for stroke patient studies (Lyden, 2017). Although the NIHSS was originally intended to identify patients for inclusion in clinical trials rather than to serve as an individual diagnostic tool, it is frequently used as a preliminary diagnostic screen for stroke patients in clinical environments (Lyden, 2017).

However, observational assessments, such as the NIHSS, rely predominantly on subjective impression of impairment levels rather than objective measurements (Meyer and Lyden, 2009; Spilker et al., 1997). While this reliance on clinical observation makes the NIHSS a simple, time-efficient method for assessing most common post-stroke deficits in patients (Goldstein et al., 1989; Goldstein and Samsa, 1997; Kasner, 2006), previous research has suggested that observational post-stroke assessment methods may not be sufficiently sensitive to visual neglect (Bickerton et al., 2011; Parton et al., 2004; Spilker et al., 1997). Observational assessments may be sufficient for detecting more severe, behaviourally apparent cases of neglect, but it is unclear whether these tests can detect less severe or less common (e.g. allocentric) subtypes of neglect (Bickerton et al., 2011; Ellis and Young, 2013; Hartman-Maeir and Katz, 1995; Muir et al., 1996).

Unlike observation, neuropsychological assessments require patients to complete tasks which provide a quantitative measure of neglect (Gottesman et al., 2010). Cancellation tasks are the standard neuropsychological approach for detecting visual neglect (Bickerton et al., 2011; Stone et al., 1992). In these tasks, patients are presented with a search matrix containing spatially-distributed stimuli and are asked to mark all target stimuli. Patients presenting visual neglect reliably fail to detect stimuli presented towards the contralesional side of space (Gottesman et al., 2010). Previous research has demonstrated that cancellation tasks are highly sensitive, and are able to reliably distinguish between egocentric and allocentric neglect (Bickerton et al., 2011;

Ellis and Young, 2013). Gottesman et al. (2010) found that including cancellation tasks alongside the NIHSS significantly added to the NIHSS' ability to predict stroke severity. Although this study demonstrates the utility of including cancellation tasks in clinical neglect assessments, it did not investigate the NIHSS' ability to detect neglect in comparison to the cancellation measures.

The NIHSS was not intended to be used as an individual diagnostic tool, but it is frequently employed as one (Lyden, 2017) It therefore remains critically important to evaluate the sensitivity of this screen for detecting post-stroke impairments.

2.1.2 Methods

Participants:

This study is a secondary analysis of cross-sectional observational data. Participants were recruited from 32 United Kingdom hospitals in the OCS-Care and OCS-tablet studies. Both studies were approved by the National Research Ethics Service (REC references 12/WM/00335 and 14/LO/0648). Patients able to be assessed within 31 days of confirmed stroke, to concentrate for 15 minutes, to provide informed consent, and to complete the NIHSS and OCS Cancellation Task within 10 days interval were included in this study.

A total of 428 stroke patients (mean age=71, SD=12.8, range=18-93, 47.6% female) were included in this study. These individuals completed the OCS an average of 7.3 days (SD=7.4, range=0-31) following their stroke and had a mean interval of 1.2 days (SD=2.1, range=0-10) days between completing the NIHSS and OCS. The NIHSS was performed before the OCS in 137/404 cases with the dates of both tests reported; while the tests were administered on the same day in 255 of these cases. Stroke types were: 284 ischemic, 47 haemorrhagic, 4 other, and 95 unreported. Lesion lateralisations were: 127 right, 113 left, 16 bilateral, 16 unknown, and 156 unreported.

Methods and Materials:

Post-stroke assessment data from the NIHSS and the OCS was considered in this investigation. The NIHSS is an 11-item scale designed to evaluate the severity of physical and cognitive

impairments (Spilker et al., 1997). This scale assigns each patient a “Stroke Severity Score” which is calculated based on the number and severity of impairments on NIHSS items. Scores range from 0-42 with 0 representing no symptoms and 42 representing the most severe level of stroke impairment. The NIHSS was administered by trained clinicians who complete each NIHSS item observationally.

The NIHSS total and two specific items - Extinction/Inattention and Visual Field - were considered in this investigation. The Extinction/Inattention Item is intended to detect extinction and visual neglect. In this item, patients who exhibit visual, auditory, tactile, or personal inattention are assigned an item score of 1 while those demonstrating profound inattention are assigned a score of 2. When clinicians are unable to detect neglect observationally, they are encouraged to test more formally to facilitate the detection of subtle deficits (Spilker et al., 1997). For example, they might raise their arms and ask patients to indicate whether the left, right, or both arms are raised. In the Visual Field Item, patients with partial hemianopia are assigned a score of 1, those with complete hemianopia are assigned scores of 2, and individuals who are completely blind are assigned scores of 3 and were excluded from this investigation.

Sensitivity is generally evaluated versus the “objective reality” of whether patients actually exhibit a given condition. However, since no absolute test of neglect exists, the OCS’ Cancellation Task was used as the best practice standard to evaluate the sensitivity of the NIHSS. The Cancellation Task has been demonstrated to be highly sensitive (94.12%, versus the Behavioural Inattention Test Star Cancellation) and reliably differentiates between egocentric and allocentric neglect (Demeyere et al., 2015; Ellis and Young, 2013). In this task, patients are presented with a search matrix of heart line drawings. One third of the hearts (N=50) contained left-lateralised gaps, one third had right gaps, and one third were complete drawings. These target and distractor stimuli are equally distributed across an A4 paper (Figure 2.1).

The Cancellation Task was administered by a trained clinician or researcher. Patients were instructed to search for and mark complete drawings while ignoring incomplete stimuli and were allowed up to two practice trials. Patients were allowed three minutes to complete the task. Egocentric neglect was scored by subtracting the number of target stimuli identified on the left of

the matrix from the number identified on the right. Allocentric neglect impairment was scored by subtracting the number of right-gap hearts identified from the number of left-gap hearts identified. Egocentric scores of >3 or <-3 and allocentric scores of >1 or <-1 are indicative of impairment, based on scoring guidelines and normative data (Demeyere et al., 2015). Total scores denoting the number of targets successfully identified were also recorded. These total scores were used to quantify the severity of egocentric neglect to resolve any potential ambiguity in the raw egocentric asymmetry scores. For example, an egocentric asymmetry score of 5 could be achieved with very severe neglect (5 items crossed out with none in the contralateral field), or very mild neglect (45 items crossed out, 15 left targets and 20 right targets).

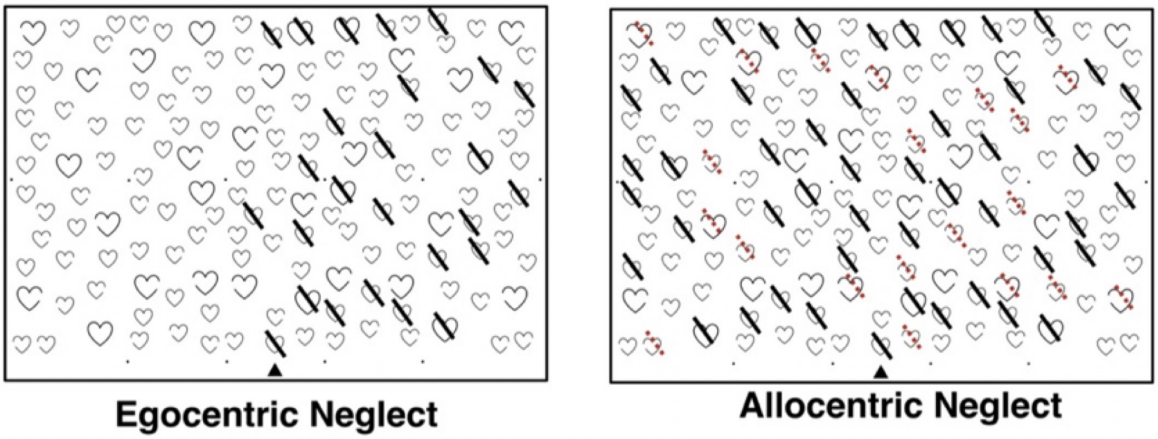


Figure 2.1: The Cancellation Task with examples of egocentric and allocentric neglect. Solid lines represent correct responses and dashed lines denote false positives.

2.1.3 Results

Neglect Prevalence as Reported by the Extinction/Inattention Item:

First, the sensitivity of the NIHSS and OCS Cancellation Task was compared. 83/428 (19.4%) of patients exhibited neglect as reported by the Extinction/Inattention Item. However, 199/428 (46.5%) patients exhibited significant neglect on the OCS. 39.4% of patients who were not diagnosed with neglect on the NIHSS exhibiting neglect on the Cancellation Task, indicating that while the NIHSS exhibits a high specificity (91.2%) for visual neglect, it is not a sensitive measure (31.6%).

Visual neglect deficits may inadvertently be captured by the Visual Field Item. 56/428 (13.1%) of patients exhibited visual field impairment on the Visual Field Item. Interestingly, the Extinction/Inattention Item was not found to be significantly more sensitive to neglect that the Visual Field Item (31.6% versus 28.1% respectively, McNemar's, X2 = 0.735, p = 0.39).

Relationship between the Severity of Neglect and Probability of Detection:

First, a regression analysis was conducted to determine the relationship between Extinction/Inattention Item sensitivity and neglect severity. Neglect patients who received higher cancellation scores (less severe neglect) were significantly less likely to be identified by the NIHSS than patients with lower cancellation scores (R2 = 0.107, F(1,42) = 5.016, p = 0.030, beta = -0.327) (Figure 2.2). However, when only the most severe neglect patients are considered (cancellation totals <10), the NIHSS was still found to have a low sensitivity (38.1%).

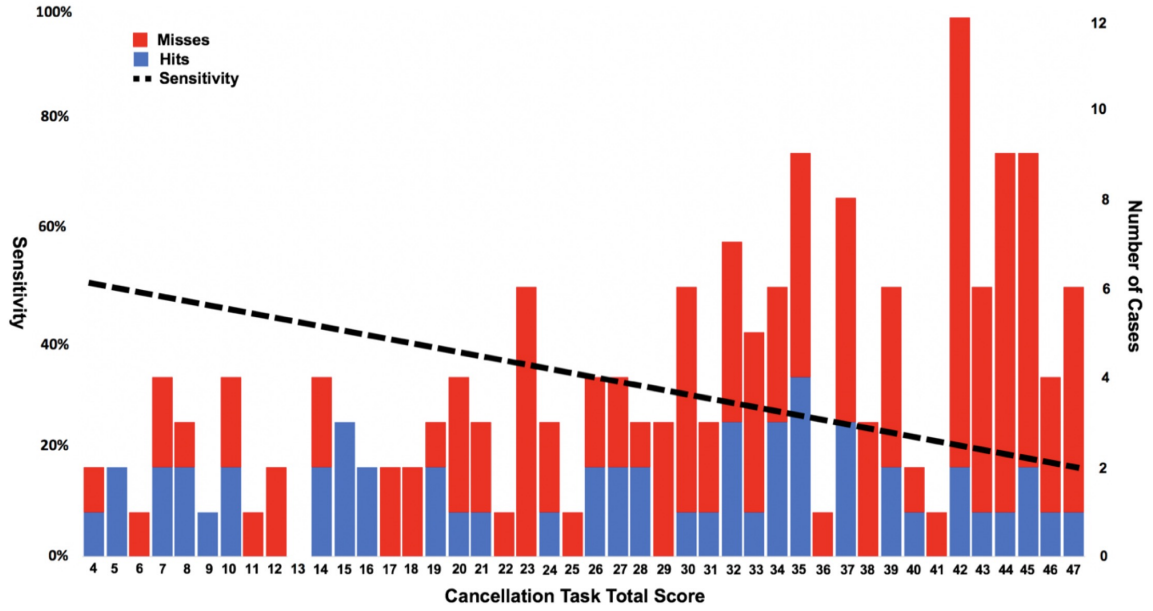


Figure 2.2: The relationship between cancellation score and NIHSS sensitivity. Number of cases of each severity is denoted by bar height (right y-axis). Cases which were successfully identified by the NIHSS are blue and missed cases are red. The sensitivity linear regression line is plotted as the dashed line.

Next, one-way ANOVA analyses were conducted to investigate the relationship between neglect severity as reported by the Cancellation Task and NIHSS detection rate for egocentric

neglect patients. Egocentric neglect alone was considered to be represented by NIHSS items, as the NIHSS is not designed to detect allocentric neglect. All tests were corrected for multiple comparisons.

There was a significant relationship between Cancellation Task total * and Extinction/Inattention Item score ($F(2,169) = 4.777$, $p = 0.010$). Post-hoc Tukey tests indicated that patients with Extinction/Inattention scores of 0 exhibited significantly less severe neglect impairments on the Cancellation Test ($M = 32.4$, $SD = 11.4$) than those assigned scores of 2 ($M = 25.4$, $SD = 11.9$, $p = 0.043$) (Figure 2.3). However, no significant difference was present in the Cancellation Scores of patients who received scores of 0 and 1 ($M = 27.1$, $SD = 13.2$, $p = 0.054$) or 1 and 2 ($p = 0.868$).

There was a significant relationship between cancellation score and Visual Item scores ($F(2,169) = 7.689$, $p = 0.001$) (Figure 2.3). Post-hoc Tukey tests demonstrated that patients with Visual Field scores of 0 exhibited a significantly less severe neglect impairment ($M = 32.7$, $SD = 11.4$) than those assigned scores of 1 ($M = 24.7$, $SD = 12.0$, $p = 0.020$) and 2 ($M = 25.2$, $SD = 15.5$, $p = 0.004$). However, there was no significant difference between the cancellation scores of patients with Visual Field scores of 1 and 2 ($p = 0.987$).

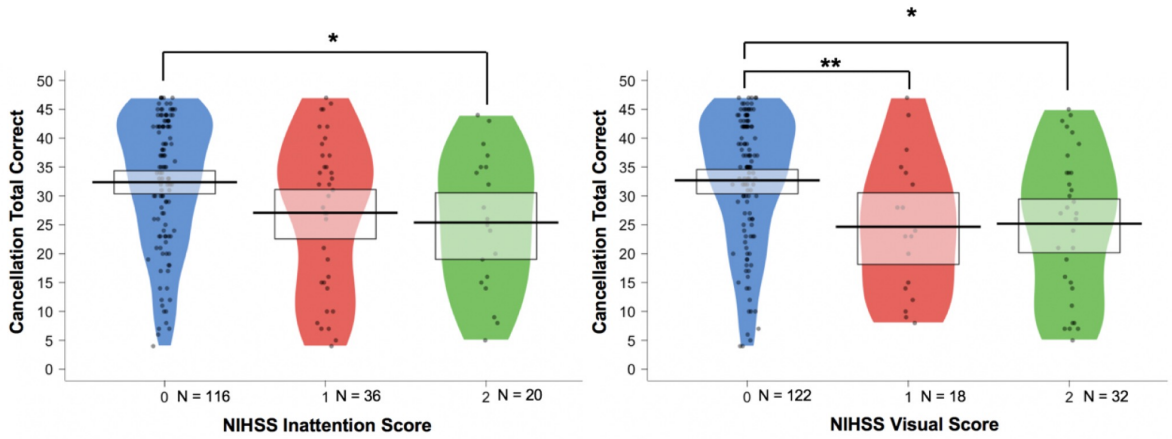


*Figure 2.3: The relationship between Inattention/Extinction and Visual Items and cancellation score in neglect patients. Score distribution is represented by plot width, points represent individual cases, and rectangles represent upper and lower quartiles. Lower cancellation scores represent more severe neglect. *=p<0.05.*

Relationship Between Visual Neglect Subtype and NIHSS Sensitivity:

Finally, sensitivity and one-way ANOVA analyses were conducted to elucidate the relation-

ship between neglect subtype and probability of NIHSS detection. The Extinction/Inattention Item was found to be more sensitive to left neglect (sensitivity = 58.3%) than to right neglect (sensitivity = 18.7%). This substantial difference in sensitivity occurred despite the fact that, in this sample, there was not a significant difference in the severity of cases of right (N = 62, M = 32.6, SD = 11.1) and left (N = 97, M = 29.1, SD = 13.0) neglect (t(157) = 1.767, p = 0.079).

There was a significant relationship of total cancellation score for Extinction/Inattention Item score categories in right neglect patients (F(2,72) = 4.345, p = 0.017), but not left neglect patients (F(2,108) = 2.469, p = 0.089). Post-hoc Tukey comparisons indicated that right neglect patients with Extinction/Inattention scores of 0 received significantly higher cancellation scores (M = 35.4, SD = 11.4) than those who received scores of 2 (M = 22.4, SD = 12.2, p = 0.047). However, there were no significant differences in cancellation scores patients who received scores of 2 and 1 (M = 27.4, SD = 10.6, p = 0.705) or 0 and 1 (p = 0.143) (Figure 2.4).

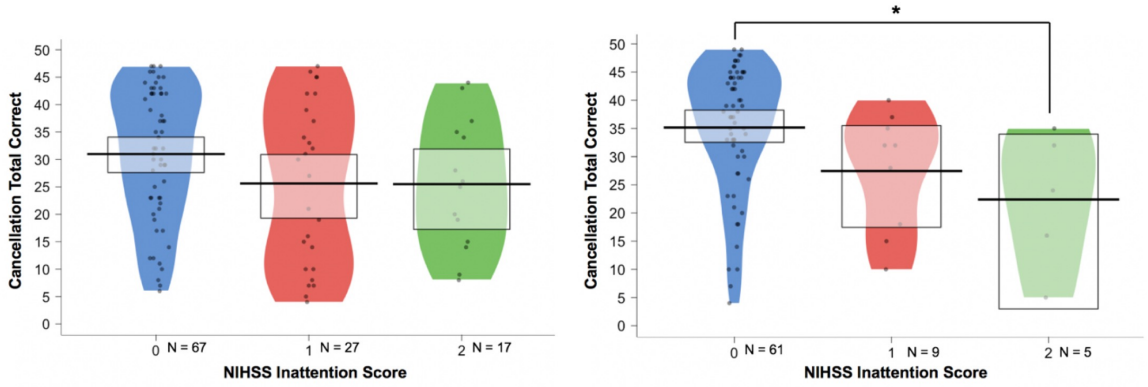


Figure 2.4: The relationship between Extinction/Inattention Score and Cancellation Total scores in patients with left (left panel) and right neglect (right panel). Lower cancellation scores denote more severe neglect.

The Extinction/Inattention Item was also found to be more sensitive to cases of cooccurring egocentric and allocentric neglect (sensitivity = 68.8%) than cases of either pure egocentric (28.8%) or pure allocentric (25.9%) neglect. There was a significant relationship between Cancellation total score and Extinction/Inattention score for pure egocentric neglect patients (F(2,115)= 3.206, p = 0.033). However, there was no relationship between Extinction/Inattention score and allocentric asymmetry for pure allocentric neglect patients (F(2,24) = 0.110, p = 0.896) or for

patients with both allocentric and egocentric neglect (F(2,51) = 1.326, p = 0.275). Post-hoc Tukey tests indicated that pure egocentric neglect patients with Extinction/Inattention scores of 0 (M = 33.8, SD = 10.6) performed significantly better on the Cancellation Task than pure egocentric patients who received scores of 2 (M = 25.4, SD = 12.9, p = 0.032) but not patients with scores of 1 (M = 30.7, SD = 13.6, p = 0.515) (Figure 2.5).

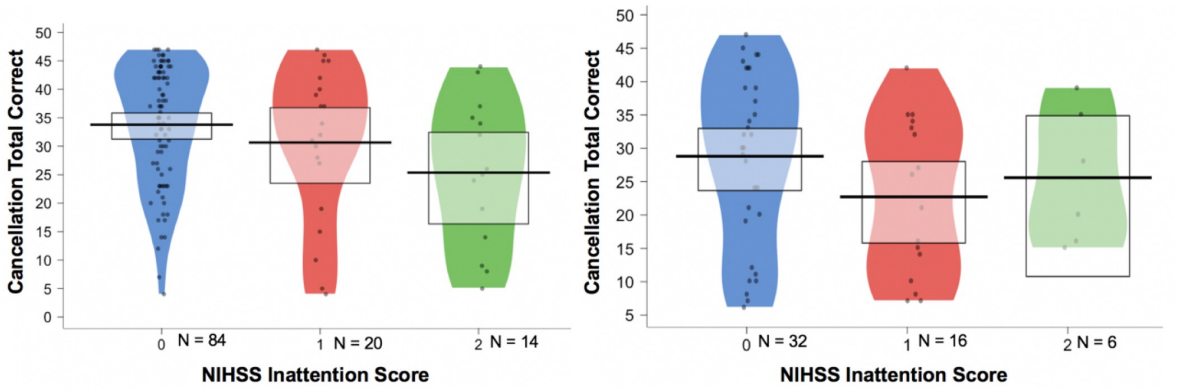


Figure 2.5: The relationship between Extinction/Inattention score and cancellation score in pure egocentric neglect (left) and both egocentric and allocentric neglect patients (right).

2.1.4 Discussion

This section's results demonstrate the differential sensitivity of observational and neuropsychological visual neglect assessments. The NIHSS was found to have very low sensitivity compared to the OCS Cancellation Task. While NIHSS was more likely to successfully identify more severe versus milder cases of visual neglect, the observational assessment frequently failed to detect even the most severe cases (41.2% missed where total accuracy <10). This was also demonstrated by the large spread of the data in each of the 3 NIHSS score categories. The NIHSS observational assessment also did not reliably identify less common occurrences of visual neglect, such as right-sided neglect and allocentric neglect. These results indicate that reliable detection of post-stroke neglect requires, at the minimum, the inclusion of a simple cancellation task.

Failure of clinical observation alone to detect neglect may also be associated with a general misunderstanding of visual neglect and a misattribution of neglect impairments to visual field

deficits (e.g. hemianopia). The Visual Field Item sensitivity was found not to differ from that of the Extinction/Inattention Item which is specifically designed to detect neglect (Spilker et al., 1997). Although general visual impairments and visuospatial neglect can co-occur (Bowen et al., 1999; Lee et al., 2008), the results of this investigation suggest that observational post-stroke assessments may not be able to reliably distinguish between these independent deficits.

This analysis also demonstrates that observational neglect assessments are more likely to detect leftward than rightward neglect, regardless of the severity. This could be explained by a potential expectation bias, as visual neglect has been most commonly characterised as a leftward deficit (Katz et al., 1999). However, several investigations have highlighted that rightward neglect deficits occur frequently following strokes (Becker and Karnath, 2007; Beis et al., 2004; Ellis and Young, 2013; Stone et al., 1992). Similarly, this study demonstrated that observational assessment was more sensitive to egocentric neglect than to allocentric neglect. Part of this difference is likely due to a difference in how egocentric and allocentric neglect are manifested in patient behaviour, but this difference may also be attributed to a lack of clinician awareness of the fractionation of neglect.

Previous research has found that simple cancellation tasks reliably distinguish between impairment caused by vision and spatial-attention problems, can differentiate egocentric and allocentric neglect impairment, and may reduce the influence of expectation biases on neglect diagnosis (Bickerton et al., 2011; Ellis and Young, 2013). While the NIHSS is undeniably a useful method for diagnosing post-stroke impairments, the results of this study strongly suggest that for detecting neglect, an additional, 3-minute neuropsychological assessment is required.

Limitations:

In this investigation, the NIHSS was always administered before the OCS. In most cases (63.3%), these assessments occurred on the same day or within three days. However, it is possible that this variance may have introduced noise into this investigation's findings. It is possible that neglect may have been more difficult to detect observationally in the first days following stroke when the patient could be bedbound with limited interactions with spatial environments. Similarly,

spontaneous recovery of neglect could have affected the data as neglect has been shown to spontaneously recover within the first ten days following stroke (Stone et al., 1992). Together, these effects may have introduced noise into this investigation's data, though it would not seem unidirectional.

Conclusions:

Simple cancellation tasks reliably distinguish between different subtypes of neglect, and provide an objective, unbiased assessment method. The findings of this study strongly suggest that observational measures of neglect overlook many cases of neglect, and that misattribution of neglect as a visual field deficit is common. We propose that the inclusion of a standard cancellation task in post-stroke assessment procedures is necessary to accurately and sensitively identify visual neglect.

2.2 Chapter 2.2: Quantifying Neglect Impairment using Cancellation Tasks

2.2.1 Introduction

Cancellation tasks are widely considered the gold standard neuropsychological approach for detecting visual neglect related deficits (Ferber amd Karnath, 2001; Hartman-Maeir and Katz, 1995; Chapter 2.1). These tasks are able to reliably detect visuospatial neglect deficits, help to avoid expectation biases, and provide quantitative neglect severity data (Bickerton et al., 2011; Demeyere et al., 2015) The latest approaches further allow differentiation between egocentric and allocentric neglect by adopting lateralised gap stimuli within the cancellation arrays (e.g. Bickerton et al., 2011; Demeyere et al., 2015; Hartman-Maeir and Katz, 1995; Huygelier et al., 2020; Ota et al., 2001). Even so, within these cancellation tasks behavioural impairments can be quantified in many different ways (e.g. Dalmaijer et al., 2015). For example, egocentric neglect severity has been quantified by summing targets found (Dalmaijer et al., 2018), subtracting number of right targets from left targets (Demeyere et al., 2015), calculating the "centre of mass" of reported targets (Rorden and Karnath, 2010), or determining the starting point (Kettunen et al., 2012; Nurmi et al., 2010) on cancellation tasks. In order to identify the most effective methods for quantifying neglect severity, it is important to understand different neglect metrics derived from these tasks and how they compare to one anther.

Egocentric neglect is traditionally quantified using response asymmetry scores (see Section One Methods). While response asymmetry metrics provide effective methods for detecting visuospatial neglect impairments (Demeyere et al., 2015; Huygelier et al., 2020; Moore et al., 2019), they may fail to capture some aspects of neglect severity. For example, an asymmetry score of 5 could be achieved with very severe neglect (5 items crossed out with none in the contralateral field), or very mild neglect (45 items crossed out, 15 left targets and 20 right targets). Centre of cancellation scores provide an alternative method for quantifying the severity of egocentric neglect (Rorden and Karnath, 2010). These scores are calculated by averaging the x-coordinate location of all reported targets to determine the "centre of mass" of each patient's responses (Rorden and Karnath, 2010). Previous investigations have also used patient starting points as a measure

of egocentric neglect severity, but the validity of this approach has not yet been evaluated in a representative sample of neglect patients (Jalas et al., 2002; Kettunen et al., 2012; Nurmi et al., 2010)

Allocentric neglect severity is traditionally quantified by summing the total number of consistently lateralised false positive responses on cancellation tasks (see Section One Methods). However, a patient who only identifies 5 targets and commits 5 allocentric errors is arguably more severely impaired than a patient who identifies 50 targets and commits 5 allocentric errors, but this range of performance possibilities is not captured by considering raw allocentric scores alone. This potential confound can be avoided by using novel proportional allocentric scores. Proportional allocentric scores are calculated by dividing the number of allocentric errors committed by the total number of correct targets found. These proportional scores compensate for the fact that raw allocentric asymmetry scores are inherently more conservative for patients who have identified fewer correct targets. However, this scoring method involves a novel metric and its utility has not yet been evaluated.

Computer-based assessments of neglect offer a potential solution to easily calculate and compare complex cancellation task metrics to more traditional scoring systems. Tablet based assessments provide detailed data such as the exact coordinates and time stamps of each patient tap which can be collated to replay and analyse response patterns. For example, Dalmaijer et al. (2018) presented a suite of open-source software, CancellationTools, which allows researchers and clinicians to flexibly administer and analyse computerised cancellation tasks. In addition to traditional response asymmetry metrics, this software automatically calculates centre of cancellation, search speed, average distance between sequential targets, intersections rate, best R (Mark et al., 2004), and a general quality of search score (Hills and Geldmacher, 1998). However, this software does not include any allocentric-specific metrics, but instead focuses exclusively on egocentric neglect biases. The purpose of this chapter is to calculate complex egocentric and allocentric neglect metrics using detailed data collected from the computerised OCS cancellation task and to compare these novel metrics to more traditionally used scoring systems.

2.2.2 Methods

Participants:

This study represents a retrospective analysis of data collected as a component of the OCS-Tablet Cognitive Screening study (REC reference 14/LO/0648). Participants were not pre-selected based on stroke type, lesion location, or behavioural phenotype in order to ensure that the sampling accurately represented the heterogeneity present within the clinical population.

Controls were recruited from the Translational Neuropsychology Group's pool of healthy ageing research volunteers. Patients were recruited on the John Radcliffe Hospital's Hyper Acute Stroke Ward following a confirmed diagnosis of stroke or TIA and completed behavioural testing at a chronic (6 month) follow-up appointment. Data from a cohort of 20 healthy, ageing controls (Age = 65.3 , SD = 11.6, range = 52-91, 53.8% female, 7.6% left handed) and 187 stroke survivors (Age = 74.3, SD = 13.1, range = 18 - 95, 48.1% Female, 11.3% left handed) was included in this investigation. Stroke types for these patients were reported as 114 ischemic, 29 haemorrhagic, 1 TIA, and 43 unreported. Stroke side was reported as 70 left, 81 right, 7 bilateral, and 29 unreported. Participants were included in the present investigation if they completed the tablet-based OCS cancellation task and were able to provide informed consent.

Materials and Procedure:

The Oxford Cognitive Screen's Cancellation Task (see Chapter 2, Section 1) was adapted to run on a tablet computer using MATLAB. Like the paper version of the OCS, the tablet task displays a search matrix of 50 complete, 50 left-gap, and 50 right-gap heart stimuli pseudorandomly scattered across a 768 x 1366 pixel tablet screen (Figure 2.6).

Participants responded by tapping on screen targets using a tablet stylus. When tapped, each target appears to have a line drawn through it, allowing patients to record their progress. Each participant was given up to two practice trials before proceeding to the full task. Participants were allowed up to three minutes to complete this task, at which time the tablet software automatically stops displaying the task stimuli. Patients were not informed of this time limit, but were requested to tell the examiner once they believed they had finished the task.

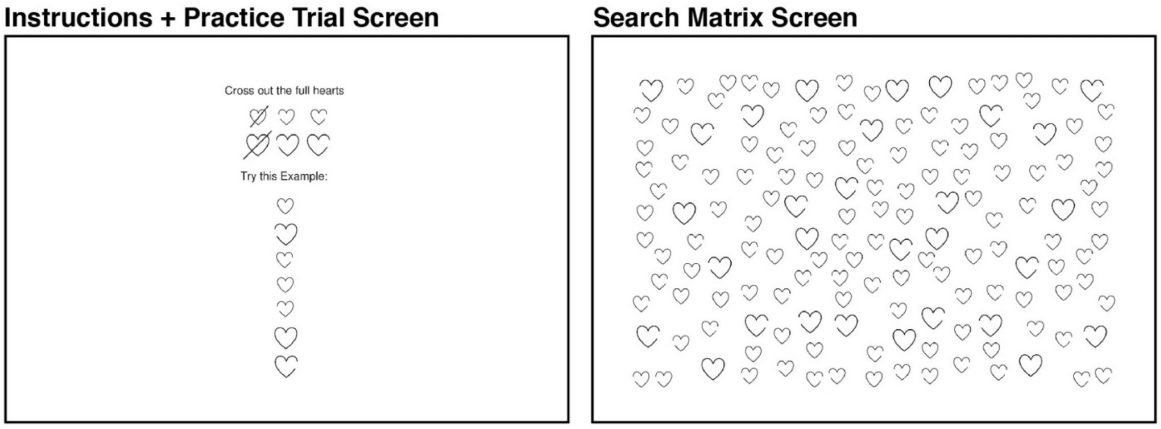


Figure 2.6: The instructions, practice trials, and search matrix stimulus display screens for the tablet version of the Oxford Cognitive Screen Cancellation Task.

Performance measures:

Basic Performance Metrics. Each touch screen response is automatically recorded as a timestamped x y coordinate with (0,0) representing the bottom left corner of the screen and (1366, 768) representing the top right corner. Each tap falling within a 10 pixel radius of a displayed stimulus was recorded as a valid response (causing the target to become marked), whilst taps outside this distance radius were not recorded as valid responses. All participant responses (including revisits and false positives) are recorded and stored in this manner. This basic data is then used to calculate task performance metrics.

Total Correct is calculated by summing all complete heart targets found by a participant whilst completing the task. If a single target was reported more than once (e.g. revisit), this target is only added to the total once, yielding a total score out of 50.

Egocentric Asymmetry Score refers to the standard egocentric severity measure used by the pen-and-paper OCS Cancellation Task. This score is calculated by subtracting the total number of correct targets found within the left-most two columns of the cancellation task (see Chapter 6, Section 1, Figure 2) from the total number of targets reported within the right-most task columns. Egocentric asymmetry scores range from -20 to 20, with negative scores representing right egocentric neglect and positive scores representing left egocentric neglect.

Allocentric Asymmetry Score refers to the standard allocentric severity measure used by the

pen-and-paper OCS Cancellation Task. This score is calculated by subtracting the total number of right-gap false positive responses from the number of left-gap false positive responses, regardless of these responses' location within the search matrix. Allocentric asymmetry scores can range from -50 to 50, with negative scores representing right allocentric neglect and positive scores representing left allocentric neglect.

Centre of Cancellation (e.g. Rorden and Karnath, 2010) represents the horizontal "centre of mass" of cancellation task responses, and is a commonly employed egocentric neglect severity measure. In this study, centre of cancellation is calculated by determining the average x-coordinate of all a participant's task responses, subtracting this value from the central x-coordinate, and reporting the resulting value as a percentage of the overall x-coordinate range. For example, a participant who reported two targets at (500, 100) and (1000, 400) would have an average x-coordinate of 750. The centre x-coordinate of the screen employed in this study was 688, so subtracting the participant's average x-coordinate from this value yields -62. Dividing this value by the full x-range (1366) yields a final centre of cancellation score of -0.046, indicating a "centre of mass" slightly (4.6%) to the right of the search matrix's centre. As in the basic asymmetry scores, negative scores represent right neglect whilst positive scores represent left neglect.

Allocentric Proportion is a novel impairment metric which unlike allocentric asymmetry, controls for how much of the total stimulus matrix was searched by each participant. This control compensates for the fact that raw allocentric asymmetry scores are inherently more conservative for patients who have identified fewer correct targets. This score is calculated by dividing the allocentric asymmetry score by the total correct score. For example, if a participant marks 50 complete, 10 left-gap, and 2 right-gap hearts, their allocentric asymmetry score (8) would be divided by 50 to yield an allocentric proportion of 0.16.

Finally, *Starting Point* is represented by the x-coordinate of each participant's first response.

Planned Analysis:

This data was analysed to address three distinct research questions. In the first analysis,

data from control patients was used to establish normative performance metrics and to determine whether these impairment thresholds significantly differed from those defined for the pen-and-paper OCS Cancellation Task. In the second analysis, neglect severity metrics were calculated and compared to identify the relative strengths and weakness of each considered scoring methodology. Specifically, traditional egocentric and allocentric response asymmetry scores were compared with centre of cancellation, proportional allocentric , and starting point scores. Impairment cut-offs were established for each of these more complex metrics and the diagnostic sensitivity/specificity was evaluated versus traditionally response asymmetry scores. In the final analysis, these scoring metrics were employed to investigate the relationship between egocentric and allocentric neglect.

2.2.3 Analysis One: Establishing a Normative Comparison Group

First, data from control participants was used to establish impairment cut-offs for the tablet cancellation task. Healthy controls were found to report an average of 48.2 targets (SD = 2.00, range = 43-50) with an average egocentric asymmetry of 0.05 (SD = 1.32, range = -3 - 2). Controls had an average allocentric asymmetry score of 0.15 (SD = 0.988, range = -2 - 3). Based on the 95th percentile of this control group performance, total scores of less than 44.3 were found to represent significant overall impairment. In this control data set, egocentric asymmetry scores of greater that 3 or less than -3 were found to represent significant egocentric neglect on the tablet task. Finally, allocentric asymmetry scores of less than -1 or greater than 2 were found to represent significant allocentric impairment.

This normative data was compared to the OCS control sample reported within Demeyere et al. (2015). This project reported normative data from 140 neurologically healthy participants (age = 65.0 (36-88), 58.6% female, 7% left handed) to establish impairment thresholds for all pen-and-paper OCS subtests. This control sample was found to report an average of 47.1 targets (SD = 2.95, range = 34-50) with an average egocentric asymmetry of -0.13 (SD = 1.37, range = -5 - 4) and an average allocentric asymmetry score of 0.02 (SD = 0.38, range = -2 – 2). Based on this performance, Demeyere et al. (2015) recommend that egocentric scores of greater than

3 or less than -3 and allocentric scores of greater than 1 or less than -1 should be employed for studies aiming to use a consistent, conservative impairment threshold.

There was a significant difference in average total score between controls assessed on the tablet and pen-and-paper task version ($t(30.6)=2.231$, $p = 0.03317$, 95% CI = 0.096 – 2.152). However, there was no significant difference in the average egocentric asymmetry ($t(24.49) = 0.560$, $p = 0.5806$, 95% CI = -0.471 – 0.823) or allocentric asymmetry score ($t(19.72) = 0.5632$, $p = 0.5657$, 95% CI = -0.334 – 0.597) between these groups. These findings suggest that performance on the tablet and pen-and-paper versions of the OCS cancellation task is largely analogous.

Analysis One Discussion:

Overall, this analysis suggests that performance on the tablet and pen-and-paper versions of the OCS Cancellation task is largely analogous for healthy ageing adults. There was no difference in egocentric/allocentric asymmetry scores between both groups. Similarly, the impairment thresholds determined from tablet and pen-and-paper task version largely agreed. Egocentric impairment cut-offs were found to be identical across task conditions, with scores of greater than 3 or less than -3 representing significant impairment. The 5th and 95th percentiles associated with allocentric asymmetry scores were found to be slightly more extreme within the tablet version (-1 vs -1 and 2 vs 1). There was also a significant difference in the average total correct and associated normative performance cut-off for controls completing the pen-and-paper versions of the OCS Task with scores. However, this difference was very small with scores of <44.2 being considered impaired on the tablet version versus scores of <42 on the paper version. This slight difference could reflect a minor difference in the difficulty of the task versions. The tablet version could potentially be slightly easier to complete due to the increased luminance or reduced dimensions of the search matrix versus the A4 pen-and-paper version. Alternatively, this difference could be a due to a comparatively small control sample (n = 20) used to calculate the tablet task impairment cut-offs versus the pen-and-paper version (n = 140). However, given that participant total scores are not generally used to diagnose neglect impairment, these potential difficulty differences do not pose a problem for the subsequent analyses on neglect specific measures.

2.2.4 Analysis Two: Exploring Measures of Neglect Impairment

The calculated tablet-specific normative impairment thresholds were then compared to patient performance in order to evaluate the prevalence of neglect impairment within this study's patient cohort. Patients reported an average of 39.7 (SD = 11.2, range = 3 - 50) targets with an average egocentric asymmetry of -0.04 (SD = 5.06, range = -19 – 15) and an average allocentric asymmetry of 0.369 (SD = 1.99, range = -4 – 11). Overall, 31.6% of participants demonstrated significant neglect with 32 participants exhibiting egocentric impairment (16 left, 16 right), 13 patients demonstrating allocentric neglect (5 left, 8 right), and 14 patients exhibiting both egocentric and allocentric neglect (4 left, 3 right, 7 left and right). See Figure 2.7 for a visualization of control and patient performance on these metrics presented alongside the impairment cut-offs.

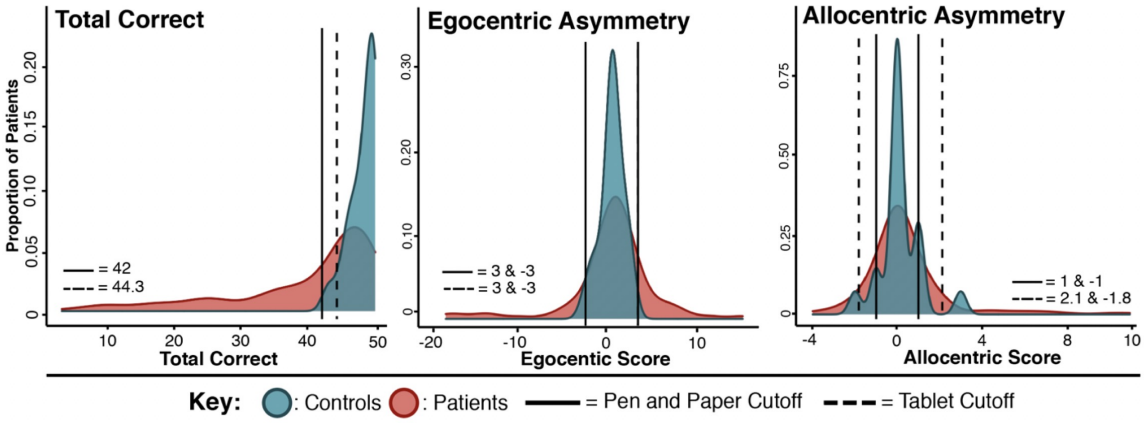


Figure 2.7: A visualization of control and patient performance on the tablet cancellation task. Solid lines represent cut-offs from the pen-and-paper analogue cancellation task while dashed lines represent new, tablet-specific impairment cut-offs.

Next, egocentric centre of cancellation scores and allocentric proportional scores were calculated and compared to traditional asymmetry metrics. Control participants were found to have an average target centre of cancellation of 0.005 (SD = 0.009, range = -0.013 – 0.024, Figure 2.8). Based on this performance, centre of cancellation scores greater than 2 standard deviations away from the mean, so scoring more than 0.0224 or less than -0.0116 were taken to represent neglect impairment (Goldman et al., 2013). Patients were found to have an average centre of cancellation of 0.008 (SD = 0.069, range = -0.276 – 0.343, Figure 2.8). A linear regres-

sion revealed that these centre of cancellation scores were highly associated with raw egocentric asymmetry scores ($F(1,185) = 533.5$, $p < 0.001$, adjusted $R2 = 0.741$). The impairment cut-offs based on control centre of cancellation scores were highly sensitive (100%) and specific (specificity = 85.1%) compared to egocentric neglect impairment as defined by traditional egocentric asymmetry scores.

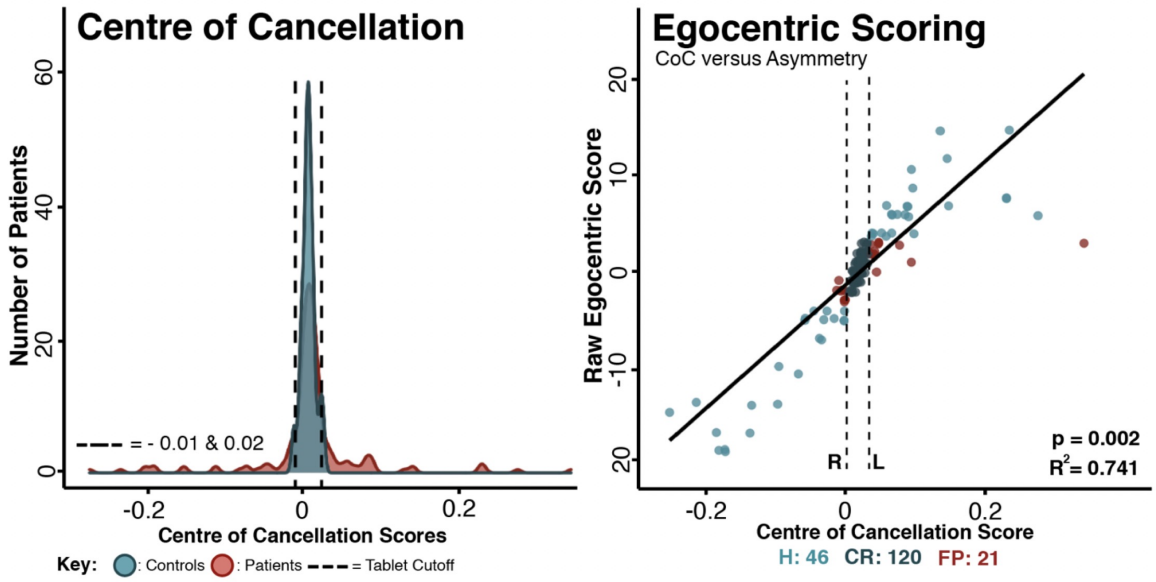


Figure 2.8: A visualization of egocentric centre of cancellation scores for controls and patients presented alongside a plot of the relationship between centre of cancellation scores and raw egocentric asymmetry scores. Raw egocentric score refers to the egocentric asymmetry score which is traditionally used to score the OCS cancellation task. H = Hits, CR = Correct Rejections, FP = False Positives, CoC = Centre of Cancellation.

Control participants were found to have an average allocentric proportion score of 0.003 (SD = 0.020, range = -0.040 – 0.06). Based on this performance, allocentric proportion scores of greater than 0.043 or less than -0.069 were taken to represent significant allocentric neglect impairment. Patients had an average allocentric proportion score of 0.013 (SD = 0.121, range = -1 – 0.714). Allocentric proportion scores were found to be associated with raw allocentric asymmetry scores within patients ($F(1,185) = 265$, $p < 0.001$, adjusted $R2 = 0.587$, Figure 2.9). Allocentric proportional scores were highly sensitive (95%) and specific (97.3%) compared to allocentric impairment as defined by raw allocentric asymmetry scores. Allocentric proportional

scores identified all allocentric patients classified as impaired by raw allocentric asymmetry, with the exception of two patients. Both these patients had committed two left allocentric neglect errors while correctly reporting a very high number of target hearts (total scores = 47 and 49). Conversely, proportional scores classified 4 patients who were unimpaired according to traditional allocentric asymmetry scores as exhibiting significant allocentric neglect. These patients had each committed a single false positive error while identifying less than or equal to 50% (total score range = 9-25) of targets present within the search matrix.

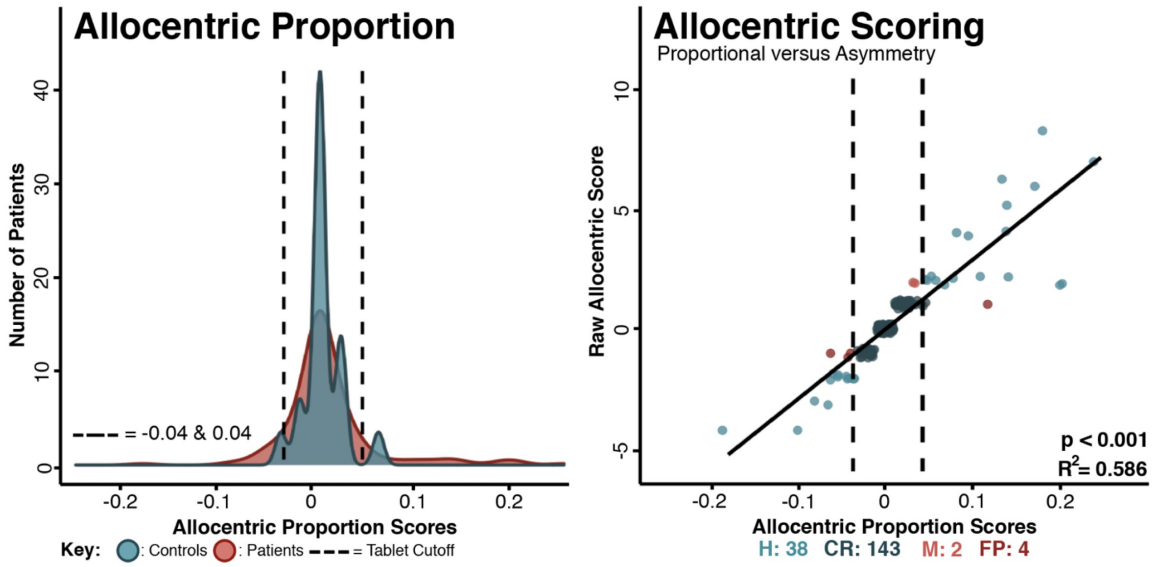


Figure 2.9: A visualization of proportional allocentric scores for controls and patients presented alongside a plot of the relationship between these proportional allocentric scores and raw allocentric asymmetry scores. H = Hits, M = Misses, CR = Correct Rejections, FP = False Positives.

Next, participant starting point's ability to distinguish between patients with left and right egocentric neglect was investigated. Typically, healthy controls were found to begin their searches in the top left corner of the search matrix (average start location = (260, 679), x-coordinate SD = 281). However, two controls employed different strategies with one beginning their search in the top right corner (1190, 720) and another near the bottom right corner (952, 276). Given this performance, starting x-coordinates greater than 821.8 (2 SD above control mean) were considered to represent significant right-ward biases, indicating left neglect. Due to the strong left-ward starting point bias within controls, the left-most possible starting point x-coordinate was within

the “normal performance” range (x = 0, z = -0.925), precluding the detection of right egocentric neglect from starting point data. The majority of patients were also found to begin their searches within the top left hand corner of the matrix (average start location = (372, 624) , x-coordinate SD = 380). Compared to normative data thresholds, 42 patients exhibited significant right-ward starting point biases, indicating significant neglect. Overall, impairment thresholds based on starting point scores were found to have a sensitivity of 25% and specificity of 78.2% to egocentric neglect impairment as defined by traditional egocentric asymmetry scores.

Given starting point’s limited ability to detect right egocentric neglect impairment, two additional quantitative analyses were conducted to further investigate the relationship between starting point and neglect impairment. Given the non-normal distribution of patient x-coordinates (Figure 2.10), a non-parametric Kruskal-Wallis ANOVA was conducted to compare the average horizontal (x-coordinate) starting position of patients with right egocentric (n = 19), left egocentric (n = 20), and no neglect (n = 125). This test found that there were no significant differences between the x-coordinate starting points of patient with left (mean x = 626, SD = 474), right (mean x = 428, SD = 441), or no neglect (mean x = 322, SD = 337, Kruskal-Wallis chi-squared = 3.4301, df = 2, p= 0.18). However, a Kendall–Theil Sen Siegel nonparametric linear regression identified a significant association between x-coordinate starting point and egocentric neglect severity as reported by centre of cancellation score (residual standard error = 0.067, df = 162, p = 0.005).

Table 2.1: A comparison of the sensitivity and specificity of the alternative neglect metrics evaluated in this analysis. Ground-truth impairment classifications are made according to asymmetry score cut-offs. CoC = Centre of Cancellation.

	Egocentric Neglect		**Allocentric Neglect**
	CoC	**Starting Point**	**Proportion**
Hits	46	10	38
False Positives	21	32	4
Misses	0	30	2
Correct Rejections	120	115	143
Sensitivity	100.0%	25.0%	95.0%
Specificity	85.1%	78.2%	97.3%

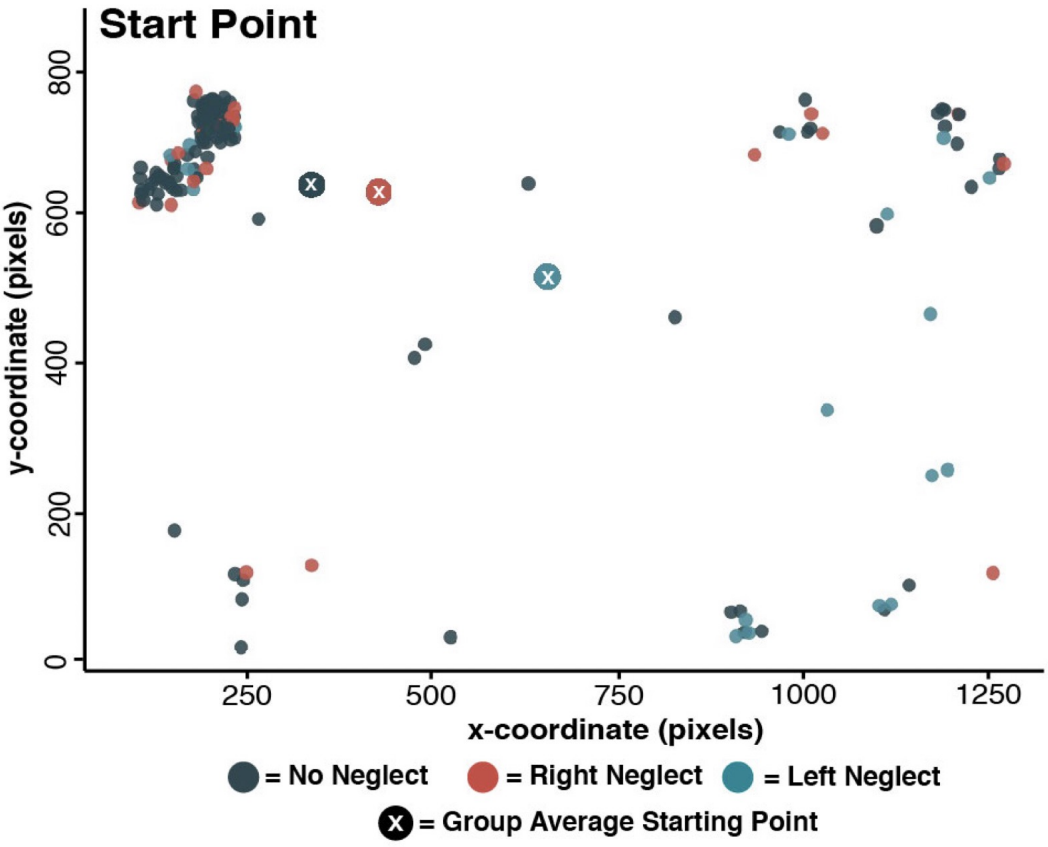


Figure 2.10: The starting points for patients with and without neglect. Each small dot represents the x y coordinates of an individual patient start point. Large, labelled dots represent the average starting point for each patient group.

Analysis Two Discussion:

The results of this analysis illustrate the strengths and weaknesses associated with employing various alternative neglect severity metrics. Both centre of cancellation and proportional allocentric scores were found to be effective, more fine-grained methods for quantifying the severity of egocentric and allocentric neglect impairment. However, starting point was not found to be able to distinguish between patients with left and right egocentric neglect or to act as a sensitive method for detecting left egocentric neglect impairment (see Table 2.1).

Centre of cancellation scores were found to exhibit extremely high sensitivity and specificity to neglect impairment compared to traditional egocentric asymmetry scores. All patients who exhibited significant egocentric neglect according to asymmetry scores were categorised as sig-

nificantly impaired according to centre of cancellation score cut-offs. Of the 21 patients who were classified as impaired according to centre of cancellation scores but not egocentric asymmetry scores, 10 had egocentric asymmetry scores of 3 or -3, just missing the asymmetry cut-off for significant impairment. The remaining false positive patients each had total scores greater than 1.5 SD below the mean of the control group (mean = 34.2, SD = 11.25), suggesting that centre of cancellation scores are more sensitive than asymmetry scores in cases where participants do not complete the full search matrix.

Similarly, allocentric proportional were found to act as a sensitive and specific method for detecting allocentric neglect impairment. Proportional allocentric scores were found to be highly associated with allocentric asymmetry scores, demonstrating a good agreement between these measures. Only 2 patients exhibited significant allocentric impairment according to asymmetry but not proportional scores. These patients had both committed 2 allocentric errors whilst achieving high total correct scores (47 and 49). Conversely, 4 patients were classified as exhibiting significant allocentric neglect according to proportional, but not asymmetry scores. These four patients had all committed a single false positive error, whilst identifying less than half of the total targets present within the search matrix. This pattern suggests that allocentric proportional scores are slightly more sensitive than asymmetry scores in cases where patients have only completed a portion of the search matrix, but are slightly more conservative than asymmetry scores in cases where patients have successfully identified most targets within the search array.

Both centre of cancellation and allocentric proportion scores are fine-grained metrics whilst traditional asymmetry scores are ordinal discrete metrics. This is a clear advantage of employing these alternative neglect metrics as employing more continuous variables improves the statistical power of many common analyses. For example, using non-normally distributed discrete behavioural metrics in lesion-symptom mapping analysis generally requires behavioural data to be binarized before an analysis can be conducted. It is well established that dichotomisation of behaviour results in a significant loss of information and statistical power compared to continuous behavioural metrics (Cohen, 1992; de Haan and Karnath, 2018). These alternative neglect metrics therefore offer a novel avenue for improving statistical power within analyses considering

neglect data.

Previous research has asserted that considering the horizontal location of each participant's starting point acts as an effective method for detecting egocentric neglect impairment (Jalas et al., 2002; Kettunen et al., 2012; Nurmi et al., 2010). Substantial variance was present within the starting points of participants with neglect, with many participants beginning their search at the top, left-hand corner of the screen, including those with left-sided neglect. Typically these patients start top left, but once at the right side of the page, don't move back to explore the left side. Multiple healthy controls and participants without neglect also were found to begin the cancellation task by selecting targets on the right side of the screen, suggesting that a starting-point based cut-off might not be able to distinguish between participants with and without neglect impairment. This investigation found that only 35.7% of patients with egocentric neglect according to asymmetry scores began their searches outside the normative boundaries established from control data. Additionally, given the strong left-ward starting point bias present within controls, starting point data was not able to identify any patients with right egocentric neglect. Although the x-coordinate starting point was found to correlate with the severity of neglect, no significant difference was present between the average starting points of patients with left, right, and no egocentric neglect. Overall, these findings strongly suggest that cancellation task starting point does not act as an effective method for distinguishing between patients with and without egocentric neglect.

Overall, the results of this analysis indicate that centre of cancellation and allocentric proportional scores act as a sensitive and specific method for quantifying the severity of neglect impairments.

2.2.5 Analysis Three: Relationship between Egocentric and Allocentric Neglect

Next, centre of cancellation and allocentric proportion metrics were used to evaluate the relationship between egocentric and allocentric neglect. There is significant debate surrounding whether allocentric neglect is best characterised as a side-effect of egocentric neglect or as an independent cognitive impairment (Demeyere and Gillebert, 2019; Karnath, 2015). The fine-grained, scores yielded by centre of cancellation and allocentric proportion metrics offer a novel

opportunity to study the relationship between these conditions in more detail.

A linear regression revealed that there was not a significant relationship between the severity of egocentric neglect and allocentric neglect within all patients ($F(1,185) = 0.182$, $p = 0.670$, adjusted $R2 < 0.001$), patients with significant neglect ($F(1,62) = 0.0763$, $p = 0.783$, adjusted $R2 = -0.0153$), and patients with both egocentric and allocentric neglect ($F(1,22) = 3.689$, $p = 0.0678$, adjusted $R2 = 0.1047$) (Figure 2.11). This analysis, along with the qualitative double dissociation present between patients presenting with only egocentric and only allocentric neglect, strongly suggests that these conditions are independent.

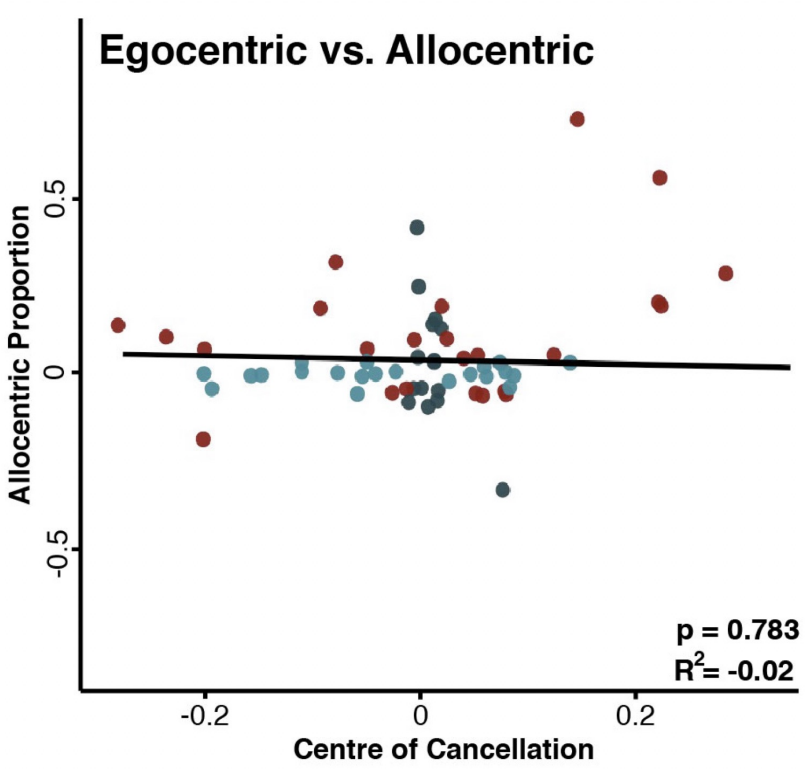


Figure 2.11: The relationship between egocentric and allocentric severity scores within neglect patients. There was no significant relationship between the severity of egocentric and allocentric neglect. Patients with egocentric neglect only are represented in light blue, patients with allocentric only are in dark blue, and patients with both deficits are visualised in red.

However, proportional allocentric scoring does not take into account the x-axis location of each individual false positive. As suggested by Driver and Halligan (1999), it is possible that the relationship between egocentric and allocentric impairment may be demonstrated by egocentric

neglect patients committing a greater proportion of allocentric errors for targets presented nearer to neglected hemispace. To investigate this possibility, the relative egocentric location of each allocentric error committed by patients with significant egocentric neglect was investigated. First, the maximum and minimum x y values for each participant were identified to determine the horizontal range of patient responses to control for egocentric neglect spatial biases. Next, and the relative location of each left and right false positive response within the searched area was then calculated using the centre of cancellation methodology.

For patients exhibiting significant left neglect, the average location of left allocentric errors was found to be 4.4% (SD = 21.6%, range = -42.5 – 45) to the left of each search's centre point. Meaning that, for these patients, allocentric errors were on average, slightly more likely to be committed nearer to the neglected hemifield. This effect was also found within patients with right neglect, with the average location of right allocentric errors at 1.64% (SD = 16.3, range = -36.3 – 27.5) to the right of the search centre point. However, there was no significant difference in the mean relative location of allocentric errors between patients with right and left neglect (t(50.6) = 1.1549, p = 0.254, CI = - 0.0164– 0.0439, Figure 2.12).

Analysis Three Discussion:

This analysis aimed to employ centre of cancellation and allocentric proportional metrics to clarify the relationship between egocentric and allocentric neglect. In previous analysis sections, egocentric and allocentric neglect were found to be double dissociated both in terms of occurrence and lateralisation (Chapter 2, Section 1). The present analysis agrees with this conclusion by demonstrating the lack of association between egocentric and allocentric severity when quantified using the proposed severity metrics. This independence is further illustrated by the demonstrated lack of egocentric bias within the location of allocentric errors. Taken together, the findings of this analysis suggest that egocentric and allocentric neglect represent independent, doubly dissociated conditions.

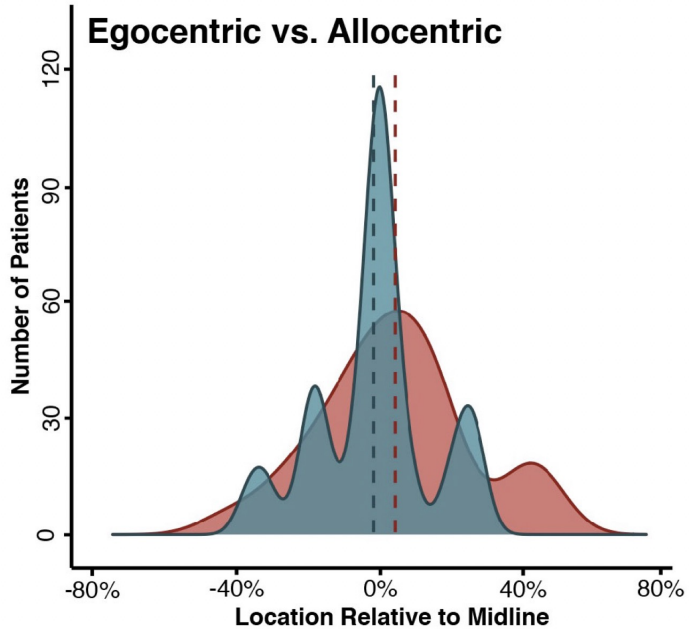


Figure 2.12: The a visualization of the average location of allocentric errors within patients with significant left and right neglect. There was no significant difference between the relative locations of left and right allocentric errors between patients with left and right egocentric/allocentric neglect.

2.2.6 Overall Discussion

The purpose of this section is to present and evaluate various neglect severity metrics which can be derived from cancellation task. More complex metrics of neglect impairment were calculated and compared to the traditional, spatial asymmetry scores employed by pen-and-paper cancellation tasks. Centre of cancellation and allocentric proportional scores were found to act as effective metrics for identifying significant neglect and quantifying the severity of these conditions. However, starting point was not found to act as an effective method for detecting egocentric neglect impairment. As in previous studies, egocentric and allocentric neglect were found to represent doubly dissociated conditions. Overall, the results of this analysis strongly suggest that employing centre of cancellation and allocentric proportional scoring allows for a more fine-grained investigation of the relationship between egocentric and allocentric neglect.

Limitations:

Neglect is a highly heterogeneous condition and many different scoring metrics have been proposed to quantify the severity of this impairment. Given this increased range of scoring methods, it is important to investigate the robustness of effects documented while using each specific scoring method. For example, it is not yet clear whether the results of a study which employed raw asymmetry scores would still hold valid if centre of cancellation scores had been used instead. Future research can aim to assess the robustness of different effects associated with neglect by employing a range of scoring methods.

Additionally, this investigation employed a comparatively small control group. Normative data from a larger and more diverse control group may help establish more effective impairment cut-offs for centre of cancellation and allocentric proportion scores. However, given that this analysis represents a retrospective analysis of existing data, data from a larger control sample was not available. Although this investigation found no significant correlation between egocentric and allocentric severity, additional Bayesian analysis is needed to draw strong conclusions from this null result.

Finally, the large majority of patients included in this investigation completed the OCS cancellation task approximately 6 months after stroke. A high proportion of neglect cases spontaneously recover within the first 6 months following stroke (Stone et al., 1992), suggesting that the neglect patients included in this investigation may not be representative of those recruited at an earlier time point. For example, this sample likely included fewer cases of severe neglect than would be present within an acute stroke sample. Additional research is needed to clarify whether the conclusions of this investigation can be replicated within an acute stroke sample.

Conclusion:

Overall, this section demonstrates that centre of cancellation and allocentric proportional scoring metrics act as an effective method for detecting and quantifying the severity of neglect impairments on the OCS Cancellation Task.

2.3 General Conclusion

The first section of this chapter demonstrates the need for objective, neuropsychological assessments in order to reliably detect and diagnose visuospatial neglect. The second section of this chapter presents and evaluates the validity of various scoring metrics which can be derived from cancellation task performance. Considered cumulatively, these studies illustrate the clinical need for standardised quantitative, neuropsychological neglect assessments.

3 Chapter 3.0: Dissociations within neglect-related reading impairments: egocentric and allocentric neglect dyslexia

Author's Note:

In line with standard CRediT author roles (Brand et al., 2015), I was responsible for Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Reviewing and Editing, and Visualisation for the project reported within this project. This section is published under the title "Dissociations within neglect-related reading impairments: Egocentric and allocentric neglect dyslexia" in the Journal of Clinical and Experimental Neuropsychology (Moore et al., 2020).

3.0 General Introduction

Previous neuropsychological research has identified two main categories of reading impairment behavioural phenotypes related to visuospatial neglect: egocentric and allocentric (Beschin et al., 2014; Ellis et al., 1987; Vallar et al., 2010; Young et al., 1991). Allocentric neglect dyslexia is characterised by consistently lateralised omission, addition, and substitution errors when reading individual words (Ellis et al., 1987; Hillis and Caramazza, 1995; Vallar et al., 2010). Conversely, patients with egocentric neglect dyslexia commit lateralised full word omissions when reading spatially presented passages of prose (Beschin et al., 2014) (Figure 3.1).

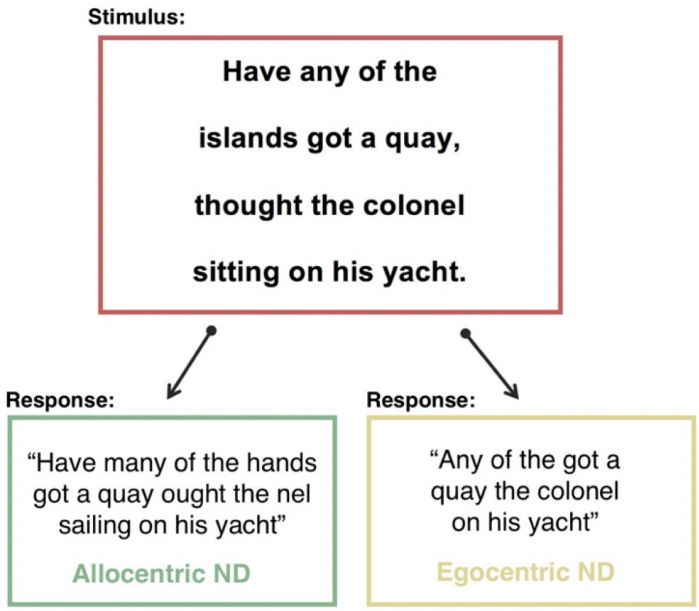


Figure 3.1: An illustration of the differential reading error pattern observed in patients with neglect dyslexia and sentence-level neglect. ND = Neglect Dyslexia.

Egocentric and allocentric neglect dyslexia can co-occur within the same patient. For example, Ellis et al. (1991) identified a patient (VB) who committed both right-lateralised letter omission errors when reading single words and full-word omission errors on the right side of lines of prose. Despite these observed associations in some patients, other studies have found dissociations, suggesting that egocentric and allocentric neglect dyslexia represent independent cognitive impairments. Several case studies have identified patients exhibiting an allocentric neglect dyslexia reading impairment in the absence of egocentric reading impairment (e.g. Friedmann

and Nachman-Katz, 2004). Friedman and Nachman-Katz (2004) identified an allocentric neglect dyslexic patient (NT) who consistently omitted the left portion of words throughout spatially presented lines of prose, but never committed full-word omission errors.

A behavioural dissociation between egocentric and allocentric neglect impairment has also been identified in group studies, notably by Beschin et al. (2014) who assessed 30 patients exhibiting left-lateralised egocentric (self-centred) visuospatial neglect deficits on a series of single word and passage reading tasks. Of these patients, 17 committed both egocentric and allocentric reading errors while 5 patients exhibited egocentric neglect dyslexia in the absence of allocentric-level impairment and 4 patients presented with allocentric neglect dyslexia in the absence of egocentric impairment. These findings illustrate that despite an apparent core egocentric visuospatial attentional deficit, egocentric and allocentric neglect dyslexia can result from spatial-attentional biases in different reference frames, supporting the conclusion that these conditions must represent independent impairments. However, it remains unclear whether these impairments are best characterised as separable consequences of a domain general visuospatial impairment or whether allocentric neglect dyslexia impairment is driven by a content-specific (word-specific) deficit.

Neglect-related reading impairments are frequently understood as side effects of visuospatial neglect rather than content-specific cognitive problems (Ellis and Young, 2013; Jackson and Coltheart, 2013; Mozer and Behrmann, 1990; Riddoch, 1990; Shallice, 1988). According to this logic, visuospatial neglect impairs the early visual processing of written stimuli's perceptual features, leading to consistently lateralised reading errors (Jackson and Coltheart, 2013; Riddoch, 1990; Shallice, 1988).This argument is supported by findings that a neglect-related reading impairment commonly co-occurs with domain-general visuospatial neglect (Lee et al., 2009; Vallar et al., 2010) and that the severity of egocentric neglect acts as a significant predictor of allocentric neglect dyslexic reading impairment (Beschin et al., 2014; Lee et al., 2009). Lee et al. (2009) assessed a cohort of patients on standardised neglect tests and a single-word reading task and found that patients exhibiting allocentric neglect dyslexia impairment had significantly more severe egocentric neglect than patients who did not make neglect dyslexia reading errors. However, this investigation and the similar study conducted by Beschin et al (2014), both did not include tests

for domain-general allocentric (object-centred) neglect, meaning that the relationship between allocentric neglect dyslexia and allocentric neglect remains unclear.

Ptak et al. (2012) investigated reading impairments in a cohort of egocentric neglect patients and found that while the prevalence of sentence-level neglect omission errors was mediated by the egocentric location of stimuli, the incidence of allocentric neglect dyslexia word reading errors was not significantly affected by where stimuli were presented in space (Ptak et al., 2012). This strongly suggests that while egocentric neglect dyslexia may be explained as a side-effect of an egocentric neglect impairment, allocentric neglect dyslexia is likely caused by a differential spatial-attentional bias. This conclusion is further supported by the findings of meta-analyses which have revealed that while allocentric neglect dyslexia does frequently co-occur with egocentric visuospatial neglect, many cases of allocentric neglect dyslexia occur in the absence of this domain-general impairment (Moore and Demeyere, 2017, 2018; Vallar et al., 2010).

However, visuospatial neglect represents a highly heterogeneous condition with some patients exhibiting spatial-attentional biases within an egocentric reference frame and others within an allocentric frame of reference (Baylis et al., 2004; Bickerton et al., 2011; Demeyere and Gillebert, 2017; Hillis and Caramazza, 1995; Chapter 1, Section 1). Patients with allocentric neglect fail to notice portions of individual objects, regardless of where objects are presented in egocentric space (Demeyere and Gillebert, 2019). This object-centred neglect impairment can potentially provide a plausible explanation for some cases of allocentric neglect dyslexia. For example, patient SP (Young et al., 1991) was found to commit similar frequencies of left allocentric neglect dyslexia errors when reading in both the left and right visual field, suggesting that the spatial bias seen in allocentric neglect dyslexia can operate independently of egocentric spatial coordinates. This error pattern can be best understood as an impairment occurring within an object-centred reference frame (Haywood and Coltheart, 2000; Hillis and Caramazza, 1995), or within a smaller attentional window (Driver and Pouget, 2000). Unfortunately, SP did not complete neglect assessments which were sensitive enough to detect and differentiate between allocentric neglect and egocentric neglect, meaning that the relationship between allocentric neglect and neglect dyslexia remains unclear.

This chapter investigates the relationship between domain-general visuospatial neglect and neglect-related reading errors. Specifically, the presented analyses aim to elucidate the relationship between egocentric and allocentric and domain-general neglect to determine whether neglect dyslexia reading errors can be adequately accounted for as a consequence of domain-general neglect impairment or whether these reading errors are best understood as an independent, content-specific impairment.

3.1 Methods

Methods/Materials:

This study considers data collected as a component of two large cognitive screening cohort studies which conducted the Birmingham Cognitive Screen (BCoS) (Humphreys et al., 2012) or the Oxford Cognitive Screen (OCS) (Demeyere et al., 2015). Both screening tools provide a multi-domain summary of cognitive impairments following brain injury. Data from these assessments' Reading, Cancellation, and Visual Field tasks was used in this experiment.

The BCoS Reading Task consists of one 14- and one 28-word sentence. The OCS Reading Task consists of one 15-word sentence. Each of these sentences is printed in size 26 font in the centre of a full A4 sheet of paper. OCS and BCoS both contain a neglect cancellation task (described in Chapter 1, Section 1) to measure both ego- and allocentric neglect (Figure 3.2).

In the Reading Tasks, each patient was asked to read the presented sentences aloud as an examiner recorded their responses. Patients who misread or failed to read more than one word on the BCoS or OCS Reading Tasks were considered to be significantly impaired following the subtests' published cut-offs. For patients with significant reading impairment, the severity of this impairment was scored as each patient's total percent of words read correctly to facilitate comparisons across the two reading tests. In the Visual Field task, the examiner sat approximately one meter in front of the patient, asked the participant to fixate on the examiner's nose, and sequentially wiggled their fingers in each of the patient's visual quadrants. Failure to report one or more of these confrontations indicated significant visual field impairment.

Neglect-Related Reading Error Identification:

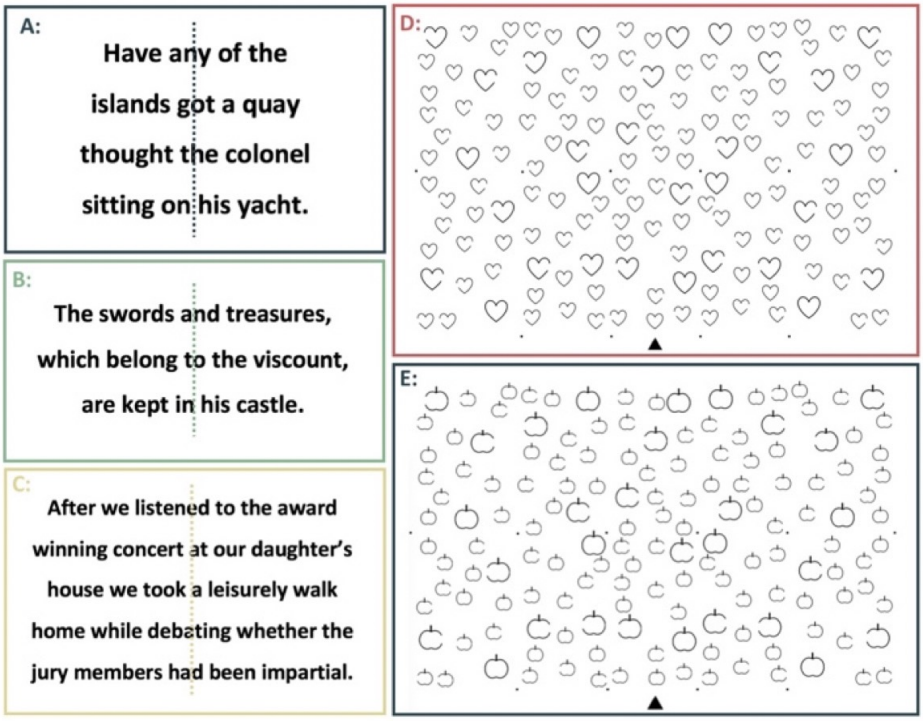


Figure 3.2: OCS and BCoS Reading Tasks and Cancellation Task stimuli. A and D are OCS stimuli while B,C and E are taken from the BCoS. Cancellation Task scoring gridline locations are denoted by the black dots within the search matrix. Sentence midpoints are denoted by dotted lines. These lines are not present during task administration, but were used to score patient performance. According to BCoS scoring guidelines, one point is assigned for correctly reading "daughter" and another for this word's corresponding possessive suffix.

Error patterns on the reading tasks were systematically analysed to identify clear cases of egocentric and allocentric neglect dyslexia. There are no existing standardised scoring procedures for diagnosing neglect-related reading impairments in stroke survivors. Therefore, this investigation employed a combination of rigorous quantitative and qualitative error evaluation procedures to identify patients with egocentric and allocentric neglect dyslexia from these brief subtests.

A multi-step filtering process (see Figure 3.3) was followed to identify patients who demonstrated neglect-related reading impairments. First, only patients with a significant reading impairment according to OCS scoring guidelines were included. Second, only patients who committed more than one reading error which was clearly characteristic of egocentric or allocentric neglect

dyslexia impairment were included. For allocentric neglect dyslexia, patients were only included if they committed two separate word reading errors demonstrating lateralised letter omission, addition, or substitution errors. For egocentric neglect dyslexia, patients were only included if they committed at least two full-word omission errors. As the reading data used in this investigation represents existing data from clinical cognitive assessments, some reading errors were scored binarily (correct/incorrect) with no qualitative error information was provided. Patients with no available qualitative information about the precise reading errors made were excluded from this investigation at this stage.

Third, potential egocentric and allocentric neglect dyslexia patients were only included if their error patterns were consistently lateralised. This was defined as demonstrating the same lateralisation in at least 80% of potential egocentric or allocentric neglect dyslexia reading errors Finally, all potential neglect dyslexia reading patterns were qualitatively and independently reviewed by all 4 authors and agreed by consensus before including each patient in subsequent analyses. See Figure 3.3 for a visualisation of this selection process and for patient exclusion counts at each stage.

This represents a very conservative approach, aimed at only including those patients with very clear impairment. Similarly, this procedure is less likely to identify cases of co-occurring egocentric and allocentric neglect dyslexia than it is to identify either deficit in isolation. This is because patients with egocentric neglect dyslexia will only perceive and respond to a portion of the presented words, making it less likely that they will commit enough allocentric errors to surpass impairment thresholds (Caramazza and Hillis, 1990; Vallar et al., 2010). Since at least two potential allocentric neglect dyslexia errors must be committed to confidently identify this reading impairment, the probability of detecting a patient exhibiting both impairments simultaneously on the OCS/BCoS reading tasks is low. However, previous research has established that egocentric and allocentric neglect dyslexia do commonly co-occur (Beschin et al., 2014; Ellis et al., 1987; Moore and Demeyere, 2017; Vallar et al., 2010). This investigation therefore explicitly aims to identify cases in which these conditions do NOT co-occur and does not attempt to make any claims about the prevalence of neglect dyslexia or what proportion of egocentric and allocentric

neglect dyslexia occur independently.

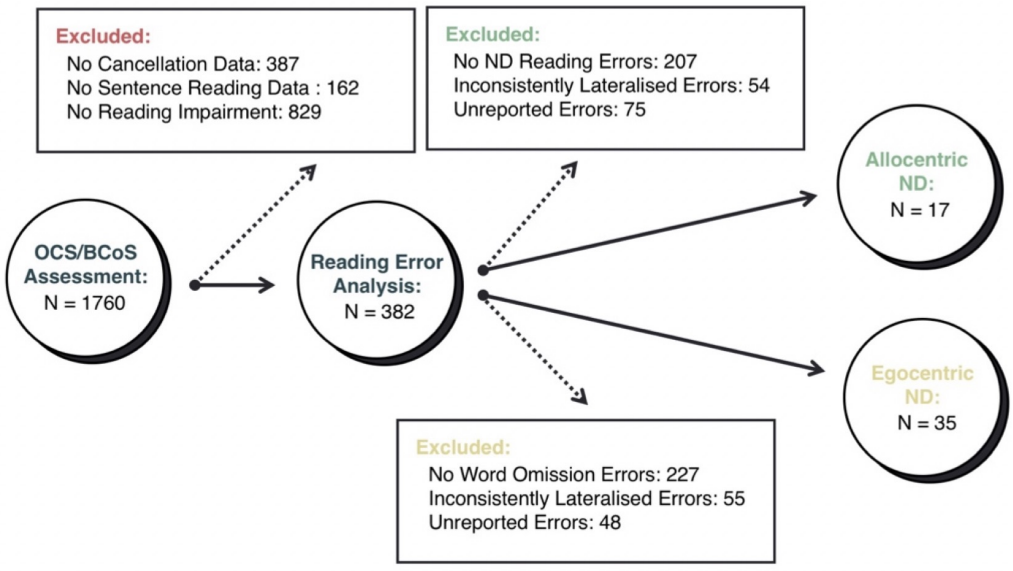


Figure 3.3: A visualisation of the neglect dyslexia and sentence-level neglect patient identification process and patient exclusion counts at each stage. ND= Neglect Dyslexia.

Participants:

The BCoS was administered to 912 subacute stroke survivors (<3 months post-stroke) at different hospital settings across the West-Midlands, as part of the BUCS study (REC reference 08/H0301/6), coordinated by the University of Birmingham between 2006-2011. The OCS was administered to a consecutive sample of 848 stroke survivors (<3 weeks post-stroke) following admission to Oxford's John Radcliffe Hospital acute stroke ward between 2012 and November 2017 as part of the Oxford Cognitive Screening programme (REC reference 11/WM/0299 and REC reference 14/LO/0648). Each participant provided verbal or written consent before beginning these cognitive assessment batteries. This resulting sample of 52 patients had an average age of 68.6 (Range = 18-92) and contained 34 (65.4%) women. See Table 3.1 for a breakdown of demographics and stroke types for each patient group.

Table 3.1: Demographics for patients with neglect dyslexia and sentence-level neglect. Unreported patient information represents missing demographics which were not recorded in medical notes. R = Right, L = Left, B = Bilateral, M = Male, F = Female, Isc = Ischemic, H = Haemorrhage, TIA = Transient Ischemic Attack.

	Patient Group		
	Neglect Dyslexia	**Sentence- Level**	**Total**
N:	17	35	52
Age:			
mean (std)	70.2 (18.4)	67.9 (13.4)	68.6 (15.1)
Gender:	14F / 3M	20F / 15M	34 F / 18 M
Hand:	15 R / 0L / 0B	27R / 2L / 1B	42R / 2L / 1B
Education:			
mean (std)	10.8 (2.08)	12.4 (3.93)	11.6 (3.52)
Stroke Side:	5R / 8L / 0B	27R / 1L / 4B	32R / 9L / 4B
Stroke Type:	9 Isc / 2H / 3 TIA	26 Isc / 3H / 2 TIA	35 Isc / 5H / 5 TIA

3.2 Results

In this sample, 17 patients with allocentric neglect dyslexia (14 right and 3 left) and 35 cases of egocentric neglect dyslexia (1 right and 34 left) were identified according to this investigation's rigorous inclusion criteria. Egocentric and allocentric neglect dyslexia were found to be behaviourally doubly dissociated with all cases of allocentric neglect dyslexia occurring independently of egocentric neglect dyslexia. Egocentric neglect dyslexia was not found to be dissociable from domain-general visuospatial neglect impairment. All 35 egocentric neglect dyslexia patients exhibited significant visuospatial neglect impairment on the Cancellation Task with 22 patients exhibiting both allocentric and egocentric neglect, 11 exhibiting significant egocentric neglect without allocentric neglect, and 2 patients presenting with only allocentric neglect with particularly severe allocentric scores of 10 and 18. All cases of egocentric and allocentric neglect in egocentric neglect dyslexia patients were found to impact the same spatial lateralisation as these patients' reading impairment.

Conversely, allocentric neglect dyslexia was found to be doubly dissociated from both egocentric and allocentric visuospatial neglect. 8 cases of right-lateralised allocentric neglect dyslexia were found to occur independently of any domain-general egocentric or allocentric neglect. There was no significant difference in the sentence reading percent correct between allocentric neglect dyslexia patients with and without neglect ($F(1,15) = 2.077$, $p = 0.17$). Of the 9 cases of allocentric neglect dyslexia which co-occurred with neglect, 2 cases (1 right and 1 left) were found to occur independently of egocentric neglect and 2 cases (both right lateralised) were found to occur in the absence of allocentric neglect. Interestingly, 2 cases involved right allocentric neglect dyslexia which occurred alongside left allocentric neglect. See Table 3.2 for a detailed breakdown per patient of the type and nature of the neglect dyslexia patient reading errors and the performance on the cancellation task, including ego- and allocentric asymmetries.

Next, a series of analyses were conducted to investigate the relationship between the severity of the visuospatial neglect within the subgroup of patients exhibiting neglect-related reading impairments. A mixed ANOVA, patients with egocentric neglect dyslexia were found to have significantly more severe egocentric ($F(1,50) = 42.6$, $p = .002$, effect size = 0.46) and allocentric

Table 3.2: Allocentric neglect dyslexia patient Reading Task and Cancellation Task performance along with basic stroke information. ICH = Intracerebral haemorrhage, TIA = Transient Ischemic Attack, NR = not reported in medical notes. ND=Neglect Dyslexia. On the cancellation task, Ego denotes the egocentric asymmetry, Allo denotes allocentric asymmetry, SL represents Sentence Level. In both asymmetry scores positive scores reflect left-sided neglect, and negative scores reflect right-sided neglect impairments. Asterix represent significant impairment.

Patient ID	Neglect Dyslexia Reading Errors			Correct	SL Lat Score	ND Side	Allo	Ego	VFD
1	thought - "though"	colonel - "colonial"		86.70%	0	R	-4	-7	/
2	thought - "though"	colonel - "colonial"	yacht - "yach"	60.00%	-2	R	-4	-7	/
3	"any"	thought - "though"	sitting - "sit"	40.00%	0	R	0	-4	/
4	thought - "though"	colonel - "color"		86.70%	0	R	2	-9	/
5	colonel - "nel'	yacht - "cht"		13.30%	2	L	4	5	Left
6	swords - "words"	treasuers - "measures"		95.20%	0	L	9	9	/
7	belong - "began" "at" jury - "journey"	castle - "case" leisurely - "leisure" members - "member"	"winner" debating - "depending" impartial - "impart"	71.40%	0	R	0	-6	Right
8	belong - "belongs" impartial - "impartable"	we - "we've"	concert - "concern"	88.10%	1	R	-5	3	/
9	islands - "island" yacht - "yache"	thought - "though"	colonel - "cur"	66.70%	-1	R	0	-1	/
10	favorite - "avorite"	trough - "rough"		86.70%	-2	L	0	-1	/
11	swords - "sword"	awards - "aweer"	impartial - "imperial"	80.90%	-3	R	0	0	/
12	treasures - "treasuries"	award - "awards"	winning - "winnings"	92.80%	-1	R	0	1	Right
13	swords - "sword"	winning - "winner"	treasures - "treasure"	90.50%	0	R	0	0	/
14	swords - "sword"	treasures - "treasure"	members - "member"	90.50%	0	R	0	1	/
15	treasures - "treasure"	leisurely - "leisure"		90.50%	-1	R	-1	0	/
16	swords - "sword" award - "awardry" impartial - "impartiate"	belong - "belongs" winning - "which"	castle - "cave" debating - "depending"	71.40%	-1	R	-1	4	/
17	treasures - "treasure"	members - "member"		95.20%	0	R	3	0	/

(F(1,50) = 8.50, p=.005, effect sixe = 0.15) neglect than patients exhibiting allocentric neglect dyslexia (Figure 3.4).

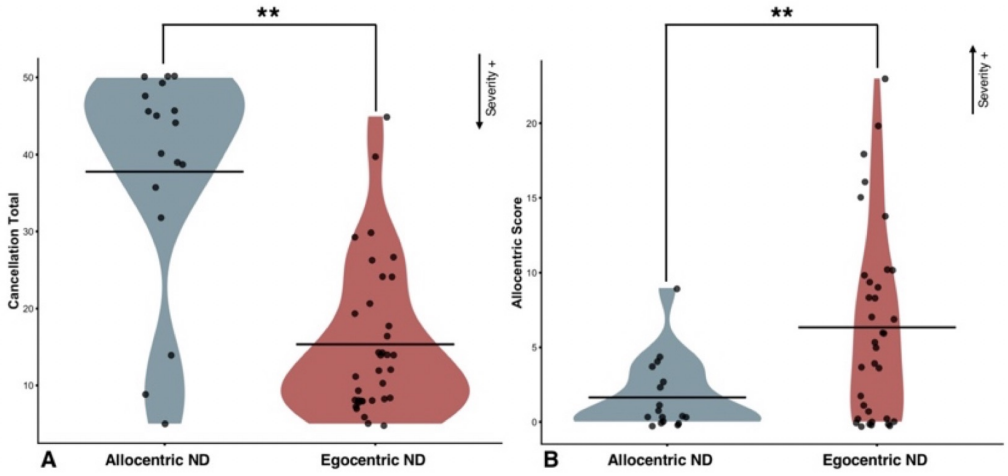


*Figure 3.4: Differences in egocentric severity (Panel A) and allocentric severity (Panel B) between patients with neglect dyslexia and sentence level neglect. Low cancellation totals represent more severe egocentric impairment. High allocentric scores represent more severe allocentric neglect. ** = p < 0.01. Shaded areas illustrate the distribution of data points.*

A subset of 37 patients completed the OCS/BCoS Visual Field Task. 25/29 sentence-level neglect patients and 3/12 neglect dyslexia patients exhibited visual field deficits when measured this way, which impacted the same side of space as their reading impairment. Only 1 allocentric neglect dyslexia patient with no neglect (total N=8) exhibited a visual field impairment.

3.3 Discussion

Egocentric and allocentric neglect dyslexia were found to represent doubly dissociated, independent cognitive impairments. Egocentric neglect dyslexia was not found to occur independently of domain-general visuospatial neglect. Alternatively, allocentric neglect dyslexia was found to be doubly dissociated from both egocentric and allocentric visuospatial neglect impairment. The results of this study suggest that allocentric neglect dyslexia cannot be fully understood as a consequence of egocentric or allocentric visuospatial impairment. In contrast, no evidence was found for a dissociation between egocentric neglect dyslexia and visuospatial neglect.

This investigation demonstrated that egocentric and allocentric neglect dyslexia represent dissociated, independent cognitive deficits, replicating and extending previous studies which also reached this conclusion about dissociable processes (Beschin et al., 2014; Ptak et al., 2012). Importantly, this dissociation is frequently not accounted for when conducting research involving these reading impairments (Galletta et al., 2014; Leff and Behrmann, 2008). Failing to differentiate between these two independent cognitive impairments may potentially confound efforts to investigate these conditions' underlying attentional biases, neural correlates, and recovery trajectories. I further extend previous research by investigating the role of object- or allocentric neglect in explaining word-centred reading impairments in allocentric neglect dyslexia.

I suggest that egocentric neglect dyslexia is best understood as a consequence of domain-general visuospatial impairment rather than an independent cognitive deficit. As in previous research (Beschin et al., 2014; Ptak et al., 2012), all cases of egocentric neglect dyslexia were found to co-occur with similarly lateralised visuospatial neglect. However, two egocentric neglect dyslexia cases occurring alongside severe allocentric but in the absence of domain-general egocentric neglect were identified in this investigation. There are several possible explanations for these cases of egocentric neglect dyslexia seemingly occurring in the absence of egocentric neglect. First, previous research has revealed that stimulus density modulates the severity of egocentric neglect impairment (Husain and Kennard, 1997; Kartsounis and Findley, 1994). It is therefore highly probable that egocentric neglect deficits may be exacerbated by the increased stimulus density and attentional demand associated with reading passages of prose compared to cancellation tasks (Riddoch, 1990). Second, it is possible that egocentric neglect dyslexia may be underpinned by more than one domain-general visuospatial impairment. For example, visual field impairments impacting one side of egocentric space are a frequent consequence of brain damage (Habekost and Starrfelt, 2006; Leff and Starrfelt, 2014). Patients with visual field impairments may struggle to scan passages of text and may therefore fail to report words presented on one side of space. Indeed, 25 patients with egocentric neglect dyslexia also failed the confrontation task. Though this may indicate a co-occurring visual field impairment, it may also simply reflect the very severe neglect, where patients fail to identify any contralesional stimuli. The OCS can

pinpoint a visual field deficit without neglect as patients with visual field deficits perform visual scanning in cancellation tasks, but patients with neglect do not. However, when both tasks are impaired, the two problems cannot be teased apart without further measures. I therefore suggest that while egocentric neglect may not be the only possible cause of egocentric neglect dyslexia impairment, this condition is best understood as a consequence of domain-general visuospatial impairment rather than a content-specific reading deficit.

In contrast, allocentric neglect dyslexia was found to be dissociated from both egocentric and allocentric visuospatial neglect. This investigation identified two patients who exhibited right allocentric neglect dyslexia which co-occurred with left allocentric neglect, illustrating that this dissociation applies not only to the occurrence of these conditions but also to their lateralisation. These findings align with previous research suggesting that some cases of allocentric neglect dyslexia represent content-specific impairments which are not caused by domain-general visuospatial deficits (Caramazza and Hillis, 1990; Friedmann and Nachman-Katz, 2004; Chapter 4). However, as some cases of allocentric neglect dyslexia were found to co-occur with domain-general neglect it seems that this explanation cannot be applied to all cases of this impairment.

These findings are in line with a conceptualisation of neglect dyslexia as a heterogenous condition with some cases being attributable to domain-general impairments and other cases to content-specific cognitive problems (Hillis and Caramazza, 1995). This data does not support a view that allocentric neglect dyslexia, in the absence of visuospatial neglect can be fully explained by other domain-general vision impairments (e.g. hemianopia) (Habekost and Starrfelt, 2006). Only 1 patient with allocentric neglect dyslexia in the absence of visuospatial neglect exhibited significant visual field impairment on the confrontation test. Additionally, visual field impairments can often be compensated for by visual scanning of written stimuli meaning that it seems unlikely that visual field impairment could explain the remaining occurrences of allocentric neglect dyslexia. Similarly, previous authors have argued that allocentric neglect dyslexia which appears to occur independently of domain-general neglect may be attributed to subtle neglect deficits which are exacerbated by the increased stimulus density and attentional demand associated with reading arrays of text (Jackson and Coltheart, 2013; Riddoch, 1990; Riddoch et

al., 1990). However, this explanation cannot account for patients who exhibit allocentric neglect dyslexia and domain-general neglect in conflicting lateralisations and therefore, at best, can only explain a subset of allocentric neglect dyslexia cases.

Previous research has provided a framework for interpreting allocentric neglect dyslexia as a content-specific impairment. Some cases of allocentric neglect dyslexia may be best understood as an impairment occurring at a graphemic-level where words' spatial information is encoded at a representational level within the orthographic lexicon (Caramazza and Hillis, 1990; Hillis and Caramazza, 1995; Jackson and Coltheart, 2013). Hillis and Caramazza (1995) propose a three-tier model of neglect dyslexia in which reading errors can occur within a retino-centric (egocentric), object-centred, or word-centred frame of reference. This model seems to neatly account for differential performance of allocentric neglect dyslexia as well as providing a theoretical framework which can help explain why some patterns of allocentric neglect dyslexia might not be related to domain-general spatial biases. Impairment to domain-general visual processes might produce a retino-centric neglect dyslexia error pattern but impairment to a graphemic level of spatial representation could plausibly result in a content-specific impairment.

Allocentric neglect dyslexia likely represents a highly heterogeneous condition with some cases being caused by domain-general impairments, content-specific impairments, or a combination of the two (Hillis and Caramazza, 1995; Moore and Demeyere, 2017; Vallar et al., 2010; Young et al., 1991). Future investigations need to account for the complexity of this syndrome if understanding of allocentric neglect dyslexia's underlying cognitive impairments is to be advanced.

Limitations:

Several potential limitations were encountered in this investigation. The primary weakness within this investigation was an inability to distinguish between stimulus-centred and word-centred neglect dyslexic reading errors (Caramazza and Hillis, 1990). Both stimulus-centred and word-centred neglect dyslexia would be expected to result in the same error types when reading normally presented passages of text and this investigation was not able to employ the orientation

manipulations necessary to distinguish between these two neglect dyslexia subtypes (Caramazza and Hillis, 1990; Hillis and Caramazza, 1995). It is plausible that the cases of allocentric neglect dyslexia which co-occurred with domain-general allocentric neglect are stimulus-centred impairments while those which occurred in the absence of (or c-occurred with opposite lateralised) allocentric neglect were word-centred neglect dyslexia. For this reason, additional research is needed to determine the underlying causes of word-centred neglect dyslexia and to evaluate whether this specific subtype of neglect dyslexia is in fact dissociable from domain-general neglect impairment.

Additionally, the OCS and BCoS are intended to serve as multidomain screening tools rather than detailed cognitive assessments. For this reason, these screens' reading tasks are comparatively very short with each patient reading between 15-42 words. These brief reading tasks, combined with the stringent criteria employed for classification, were likely only sensitive enough to detect more severe cases of neglect-related reading impairment. Similarly, these reading tasks were designed to screen for and detect several forms of acquired dyslexia and are therefore not specifically optimised for detecting neglect dyslexia. The current findings therefore cannot be employed to accurately calculate the incidence rate of neglect-related reading impairments. This limitation however, does not influence the accuracy of the conclusions regarding neglect dyslexia error patterns within the patients who were identified. Additionally, previous research has strongly suggested that administering multiple, separate tests of neglect is the most reliable method for identifying visuospatial neglect impairment in patients (Gottesman et al., 2010; Halligan et al., 1991; Huygelier et al., 2020; Lindell et al., 2007). However, as this investigation employed existing data it was not possible to include additional neglect tests.

Conclusions:

The findings of this investigation clearly demonstrate that allocentric neglect dyslexia cannot be fully explained as a consequence of allocentric visuospatial neglect. Similarly, this study suggests that neglect-related reading impairments may be best understood as a cluster of dissociable reading impairments rather than a unitary syndrome. It remains critically important to elucidate the specific cognitive mechanisms underlying neglect dyslexia which occurs in the absence of

neglect.

4 Chapter 4.0: Representation-Level Neglect Dyslexia and its Underlying Causes

Author's Note:

In line with standard CRediT author roles (Brand et al., 2015), I was responsible for conceptualisation, methodology, software, validation, formal analysis, investigation, data curation, Writing – Original Draft, Writing – Review and Editing, and Visualisation within the three single case studies reported in this chapter.

Section One is published under the title "Neglect dyslexia as a word-centred impairment: a single case study" in Cortex (Moore and Demeyere, 2018). Section Two is also published in Cortex under the title "Dissociating spatial attention from neglect dyslexia: a single case study" (Moore and Demeyere, 2020). Section Three is currently being prepared for publication.

4.0 General Introduction

Hillis and Caramazza (1995) propose a framework for three distinct levels of neglect dyslexic reading impairment affecting distinct spatial reference frames: egocentric, allocentric, and representation-level. In egocentric neglect dyslexia, patients exhibit full-word reading errors mediated by each words' location within egocentric space (Beschin et al., 2014; Hillis and Caramazza, 1995). In allocentric neglect dyslexia, patients commit letter-level errors which are unaffected by egocentric location but are instead modulated by viewer-independent, stimulus-centred biases. In representation-level neglect dyslexia, letter omission, addition, and substitution errors occur at the level of internally stored spatial representation. The previous chapter demonstrates that egocentric neglect dyslexia is best understood as a consequence of domain-general visuospatial attentional impairments. Similarly, allocentric neglect dyslexia errors likely represent a side effect of domain general allocentric neglect impairment. However, the underlying cause of representation-level neglect dyslexia and its relationship to the neglect syndrome remains unclear.

Few previous case studies have documented cases of representation-level neglect dyslexia, and many questions remain open for additional research. First, it is unclear whether this representation level error pattern can be reliably identified in a substantial proportion of cases. Second, it is not yet clear whether representation-level neglect dyslexia can be fully dissociated from visuospatial neglect. Finally, Hillis and Caramazza (1995) propose that representation-level neglect dyslexia is best characterised as visuospatial neglect which impacts stored, spatial representations of orientation-canonical stimuli. It is not yet clear whether representation-level neglect dyslexia reflects damage to a domain-general spatial attentional mechanism or is instead a reading specific deficit.

In this chapter, I will present a series of representation-level neglect dyslexia case studies aiming to elucidate the underlying causes of representation level neglect dyslexia and evaluate the validity of Hillis and Caramazza's (1995) characterisation of this impairment. Section 1 analyses reading and spatial attention abilities within a Transient Ischemic Attack patient exhibiting right lateralised representation-level neglect dyslexia in the absence of domain-general visuospatial neglect. Section 2 employs data from case a patient exhibiting right representation-

level neglect dyslexia in conjunction with left-lateralised visuospatial neglect to explore whether representation-level neglect dyslexia can be accurately characterised as an impairment of spatial attention. Specifically, this section aims to investigate the impact of attentional load manipulations within representation-level neglect dyslexia, in order to clarify this condition's relationship with the neglect syndrome. Finally, Section 3 presents data from an additional patient representation-level neglect dyslexia patient and proposes an alternative explanation for the reading impairments seen in representation-level neglect dyslexia.

4.1 Chapter 4.1: Neglect Dyslexia as a Representation-Level Impairment: Patient AB

4.1.1 Introduction

It is first critical to determine whether representation-level neglect dyslexia can be dissociated from both egocentric and allocentric domain-general neglect impairment as predicted by Hillis and Caramazza's (1995) model of neglect dyslexia. Previously documented representation-level neglect dyslexia patients have either demonstrated general visuospatial neglect (e.g. NG (Caramazza and Hillis, 1990), RB (Hillis and Caramazza, 1990), ML (Hillis and Caramazza, 1995)) or have not been adequately assessed for domain-general egocentric and allocentric visuospatial deficits (e.g. HH (Hillis and Caramazza, 1990), LHD (Schubert and McCloskey, 2013)). Similarly, studies which do not include orientation manipulations cannot adequately distinguish between cases stimulus-level and representation-level neglect dyslexia (see Chapter 3)). For this reason, the relationship between representation-level neglect dyslexia and domain-general visuospatial neglect remains unclear.

The purpose of this chapter is to employ data from a single case study of a patient demonstrating neglect dyslexia to critically evaluate representation-level neglect dyslexia's relationship with visuospatial neglect. Specifically, this study aimed to replicate Caramazza and Hillis' (1990) stimulus manipulation conditions to determine whether this patient's neglect dyslexia occurs within a representation-level frame of reference. Additionally, this study aims to investigate performance differences between lexical and non-lexical reading stimuli to determine whether representation-level neglect dyslexia can be understood as a content-specific deficit.

4.1.2 Case Report

AB was a 75-year-old woman who was admitted to the John Radcliffe Hospital's hyper-acute stroke ward after presenting with right facial weakness, right facial numbness, and dysarthria. These symptoms began at approximately 06:00 on the date of testing and had resolved by 07:00. This investigation's cognitive assessments and reading experiments were conducted between 4.5 and 5.5 hours following symptom onset. AB completed 10 years of education, was right-handed,

and reported a past medical history of epilepsy and Rheumatoid Arthritis. AB commented on having “some trouble reading” while completing routine post-stroke assessments.

AB’s diagnostic CT scan was collected at 14:37, 9 hours after initial symptom onset. This investigation identified no evidence of intracranial haemorrhage, ischaemic lesions, or space-occupying lesions. A comparison was made with an earlier CT head scan collected the previous month and no interval changes were present. AB was subsequently diagnosed with a Transient Ischemic Attack (TIA). A TIA is a temporary period of stroke-like symptoms usually lasting between a few minutes and an hour (Johnston, 2002). TIA diagnoses are comparatively rare as the majority of symptoms may resolve before patients contact or are assessed by medical professionals. (Figure 4.1).

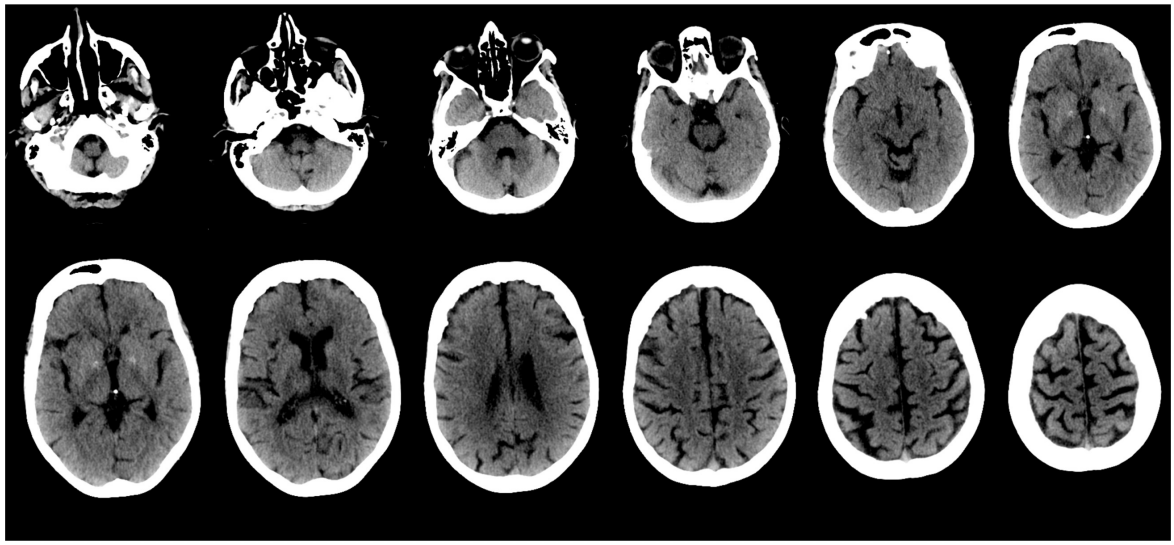


Figure 4.1: AB’s non-normalised, native space CT scan. No abnormalities were noted during clinical diagnostic assessment.

4.1.3 Methods and Materials

AB completed the Oxford Cognitive Screen (OCS) and NIH Stroke Screen (NIHSS) as a component of standardised acute stroke setting procedures. The NIHSS is a 11-item scale designed to detect and evaluate a wide range of physical and cognitive post-stroke impairments (Spilker et al., 1997). NIHSS total scores range from 0-42 with 0 representing no stroke symp-

toms and 42 representing the most severe level of stroke impairment. Cumulatively, the OCS evaluates five domains of cognition: language, memory, attention, praxis, and number processing (see www.ocs-test.org). This assessment includes a Cancellation Task to detect egocentric and allocentric visuospatial neglect impairment (see Chapter 2).

This investigation's three experimental conditions consisted of a series of reading tasks designed to detect neglect dyslexia and to determine how stimulus orientation and lexical content manipulations modulate the occurrence of neglect dyslexia reading errors. In each of these conditions, a series of written stimuli were presented sequentially and centrally on a tablet computer. This presentation program was written using MATLAB's Psychtoolbox (Brainard, 1997). Each stimulus was displayed in all capital letters in size 23 Arial font at the centre of the screen, and remained present for an unlimited duration, until a response was made by the participant. Given a viewing distance of approximately 50 cm, the viewing angle for the horizontal stimuli ranged from a 2 -degree to a 12-degree visual angle, depending on stimulus length. Responses were recorded as correct or incorrect by the examiner through a tap on the left or right side of the screen. Audio recordings of patient responses were collected and were subsequently reviewed to confirm and code error types.

Each of this investigation's three conditions included real word, pseudo-word, or number stimuli. The words and pseudo-words used in this investigation's experiments were selected so that omission or substitution of the leftmost and rightmost letters of each stimulus could potentially yield a response with lexical content. For example, the word IMPARTIAL could be misread as either "partial" or "impart" and the pseudo-word PANOW could be misread as either "pan" or "now". These words were chosen in order to increase the probability that patients would commit neglect dyslexia reading errors (Riddoch, 1990; Vallar et al., 2010). Similarly, this experiment's stimuli were intentionally selected to include many derivational affixes in order to increase the probability of neglect dyslexia reading errors. Words with suffixes and prefixes are generally more likely to produce neglect dyslexia reading errors than words without these affixes as derivational affixes can be substituted or omitted in many different combinations which still produce lexical responses (e.g. OBSESSED can potentially be misread as obsession, obsessing, obsesses,

obsess, etc.) (Riddoch, 1990; Vallar et al., 2010).

For transparency, the full list of words, numbers, and pseudo-words is included in Appendix III . All stimuli types were presented in separate experimental blocks to avoid potentially confounding effects of intermixed presentation.

Experiment One: Reading Assessment:

Here, I aimed to clarify whether AB exhibited a neglect dyslexia reading impairment. In this condition, AB was asked to read a series of 100 real presented in the normal, horizontal orientation on the tablet screen. In each of this investigation's experiments, the word stimuli were between 3 and 10 letters in length and stimulus presentation order was randomised within each word length category and these word-length categories were presented in ascending order.

Experiment Two: Orientation Manipulation:

The purpose of Experiment Two was to determine the extent to which the spatial lateralisation of AB's reading impairments was modulated by topographical orientation. First, AB was asked to read a series of words printed vertically down the centre of the tablet screen. AB was then asked to read words presented in mirror-reflected orientation (see Figure 4.2). The type and lateralisation of AB's reading errors in these orientation manipulations was compared to her reading errors in the initial reading assessment condition.

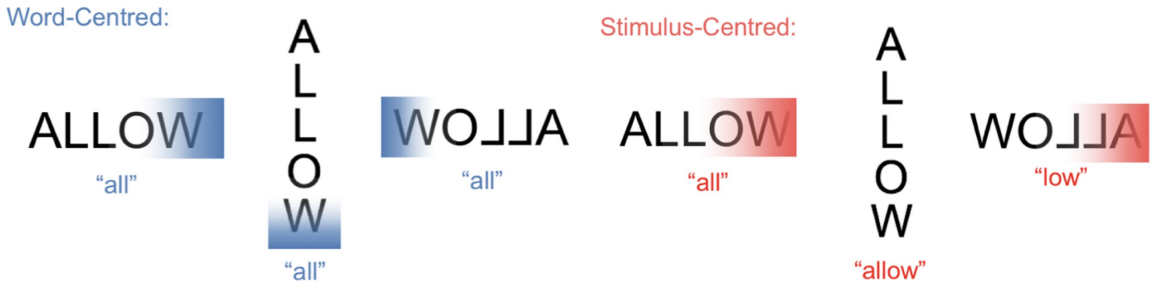


Figure 4.2: An example of the different orientation conditions with an illustration of how these conditions would be predicted to differentially impact allocentric and representation-level neglect dyslexia. "Word-centred" and "Stimulus-centred" are the terminology used by Caramazza and Hillis (1990) used to refer to representation-level and allocentric neglect dyslexia respectively.

Experiment Three: Stimulus Type:

In Experiment Three AB was asked to read a series of normally-presented pseudo-words and normally-presented numbers in order to determine whether AB's neglect dyslexia represented a content-specific or domain-general impairment. The pseudo-words in this condition consisted of 3-10 letter stimuli and the numbers consisted of equal portions of 3 and 5 digit stimuli. AB was instructed to read pseudowords "as a whole" and to name each individual digit in the number-reading condition. Pseudo-word stimuli and number stimuli were presented in separate experimental blocks and were not intermixed.

AB's performance in this condition was compared to her reading error pattern in Experiment One in order to determine the extent to which stimulus type modulated the prevalence of neglect dyslexia reading errors.

Procedure:

The procedure followed the protocol approved by the National Research Ethics Service (Reference: 14/LO/0648). AB provided informed consent and all assessments were completed by a trained examiner. In the neglect dyslexia reading assessment, AB was asked to read each presented word, pseudo-word, and number aloud while her responses were recorded. Reading errors were categorised as neglect dyslexic if they involved a letter omission, addition, or substitution affecting the terminal or initial letters of words. Reading errors were classified as visual if they involved letter translocations, omissions, additions, or substitutions which were not clearly lateralised. Errors were classified as regularisations if they involved reading a pseudo-word as a visually similar real word or the phonetically correct mispronunciation of a phonetically irregular real word. Errors which did not fall into one of these category types, were unintelligible, or involved responses that were visually and semantically unrelated to the stimuli were marked as uncategorized.

The OCS, and Experiments 1-3 were all administered sequentially and this testing was completed within one hour. AB was given short, breaks between each task to help prevent patient fatigue. AB remained alert and engaged throughout the full duration of testing.

4.1.4 Results

General Cognitive Assessment Results:

When assessed using the NIHSS, before participating in the reading experiments, AB demonstrated no inattention, motor weakness, language deficits, or other formal impairments and was therefore assigned a total NIHSS score of 0. When subsequently assessed with the OCS, immediately before participating in the reading experiments, AB exhibited impairments in number writing, calculation, and sentence reading (Figure 4.3). In the OCS number writing task, AB miss-wrote "seven hundred and eight" as "7008" and "fifteen thousand two hundred" as "150020". These "extra zero" errors are commonly seen in acute stroke, previously documented in 14.2% of a sample of 667 acute stroke survivors (Haupt et al., 2017). In the calculation task, AB answered one out of the 4 items correctly. AB also exhibited a clear reading impairment in the OCS sentence reading task (THOUGHT read as "though" and QUAY read as "quarry") and was therefore recruited to complete the battery of reading-specific assessments in this investigation.

AB exhibited no significant egocentric or allocentric (object-centred) visuospatial neglect impairment when completing the hearts cancellation task in the OCS (object asymmetry score = 0, space asymmetry score = -1, Total Correct = 35/50, Figure 4.4). However, AB did not rely on a consistent spatial search strategy in this task, but instead marked correct hearts in a random order across both sides of the page. AB was not found to exhibit any visual field deficits which may have impacted her reading abilities.

Initial Reading Assessment:

AB read 97 real words presented in the normal orientation. Overall, AB read 81/97 (83.51%) of these words correctly. Of the 16 reading errors AB committed, 15 were lateralised neglect dyslexic reading errors affecting the terminal letters (right side) of words. Four errors involved right-lateralised letter omissions (e.g. RELATED read as "relate", TOTALLY read as "total") and 11 errors involved right-lateralised letter substitutions (e.g. EVERY read as "even", PASSAGE read as "passenger"). See Table 4.1 for a summary of AB's performance on the neglect dyslexia reading assessments and see Appendix III for a full list of stimuli and reading responses.

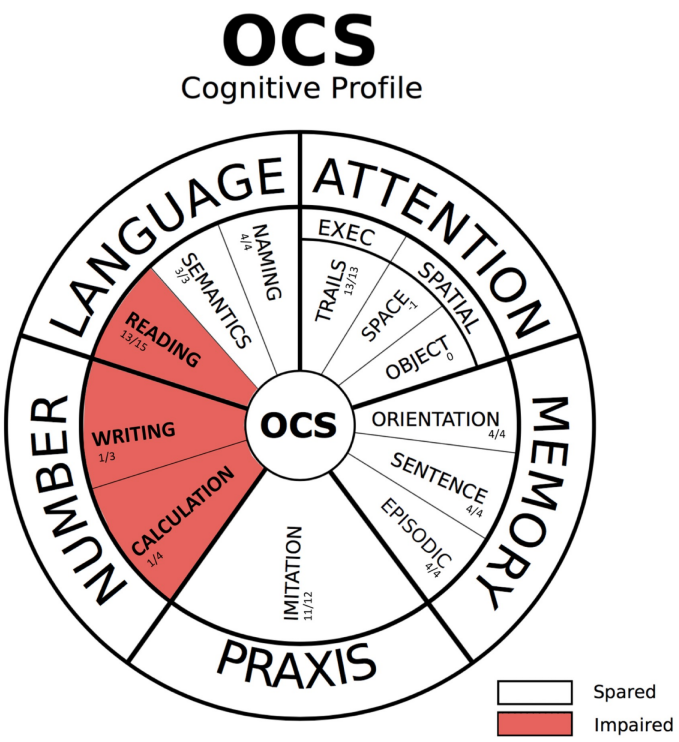


Figure 4.3: AB's Oxford Cognitive Screen performance summary. Cognitive domains are listed around the outer ring of the circle and individual tasks are denoted in the inner ring. AB's score on each task is listed within each task's segment. Scores which were below the cut-offs for impairment are denoted by shaded segments.

Orientation Manipulation Results:

When reading vertical words, AB continued to commit omission, addition, and substitution errors affecting the terminal portion of presented words. For example, AB read GLOBE as "global", SHOWN as "show", STUDIED as "study", and ADDRESSES as "address" when these words were presented printed vertically down the centre of the tablet screen. In total AB misread 9/31 vertically presented words and 6/9 of these errors were omission, addition, and substitution errors affecting the terminal letters of words. There was no significant difference between the proportion of neglect dyslexia reading errors when the stimulus was normally or vertically presented (15/97 versus 7/31 respectively; Fisher's Exact, p = 0.41).

When reading mirror-reflected words, AB exhibited lateralised neglect dyslexia errors in 5/31

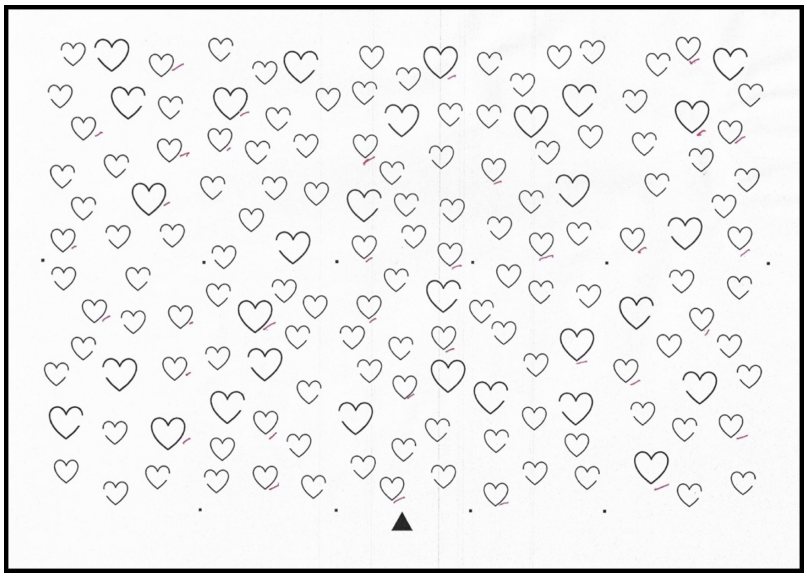


Figure 4.4: AB's completed OCS cancellation task. 35/50 target hearts were successfully identified. 14 of the correctly identified hearts were presented on the left side of space, 13 were presented on the right, and 8 were presented centrally resulting in a space asymmetry score of -1. This asymmetry score does not represent a visuospatial neglect impact.

(26.32%) of words. There was no difference in the proportion of neglect dyslexia errors in the reflected condition versus the normal orientation (15/97 versus 5/31 respectively; Fisher's Exact, p = 1). Strikingly, these errors affected the terminal portions of words, despite the fact that these normally right-lateralised portions of words were now presented in the left side of space. In this reflected condition, AB misread GROWN as "grow", THERE as "the", FORMAT as "formed", and OBSESSION as "obsess". 5/5 (100%) of AB's lateralised reading errors in the reflected condition affected the left side of egocentric space while 15/15 (100%) of AB's lateralised reading errors in the normal condition affected the right side of egocentric space.

Stimulus Type Manipulation Results:

There was a significant and absolute difference in the prevalence of neglect dyslexia reading errors when reading numbers and real words of comparable length (7/79 neglect dyslexia errors when reading 3 and 5 letter words versus 0/48 when reading numbers ; Fishers Exact, p = 0.0441) as AB did not commit any lateralised omission, addition, or substitution errors when reading numbers in the normal, vertical, and mirror-reflected conditions. AB read all numbers presented in the

Table 4.1: A general summary of AB's performance on the reading assessments incuded in this investigation.

Reading Assessment Results Summary			
	Words	**Pseudo-words**	**Numbers**
Normal Presentation			
Reading Accuracy:	81/97 (83.5%)	22/32 (68.8%)	16/16 (100%)
Neglect Dyslexia Errors:	15	1	0
Other Errors:	1	9	0
Vertical Presentation			
Reading Accuracy:	22/31 (71.0%)	12/31 (38.71%)	16/16 (100%)
Neglect Dyslexia Errors:	7	9	0
Other Errors:	2	10	0
Reflected Presentation			
Reading Accuracy:	20/31 (64.5%)	7/32 (21.9%)	9/16 (56.3%)
Neglect Dyslexia Errors:	5	6	0
Other Errors:	6	19	7

normal and vertical conditions correctly. Although AB did misread 7/16 numbers presented in the reflected condition, none of these number reading errors were characteristic of neglect dyslexia. 4/7 of AB's reflected number reading errors were transposition errors (e.g. 925 read as "952" and 259 read as "529") and the remaining 3/7 errors involved AB reporting that she could not read the presented stimuli and giving no response.

AB read 41/95 (43.2%) pseudo-words correctly. In line with existing neglect dyslexia literature (Riddoch, 1990; Vallar et al., 2010), this performance is significantly worse than AB's performance when reading real words (123/159 real words read correctly; Fisher's Exact $p < .0001$).

AB was found to exhibit a qualitatively different reading error pattern when reading pseudo-words compared to when reading real words. For example, AB misread 10/32 normally presented pseudo-words, but 9/10 of these errors were generalised visual (n = 5), regularisation (n = 1), no response (n = 2), and uncategorised (n = 1) reading errors (see Appendix). AB only committed 1 potential neglect dyslexia error when reading normally presented pseudo-words (MAB read as "mad"), which also involved a regularisation error. However, when reading normally-presented

real words, AB committed no generalised visual errors, no uncategorised errors, 1 no response error, and 15 right-lateralised neglect dyslexia errors (Figure 4.5). A qualitative difference was present between AB's real word and pseudo-word reading pattern (Figure 4.5). AB committed neglect dyslexia reading errors in 15/100 normally presented real words and 1/32 normally-presented pseudo-words. However, AB only read a comparatively small number of normally presented pseudo-words, meaning that the resulting statistical comparisons are underpowered and therefore not significant (Fischer's Exact, p = 0.1165).

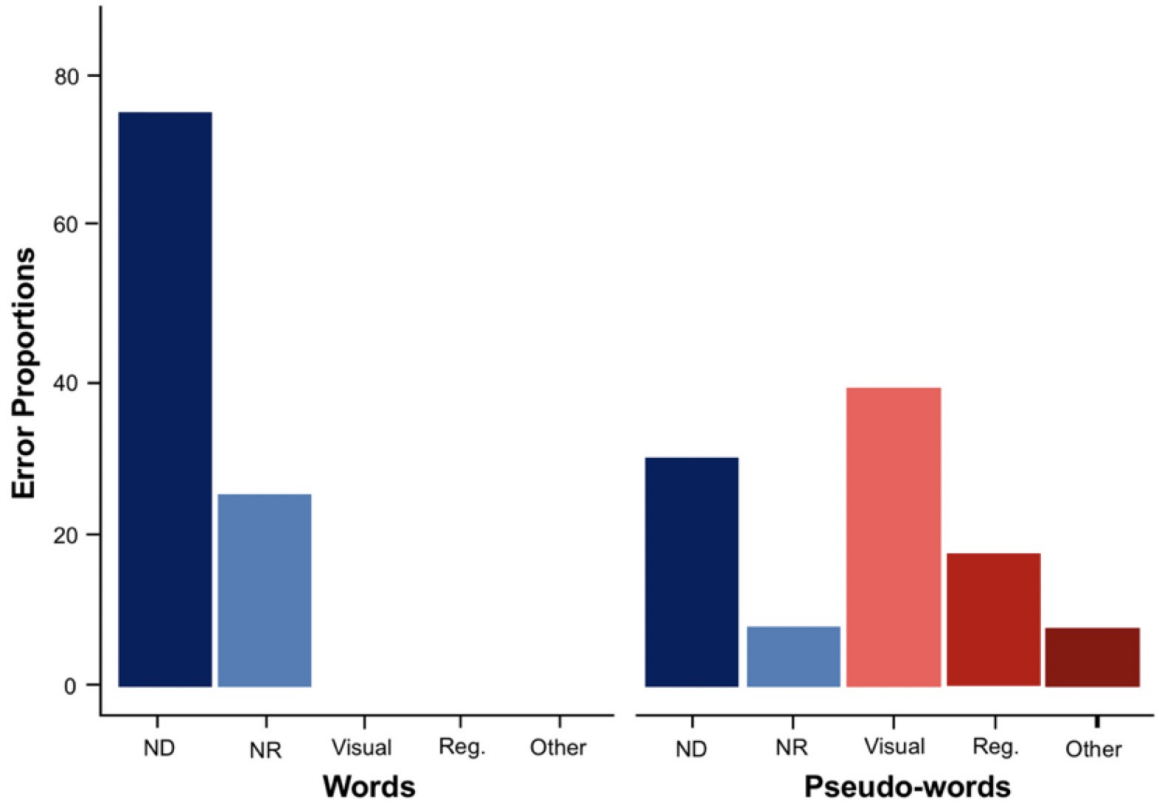


Figure 4.5: AB's distribution of different reading error types when reading real words and pronounceable pseudo-words. ND = neglect dyslexia, NR = no response, Reg. = phonemic regularisation error

Word Familiarity and Length:

A binary logistic regression revealed that AB's likelihood to commit a neglect dyslexic reading error when reading real words was significantly modulated by word length ($X^2(1) = 6.547$, $p < 0.011$), with shorter words being read more accurately than longer words. A similar model which

included both length and whether or not each word included a suffix as covariates was also found to be significant (X2(1)= 35.8 , p < 0.001). However, the inclusion of suffix category was not found to significantly improve this model (p = 0.997).

A binary logistic regression analysis revealed a significant relationship between word familiarity and AB's reading accuracy (X2= 4.78, p = 0.027), with more familiar words being read more correctly than low-frequency words (see Figure 4.6 for a distribution of the word frequencies by reading accuracy).

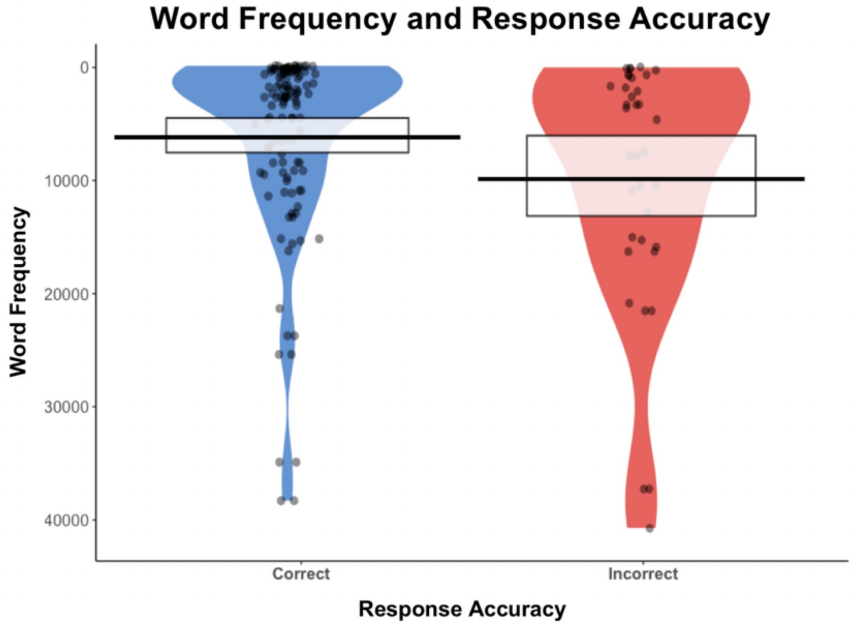


Figure 4.6: A Pirate plot (The Pirate Plot (2.0) – The RDI Plotting Choice of R Pirates – Nathaniel D. Phillips, PhD, n.d.) of the relationship between word frequency and AB's response accuracy. As learning novel words occurs through frequent encounters with these words, word frequency statistics were considered as an adequate proxy measurement of word familiarity (Osterhout et al., 2006). These word frequency scores were assigned based on the Corpus of Contemporary American English (COCA) (Davies, 2009). Words with low word frequency scores are the most frequent. Points represent individual responses, rectangles represent the upper and lower quartile, and blobs represent the spread of the distribution of responses.

4.1.5 Discussion

AB presented after a TIA and was found to exhibit right, representation-level neglect dyslexia om the absence of both egocentric and allocentric neglect. These findings demonstrate a be-

haviour dissociation between representation-level neglect dyslexia and domain-general visuospatial impairment

While AB's neglect dyslexia reading error pattern was in many ways similar to that of neglect dyslexia patient NG (Caramazza and Hillis, 1990), there are important differences between these two patients. First, NG's neglect dyslexia occurred following a left hemisphere stroke which produced substantial white matter lesions, but AB's neglect dyslexia occurred following a TIA. This is the first investigation to document a case of neglect dyslexia following a TIA. Secondly, while NG's neglect dyslexia co-occurred with profound, similarly-lateralised egocentric visuospatial neglect, AB's neglect dyslexia was found to occur independently of both egocentric and allocentric visuospatial neglect deficits, suggesting that representation-level neglect dyslexia can be dissociated from domain-general visuospatial neglect

Like NG, AB was found to commit lateralised reading errors which occurred within a representation level frame of reference. AB made neglect dyslexia errors affecting the terminal letters of individual words when reading horizontal, vertical, and mirror reflected words. Critically the location of these errors was modulated by letter's relative positions within words, not the location (left/right) they were visually presented in. Cumulatively, AB's reading error pattern within this investigation's orientation manipulation conditions strongly suggests that AB's neglect dyslexia, like NG's, is best understood as a reading deficit which occurs within the representation-level frame of reference.

Finally, AB's reading impairment was found to be content-specific. AB consistently committed right-lateralised omission, addition, and substitution errors when reading real words, this pattern was not observed when AB was asked to read numbers and pseudo-words. If AB's neglect dyslexia was a consequence of damage to a domain-general perceptual mechanism, her ability to read all alphanumeric stimuli would be expected to be equivalently impaired (Jackson and Coltheart, 2013; Riddoch et al., 1990). AB's complete lack of neglect dyslexia errors when reading numeric stimuli strongly suggests that AB's neglect dyslexia instead represents damage to a content-specific mechanism.

While the findings of this investigation imply that AB's neglect dyslexia may represent a

content-specific deficit, this implication is not without limitations. First, when reading number strings AB was asked to name each individual digit rather than to read the number as a whole. This means that AB's number reading involved serial, element-by-element parsing rather than reading stimuli "as a whole". This differential processing strategy may have resulted in numbers being less cognitively demanding to read than words or pseudo-words. Additionally, it is not quite clear how to account for the significant, but not neglect dyslexic impairment seen in AB's pseudo-word reading. One possibility is that AB could have exhibited a comorbid impairment which selectively impacted her ability to read relying on the non-lexical route. Previous research has identified neglect dyslexic patients who exhibited comorbid attentional dyslexia reading deficits (Warrington, 1991), and it therefore seems plausible that AB may have also exhibited a comorbid reading deficit selectively affecting pseudo-word reading. One other possibility is that the impaired pseudo-word reading could be linked to her other co-occurring cognitive impairments as detected with the OCS.

In the number writing portion of the OCS, AB was found to write extra zeros in numbers. A previous study of acute OCS data (Haupt et al., 2017) identified this "extra zeros" number writing impairment in 14.2% of patients and concluded that this deficit was representative of impairment in activating and employing the abstract concept of "zero", which has no corresponding semantic representation. Second, AB was found to exhibit significant calculation impairment. Finally, AB exhibited an abnormal, unstructured search strategy when completing the OCS's cancellation task. Neurologically healthy adults generally complete cancellation task in an organised, systematic manner. For example, participants frequently scan the search matrix from left to right, working their way from the top of the page to the bottom (Brucki and Nitrini, 2008; Weintraub and Mesulam, 1988). AB's failure to employ such an organised search pattern may have resulted in her substantial number of target omission errors, and suggests that AB experienced difficulty planning and employing an effective spatial search strategy.

Overall, AB was found to exhibit representation-level neglect dyslexia in the absence of domain-general visuospatial neglect, demonstrating a behavioural dissociation between these conditions.

4.2 Chapter 6.2: Dissociating Representation-Level Neglect Dyslexia from Spatial Attention: Patient CD

4.2.1 Introduction

Patient AB provides evidence that representation-level neglect dyslexia can be dissociated from both egocentric and allocentric neglect impairment. However, it remains unclear whether representation-level neglect dyslexia can be accurately characterised as a visuospatial neglect which impacts orientation-canonical representations of visual stimuli.

Several qualitative differences between representation-level neglect dyslexia and visuospatial neglect have been documented. For example, patient NG exhibited a preserved ability to name each letter in visually presented word stimuli, but committed neglect dyslexia reading errors when asked to read each word as a whole (Caramazza and Hillis, 1990). This demonstrates that patient NG was consciously aware of "neglected" stimuli, but simply did not employ this information when reading. This pattern of impairment is not clearly analogous to visuospatial neglect, as patients with visuospatial neglect are markedly unable to consciously report stimuli presented within the neglected side of space (Marshall and Halligan, 1988; Parton et al., 2004). This awareness of neglected stimuli within neglect dyslexia is also evidenced by neglect dyslexia patients' tendency to preserve word length when misreading individual words (Vallar et al., 2010). These findings demonstrate that some attributes of representation-level neglect dyslexia are not characteristic of visuospatial neglect, suggesting that these two impairments may not be as related as previously asserted.

This possibility can be further investigated by comparing the impact of visual crowding and attentional load manipulations on representation-level neglect dyslexia. The severity of visuospatial neglect has consistently been found to be modulated by attentional and perceptual manipulations. For example, patients with neglect exhibit a more severe impairment when completing dense compared to diffuse object cancellation tasks (Husain and Kennard, 1997; Trojano et al., 2009). Similarly, reducing exposure time has been found to exacerbate visuospatial biases in patients with neglect (Bonato et al., 2013; Russell et al., 2004; Russell et al., 2013). Both these manipulations have been found to impact the severity of reading impairments within a subset of

neglect dyslexia patients, suggesting an underlying spatial attentional deficit (Ellis et al., 1987; Riddoch et al., 1990). However, it is not yet clear whether these findings are generalisable to patients with representation-level neglect dyslexia.

Only a relatively small number of representation-level neglect dyslexia patients have been identified, and none of these patients have completed experiments designed to investigate the effects of attentional manipulations on their reading impairments (Caramazza and Hillis, 1990; Haywood and Coltheart, 2000; Chapter 4, Section 1). It therefore remains unclear whether representation-level neglect dyslexia is best understood as a form of representational neglect or as an impairment which may be unrelated to attention and overall visuospatial neglect. The purpose of this chapter section is to investigate the impact of attentional load manipulations within representation-level neglect dyslexia, in order to clarify this condition's relationship with the neglect syndrome.

4.2.2 Case Report

Patient CD was a 77 year-old man with no higher education (total ten years of education). Patient CD was admitted to the John Radcliffe Hospital's hyper acute stroke unit in May 2019 and was diagnosed with a right middle cerebral artery stroke. Patient CD had a complex medical history including constrictive pericarditis, pulmonary hypertension, heart failure, nystagmus, and a previous right-hemisphere middle cerebral artery stroke 2 years earlier. Following CD's most recent cerebrovascular accident, he presented with left-sided weakness and a facial droop but remained able to walk independently with the support of a stick. Patient CD reported some reading difficulties which were new following his most recent stroke. CD completed this investigation on three sequential days, beginning 13 days after admission.

Patient CD completed a routine clinical CT scan on the day of admission which demonstrated a right hemisphere ischaemic infarct centred in the basal ganglia. CD's lesion was found to primarily affect the right frontal orbital cortex and insular cortex as well as the right uncinate fasciculus and right external capsule (Figure 4.7, Table 4.2).

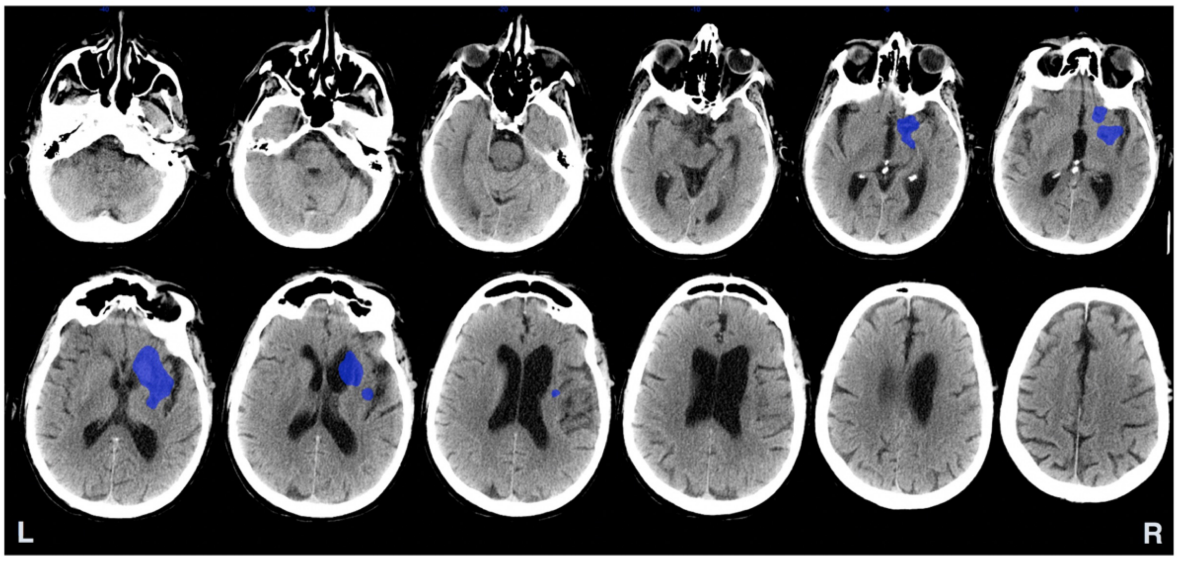


Figure 4.7: CD's native-space clinical CT scan and corresponding lesion mask.

4.2.3 Materials and Procedure

Patient CD completed the OCS as well as the initial reading assessment, orientation manipulations, and content manipulations described in Section 1 of this Chapter. CD completed a later, version of these assessments which were slightly modified from the tests used for patient AB. First, CD's version of the number string reading task employed unpronounceable consonant strings rather than digits. This change was made in order to avoid potentially confounding effects of employing both numerical and letter stimuli. Second, the exact stimuli (and number of stimuli) employed in each reading condition were modified slightly. Finally, in some cases where CD committed reading errors, CD was asked to name each individual letter in the visually presented reading stimuli. This was intended to determine whether CD's impairment (like NG (Caramazza and Hillis, 1990)) involved a low-level perceptual deficit.

In addition to these repeated reading tests, GC completed a series of additional neglect assessments and three, novel tablet-based reading assessments. See Table 4.3 for details on each conducted task, the number and type of stimuli, as well as the day of assessment. For transparency, all reading stimuli and corresponding responses are openly available on the Open Science Framework (https://osf.io/27n85/). Full reading data is included in Appendix III.

Table 4.2: Full descriptive statistics for CD's lesion mask. All ROIs are defined according to the Harvard-Oxford and Johns Hopkin's University Atlases. Fraction is the proportion of the ROI damaged, extension is the proportion of the lesion within each specific ROI. All impacted areas are within the right hemisphere.

ROI Name	Voxels	Voxels Damaged	Fraction
Uncinate fasciculus	616	485	0.787
External Capsule	8083	2379	0.294
Orbitofrontal Cortex	14694	2705	0.184
Insular Cortex	11505	1907	0.166
Parahippocampal Gyrus (Anterior Division)	8163	426	0.052
Internal Capsule Anterior Limb	4119	174	0.042
Planum Polare	4361	177	0.041
Anterior Corona Radiata	8756	136	0.016
Subcallosal Cortex	5482	63	0.011
Internal Capsule (Retrolinear Part)	3286	15	0.005
Temporal Pole	23987	101	0.004
Fornix (Cres) Stria Terminalis	1891	6	0.003
Internal Capsule (Posterior Limb)	4648	11	0.002

Neglect Tests:

CD completed the OCS cancellation task (see Chapter 2) on each testing date. CD also completed a series of simple drawing tasks in which he was asked to draw an analogue clock from memory with the hands pointing to ten past ten (Nasreddine et al., 2005) and was asked to copy a drawing of a simple scene. Finally, CD completed a computerised line bisection task. In this task a series of 100 lines ranging in length (7 cm, 9 cm, or 12 cm) were presented at one of 9 grid locations on a tablet computer screen. Patient CD was instructed to mark the centre of each line with a stylus and the distance between the actual and reported line centres was recorded in cm.

Novel Reading Assessments:

First CD, completed an Exposure Time Manipulation in which he read a series of 100 words which were only on screen for 500ms. This manipulation was derived from Riddoch et al (1990), and was intended to investigate whether the severity of neglect dyslexia is modulated by the attentional demands of reading tasks (Primativo et al., 2013; 2015). These words were the same

Table 4.3: Details of the various assessments employed in this investigation. E.T. = Exposure Time.

Reading Tests	N	Length	E.T.	Day
Reading Baseline				
Initial	100	3 - 9	Unlimited	1
Orientation Manipulations				
Vertical	75	3 - 10	Unlimited	1
Reflected	56	3 - 8	Unlimited	1
Content Manipulations				
Pseudowords	44	3 - 9	Unlimited	2
Letter Strings	43	3 - 5	Unlimited	2
Attentional Manipulations				
Location	100	5	1000ms	1
Reduced Exposure	73	3 - 9	400ms	2
Spacing Manipulations	100	7	Unlimited	3
General Neglect Tests				
OCS Hearts Cancellation				1,2,3
Clock Drawing / Figure Copy				3
Line Bisection				2,3

words as were originally presented under unlimited exposure condition in the initial reading assessment. To help prevent CD from remembering previously viewed stimuli, this manipulation was conducted 24 hours after the initial reading assessment. Next, patient CD completed a Location Manipulation. In this condition, a series of 100 5-letter words were presented either on the right or left side of the tablet screen. Each stimulus was onscreen for 1000ms. CD was asked to fixate centrally, then shift his gaze to read each stimulus as it appeared. This manipulation was designed to detect egocentric level neglect dyslexia impairments. Finally, patient CD completed a Visual Crowding Manipulation. In this test a series of 100 7-letter words were presented under unlimited exposure time. 50 of these words were presented with one space between each letter (visual angle approximately 7 degrees), and 50 were presented with three spaces separating each letter (visual angle approximately 11.5 degrees). This manipulation was conducted to determine whether visual crowding modulates the severity of neglect dyslexia in a similar way to how it has been found to modulate the severity of visuospatial neglect (Husain and Kennard, 1997; Riddoch et al., 1990)

4.2.4 Results

Cognitive Screening and General Neglect Testing:

CD exhibited significant impairment in the OCS orientation (3/4), reading (8/15), number writing (2/3, 15200 written as 50200), calculation (2/4), cancellation task (Total = 23, Egocentric Asymmetry= 13, Allocentric Asymmetry= 15), praxis (8/12), and verbal memory (1/4) on admission. The OCS cancellation task was repeated on five separate days (twice before beginning reading testing and on each day of reading testing) (Figure 4.8). Notably, CD was found to exhibit severe left allocentric neglect on each of these testing occasions (on average 15.8 left allocentric errors). Figure 4.9 presents the cancellation task CD completed immediately before beginning reading assessment. Though CD had also exhibited significant left egocentric neglect immediately after the stroke, this impairment was no longer present when the reading-specific tests were conducted 13 days later.

CD exhibited no apparent signs of visuospatial neglect when completing the clock drawing

task (on day 3), but omitted the leftmost portion of the ground line when completing the scene copy task (Figure 4.9). CD demonstrated a slight bias towards the right side of space demonstrating left inattention (M = 0.22cm, SD = 0.633, left inattention) when completing the line bisection task. This bias was not found to be significantly more pronounced for stimuli presented on the left side of the tablet screen (0.39cm, SD =0.391) than stimuli presented on the right side (0.18cm, SD = 0.653) (t(70.34) = 1.709, p = 0.0919). This finding is in line with impairment on line bisection tasks reflecting allocentric, rather than egocentric neglect impairment (Mennemeier et al., 1994) .

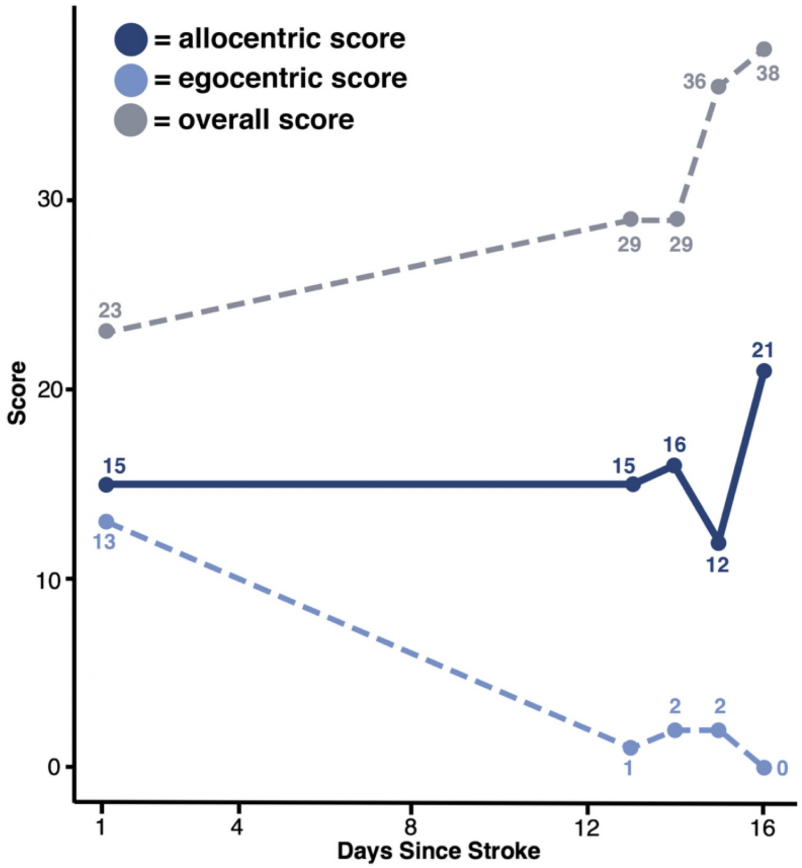


Figure 4.8: CD's performance on the OCS cancellation task across the five testing times. Reading testing was conducted between days 13 and 16 following stroke.

Initial Reading Assessment:

First, CD read a series of 100 normally presented words under unlimited exposure time. In this condition CD read 70/100 words correctly, committed 21 neglect dyslexia reading errors, and made 9 other reading errors (5 no response, 3 visual errors (non-lateralised letter omissions

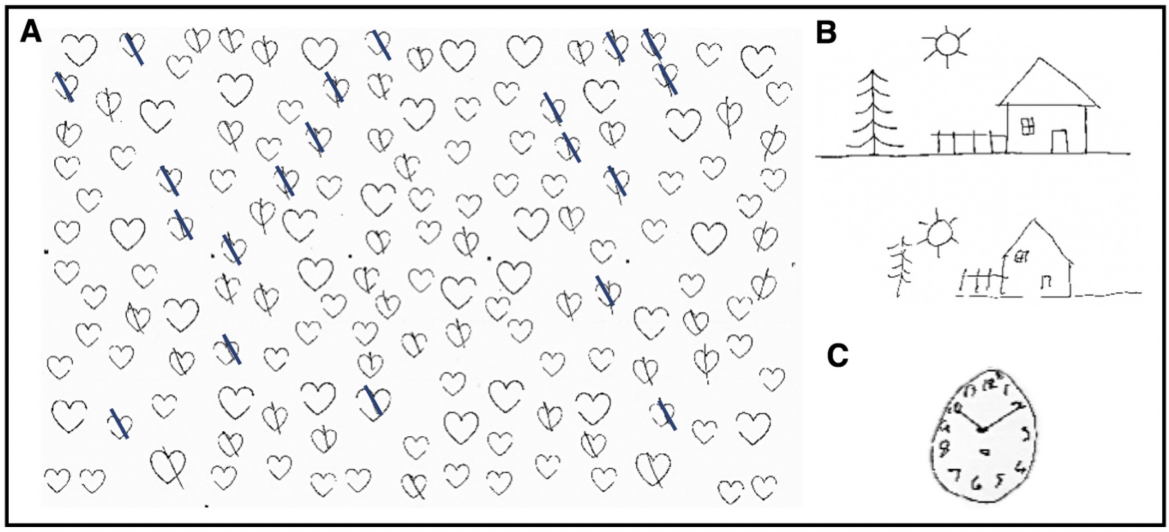


Figure 4.9: CD's cancellation task (A), scene copy (B), and clock drawing (C) performance. Left allocentric errors are highlighted in panel A. CD reported the extra dot in the centre of the clock drawing was "for winding".

or switches – e.g. MILLSTONE read as "milestone"), and 1 unintelligible response). Of CD's right neglect dyslexia reading errors, 11 involved letter substitutions (e.g. THRASHING read as "thrasher") and 10 involved letter omissions (e.g. REMISSION read as "remiss"). All but two of these omissions and substitutions (90.5%) impacted the terminal letters of words. This distribution of reading error types is consistent with previous case studies of representation-level neglect dyslexia patients (Caramazza and Hillis, 1990; Chapter 4, Section 1).

Experiment One: Reference Frame Manipulations:

Next, a series of manipulations was conducted to determine whether CD's neglect dyslexia represented a egocentric, allocentric or a representation-level reading deficit. CD's proportion of right neglect dyslexia reading errors was not found to be significantly different for stimuli presented on the right (10/50) or left (11/50) side of space ($X2(1) = 0.605$, $p = 0.437$). CD then read a series of 75 vertically presented words and 56 reflected words, presented in separate blocks. In the vertical condition, CD read 24/75 words correctly and committed 34 neglect dyslexia errors (N omission = 18, N substitution= 15, N addition = 1). All 34 neglect dyslexia errors impacted the terminal letters of individual words. Of the 17 other errors, 7 were no responses, 8 were

unintelligible responses, and 2 were non-lateralised visual errors.

In the reflected condition, CD read 20/56 words correctly and committed 29 neglect dyslexia errors (20 substitution, 9 omission). All of these lateralised errors impacted the terminal letters of words, even though these usually right-lateralised letters were now presented in the left side of egocentric space. CD also committed 5 letter-by-letter and 2 non-lateralised visual errors in the reflected reading conditions. Overall, this error pattern strongly suggests that CD's neglect dyslexia is best characterised as a representation-level reading impairment (Caramazza and Hillis, 1990; Hillis and Caramazza, 1995).

Experiment Two: Content Manipulation

Next, a series of content manipulations was conducted to investigate whether CD's neglect dyslexia represented a domain-general visual feature processing impairment or a content-specific deficit. CD was presented with a series of 43 unpronounceable letter strings and 44 pseudowords. CD read 39/43 letter strings correctly. Of the four errors committed in this condition, 3 were non-lateralised visual errors and 1 was a left-lateralised letter substitution error (LRMXT read as "A-R-M-X-T"). In the pseudoword reading condition, CD read 22/44 pseudowords correctly. Of the 22 errors committed, 4 were letter-by-letter errors, 9 were non-lateralised visual, and 9 were right-lateralised neglect dyslexia errors (7 substitutions, 2 omissions). A chi-squared test was then performed to investigate the relationship between neglect dyslexia prevalence and stimulus type. Overall, there was a significant difference in the prevalence of neglect dyslexia errors between different stimuli types ($X2(2) = 10.677$, $p = 0.005$). Post-hoc pairwise nominal independence tests revealed that while there was a significant difference in the prevalence of neglect dyslexia errors when reading letter strings and pseudowords ($p = 0.005$) and between letter string and real words ($p = 0.003$), there was no statistically significant difference between the prevalence of neglect dyslexia errors when reading real words and pseudowords ($p = 1.00$).

Experiment Three: Attentional Manipulations:

A series of attentional manipulations was conducted to investigate whether the severity of

representation-level neglect dyslexia is modulated by the same factors which modulate the severity of visuospatial neglect impairment. First, CD completed the Visual Crowding Manipulation. In this task, CD read 57/100 words correctly and committed 43 reading errors (1 unintelligible, 5 generalised visual, 5 letter-by-letter, and 32 neglect dyslexia (25 substitution, 5 omission, and 2 addition)). CD's proportion of neglect dyslexia reading errors was not found to be significantly different between the normal and wide spaced reading condition (26/51 normal versus 29/49 spaced, $X2(1) = 0.318$, $p = 0.573$).

Next, CD read a series of 73 real words presented under reduced exposure time (500ms). CD was found to read 40/73 words correctly and to commit 1 unintelligible, 12 no response, 1 non-lateralised visual, and 19 (10 substitution, 9 omission) neglect dyslexia errors. The proportion of neglect dyslexia errors committed was not found to be significantly different between the unlimited exposure and limited exposure conditions ($X2(1) = 0.350$, $p = 0.554$).

Word Length and Familiarity Analyses:

Next, the stimulus characteristics which modulated the occurrence of neglect dyslexia reading errors within real-word stimuli were investigated. A binary logistic regression was performed to determine the relationship between word length and word frequency with overall reading accuracy. Overall, this model was found to be significant ($F(401,403) = 39.531$, $p < 0.001$, AIC = 484.460) with word length acting as a significant predictor of reading accuracy ($z = -7.30$, $p < 0.001$), but not word familiarity ($p = 0.060$). A second binary logistic regression was then conducted to investigate the effect of word length and familiarity on CD's probability to specifically commit neglect dyslexic reading errors. This model was also found to be significant ($F(401,403) = 17.428$, $p < 0.001$, AIC = 469.38) with word length ($z = -4.873$, $p < 0.001$) but not word familiarity ($p = 0.096$) acting as a predictor of neglect dyslexia error commission. An additional t-test was conducted to investigate whether CD tended to misread less familiar words as more familiar targets. In cases where CD misread a target word as a real, but incorrect word, the familiarity of target words was not found to be significantly different that of CD's response ($t(302.53) = -1.265$, $p = 0.207$).

Letter-by-letter Spelling:

When shown a real word reading stimulus, CD frequently responded that he did not know what the word was. In cases where this occurred, CD was asked if he could see the individual letters within words. CD demonstrated a preserved ability to name all individual letters within words. However, when asked to read the word as a whole, CD consistently committed neglect dyslexia reading errors. For example, when shown the word RADIANS, CD reported that he did not recognise the word and was therefore prompted to name all the letters. CD correctly reported all letters within this word ("R-A-D-I-A-N-S"), but when asked to read the word as a whole he read RADIANS as "radish". Similarly, CD misread LEARNED as "legend", CLOVER as "cloves", and EVERY as "even" immediately after successfully naming all the letters within individual words. CD committed this error pattern 35 times in this investigation's real-word, unlimited exposure conditions. Audio files of these reading errors are available on the Open Science Framework (https://osf.io/27n85/).

4.2.5 Discussion

The purpose of this chapter section was to investigate the relationship between representation-level neglect dyslexia and more general aspects of spatial attention. Patient CD was found to exhibit right representation-level neglect dyslexia in conjunction with left allocentric visuospatial neglect. The severity of CD's reading impairment was not found to be modulated by attentional factors which have been found to modulate the severity of visuospatial neglect, suggesting that CD's reading impairment may not be accurately characterised as a neglect deficit. The data collected in this investigation offer a unique insight into the cognitive mechanisms subserving domain-general and reading-specific visuospatial perception.

CD's stroke was found to result in ischemic lesions to areas within the right hemisphere middle cerebral artery vascular territory, primarily the orbitofrontal and insular cortex as well as the right external capsule. Neglect dyslexia is generally associated with lesions impacting the lingual and fusiform gyri (Vallar et al., 2010), but neglect dyslexia patients exhibiting more frontal lesions (or no visible lesions) have been identified (Friedmann and Nachman-Katz, 2004; Moore

and Demeyere, 2018; Vallar et al., 2010). Cases of ipsilesional neglect impairment, like the one described here, have been previously documented, though this impairment seems comparatively rare (Cubelli et al., 1991; Kim et al., 1999; Kwon and Heilman, 1991). Kim et al., (1999) identified five cases of ipsilesional neglect and found that ipsilesional neglect impairments were associated with frontal-subcortical lesion patterns, similar to that of patient CD. Left allocentric neglect is traditionally associated with more posterior lesions impacting the angular, middle temporal, and middle occipital gyri (Chechlacz et al., 2010, 2012; Hillis and Caramazza, 1991; Medina et al., 2008), but previous research has demonstrated that damage to a surprisingly wide range of neural correlates can result in visuospatial neglect impairment (Bird, 2006; Hildebrandt et al., 2002; Karnath et al., 2002; Karnath and Rorden, 2012; Mort et al., 2003). CD's lesion data demonstrates that ipsilesional representation-level neglect dyslexia can occur, but data from additional patients is required before any firm conclusions about the neural correlates of representation-level neglect dyslexia can be drawn.

Patient CD's reading error pattern aligns closely with that of a representation-level neglect dyslexia deficit as defined by Hillis and Caramazza (1995). CD was found to commit reliable letter omission and substitution errors impacting the terminal letters of individual words, regardless of how these words were presented in space. This is the first case in which representation-level neglect has been found to co-occur with oppositely lateralised visuospatial neglect impairment. This impairment conjunction provides evidence suggesting that representation-level neglect dyslexia can be dissociated from domain-general visuospatial neglect impairment, both in occurrence and in lateralisation. Theories which characterise neglect dyslexia as a peripheral impairment caused by domain-general neglect have difficulty accounting for CD's co-occurring left allocentric neglect and right representation-level neglect dyslexia.

If the same three-level perceptual system was responsible for subserving perception of all visual stimuli, a patient with right representation-level neglect dyslexia would be expected to exhibit right allocentric neglect when completing the cancellation task, as the impairment underlying reading difficulties would also underlie perception of the heart line drawings. However, patient CD was found to exhibit a consistent, severe left-lateralised allocentric deficit when completing the

cancellation task. This impairment conjunction would not be expected if the impairment underlying representation-level neglect dyslexia also played a role in domain-general spatial attention and perception. Importantly, these findings strongly suggest that a neglect-like impairment at the level of spatially canonical internal representations does not necessarily represent damage to a domain-general system.

Further support for this conclusion is provided by CD's performance on the attentional manipulation experiments. Representation-level neglect dyslexia is thought to be analogous to both egocentric and allocentric neglect impairment, but simply within a separate reference frame. However, CD's performance on this investigation's attentional manipulations suggests that the severity of representation-level neglect is not modulated by the same factors which modulate the severity of egocentric and object-level neglect impairments. First, reducing exposure time was not found to exacerbate CD's reading impairment. Previous studies have found that reducing exposure in reading tasks appears to exacerbate the severity of domain-general neglect impairments (Riddoch et al., 1990). Second, the reduction of visual crowding was not found to significantly impact the severity of CD's reading impairment. It is well established that the severity of visuospatial neglect can be exacerbated by increasing visual crowding and density within cancellation tasks (Husain and Kennard, 1997; Kartsounis and Findley, 1994; Parton et al., 2004). It therefore follows that the effects of domain-general neglect on word reading would be expected to be ameliorated by reducing the visual density of word stimuli. This pattern was not observed within patient CD. Finally, visuospatial neglect is characterised by a marked inability to consciously report stimuli presented within neglected space (Ellis and Young, 2013; Marshall and Halligan, 1988). However, CD was able to name individual letters within words, even in cases where he committed a neglect dyslexia reading errors. Considered cumulatively, this evidence suggests that CD's reading error pattern may not be best characterised as a visuospatial neglect related deficit.

I suggest it is possible that CD's reading error pattern may represent a subtle executive function impairment rather than a strictly perceptual, neglect-related impairment. Under this hypothesis, a lack of inhibitory control might lead to CD completing the words with a more pre-potent response. CD demonstrated a preserved ability to perceive and report individual letters, but only

considered information from the left-most portions of words when reading as a whole. This impairment pattern could be in line with inference errors committed by children guessing words which they have not yet acquired lexical representations for and thus be related to a regulation deficit. For example, it is possible that CD simply lacked the self-regulation necessary to inhibit responding to presented reading stimuli until all relevant information had been processed. If this were the case, CD would be expected to respond based on information within the first-processed letters while ignoring any information presented in latter letters, resulting in apparently neglect dyslexic reading impairment. It seems possible that CD's reading performance may have been impacted by executive deficits, especially given that CD's lesion impacted basal ganglia white matter tracts which have been found to be significantly associated with executive functioning (Hua et al., 2014; Vataja et al., 2003). Further research on ipsilesional neglect dyslexia could investigate this hypothesis in more detail by including executive tasks such as the Hayling test (Bielak et al., 2006) which measure prepotent response suppression. Additional research in group studies is needed before any firm conclusions about the underlying causes of representation-level neglect dyslexia can be drawn.

Limitations:

The investigators were only able to access and assess patient CD for the duration of his hospitalisation, creating a very limited time-window for his reading error pattern to be documented. In addition, at a time so shortly after stroke, CD fatigued easily and could not sustain lengthy testing conditions. This investigation dealt with these time constraints by limiting the number of words read in each condition. This adjustment does not decrease the theoretical significance of the documented qualitative neglect dyslexia reading error pattern, but instead only lessens the statistical power of comparisons between conditions in which CD only read a small number of stimuli. Additionally, some stimuli were presented twice in the reading experiments. These repeated stimuli were intentionally included in multiple orientation conditions in order to facilitate a direct comparison between CD's exact responses for the same stimuli in multiple different topographical presentations. While carry-over effects cannot be entirely ruled out, their effects should

be minimal as each stimulus was presented a maximum of three times throughout three separate days of testing. Finally, there was no data available detailing CD's pre-morbid cognitive abilities. It is unclear whether the cognitive impairments observed in CD were directly related to his most recent stroke or whether they were residual impairments from his previous neurological events.

Previous case studies have revealed that neglect dyslexia is a highly heterogeneous condition. While some patients, have been found to exhibit neglect dyslexia impairment patterns which are similar to CD, the conclusions of this investigation cannot be generalised to all cases of neglect dyslexia (Vallar et al., 2010). There is a lack of data from standardised assessments of substantive samples of neglect dyslexia patients, precluding valid comparisons about the condition as a whole. Specifically, comparatively few detailed studies of representation-level neglect dyslexia have been conducted, making it difficult to draw generalisable conclusions. It remains unclear whether the attentional manipulation effects documented in CD can be identified in a wider sample of representation-level neglect dyslexia patients. Additional research is needed to confirm whether some cases of representation-level neglect dyslexia may be related to executive impairment rather than to visuospatial impairment.

Conclusion:

Patient CD was found to exhibit ipsilesional right representation-level neglect dyslexia in conjunction with left allocentric visuospatial neglect, illustrating a dissociation between these conditions. The severity of CD's reading impairment was not found to be modulated by attentional factors which have been found to modulate the severity of visuospatial neglect, suggesting that CD's reading impairment may not be accurately characterised as a neglect-like deficit. This data, considered in conjunction with CD's preserved ability to perceive and correctly identify individual letters implies that his reading impairment is not related to visuospatial attentional function and instead I suggest it may be related to a self-regulation executive dysfunction. However, additional research is needed to conclusively determine whether ipsilesional representation-level neglect dyslexia can be, in actuality, not a neglect-related reading impairment.

4.3 Chapter 4.3: Representation-Level Neglect Dyslexia as an Inhibitional Impairment: Patient EF

4.3.1 Introduction

Analysis of CD's reading impairment implies that representation-level neglect dyslexia is not accurately characterised as a neglect-related reading impairment. Instead, CD's performance may be related to a lack of inhibitory control. This alternate explanation has cursory support from CD's intact ability to perceive all presented letters within words and underlying lesion anatomy. However, more detailed neglect and self-inhibition assessment data is needed from additional patients before this an alternate explanation of the underlying causes of representation-level neglect dyslexia can be confidently supported or refuted.

Broadly, executive functions include the capacities for forming goals, planning, carrying out goal-directed activity, and other self-regulation activities (Diamond, 2013; Jurado and Rosselli, 2007). These deficits occur regularly following stroke, impacting approximately 28.2% of acute stroke survivors as reported by a neuropsychological Trail-Making Test (Demeyere et al., 2015). However, executive function is not a unitary function but instead is an umbrella term which encompasses multiple, dissociable cognitive functions. The pattern of impairment documented within CD more specifically suggests an impairment of self-inhibition, in which reading responses are based on information within the first-processed letters while ignoring any information presented in latter letters. If this characterisation is accurate, patients such as CD would be expected to exhibit impairment on standardised assessments assessing self-inhibition abilities.

Several standardised neuropsychological assessments aiming to assess self-regulation and self-inhibition functions are available. For example, Stroop tests can be employed to assess a patient's ability to inhibit pre-potent response (Jensen and Rohwer, 1966; Scarpina and Tagini, 2017). In a classic Stroop test, patients are shown lists of colour words printed in congruent ink colours (e.g. "BLUE" printed in blue) and incongruent colours (e.g. "BLUE" printed in red ink). Patients with self-inhibition deficits reliably struggle to inhibit the pre-potent responses within incongruent test, resulting in significantly longer reaction times an frequent mistakes in patients read the presented word rather than naming the ink colour (Kingma et al., 1996). However, given

this task's reliance on reading, additional tests are needed to confirm the role of inhibition in representation neglect dyslexia. The Hayling-Brixton Sentence Completion Test (Bielak et al., 2006) provides an ideal method for assessing self-inhibition independently of reading. In this test, participants are asked to complete sentences with clear pre-potent responses first with the relevant, related response then with an unrelated, nonsense word (Bielak et al., 2006). Patients with inhibition deficits reliably fail to provide an unrelated, nonsense response, as they are unable to supress each sentence's pre-potent responses (Bielak et al., 2006). Several other established executive function assessments require some degree of self-inhibition. In verbal and design fluency assessments (e.g. Delis et al., 2004), patients must inhibit previously provided responses in order to maximise their total number of responses. Similarly, in trail-making tests, patients must inhibit previously employed task rules when switching to a new rule set (Kopp et al., 2015; Muir et al., 2015). Overall, data from a range of standardised neuropsychological assessments can be used to quantify self-inhibition abilities and to distinguish this ability from more general executive function impairment.

Conducting a detailed analysis of the semantic and lexical characteristics of reading errors within representational-neglect dyslexia also offers a valuable approach for identifying this deficit's underlying causes. Previous research has suggested that the probability of committing a neglect dyslexia error is modulated by specific lexical characteristics of the presented word (Vallar et al., 2010). For example, words with greater numbers of derivational affixes or prefixes have been found produce a prevalence of neglect dyslexia errors (Riddoch, 1990; Vallar et al., 2010). Additional research has suggested that factors including word concreteness, orthographic neighbourhood, frequency, and familiarity may play a role in modulating the prevalence of neglect dyslexia reading errors (Riddoch, 1990; Vallar et al., 2010). If neglect dyslexia represents a perceptual impairment, visual factors such as word length would be expected to modulate the probability of less impairment on words with fewer bigram neighbours, fewer phonological neighbours, and fewer orthographic neighbours as these words would be easier to guess based on only perceiving a portion of the presented graphemes (Vallar et al., 2010). Similarly, neglect dyslexia errors would be expected to be mainly characterised by misreading longer words as shorter words, regardless

of word's high-level lexical characteristics.

Conversely, if neglect represented an inability to activate specific word representations or a generalised reading impairment, lexical-semantic factors such as lower age of acquisition, higher concreteness, and higher word frequency should decrease the occurrence of neglect dyslexia errors. In this conceptualisation, neglect dyslexia errors should be characterised by misreading words with higher ages of acquisition as responses with lower ages of acquisition. Finally, if neglect dyslexia represents a content-unspecific response inhibition deficit patients should make more errors when presented stimuli have incongruent, pre-potent responses. This implies that patients would be more likely to commit errors when reading words that are less frequent, less concrete, and have more bigram neighbours. According to this characterisation, neglect dyslexia errors should be characterised by misreading less frequent words as more frequent words and less concrete words as more concrete words. Therefore, this analysis aims to employ the lexical and sematic attributes of reading responses in neglect dyslexia to clarify the underlying cases of representation-level neglect dyslexia.

This section presents data from an additional representation-level neglect dyslexia patient, EF, who completed a series of attentional manipulations and neuropsychological assessments designed to help elucidate the specific cognitive impairments underlying representation-level neglect dyslexia. First, EF was assessed using the reading and attentional paradigms reported in Section 2 of this chapter in order to determine whether this patient's reading performance is analogous to patient CD. Next, EF completed a battery of executive function assessments aiming to identify self-inhibition impairment and to determine whether this deficit might underlie his representation-level neglect dyslexia. Finally, an analysis of the semantic and lexical attributes of EF's reading responses was conducted in order to identify additional factors predicting the occurrence of neglect dyslexia reading errors. Overall, the data and analysis presented in this chapter aims to determine whether at least some cases of representation-level neglect dyslexia can be accurately characterised as a self-inhibition rather than a spatial attentional impairment.

4.3.2 Case Report:

EF was a 71 year-old retired farm hand who had a right posterior cerebral artery stroke in May 2012. Following this stroke, EF exhibited a pronounced left-lateralised hemianopia along with left egocentric and allocentric visuospatial neglect. EF reported that he enjoyed reading, but he began to experience difficulty reading following this stroke. EF was originally recruited for research during his acute hospitalisation in 2012. At this time, EF completed the Oxford Cognitive Screen and other standard clinical assessment measures reported here. EF was identified as a potential neglect dyslexia patient and completed a more detailed reading and neuropsychological assessment during a series of chronic follow-up appointments between February and March 2020.

A routine clinical CT scan (5mm slice thickness, 32 slices) which was taken on the day of admission was retrieved in line with the study protocol. This scan demonstrated a large lesion extending throughout the right temporal, parietal, and occipital cortices as well as the underlying white matter. EF's lesion was manually delineated in native space, smoothed at 5 mm full width at half maximum in the z-direction and binarized (threshold = 0.5) using MRIcron . The scan and lesion mask were then reoriented to the anterior commissure and warped into 1x1x1 mm stereotaxic space using Statistical Parametric Mapping 12 and Clinical Toolbox functions (Brett et al., 2001; Rorden et al., 2012). This normalised lesion mask was then compared to the Harvard-Oxford cortical and Johns Hopkins University white matter atlases to formally quantify the anatomy impacted. EF's lesion was found to primarily impact the right temporal-occipital fusiform cortex (84.2%), occipital fusiform gyrus (79.4%), and intracalcarine cortex (79.1%). White matter tracts including the right sagittal stratum (93.0%), cingulum (76.6%), and posterior thalamic radiation (68.6%) were also significantly impacted. See Figure 4.10 and Table 4.4 for patient EF's clinical CT scan, lesion mask, and corresponding descriptive statistics.

4.3.3 Methods and Materials

Like AB and CD, patient EF completed a wide range of standardised neuropsychological and original assessments. First, EF completed the OCS Cancellation Task. Next, EF completed each

Table 4.4: Full descriptive statistics for EF's lesion mask. All ROIs are defined according to the Harvard-Oxford and Johns Hopkin's University Atlases. Fraction is the proportion of the ROI damaged, extension is the proportion of the lesion within each specific ROI. All impacted areas are within the right hemisphere. Only areas with a fraction > 5% are reported.

ROI Name	n Voxels	Fraction	Extension	Atlas
Sagittal stratum	3274	93.00%	3.10%	JHU
Occipital Fusiform Gyrus	11464	79.40%	9.20%	HAROX
Intracalcarine Cortex	8203	79.10%	6.60%	HAROX
Cingulum (hippocampus)	2059	76.60%	1.60%	JHU
Posterior thalamic radiation	5195	68.60%	3.60%	JHU
Inferior Temporal Gyrus temporooccipital part	8565	59.80%	5.20%	HAROX
Parahippocampal Gyrus posterior division	4070	56.80%	2.30%	HAROX
Lingual Gyrus	17881	56.40%	10.20%	HAROX
Temporal Fusiform Cortex, posterior division	7942	54.70%	4.40%	HAROX
Supracalcarine Cortex	2879	47.20%	1.40%	HAROX
Middle Temporal Gyrus posterior division	12695	45.70%	5.90%	HAROX
Retrolenticular part of internal capsule	3286	41.50%	1.40%	JHU
Fornix (cres) Stria terminalis	1891	35.30%	0.70%	JHU
Lateral Occipital Cortex inferior division	21026	34.80%	7.40%	HAROX
Superior Temporal Gyrus posterior division	10133	27.60%	2.80%	HAROX
Inferior Temporal Gyrus posterior division	11811	25.30%	3.00%	HAROX
Middle Temporal Gyrus temporooccipital part	11430	22.10%	2.60%	HAROX
Occipital Pole	29095	16.00%	4.70%	HAROX
Precuneous Cortex	26200	13.60%	3.60%	HAROX
Splenium of corpus callosum	15870	13.30%	2.10%	JHU
Parahippocampal Gyrus anterior division	8163	9.00%	0.70%	HAROX
Cuneal Cortex	6743	8.70%	0.60%	HAROX
Posterior corona radiata	5057	8.40%	0.40%	JHU
Cingulate Gyrus posterior division	12868	7.20%	0.90%	HAROX
Planum Polare	4361	7.10%	0.30%	HAROX
Cingulum (cingulate gyrus)	3808	7.00%	0.30%	JHU
Lateral Occipital Cortex superior division	47069	6.70%	3.20%	HAROX

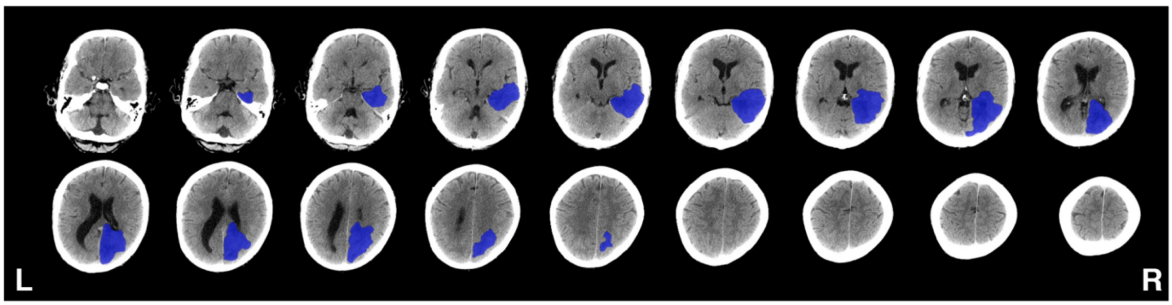


Figure 4.10: Patient EF's acute, native-space clinical CT scan and accompanying lesion mask.

of the original reading assessments described within sections 1 and 2 of this chapter. Table 4.5 provides details on the number and type of stimuli presented to EF within each of these reading tests. EF's responses to each of the reading stimuli presented in these experiments are presented in full in Appendix III.

Table 4.5: Details of the original reading assessments employed in this investigation. E.T. = Exposure Time.

Reading Tests	N	Length	E.T.
Reading Baseline			
Initial	100	3 - 9	Unlimited
Orientation Manipulations			
Vertical	60	3 - 10	Unlimited
Reflected	68	3 - 8	Unlimited
Content Manipulations			
Letter Strings	75	3 - 5	Unlimited
Attentional Manipulations			
Location	100	5	500ms
Reduced Exposure	100	3 - 9	400ms
Spacing Manipulations	100	7	Unlimited

Executive Functions Assessments:

In addition to these reading and neglect assessment, patient EF completed a number of standardised executive function assessments taken from the Hayling-Brixton Test (Bielak et al., 2006) and the Delis-Kaplan Executive Function System (DKEFS) (Delis et al., 2004). The Hayling Sentence Completion Test was used to investigate EF's ability to self-inhibit. In the first section of this standardised test, participants are instructed to listen to a series of 15 sentence fragments

and to complete the sentences with a thematically related, sensible ending (sensible completion). In the second section of this test, participants are instructed to complete 15 sentence fragments with completely unrelated endings (unconnected completion).

EF also completed the following portions of the DKEFS: Trail Making, Verbal Fluency, Design Fluency, and Colour-Word Interference subtests. Performance in all DKEFS tasks was assessed by comparing EF's performance to normative age-matched control data (Delis et al., 1983, 2004). In the Trail Making Test, the patient was asked to connect a series of numbers in ascending order then a series of letters in ascending order. Next, the patient asked to switch between these two rules to alternate between connecting a series of letters and numbers in ascending order (switching condition). The patient was allowed 5 minutes to complete each of these Trail Making tests. In the Verbal Fluency Test, the patient was given one minute name as many words as he could think of that began with a specific letters. This test was conducted three separate times with three letters (f, a, s). The patient then completed the category switching condition in which he was given one minute to name as many items as he could, alternating between the categories of fruits and furniture.

In the Design Fluency Test, the patient was shown boxes containing a mixture of filled-in and empty dots. The patient was asked to draw four lines to connect the dots in as many different ways as he could think of, while obeying a different rule in each condition. In the first condition, the patient was asked to only connect filled-in circles. In the second condition, the patient was asked to only connect empty dots. In the switching condition, the patient was asked to alternate between filled-in and empty dots within each drawing. The patient was given 60 seconds to complete each condition. In the Colour-Word Interference Test, the patient completed two baseline and one interference condition. In the first baseline, the patient was asked to name the colours of a series of colour swatches (red, green, or blue). In the second baseline, the patient was asked to read a series of colour words. Finally, in the interference condition, the patient was asked to name the ink colour of words (Stroop Task). The patient was allowed 180 seconds to complete each Colour-Word Interference condition.

Lexical and Semantic Assessment:

Next, the patient's lexical and semantic abilities were assessed using excerpts from the Psycholinguistics Assessment of Language Processing in Aphasia (PALPA) standardised neuropsychological assessment. First, the patient's comprehension of verbally presented words was assessed using the Spoken Word/Picture Matching subtest. In this test, the patient listened to a series of 40 verbally presented words and pointed to pictures which matched the meaning of each word. Next, the patient completed the Written Word/Word Matching Test in which he was asked to read a series of written words and identified each word's closest synonym from a multiple choice list. Finally, the patient completed the Regularity and Spelling Test. In this assessment, the examiner read a series of 40 words including 20 phonologically irregular words aloud and the patient was asked to spell each word from memory.

Lexical Characteristics Analysis:

Finally, the English Lexicon Project database (Balota et al., 2007) was employed to calculate lexical and semantic features of each of the word stimuli presented in this investigation's tablet-based reading assessments. This data was analysed to, first, identify lexical factors which predict the occurrence of neglect dyslexia reading errors and, second, to identify systematic differences between target and response words in cases where neglect dyslexia errors were made. This analysis included lexical/semantic variables summarising: word length, log word frequency, subtitle word frequency, orthographic neighbours, phonological neighbours, word concreteness, and semantic density.

Word length was calculated by adding the total number of letters in each presented word stimuli (lexicon mean = 8.29, range = 1-22, SD = 2.52). Word frequency was calculated based on the frequency values assigned in the hyperspace analogue to language model of lexical semantics (Burgess, 1998) with larger values representing more common words (lexicon mean = 5,636, range = 0 – 23,099,033, SD = 137,157). Given that this frequency metric produces a logarithmic score distribution, log word frequency was calculated by taking the log of the raw word frequency score (lexicon mean = 4.49, range = 0 – 17, SD = 2.89). Subtitle word frequency is an estab-

lished method for quantifying word's frequency within spoken language. This score represents each word's frequency per million words within film and television programmes (New et al., 2007) (lexicon mean = 25.23, range = 0 – 41,857, SD = 467).

Orthographic Neighbours represents the number of words which are the same length as the target word and differ by only one letter (e.g. WORD, WARD, and WORT are orthographic neighbours) (Huntsman and Lima, 2002) (lexicon mean = 1.58, range = 0-34, SD = 3.34). The Phonological Neighbours variable represents the number of words that differ by one phoneme from the target word (Luce and Pisoni, 1998) (mean = 3.43, range = 0-67, SD = 7.75). Word Concreteness represents the degree to which the semantic concept represented by a word refers to a perceptible entity (Brysbaert et al., 2014). The concreteness scores employed in this investigation are derived from Brysbaert et al. (2014) (lexicon mean = 3.11, range = 1.04 – 5, SD = 1.03). This study employs Semantic Density to represent the average proximity of semantic neighbours to each employed word within a global co-occurrence model as reported by Shaoul and Westbury (2010) (lexicon mean = 0.422, range = 0.088 – 0.724, SD = 0.155).

First, a series of 7 t-tests were used to compare the characteristics of stimuli which did and did not yield a neglect dyslexia errors across each of these metrics. Next, 7 t-tests were conducted to compare the lexical characteristics of target and response words in cases where a neglect dyslexia error was made. Given that each of these analyses include multiple comparisons, a Bonferroni correction was employed when determining significance (corrected alpha = 0.0071).

4.3.4 Results

Standardised clinical assessment data:

EF completed the OCS during acute hospitalisation in 2012. EF exhibited significant impairment in 7/11 assessed domains within this initial bedside cognitive assessment. Specifically, EF demonstrated significantly impaired performance on the picture naming, visual field, sentence reading, cancellation (egocentric), cancellation (allocentric), verbal memory, and trail making OCS subtests. Figure 4.11 provides EF's scores on each of these subtests. Notably, EF exhibited severe impairment on the Cancellation Task (total score = 5, egocentric asymmetry = 5, allocentric

asymmetry = 3). Additionally, EF demonstrated clear evidence of a left-lateralised visual field deficit on the OCS (Visual Field Test Score = 2/4).

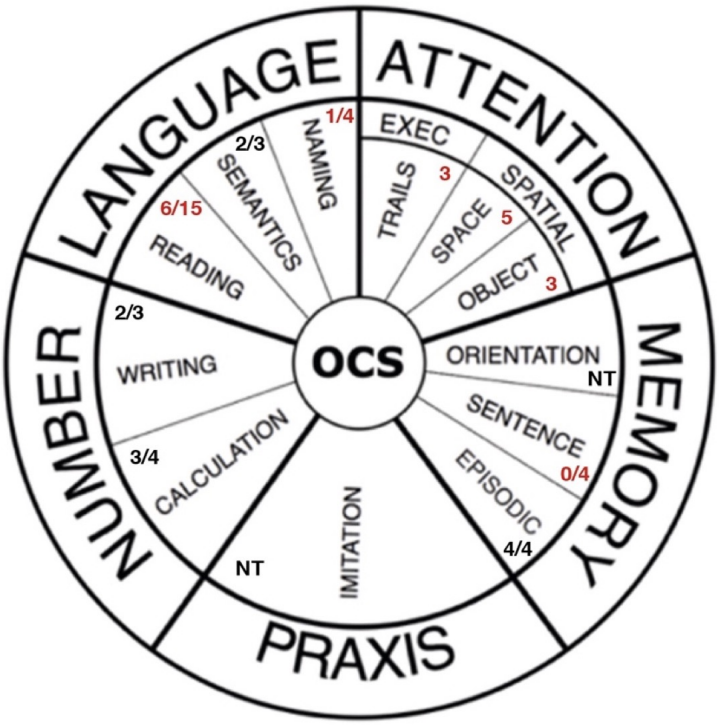


Figure 4.11: An OCS "visual snapshot" summarising EF's performance in a standard, acute cognitive assessment. Each subtest's score is listed in the relevant task subdivision. Red scores highlight impaired performance according to the normative data performance cutoffs reported by Demeyere et al. (2015).

Neglect Tests:

EF completed the OCS Hearts Cancellation Task at the beginning of each chronic testing session and was found to reliably exhibit left-lateralised visuospatial impairment. On the first testing date, EF identified 19/25 cancellation targets with and egocentric asymmetry of 15 and an allocentric asymmetry of 8. On the second testing session, EF identified 25/50 targets with an allocentric asymmetry of 3 and an egocentric asymmetry of 17 (Figure 4.12).

Reading Orientation Manipulations:

First, a series of orientation and location manipulations were conducted to determine whether EF's reading impairment operated within a egocentric, allocentric, or representation-level reference frame. EF read a series of 100 centrally presented, horizontal real words under unlimited ex-

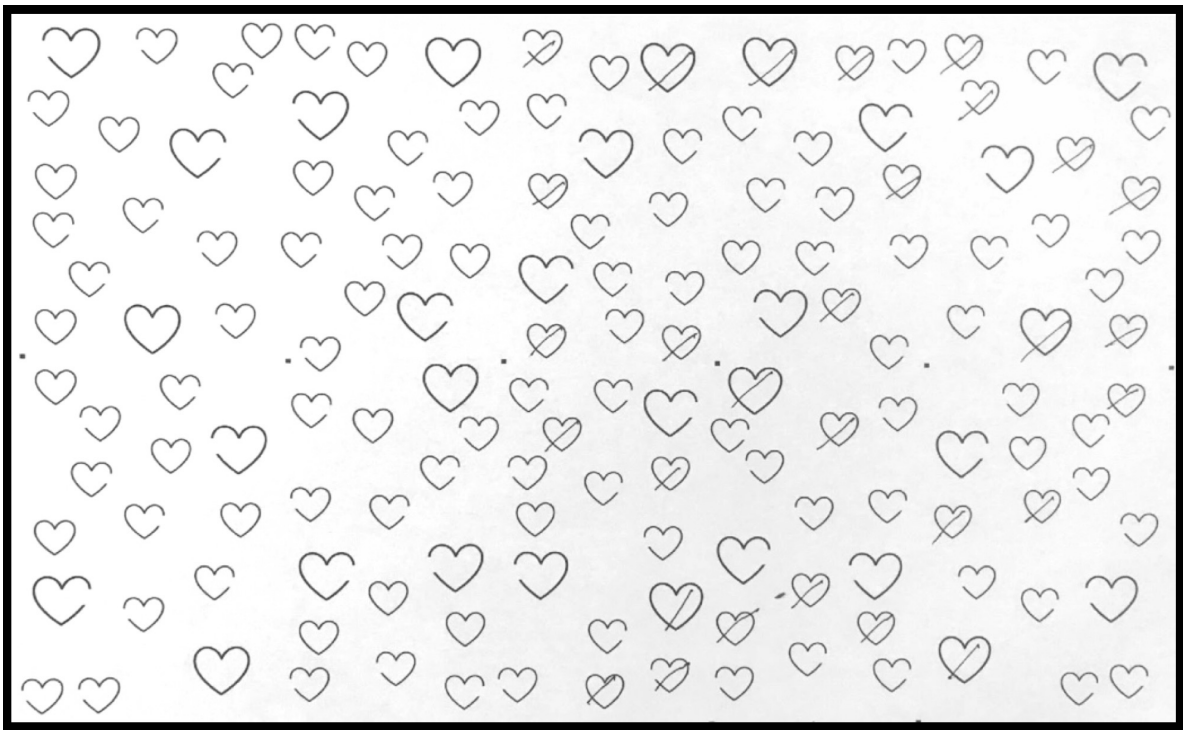


Figure 4.12: An example of EF's OCS cancellation task performance. The presented test was completed at the beginning of the second assessment session.

posure conditions. EF read 70/100 (70%) of these words correctly, with 24 right neglect dyslexia, 3 no responses, 2 unrelated, and 1 general visual reading error. For example, EF misread ADDRESSES as "address", EXCITED as "excitement", and EXAMPLE as "explain". EF read with significantly better accuracy when words were presented in the right visual field (29/50 correct) than in the left visual field (16/50 correct, $X2(1)= 6.828$, $p = 0.009$). This difference is consistent with a co-morbid left domain-general perceptual deficit. This performance was expected given EF's lesion impacted right hemisphere primary visual areas (e.g. intercalcarine sulcus) and that he exhibited clear signs of left hemianopia in acute OCS assessment. However, the proportion of neglect dyslexia reading errors was not significantly different across these two positions ($X2(1)= 0.002$, $p = 0.961$). This suggests that egocentric location mediated overall reading accuracy in EF, but this bias was not related to the occurrence of neglect dyslexia reading errors.

EF read 36/60 (60%) vertically presented words correctly and committed 1 unrelated error and 23 neglect dyslexia reading errors impacting the terminal letters of words. This lateralised er-

ror pattern is characteristic of representation-level neglect dyslexia as presenting reading stimuli vertically eliminates both egocentric and allocentric-level spatial biases. Strikingly, EF continued to commit neglect dyslexia reading errors impacting the terminal letters of stimuli when words were reflected so that these terminal portions now fell within the left visual field. EF read 14/68 (20.6%) mirror reflected words correctly, committing 29 neglect dyslexia, 10 no response, 1 unrelated, and 2 general visual errors. This impairment pattern is characteristic of right representation-level neglect dyslexia.

Serial Grapheme Identification:

Next, EF's ability to perceive individual letters within words was investigated. EF was presented with a series of 75 consonant strings and was asked to name each individual letter. EF read 73/75 letter strings with no errors, with one left-lateralised letter omission error and one right-lateralised letter visual substitution error (Q read as O).

In some cases where EF misread presented words, he was asked if he could name the individual letters within EF demonstrated a preserved ability to name all individual letters within words. However, when asked to read the word as a whole immediately after correctly naming its letters, EF consistently committed neglect dyslexia reading errors. For example, when shown the word RETIRES, EF read "retiring" and was subsequently asked to name all the letters in the stimuli. EF was able to name all letters correctly ("R-E-T-I-R-E-S"), but when immediately asked to read the word as a whole he read as "retiring". EF committed this error pattern 16 times in this investigation's real-word, unlimited exposure conditions. Anonymised audio files of these reading errors are available on the Open Science Framework (https://osf.io/vt4er/).

Reading Attentional Manipulations:

Next, a series of attentional load manipulations were conducted to investigate whether the severity of EF's neglect dyslexia was modulated by factors which have been found to modulate the severity of visuospatial neglect deficits. First, EF read a series of 100 words under reduced exposure conditions (500ms). EF was found to read 59/100 words correctly, committing 18 right

neglect dyslexia, 5 left neglect dyslexia, 4 general visual, and 14 no response errors. EF's reading accuracy in this condition was not found to be significantly different from his accuracy in unlimited exposure conditions, both in terms of total correct ($X2(1)= 2.6422$, $p = .104$) and proportion of right neglect dyslexia reading errors ($X2(1)= 0.375$, $p = 0.663$).

EF then completed a visual crowding manipulation. In this condition, EF read 50 words under normal letter-spacing condition (visual angle approximately 7 degrees) 50 words in a wide spacing condition (visual angle approximately 11.5 degrees). In the normal spacing condition, EF read 28/50 (56%) words correctly and committed 16 neglect dyslexia errors (15 right, 1 left). In the wide spacing condition. EF read 24/50 (48%) and committed 16 neglect dyslexia errors (13 right, 3 left). CD's proportion of right neglect dyslexia reading errors was not found to be significantly different between the normal and wide spaced reading condition ($X2(1) = 0.509$, $p = 0.509$). Notably, EF was found to commit a number of left neglect dyslexia reading errors within both the reduced exposure ($n = 5$) and visual crowding conditions ($n =4$). EF committed no left neglect dyslexia errors under unlimited viewing conditions, suggesting an interaction between these manipulations and EF's comorbid left domain-general visuospatial neglect. For example, EF may have been able to compensate for his left hemianopia by visual scanning under unlimited exposure conditions, but may have not been able to compensate as effectively when exposure time was reduced or viewing angle increased. However, this interaction only impacted a very small number of presented stimuli ($n = 9$).

Executive Function Assessment Results:

First, EF completed the Hayling Sentence Completion Test. EF committed no errors within the first portion (sensible completion) of this test, but was found to exhibit significant impairment within the second section (unconnected completion). In the unconnected completion test, EF provided 4 unconnected (correct), 3 directly connected, and 8 somewhat connected responses, yielding a total score of 34. According to this test's normative scoring guidelines, this score represents severe self-inhibition impairment.

Next, EF completed a number of subtests taken from the DKEFS. EF performed within the

normal range within the Verbal Fluency Task's letter fluency condition (score = 32). In the DKEFS Trail-Making Test, EF was able to accurately complete both the number-sequencing and letter-sequencing tests accurately, but exhibited significant impairment within the number-letter switching condition (Figure 4.13). Similarly, EF was found to be impaired compared to controls within the switching condition of the DKEFS design fluency test versus the non-switching conditions (scaled score = 10, contrast score = -15). In the DKEFS Colour-Word Interference Test, EF performed within the normal range for naming colour swatches (0 errors) and reading colour words (2 omission errors). However, EF was found to exhibit mild, but significant impairment (5 uncorrected errors) within the inhibition (Stroop task) condition.

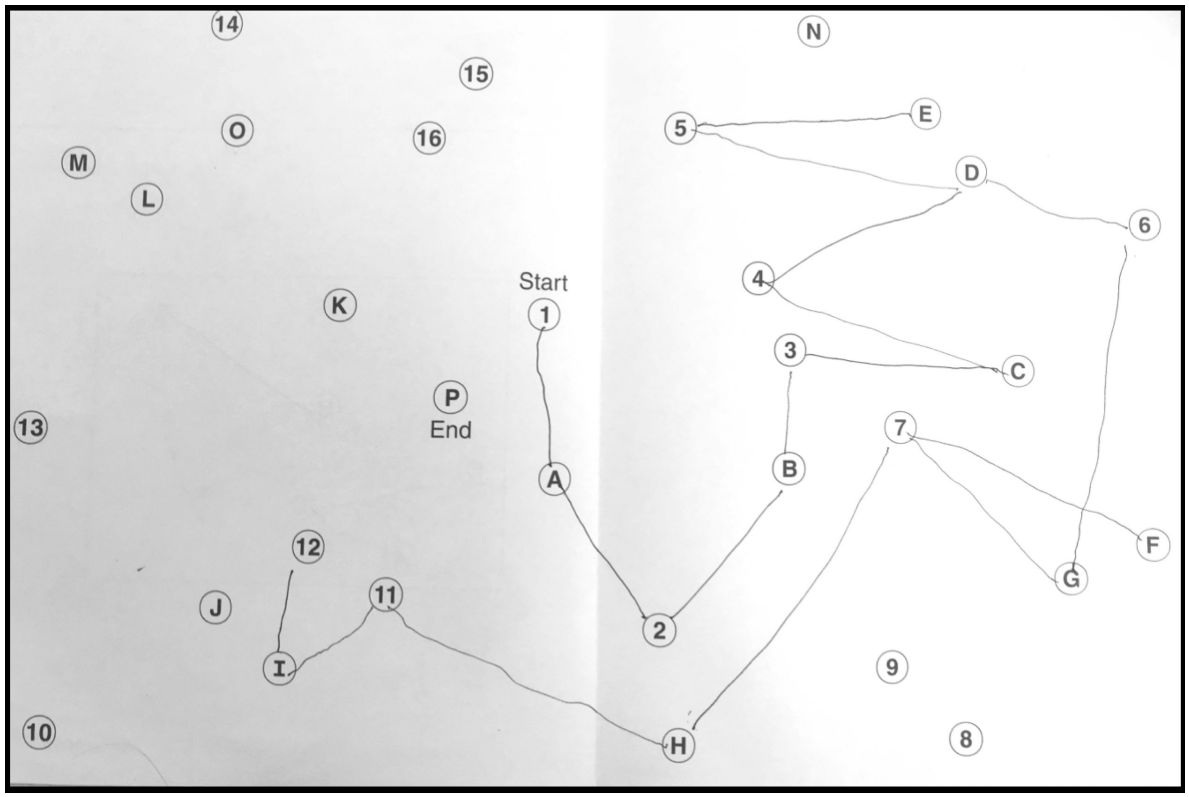


Figure 4.13: EF's performance on the DKEFS number/letter switching task.

Lexical and Semantic Assessment Results:

Next, EF completed a series of PALPA subtests. EF was found to perform within the normal range within the PALPA spoken Word/Picture matching test (score = 36/40). In this task, EF committed 3 close semantic, 1 distant semantic, and 1 visual error. In the written Word/Word

Matching PALPA subtest, EF matched 13/15 highly imaginable (no impairment) and 11/15 low imaginability (minor impairment) words correctly. All errors on these tests involved semantically similar distractors. Overall, EF's performance on this these tasks suggests an intact ability to understand the meaning of verbally presented and written words.

Finally, EF completed the PALPA Regularity and Spelling Subtest. EF exhibited clear impairment on this test, spelling only 12/40 words correctly. EF was comparatively more impaired when spelling phonologically irregular words (2/20 correct) versus regular words (10/20). Similarly, the majority of EF's spelling errors (n = 13) involved phonetic transcoding regularisations (e.g. SQUIRREL spelled as "s-q-e-r-a-l"). In this task, EF committed 7 potentially right neglect dyslexic spelling errors (e.g. CASTLE spelled as "c-a-s-t-e-r"). However, it is inherently easier to name the first letters of words than the last letters and these potentially neglect dyslexic errors make up only a small portion of EF's spelling errors. Given these findings, EF's spelling impairment seems to be more strongly modulated by phonological regularity rather than right neglect dyslexia errors.

Lexical Characteristics Analysis:

7 t-tests were then conducted to identify systematic lexical characteristic differences between word stimuli which did and did not produce neglect dyslexia reading errors. Each of these analyses employed response accuracy as a grouping variable. These analyses employed a Bonferroni correction (alpha level = 0.007) Target words which produced errors were found to have significantly greater length ($t(184.8) = -3.43$, $p < 0.001$, 95% CI = -1.22 - -0.328) than words which were read correctly. Conversely target words were read incorrectly had significantly lower frequency ($t(199.9) = 2.817$, $p = 0.005$, 95% CI = 0.196 – 1.110) and concreteness rating ($t(175.91) = 3.986$, $p < 0.001$, 95% CI = 0.271 – 0.804) as well as fewer orthographic (($t(229.91) = 2.997$, $p = 0.003$, 95% CI = 0.716 – 3.466) neighbours than words which were read correctly. Subtitle word frequency ($t(285.5) = 2.552$, $p = 0.011$, 95% CI = 43.5 – 337.0), phonological neighbours (($t(202.09) = 2.229$, $p = 0.0269$, 95% CI = 0.313 – 5.098), and semantic density ($t(166.02) = 1.709$, $p = 0.089$, 95% CI = -0.003 – 0.045) were not found to be significantly different between

words which were and were not read correctly (Figure 4.14).

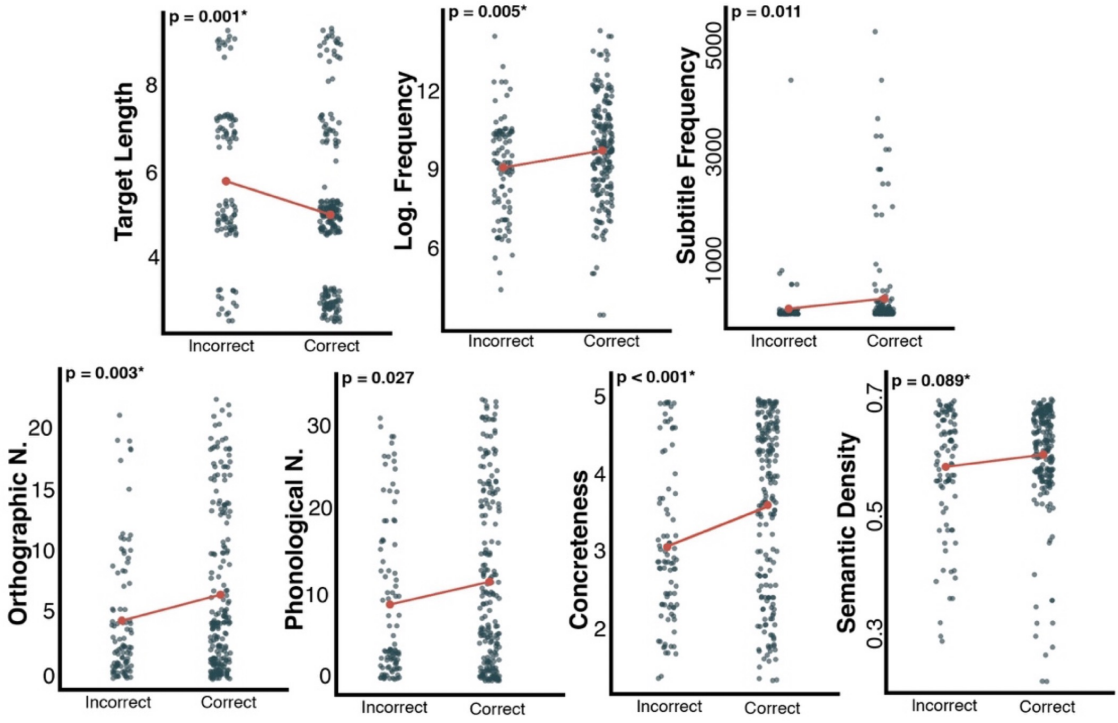


Figure 4.14: Differences in lexical characteristics between words which were read correctly and incorrectly. Comparisons surviving correction for multiple comparisons are starred. N = Neighbours. Blue points represent responses whilst red points represent group means. Red lines highlight difference in means between correct and incorrect response comparison groups.

Next, 7 additional t-tests were then conducted to identify systematic lexical characteristic differences between target and response words in cases where presented stimuli were not read correctly. These analyses included data from all incorrectly read words. Each of these analyses employed response accuracy as a grouping variable and employed a Bonferroni correction (alpha level = 0.007). Word Frequency was found to be significantly higher for response words (mean = 9.7) than target words (mean = 8.8)in cases where EF made an error ($t(216.7) = -3.499$, $p < 0.001$, 95% CI = -1.29 – -0.36). Critically, this finding indicates that EF consistently misreads targets as words which are more frequent. All other considered lexical metrics were not found to be significantly different between target and response words (Figure 4.15).

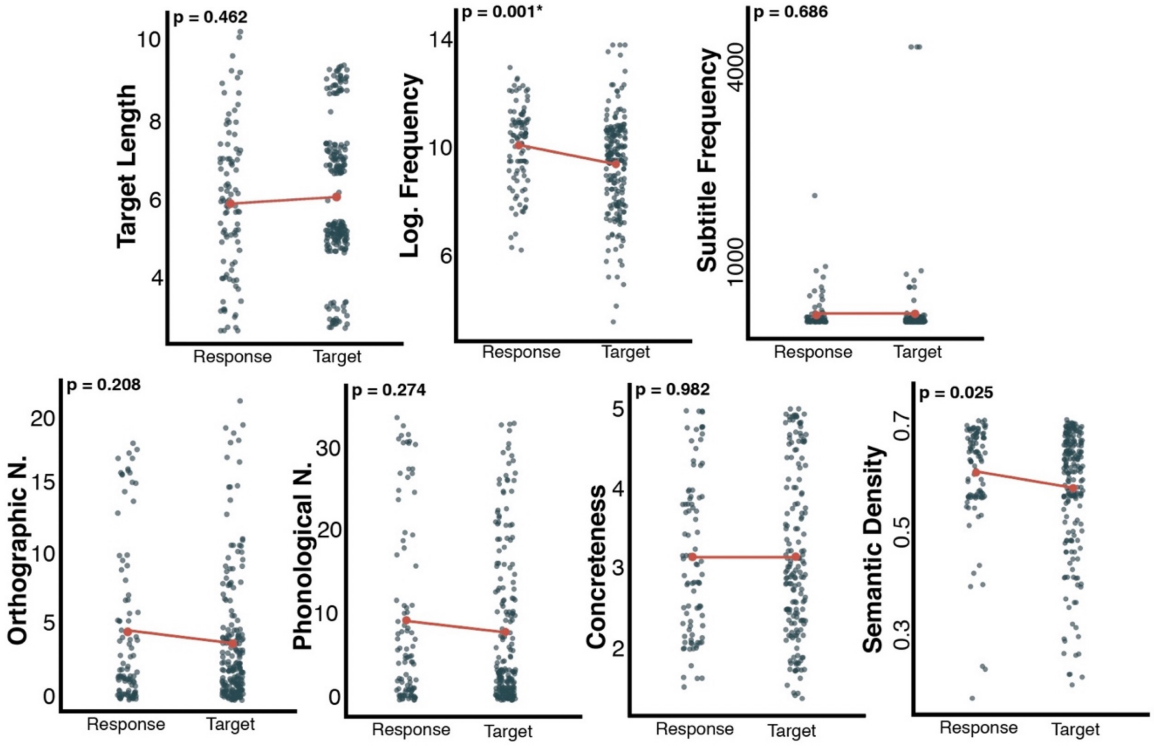


Figure 4.15: Differences in lexical characteristics between target and response words in cases where EF committed a reading error. Comparisons surviving correction for multiple comparisons are starred. N = Neighbours. Blue points represent individual words whilst red points represent group means. Red lines highlight difference in means between target and response words.

4.3.5 Discussion

The purpose of this case study was to determine the specific cognitive impairment underlying representation-level neglect dyslexia. Like patient CD, patient EF was found to exhibit right, representation-level neglect dyslexia in conjunction with left-lateralised domain-general neglect impairments and left hemianopia. EF's reading impairment cannot be accurately conceptualised as a spatial attention deficit, as it was not modulated by attentional parameters which have been reliably demonstrated to regulate the severity of visuospatial neglect deficits. However, EF exhibited a clear executive function deficit within various standardised task-switching and self-inhibition neuropsychological assessments. Taken together, the data collected in this investigation suggests that the representation-level neglect dyslexia documented within this study may be better conceptualised as an "inhibitional dyslexia" deficit rather than a component of the neglect syn-

Table 4.6: A summary of EF's performance on each of the metrics included in this case study.

Reading Tests	
Reading Baseline	
Horizontal Words	Right Neglect Dyslexia
Orientation Manipulations	
Vertical Words	Right Neglect Dyslexia
Reflected Words	Right Neglect Dyslexia
Content Manipulations	
Letter Strings	No Neglect Dyslexia
Attentional Manipulations	
Location	No Difference across Presentation Locations
Reduced Exposure	No Difference from Horizontal Performance
Spacing Manipulations	No Difference between Spacing Conditions
Serial Grapheme Identification	Intact
OCS Visuospatial Tests	
OCS Hearts Cancellation	Left Egocentirc and Allocentric Neglect
Visual Field Test	Left Hemianopia
Executive Function / Inhibition	
DKEFS Verbal Fluency	Not Impaired (non-switching conditions)
DKEFS Trail-Making	Unimpaired Sequencing, Impaired Rule-Switching
DKEFS Design Fluency	Impaired on Switching but not Non-Switching Trials
DKEFS Stroop	Mild Impairment on Inhibition Condition
Hayling-Brixton Inhibition	Severe Inhibition Impairment
Semantic / Lexical Tests	
PALPA Spoken Word/Picture Matching	Unimpaired
PALPA Written Word/Word Matching	Unimpaired
PALPA Regularity and Spelling	Impaired (Worse on Irregular Words)
Lexical Factors (Target vs. Responses)	Response Words more Frequent than Targets

drome.

EF's behavioural phenotype was largely analogous to the behavioural pattern documented within patient CD. Both patients exhibited representation-level neglect dyslexia in conjunction with oppositely lateralised visuospatial neglect. EF also demonstrated significant early visual processing impairment in the form of left-lateralised hemianopia. Both patients were able to reliably name individual letters as a whole, but committed neglect dyslexia errors when subsequently asked to read presented words as a whole. Importantly, both CD and EF's impairment severity was not found to be modulated by attentional parameters which impact the severity of spatial attention deficits. These findings strongly suggest that like CD, patient EF's reading impairment cannot be explained as a side-effect of visuospatial neglect. Therefore, the majority of assessments included in this investigation were selected to explore alternate explanations for EF's reading impairment.

First, EF completed a series of standardised tasks aiming to investigate his lexical and semantic abilities. These tests were included in order to confirm whether EF was reliably able to read and understand written content. EF demonstrated an intact comprehension of verbally and visually presented words. EF exhibited an impaired ability to spell auditory words. However, this performance was not consistently lateralised. EF committed spelling errors impacting both the terminal and initial letters of words. Notably, EF's spelling errors consisted mostly of phonological regularisations (e.g. GHOST spelled as "g-o-s-t-") rather than lateralised omissions. This error pattern is qualitatively different than the spelling pattern reported for patient NG, who was found to commit consistently lateralised neglect dyslexia errors when spelling as well as when reading written words (Caramazza and Hillis, 1990). However, this previous study does not take into account that it is inherently easier to spell initial letters of words rather than the terminal letters (Jackson and Coltheart, 2013). This is due to the fact that the probability of committing a letter addition or omission error when spelling increases as the number of letters named increased. It is also inherently easier to name the first letter in words than it is to name the last letter. For example, patient EF misspelled the word ELEPHANT as "e-l-f-u-n-t". Technically, this error could be considered to be a right neglect dyslexia errors as all letters to the right of a "neglect point" do not match the target letters. A portion of this misalignment was due to the early omission of an e, coupled with

a phonetic regularisation of “p-h” to “f”. However, this error is more accurately summarised as a phonetic regularisation error. A similarly detailed analysis of NG’s specific spelling errors is not presented, suggesting that additional analysis is needed to confirm that NG’s spelling pattern is best understood as a neglect deficit.

Notably, EF’s tendency to commit phonetic regularisation errors when spelling strongly suggests that EF exhibits difficulty accessing orthographic representations of words (Jackson and Coltheart, 2013). Orthographic representations of words are accessed through the lexical route to reading (Jackson and Coltheart, 2013). Phonetic regularisation errors are committed when patients do not read through this lexical route, but instead rely upon stored grapheme-phoneme correspondence rules when reading aloud (Jackson and Coltheart, 2013). This non-lexical reading is a serial rather than a parallel process, and is not normally relied upon by healthy readers encountering known words (Jackson and Coltheart, 2013). This observation is important to consider in the context of EF’s reading impairment pattern.

EF was found to be able to name each individual letter within presented words, but reliably committed neglect dyslexia reading errors when subsequently asked to read the presented word as a whole. This pattern exhibits a selective deficit of parallel processing in reading, with an intact ability to serially process graphemes (Ellis and Young, 2013; Jackson and Coltheart, 2013; Shallice, 1988). This finding suggests that EF’s non-lexical route to reading is largely intact, but that errors occur while attempting to process words as a whole. The process of individually naming individual letters does not require patients to inhibit prepotent responses (Ellis and Young, 2013; Jackson and Coltheart, 2013). However, when reading words as a whole patients must serially process letters, accumulating evidence and inhibiting pre-potent responses based on incomplete data in order to give a correct response. A selective deficit impacting “reading words as whole” could be caused by an underlying inability to inhibit prepotent responses associated with the first-perceived letters, resulting in reading based on incomplete visual information. Further evidence for this possibility is provided by considering EF’s performance on the standardised executive function tasks within this investigation.

A range of lexical and semantic factors were found to significantly differ across words which

EF read correctly and incorrectly. Words which were misread had more letters, lower frequency, lower concreteness, and fewer orthographic neighbours than words which were read correctly. This finding likely represents a general "difficulty" effect in which words that are more challenging to read were more likely to be misread. Subtitle word frequency, number of phonological neighbours, and semantic density were not found to be significantly different between words which were read correctly and incorrectly. Critically, in cases where EF committed a reading error, he was found to systematically produce a response word which with a higher frequency score than the presented target word. No other investigated lexical characteristic was found to be significantly different between EF's target and response words. This error pattern is in line with an the characterisation of EF's impairment as a self-inhibition deficit, as it may represent an inability in inhibit more frequent and therefore comparatively pre-potent reading responses.

EF completed a variety of standardised executive function assessments revealing selective task-switching and self-inhibition deficits. EF demonstrated an intact ability to complete number/letter-sequencing tests, but presented with significant impairment within task-switching variation of this task. Similarly, EF exhibited selective impairment within the design fluency test's rule switching condition. This pattern is characteristic of a patient with set-switching impairment (Diamond, 2013; Jurado and Rosselli, 2007). EF also demonstrated a self-inhibition deficit within the DKEFS Colour-Word interference and Hayling sentence completion tasks. In the Colour-Word Interference Task, EF performed within the normal range for naming colour swatches and reading colour words but demonstrated significant impairment within the inhibition condition. In the Hayling, EF committed no errors within the sensible completion but was found to exhibit severe impairment within the unconnected completion test. EF's qualitative failure within these tasks provides strong evidence of an inability to inhibit pre-potent responses.

It is possible that this inhibitional impairment is responsible for EF's reading errors. Successful mapping of visual word forms to orthographic representations requires participants to inhibit pre-potent responses. For example, reading the word COVEN aloud requires a reader to inhibit visually similar, but more frequent orthographic neighbours including OVEN and COVE in order to correctly read the word (Balota et al., 2007). Given that EF exhibits a clear inhibition deficit,

it is plausible that he struggles to inhibit visually similar orthographic neighbours of target words. However, this inhibition deficit alone cannot account for the consistent lateralisation of EF's errors. EF's reading pattern suggests that he employs a serial, rather than parallel reading strategy. In a serial strategy, the initial letters of words are the first to be processed and mapped to orthographic representations. It is possible that this abnormal serial processing may interact with EF's inhibition deficit to produce consistently lateralised reading errors. The initial letters of many words may be common across a number of orthographic neighbours, meaning that readers have to inhibit inaccurate mappings to initial letter orthographic neighbours in order to serially read words (Jackson and Coltheart, 2013). It is therefore plausible that EF is unable to inhibit incorrect lexical mappings based on partial visual information, yielding apparent representation-level neglect dyslexia. This explanation can account for many of the behavioural patterns observed within representational neglect dyslexia. First, this inhibitional dyslexia deficit should be insensitive to topographical manipulations. If responses are based on the first letters perceived, error patterns would not be expected to change based on stimulus orientation. Second, this account would help explain why representation-level neglect dyslexia patients have been found to misread stimulus words as more familiar response words. A tendency to misread less familiar words as more familiar words could very likely be a behavioural symptom of a general inability to inhibit pre-potent responses (Jackson and Coltheart, 2013). Third, conceptualising representational-neglect dyslexia as an inhibitional deficit could help account for why this condition has been found to differentially impact lexical and non-lexical stimuli. Some patient with neglect dyslexia have been found to exhibit qualitatively different error patterns when reading real words and pronounceable pseudowords (see Chapter 4, Sections 1-2). This heterogeneity could be explained by the comparative dearth of a visually similar pre-potent response for many pseudowords.

Taken together, the data presented in this case study strongly suggests that at least some cases of representation-level neglect dyslexia may be better understood as "inhibitional dyslexia" rather than a component of the neglect syndrome. However, additional research is needed to confirm this hypothesis. Its is unclear whether EF's error pattern is representative of all patients with representation-level neglect dyslexia. It is possible that apparent representation-level neglect

dyslexia is a common behavioural symptom of multiple underlying causes. For example, a subset of neglect dyslexia patients may exhibit behavioural patterns which match the predictions of Hillis and Caramazza's (1995) model, while others may not. For this reason, future research should conduct standardised assessments of groups of representation-level neglect dyslexia patients in order to facilitate conclusions pertaining to the disorder as a whole and more clearly define potential behavioural subtypes.

Limitations:

The findings of this investigation illustrate a clear co-morbidity between self-inhibition impairment and representation-level neglect dyslexia. However, additional research is needed to confirm the causal link between these impairments. Future research can aim to design experimental paradigms which determine the degree to which pre-potent reading responses can be successfully inhibited in controls, patients with neglect, and patients with suspected inhibitional dyslexia.

Conclusions:

Overall, the data presented within this section strongly suggests that at least some cases of representation-level neglect dyslexia should not be conceptualised as a component of the neglect syndrome, but instead represents an independent, inhibitional deficit. Additional research is needed to confirm the causal link between domain-general inhibitional impairments and potential inhibitional dyslexia error patterns.

Table 4.7: A general summary of domain-general visuospatial abilities and reading assessment performance for the single case studies reported in this chapter. TIA = Transient Ischemic Attack, MCA = Middle Cerebral Artery, PCA = Posterior Cerebral Artery, Ego = Egocentric Neglect, Allo = Allocentric Neglect, R = Right, L = Left, ND = Neglect Dyslexia, - = Not Tested, No Dif. = no statistically significant difference in the prevalence of neglect dyslexia errors between the condition and the relevant comparison condition. Letter Naming refers to the behavioural pattern of successfully naming all letters in a presented word then subsequently committing a neglect dyslexia error.

	Domain-General				Reading Assessments							
Patient	**Stroke**	**Ego.**	**Allo.**	**VFD**	**Horizontal**	**Vertical**	**Reflected**	**String/Number**	**Location**	**Reduced**	**Spaced**	**Letter Naming**
AB	TIA	None	None	None	R ND	R ND	R ND	No ND	-	-	-	-
CD	R MCA	L	L	-	R ND	R ND	R ND	No ND	No Dif.	No Dif.	No Dif.	Yes
EF	R PCA	L	L	L	R ND	R ND	R ND	No ND	No Dif.	No Dif.	No Dif.	Yes

4.4 Future Directions: Confirming Inhibitional Dyslexia

The case study of patient EF provides strong evidence that representation-level neglect dyslexia co-occurred with a deficit in self-inhibition. Importantly, this evidence is purely correlational and additional research is needed to establish a causal link between underlying inhibition deficits and apparent representation-level reading errors. Future experiments could aim to establish this causal link by designing a novel reading task designed to pit semantic priming against visual word form information. For example, patients with neglect dyslexia could be asked to read a series of simple sentences within four semantic conditions: congruent, incongruent, right incongruent, and left incongruent (Figure 4.16). Congruent sentences will contain a final, critical word which is semantically similar to the rest of the sentence. Incongruent trials contain a critical stimulus which is semantically and visually unrelated to a reasonable response. Right incongruent trials contain semantically unrelated critical stimuli which are visually similar to the initial, but not terminal letters of a semantically appropriate response. Similarly, left incongruent trials contain stimuli which are semantically unrelated, but contain identical initial letters to a semantically appropriate response.

This paradigm should be tested on healthy aging controls and patients with suspected inhibition dyslexia. A patient with inhibition dyslexia would be expected to perform similarly to controls within the semantically similar trials and worse than controls within all other trials. More specifically, patients with inhibitional dyslexia would be expected to commit a higher proportion of errors in cases which involved semantically incongruent critical words with visually similar initial letters due to the combined semantic priming of the sentence and visual priming of the initially perceived letters. This effect should be less pronounced in cases where semantically incongruent words have visually similar terminal letters. This paradigm could also be used to compare reading patterns between patients with domain-general allocentric neglect and inhibitional dyslexia. Patients with a pure spatial attention deficit would be expected to commit some level of neglect dyslexia errors, but the frequency of these errors should not be as strongly modulated by semantic incongruency as in patients with inhibitional dyslexia. In summary incongruent semantic priming would be expected to reduce reading accuracy within all participants, but the magnitude of this effect

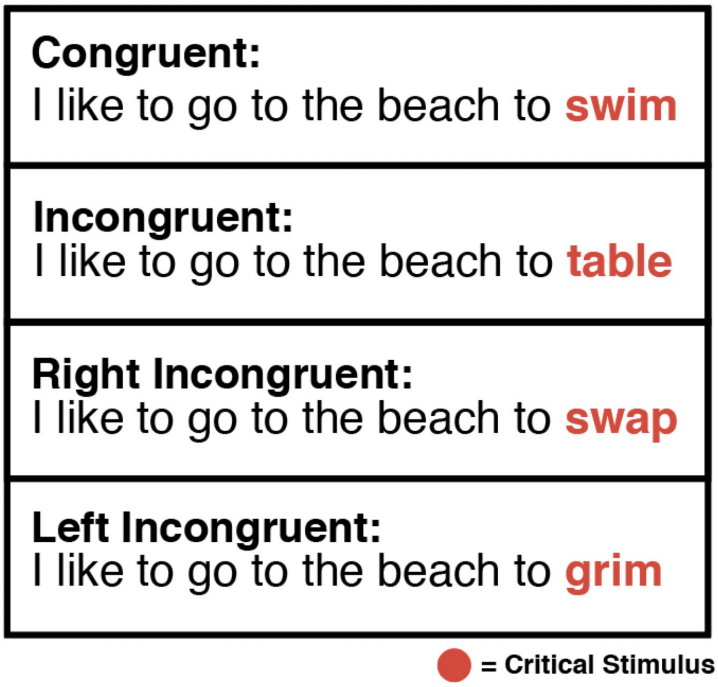


Figure 4.16: A visualisation of the various conditions within the proposed semantic/visual priming reading paradigm.

should be stronger within patients with an inhibition deficit.

The case study data presented within this chapter presents strong evidence that representation-level neglect dyslexia cannot be characterised as a direct consequence of visuospatial neglect impairment within Hillis and Caramazza's (1995) proposed representational spatial reference frame. This finding demonstrates potential weaknesses within Hillis and Caramazza's (1995) three-tier model of neglect. Mainly, these findings suggest that it is plausible Hillis and Caramazza's (1995) proposed third, representational level of neglect impairment may not exist as neglect dyslexia errors which impact this frame of reference may be better explained by impairments unrelated to spatial attention. However, additional research is needed to investigate this possibility more thoroughly.

One of the key predictions of Hillis and Caramazza's (1995) model is that the three-tier reference frame system supports perception of all stimuli, regardless of stimuli content. This claim implies that representational-level neglect errors should be able to impact non-orthographic as well as orthographic stimuli. Previous research which has aimed to document representational

neglect errors within non-orthographic stimuli has been largely confounded by a reliance on stimuli which are not linked to existing, orientation canonical spatial representations (Cubelli and Speri, 2001; Savazzi, 2003). Similarly, research which has investigated neglect imagined spatial scenes has succeeded in identifying representational neglect which occurs with respect to imagined viewpoint (Bisiach and Luzzatti, 1978), but has not identified the orientation-insensitive pattern of representational neglect predicted by Hillis and Caramazza (1995). Additional research is needed to confirm whether or not Hillis and Caramazza's (1995) theorised pattern of rotation-insensitive representational neglect can occur within non-orthographic stimuli.

Future investigations can aim to design novel, behavioural paradigms which can reliably distinguish between neglect occurring within each of Hillis and Caramazza's (1995) three proposed reference frames. For example, a variation of the OCS Cancellation Task could be employed to detect egocentric, allocentric, and representation-level neglect within stoke survivors. In this task, heart stimuli could be presented in various orientations (Figure 4.17). In this task, egocentric neglect impairment can be defined as a significant difference in the proportion of stimuli correctly identified within the right and left side of the search matrix Similarly, allocentric neglect could be defined as a significant difference in the proportion of correct responses in cases where heart gaps were presented on the perceived left and right side of stimulus. Finally, representational level neglect can be defined as a significant difference in the proportion of correct responses in cases where gaps were present within the stimuli's canonical left and right side (Figure 4.18). In line with Hillis and Caramazza's (1995) theory, these impairment definitions allow for patients to exhibit impairment within multiple reference frames simultaneously. This novel paradigm can be employed to investigate whether Hillis and Caramazza's (1995) theorised pattern of rotation-insensitive representational neglect can occur within non-orthographic stimuli.

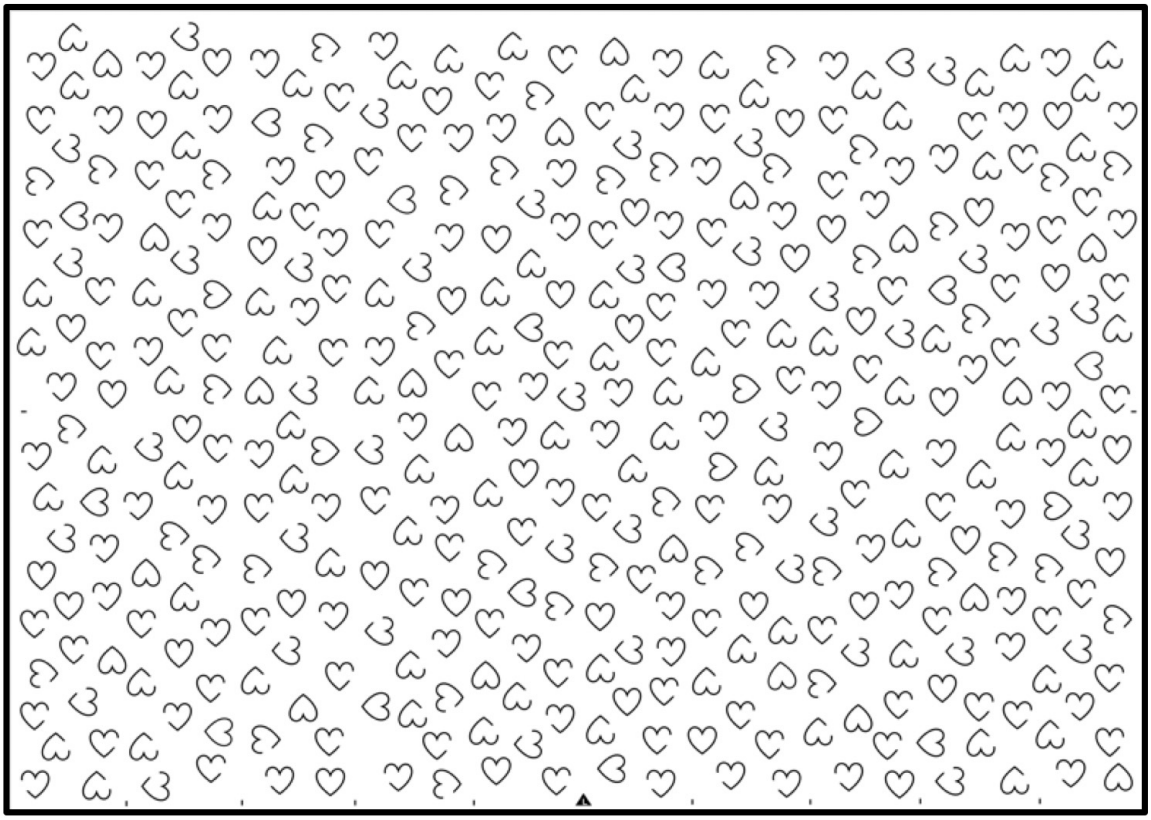


Figure 4.17: A novel cancellation task designed to detect representation-level neglect deficits within non-orthographic stimuli.

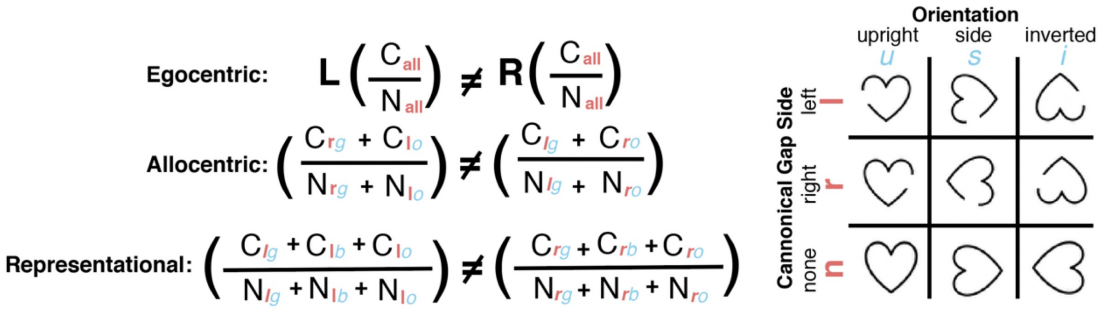


Figure 4.18: The equations used to define neglect impairment within each of Hillis and Caramazza (1995) proposed reference frames. Number of correct answers is represented by "C" whilst number of stimuli presented is denoted by "N". Subscripts denote which type of stimuli are counted within each summary statistic. Upper case letters denote whether targets are presented on the left or right (L/R) side of the stimulus display.

4.5 General Conclusion

The data and analyses presented within this chapter highlight several potential weaknesses within Hillis and Caramazza's (1995) thee-tier theory of visuospatial neglect. First, representation-level errors in orthographic stimuli were found to occur independently of representation-level neglect impairment within non-orthographic stimuli. Second, the severity of representation-level neglect was not found to be modulated by factors which have been reliably shown to modulate the severity of neglect deficits. Third, the specific behavioural profile associated with representation-level error within orthographic stimuli seems to be better accounted for as an inhibition deficit rather than a spatial attentional impairment. Considered cumulatively, these findings suggest that Hillis and Caramazza's (1995) three-tier theory of neglect should be revisited and revised.

5 Chapter 5.0: The Neural Correlates of Visuospatial Neglect

Author's Note:

In line with standard CRediT author roles (Brand et al., 2015), I was responsible for Methodology, Software, Formal Analysis, Investigation, Resources, Data Curation, Writing -Original Draft, Writing – Reviewing and Editing, and Visualisation for the project reported within this chapter. This study is currently under review at Neuropsycholgia under the title "Right- and Left-Lateralised Neglect are not Anatomically Homologous: A Voxel-Lesion Symptom Mapping Study" and is available as a pre-print (DOI: 10.31234/osf.io/4kyf8).

5.0 General Introduction

Visuospatial neglect is most commonly characterised as a left-lateralised spatial attentional deficit which occurs following damage to right hemisphere temporo-parietal areas (Chechlacz et al., 2012; Parton et al., 2004). Although visuospatial neglect is typically considered more severe and long lasting following right hemisphere lesions, visuospatial neglect also occurs frequently following left hemisphere damage (Demeyere and Gillebert, 2019; Stone et al., 1992; Stone et al., 1993; Suchan and Karnath, 2011; Ten Brink et al., 2017). For example, Demeyere and Gillebert (2019) conducted standardised neglect testing in a large, representative acute stroke cohort and found and right-lateralised visuospatial neglect incidence of 35% of participants. In addition, neglect is a highly heterogeneous condition and can selectively impact egocentric or allocentric reference frames (Binder et al., 1992; Demeyere and Gillebert, 2019; Stone et al., 1992; Ten Brink et al., 2017). It is necesary to acknowledge this behavioural heterogeneity when investigating the neural correlates of the neglect syndrome in order to gain a more detailed understanding of the anatomy of spatial attention.

Previous studies have primarily focused on identifying the neural correlates of left-lateralised egocentric neglect in patients with right hemisphere damage. Left egocentric neglect has been shown to be associated with structural damage to right hemisphere regions surrounding the sylvian fissure, such as the temporoparietal junction and right superior temporal gyrus (Chechlacz et al., 2010, 2012; Hillis, 2005; Karnath et al., 2004; Molenberghs et al., 2012; Mort et al., 2003; Vossel et al., 2011) though a wide range of lesion patterns have been implicated. For example, Mort and colleagues (2003) suggested that damage to the right angular gyrus and parahippocampal region was critical, and Bird et al (2006) additionally found that the white matter ROIs connecting these areas were implicated in neglect. Karnath et al., (2002) found that damage to subcortical structures including the right putamen, pulvinar, and caudate nucleus was associated with left egocentric neglect impairment. In addition, visuospatial neglect has also been found in a number of patients with damage confined to the cerebellum (Hildebrandt et al., 2002; Kim et al., 2008; Silveri, 2001). This heterogeneity in results has led to the hypothesis that visuospatial neglect represents a disconnection syndrome (Bartolomeo et al., 2007) and this claim has been supported

by studies linking left visuospatial neglect to damage to the right superior longitudinal (He et al., 2007; de Schotten et al., 2008), inferior longitudinal (Bird, 2006), and inferior fronto-occipital fasciculi (Urbanski et al., 2008). A portion of the varied findings may also be explained by differential study populations, lesion coverage, neglect tests used and time between stroke and test. In addition, treating visuospatial neglect as a heterogenous syndrome rather than a unitary behavioural deficit may help disentangle some of these findings.

Previous lesion mapping investigations which have considered egocentric and allocentric neglect as independent constructs have consistently identified distinct neural correlates associated with each of these deficits (Chechlacz et al., 2010, 2012; Medina et al., 2008; Ptak et al., 2012). Medina et al. (2008) found that left egocentric neglect was associated with hypoperfusion within right hemisphere dorsal stream areas (e.g. the supramarginal gyrus) while allocentric impairment was associated with damage to areas of the ventral visual processing stream (e.g. the posterior inferior temporal gyrus). Similarly, Hillis et al. (2005) found that damage to the right superior temporal gyrus was implicated in allocentric neglect while damage to the right angular gyrus was predictive of egocentric neglect impairment. Chechlacz et al. (2012) conducted an anatomical likelihood estimate meta-analysis of 1306 neglect patients from 32 different lesion-symptom mapping studies which concluded that egocentric symptoms are associated with damage to the perisylvian network (e.g. pre- and postcentral, supramarginal, and superior temporal gyri) while allocentric symptoms are associated with more posterior lesions impacting the angular, middle temporal, and middle occipital gyri. These findings support the characterisation of neglect as a cluster of distinct impairments rather than a unitary syndrome. However, these investigations focused exclusively on patients with left neglect following right hemisphere damage.

Few previous studies have investigated the neural correlates of visuospatial neglect following left hemisphere lesions. Suchan and Karnath (2011) conducted a lesion-symptom mapping analysis investigating the neural correlates of neglect following left hemisphere lesions. This investigation identified 11 patients with neglect and found that it was most strongly associated with damage to voxels within the left superior and middle temporal gyri, inferior parietal lobule, and insular cortex (Suchan and Karnath, 2011). Similarly, Beume et al. (2017) found that damage to

the left superior and middle temporal gyrus, temporal pole, frontal operculum, and insula were the strongest predictors of right egocentric neglect within a cohort of 121 left hemisphere patients (21 with neglect). Additional studies have aimed to investigate the neural correlates of right egocentric neglect following left-hemisphere lesions, but these studies have employed categorical lesion comparisons (e.g. vascular territory, stroke severity) instead of more detailed voxel-wise analyses (Beis et al., 2004; Maeshima et al., 1992; Ogden, 1985; Ringman et al., 2004). Notably, no previous investigation has identified a statistically significant relationship between any brain area and allocentric neglect impairment. Kleinman et al. (2007) investigated the anatomy of right allocentric neglect following left hemisphere damage. This study found that 2 of the 3 included patients exhibiting allocentric neglect in the absence of egocentric neglect had damage to Brodmann's areas 18, 19, and 37 in a descriptive overlay analysis (Kleinman et al, 2007).

Suchan and Karnath (2011) propose that neglect occurs following damage to left hemisphere homologues to right-hemisphere spatial orienting areas. According to this theory, representation of spatial orienting in left hemisphere areas is thought to be a subdominant remnant of more primitive neural structure in humans. However, it is not yet clear whether this is an accurate characterisation of right neglect. Previous research has suggested that at least a portion of right-lateralised egocentric neglect cases occur following ipsilesional right hemisphere lesions (Agrell et al., 1997; Kim et al., 1999; Kwon et al., 2012; Weintraub and Mesulam, 1987; Williamson et al., 2018). For example, Kim et al. (1999) assessed 30 right hemisphere stroke survivors on a line bisection task and identified 5 patients exhibiting ipsilesional (right) egocentric neglect deficits. This ipsilesional neglect could not be explained as a compensatory strategy, as these patients did not initially present with contralesional neglect impairment (Kim et al., 1999). Patients with ipsilesional neglect were found to have damage to right hemisphere fronto-subcortical circuits, suggesting that the right hemisphere may play a role in maintaining attention to ipsilesional hemispace. This finding is in line with the current understanding that the right hemisphere plays a role in distributing attention across both the right and left visual fields while the left hemisphere solely attends to contralesional hemispace (de Schotten et al., 2011; Weintraub and Mesulam, 1987). However, it is not yet clear what implications this finding has concerning the overall anatomy of right egocentric

neglect.

Most previous research investigating either right or left visuospatial neglect has systematically excluded patients exhibiting ipsilesional deficits and have only analysed the implicated anatomy within a single hemisphere. Given that at least some cases of neglect have been found to ipsilesional, we suggest that is important to account for this heterogeneity by considering the full brain in lesion symptom mapping analyses within an unbiased cohort. The purpose of the present investigation is thus to conduct whole-brain voxel-based lesion symptom mapping analyses to identify the distinct neural correlates of left and right egocentric and allocentric neglect. Notably, the present investigation is the single largest whole brain lesion-mapping study to be conducted on visuospatial neglect as well as being the first to investigate the neural correlates of right allocentric neglect. Alongside conducting data-driven VLSM analyses, this study aims to investigate whether right-lateralised neglect is subserved by left hemisphere homologues of regions critical for left-lateralised neglect following right hemisphere damage.

5.1 Methods

Participants:

This investigation considered existing data from a cohort of acute stroke survivors recruited as a component of the OCS-Tablet, OCS-Recovery, and OCS-Care studies (NHS REC reference 14/LO/0648, 18/SC/0550, and 12/WM/00335) (Demeyere et al., 2015, 2019). These studies recruited and examined a continuous sample of stroke survivors in 38 hospitals throughout the United Kingdom. Each included study employed limited exclusion criteria to only exclude patients who would not be able to concentrate for 10 minutes as judged by the multidisciplinary team. The OCS was specifically designed to be inclusive for patients with aphasia (see Demeyere et al 2016; Mancuso et al., 2018). Patients with severe deficits in understanding task instructions however would still not have been able to complete the task and so indeed will not have been included in the present study. All participants provided informed consent in accordance with the Declaration of Helsinki. Participants were included in this investigation if they had a confirmed diagnosis of acute stroke, were able to remain alert for 20 minutes, were at least 18 years of

age, and were able to provide informed consent. Participants were not pre-selected based on behavioural pathology or lesion location.

641 patients met initial inclusion criteria. Patients with no acute routine clinical imaging (n = 40) or acute OCS data (n = 26) were excluded. All patients with evidence of previous strokes (n = 99) or with total scores of less than 5 on the OCS Cancellation task (n = 21) were also excluded. Finally, 9 patients who exhibited comorbid right and left neglect deficits (e.g. right egocentric and left allocentric neglect) were excluded. All patients classed as "bilateral" exhibit evidence of a single, spatially-contiguous lesion which partially crosses the midline. These patients are explicitly included in this investigation, as excluding patients with these damage patterns would preclude the identification of any significant neural correlates within similar regions which are most frequently impacted by strokes which cross the anatomical midline. For example, many pontine and large cerebellar strokes cross the midline due to the vascular anatomy of these regions. For this reason, patients were not pre-selected based on stroke location.

A total of 446 patients (average age = 71.5 (sd = 13.1), 44.5% female, 9.1% left handed) met all inclusion criteria for this investigation. This sample included 345 ischemic and 101 haemorrhagic stroke patients (224 R, 191 L, 31 Bilateral). The average stroke-test interval was 5.85 days (sd = 5.99) with 76.8% of patients completing behavioural testing within the first week following stroke. Similarly, the average stroke-scan interval was 1.67 days (sd = 3.73) with 93.9% of patients completing their relevant clinical scan within the first week following stroke. See Table 5.1 for a detailed breakdown of patient clinical characteristics.

Table 5.1: A breakdown of the clinical characteristics of patients within each VLSM analysis group. Test Date reports the interval between stroke and behavioural testing in days. Scan Date reports the interval between stroke and neuroimaging data collection in days. Lesion sizes are reported in cm3. Standard deviations are provided in parentheses. L = Left, R = Right, B = Bilateral, Ego = Egocentric, Allo = Allocentric.

	Demographics						Lesion Details				Behaviour		
	N	Age	Female	L Handed	Test Data	Scan Date	Size	L	R	B	Total	Ego Score	Allo Score
Left Ego	58	72.9 (11.6)	55.2%	15.4%	6.2 (6.5)	1.4 (3.24)	5.9 (5.8)	6	48	4	26.8 (11.4)	0.72 (0.56)	0 (0.03)
Left Allo	27	72.0 (13.8)	48.1%	10.5%	4.5 (6.2)	2.6 (4.0)	5.5 (7.2)	8	17	2	32.4 (14.5)	0 (0.1)	0.2 (0.2)
Left Ego & Allo	42	74.5 (10.9)	38.1%	0.0%	5.6 (5.7)	1.4 (2.3)	10.9 (11.1)	2	39	1	17.4 (11.3)	1.30 (0.63)	0.48 (.30)
Right Ego	31	72.5 (10.6)	51.6%	13.3%	5.9 (5.7)	1.1 (1.7)	3.39 (43.2)	22	8	1	31.8 (10.4)	-0.50 (0.12)	0.02 (0.04)
Right Allo	28	73.6 (13.7)	46.4%	18.8%	5.4 (4.2)	3.2 (5.1)	5.93 (9.02)	19	7	2	36.4 (13.6)	-0.03 (0.12)	-0.11 (0.09)
Right Ego & Allo	11	78.7 (7.3)	63.6%	0.0%	5.1 (5.4)	2.4 (3.0)	4.3 (7.1)	5	4	2	24.0 (10.6)	-0.91 (0.63)	-0.21 (0.12)
No Neglect	249	69.8 (14.0)	40.0%	8.3%	6.0 (6.1)	1.6 (4.1)	3.0 (4.5)	101	129	19	40.6 (10.6)	0.00 (0.11)	0.00 (0.03)

Behavioural Data:

Data from the OCS Hearts Cancellation Task was considered in this investigation. The Hearts Cancellation Task is a standard neuropsychological assessment designed to detect and differentiate between egocentric and visuospatial neglect impairments (Figure 5.1). This test has been demonstrated to be highly sensitive to neglect impairment (94.12%, versus the Behavioural Inattention Test Star Cancellation – Demeyere et al., 2015). In this task, patients are presented with line drawings of 150 hearts (50 complete, 50 left-gap, 50 right-gap) pseudorandomly scattered across an A4 sheet of paper (Figure 5.1). Patients are instructed to cross off all complete hearts while ignoring incomplete distractor stimuli and are allowed three minutes to complete this task.

According to normative OCS impairment thresholds, egocentric scores greater than 3 or less than -3 and allocentric scores greater than 1 or less than -1 represent significant impairment (Demeyere et al., 2015). These standard thresholds were used to binarize impairment categorisations (e.g. Table 5.1). However, more fine-grained continuous measures were used to quantify impairment severity for VLSM analysis. In the VLSM analyses, egocentric severity was quantified using a centre of cancellation measure (Rorden and Karnath, 2010). This metric was calculated by assigning each target a numeric weight based on location along the right/left axis, and averaging these weights (see (Huygelier et al., 2020; Chaper 1, Section 2) . Similarly, allocentric asymmetry was quantified by dividing the number of consistently-lateralised false positive responses by the number of reported targets (see Chapter 2, Section 2).

Lesion Data:

The extent and location of patient lesions was quantified using clinical CT (n = 376) and MR (61 T2, 3 T1, 6 FLAIR) whole-brain scans obtained as a component of routine post-stroke clinical imaging. The validity of employing this routine clinical imaging for VLSM analysis of post-stroke cognitive impairment has recently been established in a large, multi-domain VLSM study (Moore and Demeyere, Under Review (Appendix I)). Patient lesions were manually delineated on native space scans using MRIcron (McCausland Center for Brain Imaging, Columbia, SC, USA) by in-

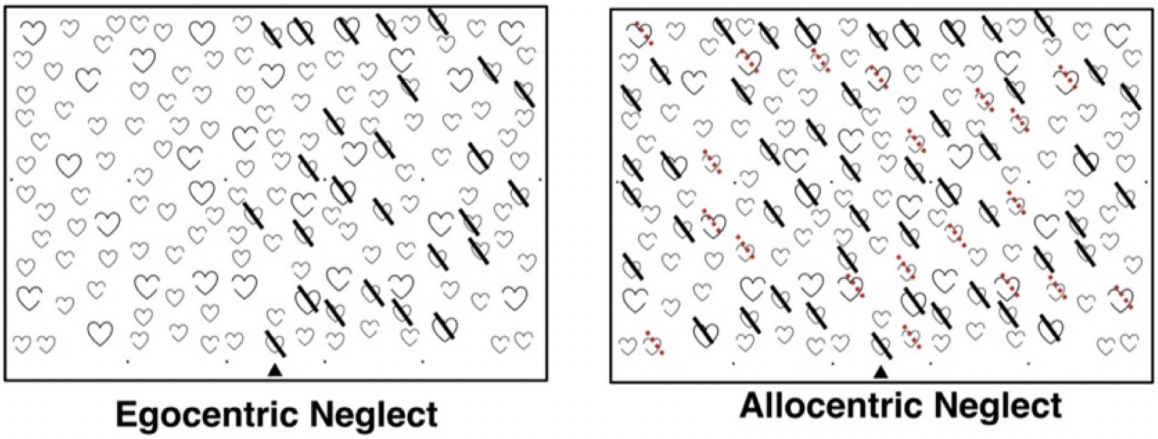


Figure 5.1: An example of egocentric/allocentric neglect impairment as captured by the Oxford Cognitive Screen's Hearts Cancellation Task. Patients with egocentric neglect omit targets on one side of the page while patients with allocentric neglect commit consistently lateralised false positive errors.

vestigators who were blind to behavioural results (Varjacic et al., 2018). All lesion masks were smoothed at 5 mm full width at half maximum in the z-direction and binarised using a .5 threshold. These scans and lesion masks were then reoriented to the anterior commissure and warped into 1×1×1 mm stereotaxic space using the Statistical Parametric Mapping 12 and Clinical Toolbox (Ashburner et al., 2016) functions. All normalised scans and lesions were visually inspected for quality before conducting lesion mapping analyses.

Planned Analysis:

Four VLSM analyses were conducted to determine the neural correlates egocentric and allocentric neglect within patients exhibiting left and right visuospatial neglect. These VLSM analyses were conducted on a theory-blind voxel-wise basis using the MATLAB package NiiStat (https://github.com/neurolabusc/NiiStat). Given that continuous impairment severity metrics were employed, this software employed one-tailed pooled-variance t-tests to evaluate voxel significance. Only voxels which were lesioned in a minimum of 10 patients were considered (n = 589,216, Figure 5.2). These analyses employed a highly conservative Bonferroni correction (corrected alpha = 8.49x10-8, z-cut = 5.23) and controlled for lesion volume. Lesion anatomy was evaluated versus the Harvard-Oxford Cortical (Desikan et al., 2006) and John's Hopkins Univer-

sity White Matter (Mori et al., 2005; Wakana et al., 2007) atlases.

Finally, the voxel maps produced by each VLSM analysis were compared to analyse the degree of overlap between voxels associated with different neglect impairments. Specifically, voxel maps for similarly-lateralised egocentric and allocentric neglect were compared to confirm whether these conditions can be dissociated at an anatomical level. Next, the voxel maps associated with left hemisphere neglect impairments were inverted to overlay with their right-hemisphere homologues in order to quantify the degree of similarity between the correlates of right and left hemisphere neglect. All analysis output files and behavioural data are openly available on the Open Science Framework (Foster and Deardorff, 2017) (https://osf.io/vf9ew/). All additional data is available upon request. No part of this study or analysis was preregistered prior to this research being conducted.

5.2 Results

Figure 5.2 presents the lesion overlay for all 446 participants within the voxels included in VLSM analysis. The highest lesion overlap (n = 69) was present within the MCA territory. In line with previous findings, patients with neglect (defined as any impairment on the ego and/or allocentric measures, n = 197) were found to have significantly larger lesions than participants without neglect (mean volume 51.57 voxels versus 24.12 respectively, $t(445)=14.793$, $p < 0.001$). A one-way ANOVA analysis revealed a significant relationship between neglect type and lesion volume ($F(5,191) = 4.026$, $p = 0.002$). Post-hoc Tukey HSD tests revealed that this effect was driven by a significant difference in severity between patients with left egocentric and both left neglect types (47.4 vs 87.3, $p = 0.224$) and a significant difference in volume between patients with right egocentric and both left impairments (27.2 vs 87.3, $p < 0.001$). All other conducted volume comparisons were not significant. Notably, 35/197 (17.8%) of included neglect patients demonstrated ipsilesional neglect impairment. Figure 5.3 presents descriptive lesion overlays of patients in each of these behavioural impairment categories.

VLSM Analysis:

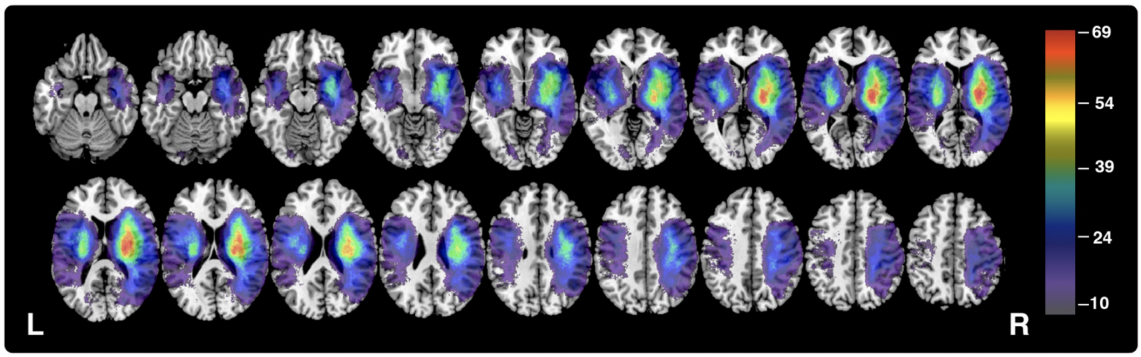


Figure 5.2: Lesion overlay for the total sample of 446 participants. Colour represents number of patient lesions overlapping within each region. Only regions with a minimum overlap of 10 are visualised (MNI z coordinates -44 – 66). The voxels highlighted in this visualisation are tested in all reported VLSM analyses.

First, two VLSM analysis were conducted to identify the neural correlates of left egocentric and left allocentric neglect (Figure 5.4, Figure 5.5). VLSM analysis of left egocentric neglect yielded 11,526 significant voxels with the peak z-score (z = 7.392) centred within the left parietal operculum (MNI 39 -34 19). This significant voxel cluster impacted a number of left temporo-pareital cortical areas including the supramarginal gyrus, and planum temporale, lateral occipital cortex (superior division). Voxels within underlying white mater ROIs including the internal capsule (posterior and retrolenticular parts), tapetum, and posterior corona radiata were also significantly associated with left egocentric neglect impairment. Full anatomical statistics of significant voxels are reported in Table 5.2.

Conversely, VLSM analysis of right egocentric neglect yielded 1,556 significant voxels with the peak z-score (z = 7.151) located within the left occipital fusiform gyrus (MNI -17 -74 37). Significant voxels were organised in two distinct clusters. The posterior cluster impacted occipital cortical areas including the intercalcarine cortex, lingual gyrus, and supracalcarine cortex. Voxels within the left posterior thalamic radiation and corpus callosum (splenium) were also significantly associated with right egocentric neglect impairment. The more anterior cluster impacted subcortical areas underlying the left insular cortex, primarily the anterior putamen.

To evaluate anatomical overlap between left and right egocentric neglect, the left hemisphere voxels which were found to be significantly associated with right neglect were superimposed on

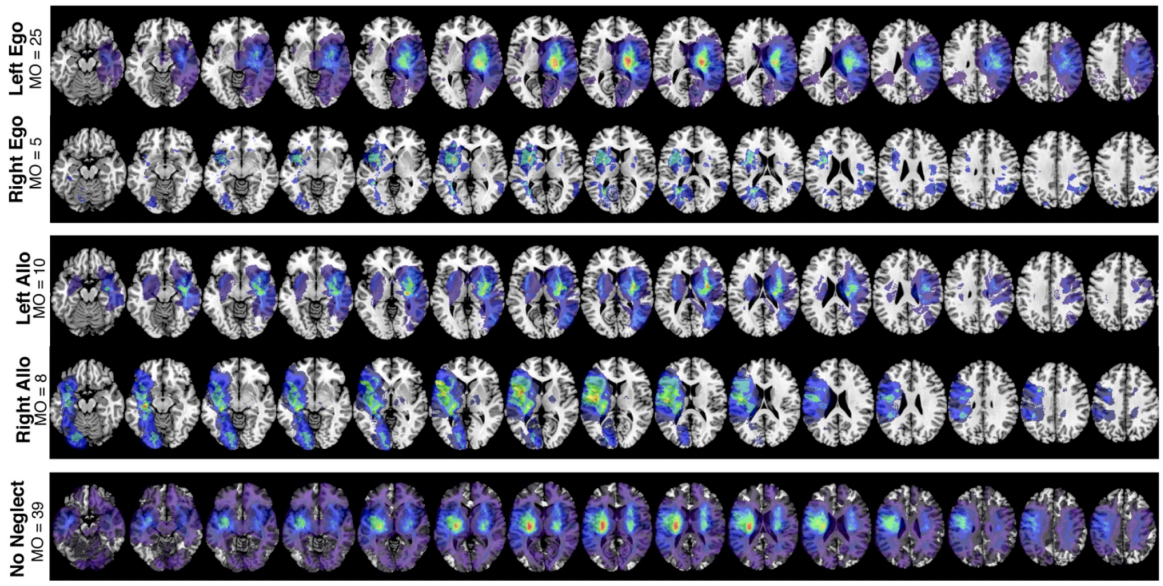


Figure 5.3: Lesion overlays for each of the behavioural groups considered within this investigation. Regions with at least one lesion present are visualised.(MNI z coordinates -44 – 66)

the homologous voxels within the right hemisphere. Only one voxel of overlap was present between the voxels associated with left egocentric neglect and the right hemisphere homologues of voxels associated with right egocentric neglect impairment. This voxel was centred near the inferior medial border of the lateral occipital cortex (superior division).

VLSM analysis of left allocentric neglect impairment yielded 3968 significant voxels with a peak z-score of 7.150 centred within the superior division of the right lateral occipital cortex (MNI 25 -65 59). The significant voxels were largely grouped in three clusters. First, a cluster of significant voxels was present within the lateral occipital cortex. This cluster partially overlapped with voxels associated with left egocentric neglect, but included a number of distinct, more inferior voxels which were not found to be associated with left egocentric impairment. Next, a cluster of significant voxels was centred on the border between the post-central gyrus and the anterior division of the supramarginal gyrus. A third, more anterior cluster of significant voxels was located on the inferior border between the planum temporale, temporal pole, posterior temporal fusiform cortex, and anterior parahippocampal gyrus. Overall, 6.45% of significant voxels were associated with both left egocentric and left allocentric neglect. These overlapping voxels were centred within

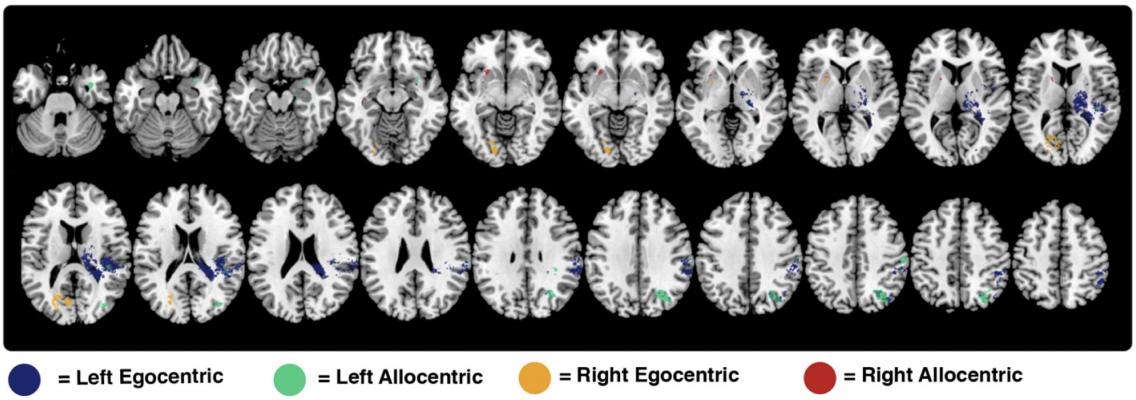


Figure 5.4: A visualisation of the significant voxels yielded by VLSM analysis of left/right egocentirc and allocentric neglect.

the lateral occipital cortex (superior division) and planum temporale.

Finally, VLSM analysis of right allocentric neglect yielded 203 significant voxels with a peak z value (z= 5.949) located within the anterior limb of the left internal capsule. This cluster impacted the external capsule. In total, there was 0.34% overlap between the voxels significantly associated with right allocentric and right egocentric neglect. These 6 overlapping voxels were located within the white matter underlying the right insular cortex.

The left hemisphere voxels associated with right allocentric neglect were then superimposed on their right hemisphere homologous to evaluate the anatomical overlap between left and right allocentric neglect. No common voxels were present within this comparison.

5.3 Discussion

The purpose of the present study was to identify the neural correlates of left and right lateralised visuospatial neglect in a large, representative sample of acute stroke survivors and to determine whether right lateralised neglect is subserved by homologous areas underlying left-lateralised neglect following right hemisphere damage. As in previous studies, left egocentric neglect was found to be most strongly associated with damage to the right temporoparietal area while left allocentric neglect was associated with distinct, more posterior and inferior (or ventral) lesion sites. Conversely, right egocentric neglect was found to be most strongly associated with

Table 5.2: Detailed anatomical descriptions of the significant voxel clusters identified in each individual VLSM analysis. Starred ROIs contain the peak z-values for each VLSM test. Full anatomical descriptions for each voxel cluster are available on the Open Science Framework. Fraction represents the proportion of each ROI covered by each significant z-statistic map. All anatomical areas are defined based on the Harvard-Oxford Cortical Atlas (HAROX) and the Johns Hopkins University White Matter Atlas (JHU). Hem = hemisphere (Left/Right). Nsig = number of significant voxels within each ROI

Left Egocentric	**Hem.**	**Nsig**	**Fraction**	**Atlas**
Supramarginal Gyrus (Posterior Division)	R	1698	11.37%	HAROX
Planum Temporale	R	1087	20.43%	HAROX
Parietal Operculum Cortex*	R	972	17.94%	HAROX
Lateral Occipital Cortex (Superior Division)	R	946	2.01%	HAROX
Supramarginal Gyrus (Anterior Division)	R	696	8.77%	HAROX
Internal Capsule (Posterior Limb)	R	633	13.62%	JHU
Tapetum	R	552	62.80%	JHU
Internal Capsule (Retrolenticular Part)	R	408	12.42%	JHU
Heschl's Gyrus	R	257	7.90%	HAROX
Corona Radiata (Posterior)	R	237	4.69%	JHU
Angular Gyrus	R	209	1.44%	HAROX
Splenium of Corpus Callosum	R	192	1.21%	JHU
Posterior thalamic Radiation	R	173	3.33%	JHU
Superior Longitudinal Fasciculus	R	74	0.78%	JHU
Insular Cortex	R	48	0.42%	HAROX
Central Opercular Cortex	R	30	0.35%	HAROX
Superior Temporal Gyrus (Posterior Division)	R	29	0.29%	HAROX
Fornix (cres) Stria terminalis	R	23	1.22%	JHU
External capsule	R	18	0.22%	JHU
Body of Corpus Callosum	R	11	0.07%	JHU
Left Allocentric				
Lateral Occipital Cortex (Superior Division)*	R	2589	5.50%	HAROX
Supramarginal Gyrus (Anterior Division)	R	189	2.38%	HAROX
Planum Temporale	R	157	2.95%	HAROX
Superior Parietal Lobule	R	101	0.63%	HAROX
Temporal Pole	R	74	0.31%	HAROX
Postcentral Gyrus	R	63	0.19%	HAROX
Uncinate Fasciculus	R	63	10.23%	JHU
Supramarginal Gyrus (Posterior Division)	R	55	0.37%	HAROX
Superior Longitudinal Fasciculus	R	41	0.43%	JHU
Parietal Operculum Cortex	R	28	0.52%	HAROX
Temporal Fusiform Cortex (Posterior Division)	R	28	0.35%	HAROX
Precuneous Cortex	R	26	0.10%	HAROX
Inferior Temporal Gyrus (Posterior Division)	R	25	0.21%	HAROX
Insular Cortex	R	20	0.17%	HAROX
Parahippocampal Gyrus (Anterior Division)	R	19	0.23%	HAROX
Middle Temporal Gyrus (Posterior Division)	R	18	0.14%	HAROX
External Capsule	R	15	0.19%	JHU
Planum Polare	R	11	0.25%	HAROX
Right Egocentric				
Intracalcarine Cortex	L	381	5.50%	HAROX
Occipital Fusiform Gyrus*	L	275	2.22%	HAROX
Lingual Gyrus	L	271	1.72%	HAROX
Supracalcarine Cortex	L	186	5.60%	HAROX
Lateral Occipital Cortex (Superior Division)	L	91	0.20%	HAROX
Posterior Thalamic Radiation	L	43	0.80%	JHU
Splenium of Corpus Callosum	L	24	0.15%	JHU
Cuneal Cortex	L	17	0.28%	HAROX
Right Allocentric				
External capsule	L	118	1.46%	JHU
Internal Capsule (Anterior Limb)*	L	56	1.40%	JHU

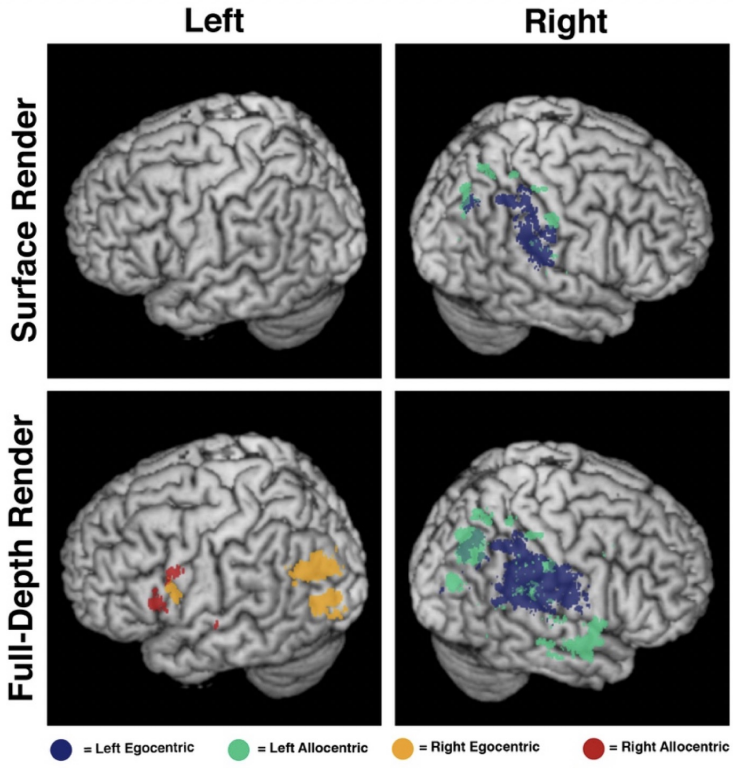


Figure 5.5: A 3D render of significant voxels for each conducted comparison. The surface render visualises all voxels within 4 voxels of the brain surface. The full-depth render visualises all significant voxels, regardless of depth.

damage to left hemisphere occipital areas while right allocentric neglect was related to damage to voxels within the left internal capsule white matter. While there was some degree of overlap (6.45%) between the neural correlates associated with left egocentric and left allocentric neglect, the voxels associated with right egocentric and right allocentric neglect demonstrated less than 0.5% overlap. The right hemisphere homologues of the regions associated with right allocentric neglect did not overlap with the regions associated with left allocentric neglect. Similarly, only one voxel of overlap was present between the regions associated with left egocentric neglect and the right hemisphere homologues of voxels associated with right egocentric neglect impairment. These findings provide important novel insights into the neural correlates of spatial attention.

The behavioural data collected in this investigation provides a clear demonstration of heterogeneity within the neglect syndrome. Within the consecutive sample included in this investigation

28.5% exhibited right-lateralised and 15.7% exhibited left-lateralised neglect. This finding is in line with previous research demonstrating that neglect deficits regularly occur following both right and left hemisphere damage (Stone et al., 1992; Ten Brink et al., 2017). Similarly, as in previous studies, egocentric and allocentric neglect were found to be behaviourally doubly dissociated (Chechlacz et al., 2010, 2012). Notably, 17.8% of the neglect patients identified in this investigation exhibited ipsilesional neglect deficits. Previous VLSM studies have generally included a specific subset of neglect patients, rather than a broad, representative sample. For example, may previous investigations have excluded all left hemisphere or ipsilesional neglect patients, and have not distinguished between egocentric and allocentric neglect impairment (Chechlacz et al., 2012; Molenberghs et al., 2012; Suchan and Karnath, 2011). It is critically important to adequately represent this variety within experimental subsets in order to produce generalisable results which can further fundamental understanding of the neglect syndrome as a whole.

Left egocentric neglect was primarily associated with damage within the right temporo-parietal cortex and underlying white matter while left allocentric neglect was found to be associated with distinct voxel clusters. These distinct clusters were centred within the left lateral occipital cortex and the inferior border of the anterior parahippocampal gyrus. A third cluster of significant voxels was present on the border between the post-central gyrus and the anterior division of the supramarginal gyrus. This third cluster largely overlapped with voxels found to be significantly associated with left egocentric neglect impairment. These findings are in line with previous findings suggesting that left egocentric and allocentric neglect are associated with distinct but overlapping regions. Some degree of this overlap may be accounted for by the common co-occurrence of left egocentric and allocentric neglect, with 42 (9.4%) patients included in these analyses exhibiting both impairments. These results suggest that the common co-occurrence of egocentric and allocentric neglect is likely due to their distinct neural correlates' anatomical proximity rather than being indicative of a common underlying mechanism. This finding aligns well with existing literature (Chechlacz et al., 2010, 2012; Medina et al., 2008, 2008; Ptak et al., 2012) and provides additional evidence suggesting that egocentric and allocentric neglect represent doubly dissociated, independent cognitive impairments.

Conversely, right egocentric neglect was most strongly predicted by damage to left hemisphere occipital areas including the intercalcarine, lingual, and occipital fusiform cortices. These results contrast with previously reported results which have identified correlates of right egocentric neglect within left frontotemporal cortical areas. However, this disagreement can be largely accounted for by the differences in methodologies employed by these studies. First, previous investigations have restricted analyses to the left hemisphere, precluding detection of any right hemisphere correlates (Beume et al., 2017; Suchan and Karnath, 2011). Second, Suchan and Karnath (2011) did not explicitly distinguish between egocentric and allocentric neglect. This investigation quantified allocentric-level biases within a figure copy task, but grouped patients into "neglect" and "no neglect" VLSM analysis groups regardless of the type of neglect impairment exhibited. This "neglect" group may have then included a combination of patients with pure egocentric, pure allocentric, and both egocentric and allocentric neglect. Previous research has established that left egocentric and allocentric neglect are associated with distinct neural correlates. It therefore seems likely that similar variation exists within right neglect, meaning that failing to distinguish between egocentric and allocentric neglect may likely introduce confounding noise into anatomical analyses.

Notably, right egocentric neglect was associated with damage to areas which are traditionally associated with lateralised visual rather than attentional impairments. Specifically, voxels within the primary visual cortex (intercalcarine cortex) were found to be associated with right egocentric neglect impairment. The OCS cancellation task reliably distinguishes between neglect and low-level visual impairments, as patients with visual impairment retain the ability to visually scan the search matrix whilst patients with neglect do not (Demeyere et al., 2015). Previous research has demonstrated that occipital areas, including those found to be associated with right egocentric neglect, may play a key role in directing visual attention (Vilares et al., 2012). For example, Vilares et al. (2012) found that a cluster of voxels centred within the superior occipital cortex and extending into the calcarine sulcus and lingual gyrus was responsible for encoding salience-based aspects of visual attention. These regions were also found to be associated with right egocentric neglect, implying a degree of functional overlap. Alternatively, it is possible that the association

between the intercalcarine cortex and egocentric neglect is indicative of a general association between PCA strokes and egocentric neglect. Additional research is needed to determine the exact mechanisms underlying right egocentric neglect in order to further understand the functional role of these posterior lesion sites.

Previous research investigating the neural correlates of right egocentric neglect has generally concluded that this impairment is associated with damage to more anterior temporo-parietal areas rather than the occipital areas identified in this investigation (Beume et al., 2017; Suchan and Karnath, 2011). This discrepancy can be largely accounted for by methodological differences. First, previous analyses have considered a restricted sample of neglect patients (n = 11, n = 21) with exclusively left hemisphere damage while the present study conducted whole-brain analyses on a much larger sample of right egocentric neglect patients (n = 42). In previous studies, the vast majority of patients have exhibited MCA territory strokes, with limited overlap present in the regions found to be associated with neglect in the present study (Beume et al., 2017; Suchan and Karnath, 2011). This is in line with the clinical picture of the majority of patients exhibiting MCA damage, but precludes testing the role of more posterior lesion sites in right egocentric neglect impairment. However, it necessary to include a larger sample with more diverse lesions in order to gain a more accurate understanding of right egocentric neglect.

Finally, the present study explicitly distinguished between egocentric and allocentric neglect impairment. Suchan and Karnath (2011) did include behavioural tests of allocentric-level impairment, but did not conduct VLSM analyses which distinguished between egocentric and allocentric neglect. Given that right allocentric neglect was found to be associated with more anterior fronto-temporal regions, failing to exclude these patients from an analysis of right egocentric neglect would be expected to bias results towards these anterior areas. This is due to the fact that VLSM is most effectively able to identify the correlates of functions which are associated with a single, spatially contiguous correlate and tends to “average” across spatially distinct correlates (Bates et al., 2003; de Haan and Karnath, 2018). This “averaging” effect is particularly prominent when small samples of impaired patients are used (de Haan and Karnath, 2018). In the present study, this effect was carefully controlled for by regressing out lesion volume and employing an extremely

conservative correction for multiple comparisons.

Overall, the findings of this experiment strongly suggest that right egocentric neglect cannot be accurately conceptualised as resulting from damage to left-hemisphere homologues of traditional right spatial attention areas. Damage to right hemisphere homologues of the left hemisphere voxels implicated in right egocentric was not found to be associated with left egocentric impairment. Some degree of this disagreement can be accounted for by differences in the VLSM analyses, given that both analyses included a different lesion overlay patterns (Figure 5.2). This diversity implies that even if right and left egocentric were exactly homologous, some degree of disagreement would be present in the VLSM results. However, this inherent noise would not be expected to result in the clear, qualitative differences between right and left egocentric neglect documented in this investigation. Left egocentric neglect was largely associated with damage to temporo-parietal areas while right egocentric impairment was associated with posterior occipital regions. This diversity implies that egocentric neglect is best understood as a common symptom of multiple underlying lesion patterns, rather than a unitary syndrome. It is important for future research to take this anatomical and behavioural diversity into account in order to produce findings which can help further fundamental understanding of the neglect syndrome as a whole. Additionally, future research is needed in order to determine how right-lateralised egocentric neglect mechanistically differs from left-lateralised neglect deficits.

Notably, the present study is the first to conduct statistical analyses aiming to identify the neural correlates of right allocentric neglect. This deficit was found to be significantly associated with a small cluster of voxels centred within right external capsule. This finding differs from the previously reported results of Kleinman et al. (2007). This discrepancy is likely due to the present study's comparatively larger sample of allocentric neglect patients (39 patients versus 3 patients) and use of quantitative statistical analyses rather than qualitative lesion descriptions. Inferior temporo-frontal cortical regions have been consistently associated with object-level perceptual processes and is a key anatomical component of the ventral visual processing stream (Borowsky et al., 2007; Grill-Spector, 2003; Quiroga et al., 2005). It is plausible that damage to the external and internal capsule white matter ROIs disrupts communication with these areas, resulting in

allocentric neglect impairment. However, there was no overlap between the neural correlates of left and right allocentric neglect. This suggests that the allocentric level spatial-attentional system is not homologous across hemispheres. Additional research is therefore needed to provide a more detailed characterisation of the neural correlates of allocentric-level visual attention in order to better understand the exact mechanisms which underly this condition.

Considered cumulatively, the results of the present investigation support the characterisation of visuospatial neglect as a heterogenous cluster of impairments rather than a unitary syndrome. Similarly, the consistent involvement of damage to white matter ROIs in egocentric/allocentric neglect supports previous assertions that neglect represents a disconnection syndrome in which neglect symptoms with distinct cortical correlates may be linked back to common white matter damage. Future investigations need to account for this heterogeneity. Studies which do not account for differences between left/right or egocentric/allocentric neglect deficits may risk producing overgeneralised results confounded by considering distinct behavioural deficits as a single, unitary impairment. The inclusion of large, representative patient samples assessed for both egocentric and allocentric level neglect impairment is critical in order to facilitate valid conclusions about the neglect syndrome as a whole.

Limitations:

This investigation exclusively employed routinely collected clinical neuroimaging and behavioural data. While this approach allowed for the inclusion of the largest number of patients in any neglect VLSM study, this methodology is not without limitations. Acute lesions develop over time and are often not fully visible on acute CT imaging (González, 2005; Merino and Warach, 2010). Ideally, more high-resolution imaging data from T2 MRI or DWI scans would be employed to quantify lesion anatomy. Given that this investigation employed routinely collected clinical imaging, these higher quality scans were only available for a subset of the included patients.

However, previous investigations have repeatedly demonstrated the feasibility of employing acute CT scan data for VLSM analysis (Chechlacz et al., 2010; de Haan and Karnath, 2018; Varjačić et al., 2018). Regardless of imaging modality, there is inherently some degree of mea-

surement error present within creating binarized, quantitative lesion masks from uncertain clinical data. The impact of this error has been minimised by including only lesion masks which were confirmed by trained researchers and by using extremely strict Bonferroni corrections when conducting VLSM analysis. Additionally, previous research has suggested that it is generally best to diagnose neglect based on agreement between multiple or repeated neuropsychological tests as no single neuropsychological test is perfectly sensitive to neglect impairment (Azouvi et al., 2002; Huygelier et al., 2020; Lindell et al., 2007). Though additional and potentially computerised measures may have provided a more sensitive measure, the acute nature and relatively severe neglect impairments combined with a sensitive cancellation task provides confidence in the methods employed. In addition, careful consideration of sensitivity and specificity of measures used and ensuring a balance between high inclusivity with low burden tasks, and reducing potential false positives (Huygelier et al., 2020). However, given this investigation represents a retrospective analysis of routinely collected data, no additional neglect behavioural assessment data were available.

VLSM is inherently better at identifying the neural correlates of deficits which are subserved by a single, spatially coherent neural correlate (Gajardo-Vidal et al., 2018). Given that visuospatial neglect deficits likely involve disconnection syndromes rather than a single critical lesion site, additional research using a range of analysis techniques is needed to further clarify the underlying networks implicated in spatial attentional deficits. In addition to impacting different spatial reference frames, Patients with visuospatial neglect can exhibit a diverse range of location or modality- specific behavioural phenotypes and functional outcomes (Agrell et al., 2016; Aimola et al., 2012; Connine et al., 1990; Laplane and Degos, 1983; Ten Brink et al., 2019). Future research is needed to specifically identify the neural correlates of these additional neglect subtypes.

Conclusions:

The findings of this investigation elucidate the distinct neural correlates of right and left visuospatial neglect deficits in a large, representative sample of stroke survivors. The findings pertaining to left egocentric/allocentric neglect align with and replicate findings from existing liter-

ature. With regards to the critical neuro-anatomy underlying right-lateralised visuospatial neglect, where little research exists, we found right egocentric neglect to be most strongly predicted by damage to voxels within the posterior occipital cortex. Importantly, right neglect should not be characterised as a consequence of damage to left-hemisphere homologues of the right hemisphere attentional systems, but instead may represent a common behavioural consequence of multiple underlying causes. Notably, this is the first study to identify the neural correlates of right allocentric neglect in the left internal/external capsule white matter. Cumulatively, these findings provide novel insight into the neural correlates of spatial attention.

6 Chapter 6.0: Visuospatial Neglect as a Predictor of Poor Long-Term Functional Outcome

Author's Note:

In line with standard CRediT author roles (Brand et al., 2015), I was responsible for Formal Analysis, Data Curation, Writing - Original Draft, Writing - Reviewing and Editing, and Visualising the material presented within Section One of this Chapter. This content of this section is accepted for publication under the title "Visuospatial neglect: recovery and functional outcome after 6 months" in Neurorehabilitation and Neural Repair (Moore et al, 2021).

Section Two represents a represents a retrospective analysis of existing data in which I was responsible for project conceptualisation, methodology (development + design), Software (designing and implementing computer programs), Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Reviewing and Editing, and Visualising. This project is accepted for publication in the Journal of Neurology and is available as a preprint (Moore and Demeyere, MedRxiv, https://doi.org/ 10.1101/2021.03.29.21254222).

Section Three is a retrospective analysis of existing data in which I was responsible for Formal Analysis (quantitative data), Writing – Original Draft, Writing – Reviewing and Editing, and Visualising. Notably, the coding and thematic qualitative analysis of therapist notes reported in this section was performed by undergraduate researcher Rebecca Driscoll in fulfilment of her research project, and graduate research assistant Michael Colwell, under supervision of qualitative analysis expert and collaborator Dr Olivia Hewitt. This paper is under review for publication in Neuropsychological Rehabilitation.

6.0 General Introduction

Previous research has demonstrated that the occurrence of acute visuospatial neglect acts as a predictor of poor long term functional outcomes, such as instrumental activities of daily life. However, it is unclear whether these findings can be generalised to patients exhibiting different types of neglect impairments, and to what extent specific daily tasks can be affected. Does the severity of the neglect impairment as assessed with formal, abstract neuropsychological testing align with severity of impacts on a range of everyday life activities. Section 1 of this chapter aims to investigate how acute egocentric and allocentric neglect severity scores differentially act as predictors of long-term recovery outcomes. Section 2 investigates the robustness of this finding and presents a novel multiverse analysis aiming to determine whether findings pertaining to the association between neglect and poor long term functional outcome can be generalised across patient groups selected using different inclusion criteria. Finally, Section 3 presents a mixed methods analysis of the specific behavioural impairment profile associated with visuospatial neglect in functional assessments conducted by Occupational Therapists in an acute stroke setting. Cumulatively, these studies provide novel insight into the impact of different types of visuospatial neglect on patient functional outcome.

6.1 Chapter 3.1: Visuospatial Neglect Recovery and Functional Outcome at 6 Months

6.1.1 Introduction

The neglect syndrome is represented by a highly heterogeneous group of symptoms and contains many subtypes (Bickerton et al., 2011; Li et al., 2014; Stone et al., 1993). Although visuospatial neglect is a common consequence of stroke, it is not yet clear whether different subtypes of neglect follow similar recovery trajectories or whether neglect subtypes are differentially associated with poor long-term functional outcomes.

The occurrence of post-stroke cognitive impairments has been strongly associated with reduced quality of life throughout recovery (Jehkonen et al., 2000a; Katz et al., 1999; Langhammer et al., 2016; Nys et al., 2006). However, not all cognitive deficits appear to affect quality of life and functional recovery to the same extent. Previous research has demonstrated that patients who experience visuospatial neglect following stroke are significantly more likely to report higher levels of functional impairment and lower quality of life than patients without visuospatial neglect impairment (Cherney et al., 2001; Jehkonen et al., 2000a; Katz et al., 1999). This particularly robust effect has been documented across multiple different timepoints using a wide range of functional outcome measures. For example, Jehkonen et al. (2000a) found that performance on the Behavioural Inattention Test was the single best predictor (compared to hemianopia, age, and verbal memory) of poor functional outcome at 3, 6 and 12 month follow-up appointments. Cherney et al. (2001) determined that higher neglect severity was predictive of lower Functional Independence Measure scores at admission, discharge, and 3 month follow-up. Katz et al. (1999) found that acute neglect was associated with lower scores on various activities of daily living measurements as well as on standardised cognitive measures throughout the first five months following stroke. Similarly, Buxbaum et al. (2004) concluded that the occurrence of neglect deficits predicted poor recovery outcome following stroke over and above general stroke severity metrics. These findings demonstrate that the occurrence of visuospatial neglect acts as a significant predictor of functional recovery outcome.

However, neglect is not a unitary syndrome. Following stroke, patients can exhibit visuospa-

tial neglect within a egocentric and/or allocentric reference frame (Bickerton et al., 2011, 2011; Chechlacz et al., 2012; Demeyere and Gillebert, 2017; Humphreys et al., 2013; Li et al., 2014; Ota et al., 2001). While egocentric and allocentric neglect do frequently co-occur, these conditions have been demonstrated to represent doubly-dissociated, independent cognitive impairments (Bickerton et al., 2011; Costello and Warrington, 1987; Cubelli et al., 1991; Demeyere and Gillebert, 2017). Importantly, additional subtypes of neglect have been documented. Patients can selectively exhibit neglect within peri-personal (near space) and extra-personal space (Committeri et al., 2007, 2018; Ten Brink et al., 2019; Vallar, 2001). Patients have also been found to exhibit spatial attentional biases in additional sensory modalities including auditory neglect (Bellmann et al., 2001; Guilbert et al., 2016; Gutschalk and Dykstra, 2015) and motor neglect (Laplane and Degos, 1983; Punt and Riddoch, 2006; Triggs et al., 1994). However, standardised neuropsychological tests which can reliably detect and differentiate between these additional neglect subtypes are not commonly employed in clinical environments (Checketts et al., 2020; Evald et al., 2020; Rabin et al., 2016). For this reason, this analysis will focus on exploring the recovery trajectories of egocentric and allocentric neglect. The present study aims to investigate only differences between egocentric and allocentric neglect with the implication being that if these two subtypes recover differentially, additional research will be needed to investigate whether these differences are also present within other subtypes of neglect.

Previous research has suggested that patients with egocentric and allocentric neglect may exhibit differing levels of functional impairment. Bickerton et al. (2011) found that patients with allocentric neglect scored significantly lower (e.g. worse functional performance) on the Barthel Index activities of daily life measurement (Quinn et al., 2011) compared to patients with egocentric neglect at a single, subacute time point. In this study, patients with both allocentric and egocentric neglect also reported significantly higher levels of depression on the Hospital Anxiety and Depression Scale than patients with either egocentric or allocentric neglect alone (Bickerton et al., 2011).

Similarly, patients with left and right neglect may exhibit differing levels of functional impairment. Ten Brink et al. (2017) investigated the relationship between neglect lateralisation and

performance on various cognitive and physical independence measures in a cohort of 335 acute stroke survivors. This study found that left-lateralised neglect impairment was more severe than right-lateralised neglect as assessed by both neuropsychological and observational measures. However, patients with right neglect exhibited lower scores on the Mini Mental State Examination (Folstein et al., 1983; Tombaugh and McIntyre, 1992) than patients without neglect (potentially through a co-occurring language deficit) and were more likely to exhibit impaired balance than patients with left neglect (Ten Brink et al., 2017). These findings suggest that the association between neglect and functional impairment may depend on the reference frame and lateralisation of neglect. However, these studies only employed data from a single timepoint acutely post stroke.

Overall, previous studies which have tracked neglect recovery over time have found that the majority of neglect cases recover within the first six months following stroke (Demeyere and Gillebert, 2019; Nijboer et al., 2013; Stone et al., 1992). Nijboer et al. (2013) found that time post-stroke was a key and independent predictor of visuospatial neglect recovery, with 54% of patients recovering within the first 12 weeks and around 60% recovered within the first year. A subsequent study found that clinical characteristics including neglect severity, stroke severity, and severity of comorbid stoke deficits did not act as significant predictors of neglect recovery over the first 26 weeks following stroke (Nijboer et al., 2018). These studies provide important insight into the recovery trajectory of neglect as a whole, but do not distinguish between egocentric and allocentric neglect deficits. Several previous studies have investigated how different neglect subtypes recover over time. Stone et al (1992) in a group of 68 patients with neglect, found that neglect following right hemisphere damage (N=34) was significantly slower to improve and less likely to fully recover than neglect following left hemisphere lesions (N=34) over the first six months following stroke. Demeyere and Gillebert (2019) found that of the 160 patients with follow up data 81% of egocentric neglect (11 impaired at follow up versus 55 impaired at the stage) and 71% of allocentric neglect cases (10 chronic versus 39 acute) recovered within six months following stroke. Overall, a high proportion of visuospatial neglect cases were found to spontaneously recover within the first six months following stroke (Demeyere and Gillebert, 2017; Stone et al., 1992), but this relationship may not be equivalently true for different neglect lateralisations and

reference frames.

Previous research has suggested that some stroke-related deficits follow a proportional recovery rule in which the amount of improved function is proportional to the initial degree of function loss (Marchi et al., 2017; Smith et al., 2017). However, it is not yet clear whether egocentric and allocentric visuospatial neglect follow this proportional recovery pattern (Bonkhoff et al., 2019; Hope et al., 2019). If neglect impairments follow a proportional recovery rule, neglect cases which are initially more severe should be less likely to fully recover than less severe cases (Marchi et al., 2017; Smith et al., 2017). Conversely, if neglect does not follow a proportional recovery pattern, the initial severity of neglect would not be expected to differentiate between patients who do and do not recover over time. Similarly, it is important to investigate differences in rates of improvement over time across different neglect subtypes. For example, it is possible that patients with milder deficits improve gradually over time while patients with severe impairments do not experience any improvement. Alternatively, it is possible that all patients with neglect exhibit the same rate of change in severity over time, regardless of the severity of their initial deficits. It is therefore critically important to better characterise recovery trajectories in different neglect subtypes in order to identify the specific patients who are least likely to fully recover.

Previous investigations into neglect recovery trajectories have not considered the interaction between neglect subtype and lateralisation when attempting to elucidate the predictive relationships between these acute factors and long-term recovery outcomes. Here, for the first time, we present data from a large and representative longitudinal sample of stroke survivors to attempt to disentangle how complex acute neglect behavioural phenotypes predict longer-term recovery outcomes, both in terms of long-lasting neglect symptoms as well as broader functional outcomes related to activities of daily life and participation.

The present study aims to analyse data from a large and representative sample of stroke survivors to elucidate how complex neglect behavioural phenotypes predict long-term outcomes, both in terms of neglect recovery and broader functional outcomes. Notably, this study is the largest single investigation on the recovery of neglect and the first to evaluate longitudinal differences between different neglect subtypes. The first section of this chapter aims to investigate

which specific acute neglect characteristics are predictive of neglect recovery and chronic functional outcomes.

6.1.2 Methods

Participants:

This project represents a secondary analysis of data collected within the Oxford Cognitive Screen (OCS) (Demeyere et al., 2015), OCS-Tablet, and OCS-Care (Demeyere et al., 2019) studies from 2015-2019. These study protocols were reviewed and approved by the National Research Ethics Committee (UK) (References: 11/WM/0299, 14/LO/0648, and 12/WM/00335 respectively). Each study included acute cognitive screening (T1) and 6 month follow-ups (T2). Patients were included in this analysis if Cancellation Task data was available from both timepoints and they had completed the Stroke Impact Scale (SIS) at timepoint 2 (Figure 6.1). A total of 400 patients (mean age=70.6 (SD= 12.2), 47% female, mean years of education = 12 years (SD = 2.78), 6% left handed) were included in this study. As reported by patient clinical notes, this sample included 322 ischemic, 57 haemorrhagic, and 21 not reported stroke types. Lesion sides were reported as 197 right, 157 left, 29 bilateral, and 17 not reported. The average stroke-test interval was 9.9 (SD=11.9) days at T1 and the average National Institutes of Health Stroke Scale (NIHSS) total scores was found to be 3.82 (SD = 3.94, range = 0 -22). Table 1 presents a full summary of demographic and stroke information for the patients in this study with and without significant neglect impairment. Table 6.1 presents a full summary of demographic and stroke information for the patients in this study with and without significant neglect impairment.

Due to the high exclusion rate within this secondary analysis (60.8% of the originally considered cohort), a series of analyses were conducted to determine whether the included neglect sample was representative of the full acute cohort assessed. The proportion of patients with neglect within all acute patients (n =1020, 44.5%) was found to be significantly higher than that within the included sample (n = 400, 35.5%) ($X2= 5.579$, $p = 0.0182$). However, there was no significant difference between the egocentric ($t(265.79) = 0.627$, $p = 0.5312$, 95% CI = -0.974 – 1.884) or allocentric ($t(230.24) = 0.720$, $p = 0.472$, 95% CI = -0.563 – 1.211) asymmetry scores

between neglect patients who were and were not included in the final sample.

Table 6.1: Demographics and Stroke Information for the patients with and without neglect. Means are reported alongside standard deviations (in parentheses).

	Neglect (n = 142)	**No Neglect (n = 258)**
Age (years):	72.1 (12.6)	69.8 (11.9)
Percent Female:	47.90%	46.50%
Education (years):	11.6 (2.5)	12.2 (2.9)
Percent Left Handed:	7.80%	11.30%
Stroke Side:		
Right	58	76
Left	42	76
Bilateral	6	11
NR/Unknown	36	95
Stroke Type:		
Ischemic	89	158
Haemorrhagic	14	34
NR	39	66
Stoke/Test Interval (days):	9.4 (10.9)	10.2 (12.3)

Procedures:

The behavioural analyses conducted in this investigation aim to 1) determine which neglect factors predict presence of chronic neglect and 2) investigate the interaction between acute neglect type, lateralisation, severity with long-term SIS score. Data from standardised Cancellation Tasks and the Stroke Impact Scale questionnaire were considered in this investigation. Participants completed either the OCS or Birmingham Cognitive Screen Cancellation Task (Bickerton et al., 2011; Humphreys et al., 2012) in pen and paper format. These assessments are parallel versions of a standardised assessment aiming to detect egocentric and allocentric visuospatial neglect and do not aim to quantify additional neglect impairments (e.g. motor or auditory neglect). Each cancellation task consists of similarly structured search matrices containing complete, right-gap, and left-gap line drawings. In these tasks, patients were instructed to mark complete drawings while ignoring incomplete stimuli. Patients completed two practice trials and were given three minutes to complete the Cancellation Task. These Cancellation Tasks have been demonstrated to be sensitive and reliable measures for detecting and differentiating between allocentric and ego-

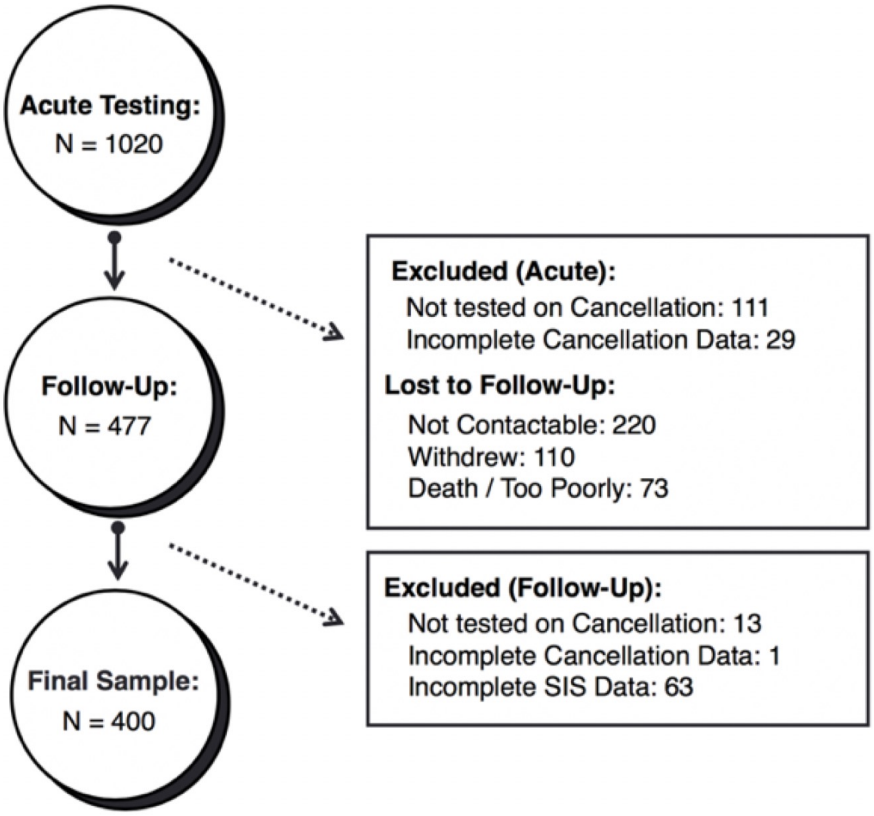


Figure 6.1: A summary of patient exclusion criteria and dropout counts at each stage.

centric deficits (Bickerton et al., 2011; Demeyere and Gillebert, 2019) (Figure 6.2). The Stroke Impact Scale (SIS) is a self-report questionnaire assessing stroke-specific functional outcome domains (Duncan et al., 2003; Duncan et al., 1999). This investigation employed version 3.0 of this scale, which includes 59 questions across 8 domains (physical weakness, memory, mood, communication, activities of daily living, mobility, affected hand, and participation). Each question is responded to on a 5-level Likert scale. The SIS exhibits high test-retest validity, correlates strongly with other established measures, and is sensitive to changes.

Participants completed the Cancellation Task at timepoints 1 and 2. The presence of egocentric neglect is scored by subtracting the number of targets identified on the left from those on the right. Egocentric asymmetry more extreme than +3(left neglect)/-3(right neglect) in conjunction with total scores of less than 42/50 was considered to represent significant neglect impairment (Demeyere and Gillebert, 2019). Egocentric neglect severity was calculated though a

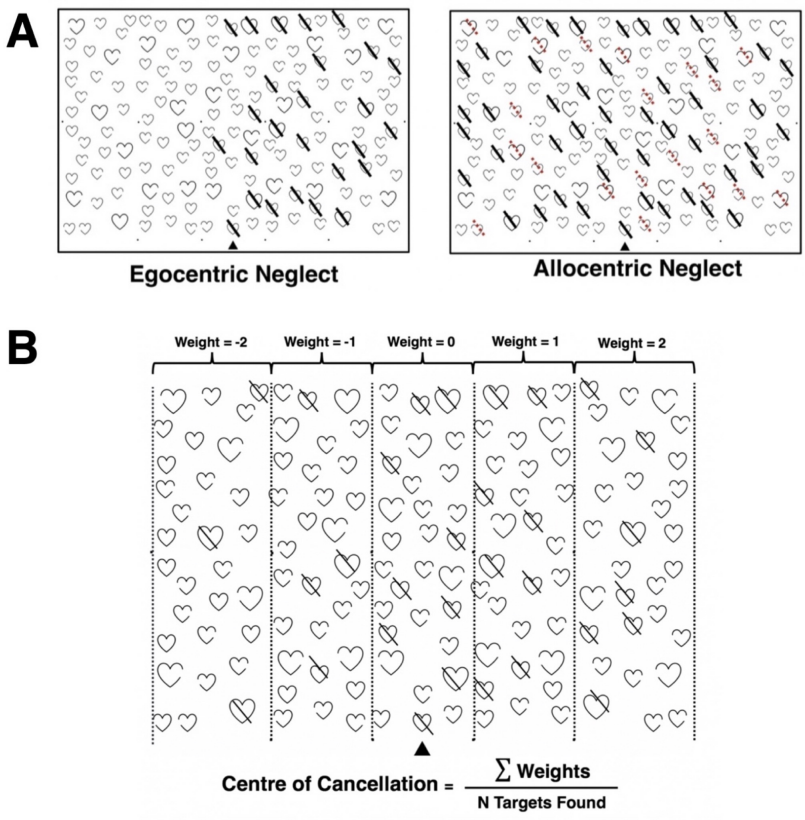


Figure 6.2: A visualisation of egocentric and allocentric neglect deficits as detected by the OCS cancellation task (Panel A). Patients with egocentric neglect fail to report targets on one side of space while patients with allocentric neglect commit consistently lateralised false positive errors (highlighted in red). Panel B presents the task scoring grid, corresponding error weights, and equation for calculating centre of cancellation neglect severity scores.

centre of cancellation (CoC) score (see Chapter 2, Section 2). This score was calculated by assigning each response a numerical weight according to its horizontal location, the average response weight determines the CoC. Allocentric neglect impairment was quantified by subtracting the number of right-gap and left-gap false positives. Allocentric asymmetry more extreme than -1 (right neglect) or 1 (left neglect) represents significant impairment (Demeyere et al., 2015). Allocentric severity is scored as the proportion of allocentric errors committed to number of targets successfully identified.

Participants also completed the SIS at timepoint 2. Total SIS score was calculated by formatting all Likert responses so that low scores represent poor outcomes (e.g. 1 = “could not do at all” and 5 = “not difficult at all”) and subsequently summing all numeric responses(Duncan et

al., 2003). All data collected in this investigation has been made openly available on the Open Science Framework (Foster and Deardorff, 2017) (https://osf.io/wm8v3/).

Statistical Analysis:

All comparisons control for age, sex, stroke severity (NIHSS total), education, and stroke side when applicable. First, two chi-squared tests were performed to determine whether the proportion of patients whose neglect impairment was unrecovered versus recovered at follow-up assessment was equivalent across neglect subtypes and lateralisations. Next, two t-tests (separately for egocentric and allocentric) were conducted to determine whether unrecovered patients initially had more severe impairments at T1. Finally, two repeated-measures ANOVAS (one for egocentric and allocentric) were performed to investigate whether the magnitude of the change in neglect severity between T1 and T2 is proportional for patients with different impairment lateralisation, and with/without chronic neglect. Each ANOVA included: presence/absence of chronic neglect, neglect lateralisation, age, sex, education, and stroke severity (NIHSS total). .

To investigate the second research question, a multiple regression was performed to determine the relationship between acute neglect severity and follow-up functional outcome (SIS score). This regression includes egocentric and allocentric severity, impairment lateralisation, age, sex, stroke severity, handedness, and education as covariates, and evaluates these metrics for co-linearity using Durbin-Watson testing and Variance Inflation Factor analyses. Finally, an ANOVA was conducted to determine whether patients exhibiting different acute neglect subtypes/lateralisations reported significantly different follow-up SIS score.

6.1.3 Results

Neglect Prevalence and Recovery:

142/400 (35.5%) patients exhibited significant neglect at T1. 71 (50%) of these cases involved only egocentric neglect, 41 (28.9%) only allocentric, and 30 (21.1%) cases involved co-occurring egocentric and allocentric impairments. 78 (54.9%) cases were left-lateralised, 57 (40.1%) impacted the right side of space, and 7(4.9%) involved right and left deficits which co-occurred (Costello and Warrington, 1987; Humphreys and Riddoch, 1994). There was a significant difference in stroke severity between patients with egocentric (mean NIHSS score= 4.22) and allocentric (mean NIHSS score = 11.96) in this sample ($t(36.64) = -3.306, p = 0.002$, CI: -12.48 – 2.99). At follow-up, 98/142 (69%) neglect cases had fully recovered. There was no significant difference in the proportion of patients recovered between egocentric and allocentric neglect ($X2(1)=0.66$, $p=0.418$). Similarly, there was no significant association between the lateralisation of neglect and probability of neglect recovery ($X2(2)=0.781$, $p= 0.677$) (Figure 6.3).

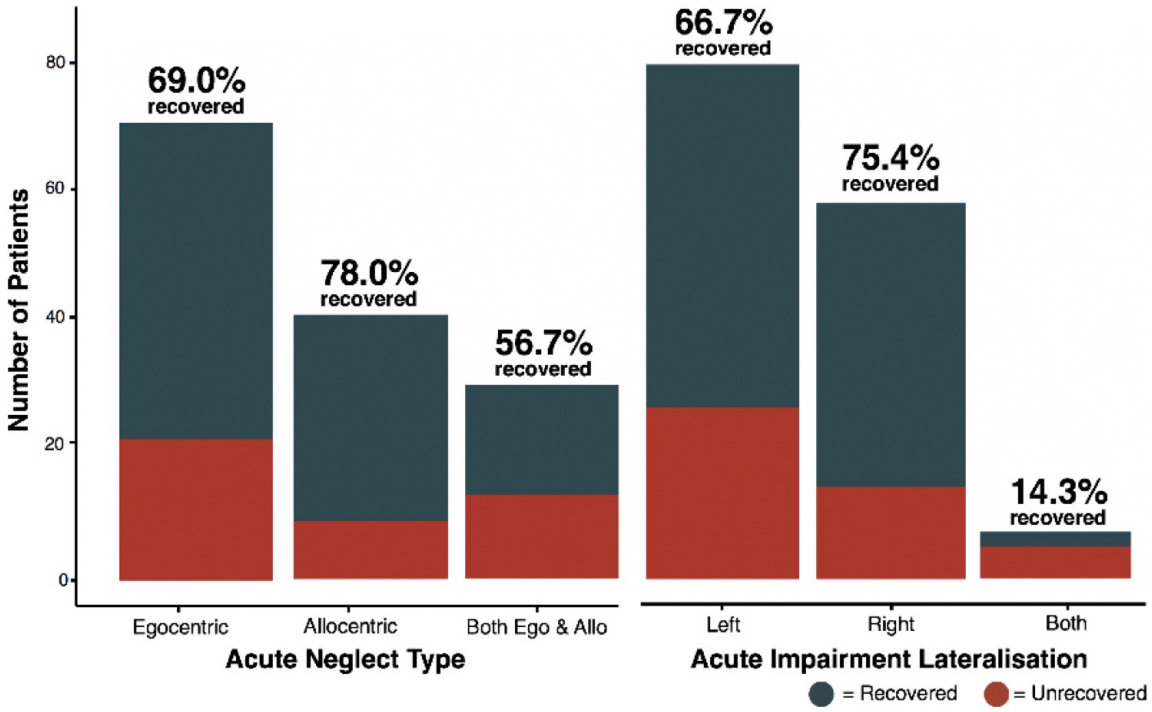


Figure 6.3: Recovery proportions for each neglect subtype and for each lateralisation of neglect, demonstrating no reliable sub-group differences in proportion of neglect impairment at 6 months. Red areas represent patients who had not recovered by follow-up assessment.

Patients with chronic egocentric neglect had significantly more severe acute impairment than those who recovered, (t(34.933)= -2.288, p=0.028), suggesting that egocentric neglect follows a proportional recovery pattern. However, there was no difference in the severity of acute impairment between allocentric patients who did and did not recover (t(22.633= -1.373. p=0.183), suggesting that allocentric neglect follows a non-proportional recovery pattern.

Within egocentric neglect, there was a significant main effect of neglect recovery outcome with more severe cases being less likely to recover than milder cases (F(1,190)=18.311, p<0.001, eta squared=0.115). There was also a significant main effect of stroke severity (F(1,190) = 8.576, p = 0.004, eta squared= 0.54). However, no significant interaction effects were present between change in neglect severity over time and the presence of chronic neglect (F(1,190)=0.003, p=0.985) or between neglect lateralisation and the presence of chronic neglect (F(1,190)=0.2003, p=0.6556). These findings suggest that patients with egocentric neglect exhibit proportional re-

covery and that the rate of recovery is not different for patients with more and less severe neglect, regardless of lateralisation (see Figure 6.4).

Within allocentric neglect, there was a significant interaction effect of change in neglect severity between timepoints and the presence of chronic neglect ($F(1,130)=9.1927$, $p= 0.004$, effect size 2=0.096), demonstrating that allocentric cases do not recover at the same rate. In this analysis there was no significant main effect of stroke severity ($F(1,130) = 3.65$, $p = 0.611$, eta squared= 0.004). Finally, there was no significant interaction effect between lateralisation and the incidence of chronic neglect ($F(1,130)=0.136$, $p=0.713$, eta squared=0.001), suggesting that patients with right and left allocentric neglect do recover at similar rates.

Which factors predict chronic SIS scores?

At the 6 month follow up, patients reported an average SIS total score of 223/300 (SD=44.3, Range=41-295), with lower scores indicating poorer outcome. A multiple regression was performed to investigate the relationship between neglect severity and functional outcome (SIS). This regression included egocentric and allocentric severity, impairment lateralisation, age, sex, stroke severity (NIHSS Score), handedness, and education as covariates (max VIF=1.28, Durbin-Watson=2.17). Overall, this model was found to be significant ($F(9,300)=4.742$, $p<0.001$, adjusted $R2=0.098$, Figure 6.5). Acute allocentric neglect severity ($p=0.006$, Cohen's $f=0.15$) and stroke severity ($p < 0.001$, Cohen's $f=0.23$) were found to be significant predictors of lower functional outcome. Notably, acute egocentric severity did not act as a significant predictor of long-term SIS ($p=0.217$).

Finally, an ANOVA was conducted to investigate the interactions between acute neglect category/lateralisation and chronic SIS. There was a significant overall effect between neglect subtype and SIS score ($F(9,383)=3.393$, $p=0.018$, effect size=0.026). However, there were no significant post-hoc paired differences between different neglect categories (Figure 6.6).

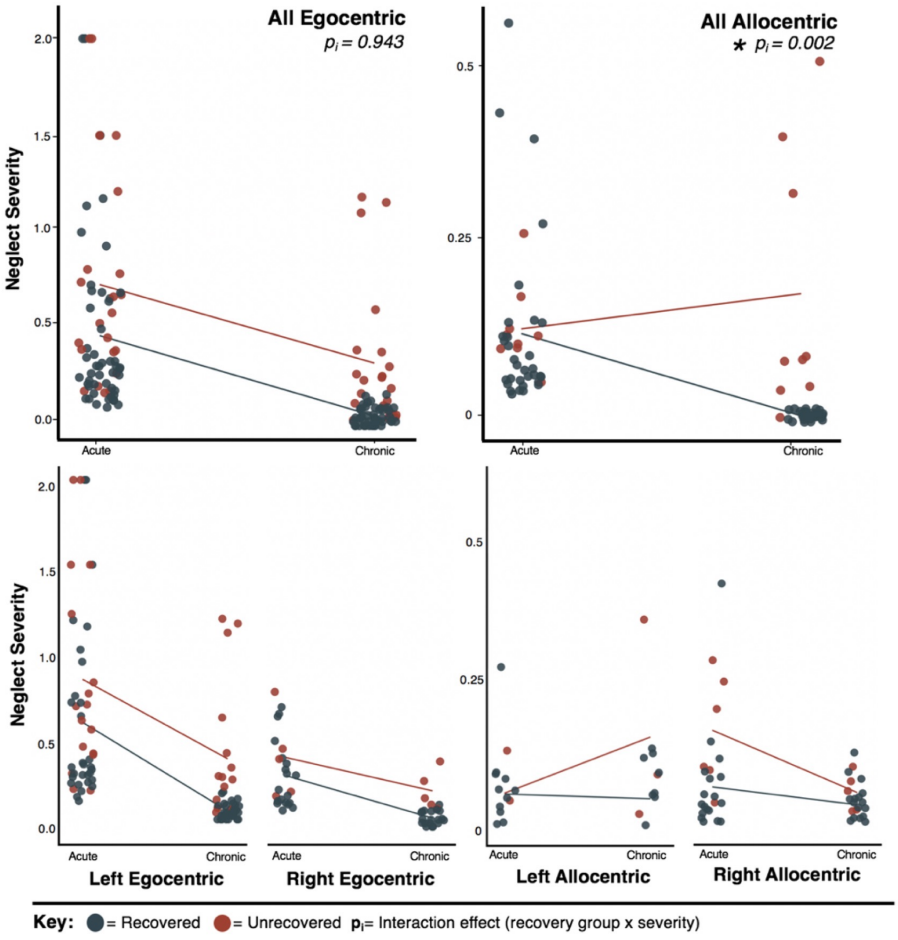


Figure 6.4: The relationship between egocentric neglect severity and allocentric neglect severity (as expressed through absolute values for centre of cancellation) and chronic SIS score. Patients with no neglect have not been plotted in this visualisation. See Figure 3.1.5 for an illustration of the distribution of SIS scores in patients with no neglect.

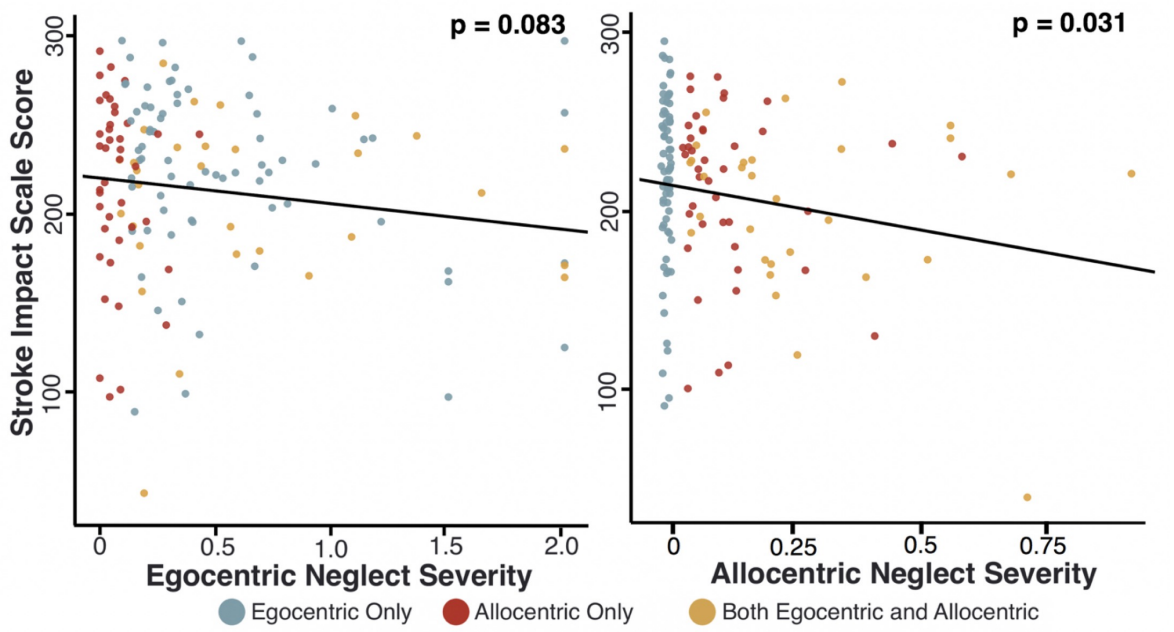


Figure 6.5: The relationship between egocentric neglect severity and allocentric neglect severity (as expressed through absolute values for centre of cancellation) and chronic SIS score. Patients with no neglect have not been plotted in this visualisation. See Figure 6.6 for an illustration of the distribution of SIS scores in patients with no neglect.

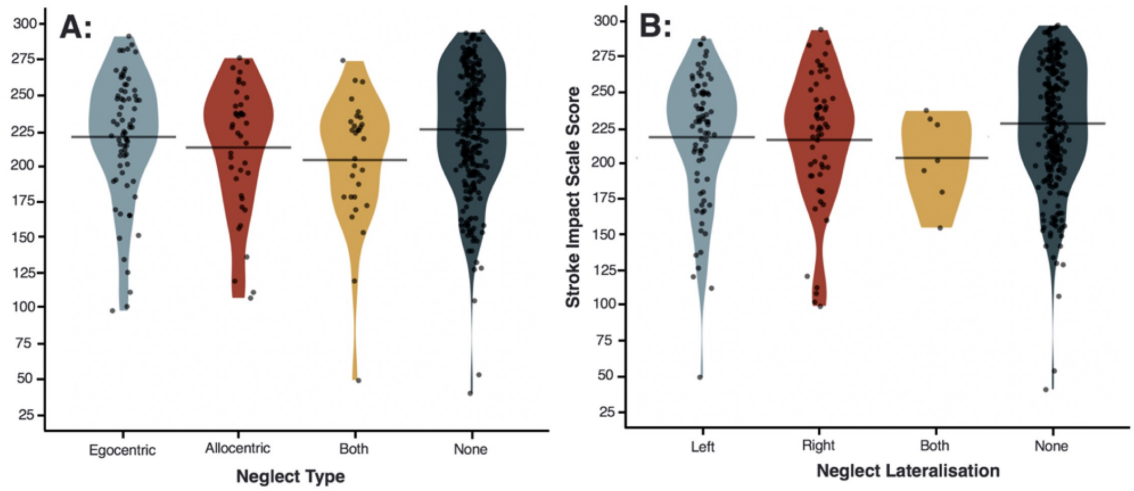


Figure 6.6: The relationship between acute neglect category (Panel A) and lateralisation (Panel B) and chronic SIS score.

6.1.4 Discussion

This study aimed to determine whether visuospatial neglect subtypes act as predictors of long-term outcomes, both with regards to neglect recovery and to broad functional outcomes. Egocentric and allocentric neglect occurred frequently in the acute stroke population and represented doubly dissociated conditions. Both left- and right lateralised neglect deficits were common and, in line with expectations (Ten Brink et al., 2017), left-lateralised neglect was more severe than right neglect. Egocentric neglect exhibited proportional recovery with the severity of acute impairment predicting the severity of chronic impairment. However, allocentric neglect was not found to recover proportionally with a subset of patients remaining unchanged or getting worse over time, regardless of initial severity. The severity of acute allocentric, but not egocentric, neglect acted as a significant predictor of long-term functional outcome. These results highlight the importance of standardised, neuropsychological assessment of post-stroke visuospatial impairments to improve the sensitivity of neglect detection and provide quantitative severity information which can be used to predict functional outcome trajectory and guide intervention pathways.

The results of the present study suggest that egocentric neglect's initial severity modulates the probability of its recovery. Egocentric patients who recovered had less severe acute neglect than patients presenting with chronic neglect at 6 months. Importantly, the rate of egocentric improvement was not different between patients whose impairments did and did not recover. This effect held for patients exhibiting right and left egocentric neglect over and above generalised stroke severity. These findings align with previous studies documenting proportional recovery in egocentric neglect and suggesting that acute severity may be the best indicator of the probability of egocentric neglect recovery (Marchi et al., 2017; Stone et al., 1992).

However, proportional recovery was not found to be present within patients with allocentric neglect. Allocentric patients who recovered by 6 months were not initially less severely impaired than patients whose allocentric neglect did not recover. This pattern is characteristic of non-proportional recovery (Bonkhoff et al., 2019; Hope et al., 2019; Smith et al., 2017). This non-proportional recovery pattern within allocentric neglect aligns well with recent research suggesting that not all post-stroke impairments follow the proportional recovery rule (Bonkhoff et al.,

2019; Hope et al., 2019). Additionally, unrecovered allocentric patients were found to exhibit a significantly different recovery rate than patients whose allocentric neglect did recover. Notably, although patients with allocentric neglect had significantly higher stroke severity than patients with egocentric neglect, stroke severity was not found to significantly predict which cases of allocentric neglect recovered over time. Considered cumulatively, these findings suggest that it is not yet clear how to predict which patients with allocentric neglect will and will not recover from their neglect impairment.

Future research can aim to investigate the recovery of allocentric neglect in more detail, as it appears that this subtype of neglect is more likely to lead to a chronic neglect impairment. Similarly, it is important for future studies to aim to identify additional factors such as behavioural profile or comorbid cognitive impairments which may help distinguish between allocentric neglect patients who do and do not spontaneously recovery. This investigation also considered the impact of neglect lateralisation and severity on functional outcome. With regards to lateralisation, interestingly, there was no significant difference in functional impairment levels reported by patients with right and left lateralised neglect, despite the finding that left neglect was significantly more severe than right neglect on neuropsychological assessments. This effect has been previously identified (Ten Brink et al., 2017), but it is not clear which factors are responsible for driving it. It seems plausible that right neglect may result in a disproportionally high impact on functional activity relative to impairment severity, as left hemisphere damage may be more likely to reduce patient's ability to use their dominant hand, and include language and communication impairments which may affect overall functional outcomes in a broad measure such as the SIS. Further research is needed to investigate this possibility in detail.

The quantitative severity of acute allocentric neglect impairment was found to act as a significant predictor of poor long-term functional outcome while the severity of acute egocentric neglect was not. Patients with more severe allocentric neglect at the acute timepoint were found to report higher levels of domain-general functional impairment at chronic assessment, regardless of whether or not their neglect had recovered. This effect could potentially be explained by a comparatively more severe impact of allocentric neglect impairment on daily life activities. Patients with

egocentric neglect may be able to orient or adjust their environments to help compensate for their neglect, but it is unclear whether patients with allocentric-level deficits would benefit from similar compensation strategies. Similarly, allocentric neglect may impact performance within specific activities (e.g. reading individual words, identifying/manipulating objects) which may be comparatively unaffected by egocentric neglect. Additional research is needed to clarify how egocentric and allocentric neglect deficits differentially impact on functional activities.

Considered cumulatively, the findings of this study emphasize the importance of employing standardised, neuropsychological assessments of neglect within clinical environments. Detecting and determining the severity of allocentric neglect can help identify patients which are least likely to spontaneously recover and are most likely to experience lower levels of functional outcome, but this impairment is not commonly screened for after stroke. However, many commonly used neglect assessments are not able to reliably detect allocentric neglect, resulting in the omission of information which can help identify patients likely to experience poorer functional outcomes. Implementing standardised administration of neuropsychological neglect assessments is critically important in order to sensitively detect neglect impairments, to assign quantitative neglect severity scores, and to identify neglect patients who are most likely to benefit from targeted neglect-specific rehabilitation programmes (Bickerton et al., 2011; Demeyere et al., 2015; Ota et al., 2001). Based on the current data, neglect intervention research may need to focus on rehabilitation specifically for those with more severe neglect impairments and those with allocentric neglect.

This investigation also highlights the need for future neglect research to accurately represent the diversity of neglect behavioural impairments to produce generalisable findings. Studies which consider only a restricted subset of neglect impairment (e.g. restricting sample to only left egocentric neglect after right hemisphere damage) are likely not representative of neglect as a whole and as it presents in acute clinical settings. Differences in patient inclusion criteria can help explain why many past investigations have provided conflicting findings pertaining to the prevalence (Bowen et al., 1999; Rorden and Karnath, 2010; Stone et al., 1993), underlying neural mechanisms (Chechlacz, Rotshtein, and Humphreys, 2012; Karnath et al., 2002; Karnath and Rorden, 2012), and functional impact of neglect impairment (Cherney et al., 2001; Jehkonen et

al., 2000a; Katz et al., 1999). Similarly, future investigations should aim to determine whether neglect uniformly impacts across all aspects of functional recovery, or whether a single component of this broad, encompassing concept (e.g. activities of daily living, mood) may be responsible for driving the predictive relationship between neglect and poor functional outcome. It is therefore critically important for future neglect research to adequately represent this syndrome's behavioural diversity as conceptualising neglect as a unitary syndrome rather than a cluster of interrelated impairments may preclude valid conclusions about the disorder as a whole.

Most importantly, the findings of this investigation reveal that patients with allocentric neglect may represent a key group for research for targeted, neglect-specific rehabilitation. The vast majority of existing neglect rehabilitation strategies are designed to ameliorate the effects of egocentric neglect (Bowen and Lincoln, 2007; Ten Brink, Visser-Meily, et al., 2017; Yang et al., 2013). It seems likely that many of these strategies would be ineffective for patients with allocentric impairment. For example, rehabilitation strategies such as prism adaptation help shift attention towards a neglected hemifield but would likely not impact an attentional bias which is not mediated by viewer-centred impairments (Bowen and Lincoln, 2007). Pharmaceutical and transcranial stimulation based rehabilitation strategies may face similar challenges (Yang et al., 2013). However, some rehabilitation studies which could plausible impact the severity of both egocentric and allocentric neglect have been proposed (Yang et al., 2013). Approaches based on phasic alerting (Robertson et al., 1998), vestibular stimulation (Agrell et al., 2013), neck muscle vibration (Johannsen et al., 2003), or motor feedback training (Rossit et al., 2019) seem potentially appropriate for ameliorating allocentric neglect symptoms. However, the impact of these rehabilitation therapies on allocentric-level attentional biases have not yet been adequately investigated in large and representative samples of neglect patients. It is not clear how allocentric neglect impacts behaviour, and understanding this impact is likely a necessary precursor to identifying effective rehabilitation strategies.

Limitations:

SIS scores are self-reported and are therefore vulnerable to response biases. In addition,

some visuospatial neglect patients may also exhibit anosognosia (Vossel et al., 2013). Nevertheless, this association may influence functional self-report data and lead to some underestimation of functional impairment levels. Given that this study is a secondary analysis, the large sample data came at the cost of detailed stroke and additional potentially informative data. For example, T1 functional assessments, tests for additional neglect signs (e.g. anosognosia), rehabilitation programme information, detailed stroke anatomy, or diagnoses of additional neglect subtypes were not available.

Importantly, egocentric and allocentric neglect are not the only subtypes of visuospatial neglect. Given that this investigation demonstrated that egocentric and allocentric neglect may follow different recovery trajectories, it seems plausible that other neglect subtypes, not considered within this investigation, may be differentially associated with long term recovery as well. Future research should therefore aim to elucidate the recovery trajectories associated with additional visuospatial neglect subtypes.

Critically, this investigation aimed to determine predictors rather than causes of poor recovery outcome. The identified significant relationship between acute allocentric neglect and poor recovery outcome should therefore not be interpreted as a causal relationship but instead as a correlational effect which may help clinicians predict which patients may experience reduced functional outcome in later stroke recovery phases. A number of factors including overall stroke severity, age of onset, cognitive reserve, and psychosocial factors have been shown to be significantly related to stroke recovery trajectories (Colantonio et al., 1993; Hankey et al., 2007; Loewen and Anderson, 1990). Additionally, comorbid cognitive and physical impairments including motor and sensory impairments may act as important predictors of recovery outcomes (Hankey et al., 2007). For this reason, any individual factor noted here, should not be understood as a standalone predictor of stroke recovery but instead only explains a small portion of variance. Clinicians should therefore employ a wholistic approach considering the impact multiple factors such as overall stroke severity, age of onset, co-morbid impairments, cognitive reserve, and psychosocial factors rather than any one source of information to make informed prognoses.

Importantly, this study does not aim to develop a quantitative prognostic model, but instead to

investigate whether specific neglect subtypes are differentially associated with lasting impairment and functional outcomes.

Conclusion: The findings of this section illustrate that considering the subtype and quantitative severity of visuospatial neglect provides information which can be applied to identify patients who are more likely to end up living with chronic neglect. These findings highlight the need for standardised neuropsychological neglect assessments and for the development of allocentric-specific rehabilitation strategies.

6.2 Chapter 3.2: A Multiverse Analysis of the Relationship between Visuospatial Neglect and Poor Functional Recovery Outcome

6.2.1 Introduction

Conducting any research study inevitably involves choosing a specific analysis design from a multitude of possible methodologies. It is often unclear how these inherent, yet arbitrary methodological choices ultimately impact the final conclusions of any single study. It is plausible that the results of any one individual analysis can be drastically skewed, and therefore unrepresentative due to the specific combination of methodological choices made by the researchers. Due to this possibility, it is not yet clear whether the relationship between neglect and poor functional outcome is a robust effect present across various patient groups and outcome measures or whether this relationship is an ungeneralizable, statistical abnormality created by the specific combination of methodological choices employed. This section aims to employ multiverse analysis to evaluate the robustness and generalisability of the predictive relationship between neglect and poor functional outcome.

Multiverse analysis provides an ideal methodology for evaluating the impact of arbitrary design choices on the conclusions of neurological research (Dragicevic et al., 2019; Steegen et al., 2016). In a multiverse analysis, a large number of potential datasets are generated by making each possible permutation of reasonable methodological choices within a single experiment. Each of these datasets are then independently analysed, and the cumulative results are used to evaluate the overall robustness of the effect of interest. Critically, multiverse analysis clarifies which specific methodological choices may lead to significant effects. This analysis technique provides a useful method for evaluating the impact arbitrary inclusion criteria, outcome measure, and analysis choices have on the conclusions of research within neurological populations.

A substantial body of evidence has found that the occurrence of acute visuospatial neglect acts as a strong predictor of poor functional recovery outcome in stroke survivors (Bickerton et al., 2011; Cherney et al., 2001; Jehkonen et al., 2000b; Katz et al., 1999). However, each previous investigation on this topic has made specific methodological choices which may potentially have a significant impact on the study's results. For example, some previous investigations of relationship

between acute visual neglect and poor functional outcome have included a sample restricted to only patients with right hemisphere damage (Jehkonen et al., 2000b). Neglect following right damage is significantly more severe than neglect following left lesions (Bickerton et al., 2011; Stone et al., 1992; Ten Brink et al., 2017). Therefore, including only right hemisphere patients in visuospatial neglect studies could potentially result in a sample which is biased towards more severe neglect cases.

Similarly, previous studies have included samples of neglect patients recruited at different timepoints following stroke (Bickerton et al., 2011; Nys et al., 2006). Previous research has suggested that neglect follows a non-linear recovery trajectory throughout the first six months following stroke, with most spontaneous recovery occurring within the first ten days following stroke (Stone et al., 1992). This suggests that the "neglect" groups within more acute samples will include patients which will have recovered by later timepoints and would therefore not be included in the "neglect" groups of studies who recruit patients at a later timepoint. Finally, many studies investigating the relationship between neglect and functional outcome have exclusively included patients with egocentric neglect and have not included tests of allocentric neglect (Cherney et al., 2001; Jehkonen et al., 2000b; Nys et al., 2006; Stone et al., 1992). It therefore remains whether these restricted and potentially biased samples are adequately representative of neglect.

Given that research investigating the predictive relationship between neglect and poor functional outcome in stroke survivors inherently requires such a wide range of methodological choices, this topic of research is ideal for investigating the utility of multiverse analysis techniques within neurological patient research. The purpose of this study is to demonstrate the utility of multiverse analysis techniques for evaluating the robustness and generalisability of effects documented within neurological populations.

6.2.2 Methods

This project represents a secondary analysis of longitudinal data collected as part of the Oxford Cognitive Screen (OCS) study (Demeyere et al., 2015 - REC reference 11/WM/0299), OCS-Tablet Cognitive Screening study (REC reference 14/LO/0648) and OCS-Care study (Demeyere

et al., 2019 – REC reference 12/WM/00335). All 3 studies included acute cognitive screening and 6 month follow ups. All patients provided informed consent in line with the Declaration of Helsinki.

Participants:

Participants were included in this investigation if they had completed the OCS Cancellation Task during initial hospitalisation and had completed at least one functional outcome measure during either acute hospitalisation or follow-up.

Importantly, to accurately reflect the clinical reality in stroke, patients were not excluded based on stroke type, stroke side, or pre-existing neurological conditions, such as previous stroke. A total of 1159 patients (mean age = 72.5 years (SD = 13.7, range = 18-97), 45.1% female, average education = 11.9 years (SD = 3.82), 7.8% left handed) were included in this study. These participants had an average NIHSS score of 3 (SD = 3.82 , range = 0 - 22).

Stroke types of the final sample were reported as 909 ischemic, 173 haemorrhagic, 20 TIA, 6 unknown, and 51 not reported. Lesion sides were reported as 466 right, 415 left, 62 bilateral, 148 not visible, and 68 not reported. The average stroke-test interval was 8.1 days (SD = 15.4) days. This participant group was divided into 400 subgroups, each selected based on a plausible combination of lesion location, stroke type, assessment time, and minimum score inclusion criteria (Table 6.2).

Table 6.2: A visualisation of the four different grouping factors considered when creating multiverse subsamples. For each subsample, one option from each grouping factor was selected, yielding 400 unique patient groups. Hem = Hemisphere, d = days, m = months

Inclusion Criteria				**Impairment Definition**	
Lesion Location	**Stroke Type**	**Assessment Time**		**Neglect Definition**	**Scoring Criteria**
Right Hem.	Ischemic	<7 d	< 2 M	Egocentric Only	Total Score <42 +
Left Hem.	Haemorrhagic	<14 d	> 1 M	Allocentirc Only	Asymmetry
Not Bilateral	Not a TIA	>7d & <1M	Known Time	Both Ego + Allo	
Any Visible	Any Known	< 1 M	Unrestricted	Any Neglect	Asymmetry Only
Unrestricted	Unrestricted				

Materials:

Each participant in this investigation completed the OCS Cancellation task (Demeyere et al.,

2015) acutely and at least one standardised functional outcome measure at 6 months follow-up. Here we considered measures of activities of daily life (including subscales), level of remaining stroke severity, measures of mood, and measures of quality of life. See Table 6.3 for a full list of all considered functional outcome measures. Given that not all previous investigations have considered both egocentric and allocentric neglect impairment, four different methods for grouping participants into neglect/no neglect groups were employed. In the first instance, egocentric impairment alone was considered as the "neglect" category while all other patients were categorised as "no neglect". Next, allocentric neglect impairment alone was considered. In a third grouping, patients were required to exhibit both allocentric and egocentric neglect to be added to the "neglect" group. In the final instance, patients with any neglect impairment, regardless of the type, were grouped into the "neglect" group.

Planned Analysis:

Multiverse analysis was employed to compare the level of functional impairment in patients with and without neglect. Multiverse analysis involves multiple permutations of any single base analysis (e.g. regression, t-test, ANOVA). Given this investigation aims to compare a series of continuous variables (e.g. outcome measures) between two categorical groups (neglect vs. no neglect), a t-test base analysis was employed. This base t-test analysis was performed for each possible permutation patient group (n = 200), method of grouping neglect/no neglect patients (n = 4), outcome measure (n = 16), and scoring method (n = 2) yielding 25,600 individual t-tests. Of these tests, only combinations leading to comparisons involving at least 5 neglect and 5 no-neglect participants were considered in subsequent analyses, resulting in a final sample of 18,898 valid comparisons. In line with multiverse methodology, and given that this analysis aims to simulate the findings of all potential individual analyses which could be conducted in isolation, no correction for multiple comparisons are employed (Dragicevic et al., 2019; Steegen et al., 2016).

First, a specification curve analysis (Simonsohn et al., 2019) was conducted to evaluate the directionality and robustness of differences between participants with and without neglect. This analysis employed a null curve created by conducting all potential t-test analyses, but with partic-

Table 6.3: A list of the outcome measures considered within this investigation. N represents the number of participants for which data was available for each outcome measure. The Time column reports whether the assessment was delivered during acute hospitalization or at 6-month follow up. SIS = Stroke Impact Scale, NIHSS = National Institute of Health Stroke Scale, ADL = Activities of Daily Living, IADL = Instrumental Activities of Daily Living, HADS = Hospital Anxiety and Depression Scale. Max scores which are marked with a star denote tests in which a higher score represent worse functional outcome. These scores are inverted in all subsequent analyses. SIS total is the combined total of all SIS subtests. SIS ADL Total is the combined total of both SIS ADL measures.

Measure	Reference	Max Score	Time	N	Mean (SD)
SIS Total	(Duncan et al., 1999)	300	Follow-up	465	222.3 (46.3)
SIS ADL Total	(Duncan et al., 1999)	90	Follow-up	462	66.2 (17.5)
SIS Physical Weakness	(Duncan et al., 1999)	20	Follow-up	451	14.5 (4.5)
SIS Memory	(Duncan et al., 1999)	35	Follow-up	465	28.8 (6.2)
SIS Mood	(Duncan et al., 1999)	45	Follow-up	462	32.7 (6.4)
SIS Communication	(Duncan et al., 1999)	35	Follow-up	460	31.0 (5.0)
SIS Mobility	(Duncan et al., 1999)	45	Follow-up	464	34.2 (9.8)
SIS ADL	(Duncan et al., 1999)	45	Follow-up	462	39.2 (10.1)
SIS Affected Hand	(Duncan et al., 1999)	25	Follow-up	449	17.5 (6.9)
SIS IADL	(Duncan et al., 1999)	45	Follow-up	457	27.4 (9.05)
NIHSS	(Lyden, 2017)	42	Acute	319	4.3 (3.8)
Quality of Life	(Al-Janabi et al., 2012)	20	Follow-up	519	15.2 (3.1)
HADS Depression	(Bjelland et al., 2002)	21	Follow-up	491	5.5 (4.0)
HADS Anxiety	(Bjelland et al., 2002)	21	Follow-up	484	6.2 (3.9)
Carer Strain Index	(Robinson, 1983)	13	Follow-up	145	7.6 (5.7)
Barthel Index	(Quinn et al., 2011)	100	Acute	517	17.4 (4.1)

ipants randomly allocated to neglect/no neglect comparison groups. The overall generalisability of acute neglect's relationship with poor functional outcome was analysed by first evaluating the overall proportion of conducted comparisons met traditional significance thresholds. Subsequent analyses aimed to identify sources of biases within these significant results by comparing average effect sizes across comparisons which employed different selection criteria.

6.2.3 Results

Specification Curve Analysis:

First, a specification curve analysis was conducted (Figure 6.7). Given the standard alpha level of 0.05, if no effect was present within the analysed data, approximately 5% of comparisons would be expected to yield significant results. However, 33.9% of the conducted comparisons were found to be statistically significant. These significant comparisons had an average effect size of -0.485 (SD = 0.327, range = -3.87 – 0.552, 25th Quantile = -0.523, 75th Quantile = -0.334). This negative overall effect size indicates that as a whole, neglect was found to be associated with poorer performance across the various functional outcome measures.

The robustness of this result was then evaluated by comparing this experimental specification curve to a null curve. The null curve representing randomly-allocated comparisons contained 3272/19200 (17.0%) significant results with an average effect size of 0.163 (SD = 0.387, range = -1.23 – 1.12, 25th Quantile = -0.239, 75th Quantile = 0.375). 99.9% of statistically significant experimental curve comparisons were found to fall below the null curve 25th quantile boundary (Figure 6.7). In line with interpretations of the null curve in Simonsohn et al. (2019), this finding illustrates that the relationship between neglect and poor functional outcome is highly robust and significant across may possible methodological combinations.

Evaluating the Impact of Methodological Decisions:

Despite the robustness of the relationship between neglect and poor functional outcome, significant variance was present within the effect sizes of individual significant comparisons. For this reason, additional analyses were conducted to evaluate the impact of specific methodological

choices on resulting effect sizes.

Given that the number of participants with available data was found to vary dramatically across outcome measures, the impact of sample size on the proportion of significant results was then investigated. Comparisons involving less than 100 participants were found to yield only 12.1% significant results while 46.5% of comparisons with 200-299 participants, and 100% of the comparisons including more than 500 participants yielded significant results. Figure 6.8 presents a visualisation of the relationship between sample size and proportion of significant results.

Next, the impact of using different outcome measures was evaluated. Average effect sizes were found to vary across outcome measures ranging from -0.28 (HADS Depression) to -0.68 (NIHSS). Overall, comparisons involving HADS Depression (M = -0.28, SD = 0.08), SIS IADL (M = -0.32, SD = 0.07), SIS Mood (M = -0.40, SD = 0.16) and Quality of Life (M = -0.34, SD = 0.09) were found to result in the weakest effects and comparisons involving NIHSS (M = -0.68, SD = 0.29), SIS ADL (M = -0.63, SD = 0.22), SIS Total (M = -0.57, SD = 0.41), and SIS Communication (M = -0.55, SD = 0.63) were found to be the strongest (Figure 6.9). However, comparisons involving SIS ADL, SIS ADL Total, SIS Physical Weakness, and SIS Total were found to yield the highest proportion of significant results (Figure 6.9).

The Impact of Significant Choice Combinations:

Figure 6.10 presents a visualisation of the impact of specific methodological choice combinations on comparison effect size. Given that many of the conducted comparisons involve small sample sizes which are associated with unreliable effect sizes (Kühberger et al., 2014; Lakens and Evers, 2014) , only comparisons involving samples of at least 108 participants are included in this comparison (n = 13,736). This inclusion threshold was determined by calculating the minimum sample size needed to detect the average significant effect size (-0.485) with a power of 0.80.

Overall, the choice of outcome measure was found to have the greatest impact on comparison effect size across choice combinations with the average effect size ranging between -0.464 (SIS ADL) and -.0.113 (HADS Depression). Notably, these consistently negative average effect

sizes demonstrate that acute neglect was associated with poor performance across all employed outcome measures. Other selection criteria led to similar ranges in average effect size. Comparisons which included all patients, regardless of lesion type resulted in stronger effects (mean effect = -0.310) than those which included patients with only right (-0.284) or left (-0.259) hemisphere damage (Figure 6.10). Similarly, analyses which considered allocentric neglect impairment generally resulted in stronger effects than those which considered only egocentric neglect impairment (-0.250). Comparisons which required participants to have significant asymmetry scores as well as total scores of <42 in order to be classified as exhibiting egocentric neglect (mean = -0.328) resulted in stronger average effect sizes than those which only required significant asymmetry scores (mean = -0.268). Assessment time and stroke type and selection criteria resulted in comparatively little variance within average effect sizes.

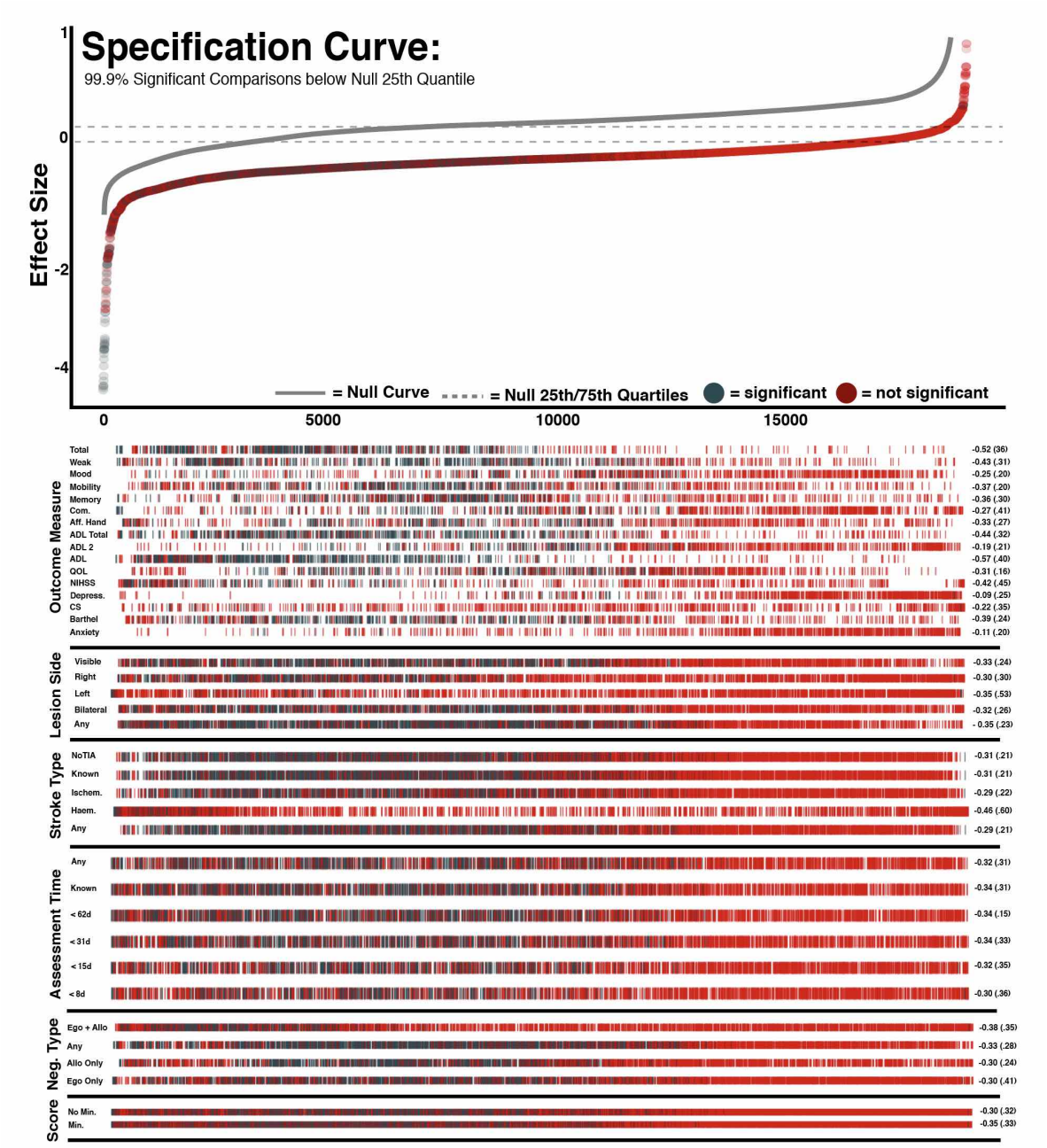


Figure 6.7: The upper panel presents a specification curve analysis presenting the effect sizes of all experimental and null comparisons ranked in order of size on the x-axis. Significant comparisons are represented in blue, insignificant results are visualised in red, and null curve comparisons are represented in grey. Dotted lines denote the 25th and 75th quantile of the null curve. 99.9% of experimental comparisons fell below the 25th quantile of the null curve, suggesting that neglect illustrates that the relationship between neglect and poor functional outcome is highly robust and significant across may possible methodological combinations. The lower panels visualise each specific combination of methodological comparisons used in each individual comparison. The average effect size and standard deviation of comparisons using each methodological option are listed to the right of each row. CS = Carer Strain, QOL = Quality of Life, ADL 2 = SIS Instrumental ADL, Com. = SIS communication, AffHand = SIS Affected Hand, Weak = SIS Physical Weakness, Not BL = Not Bilateral, Ego = Egocentric, Allo = Allocentric.

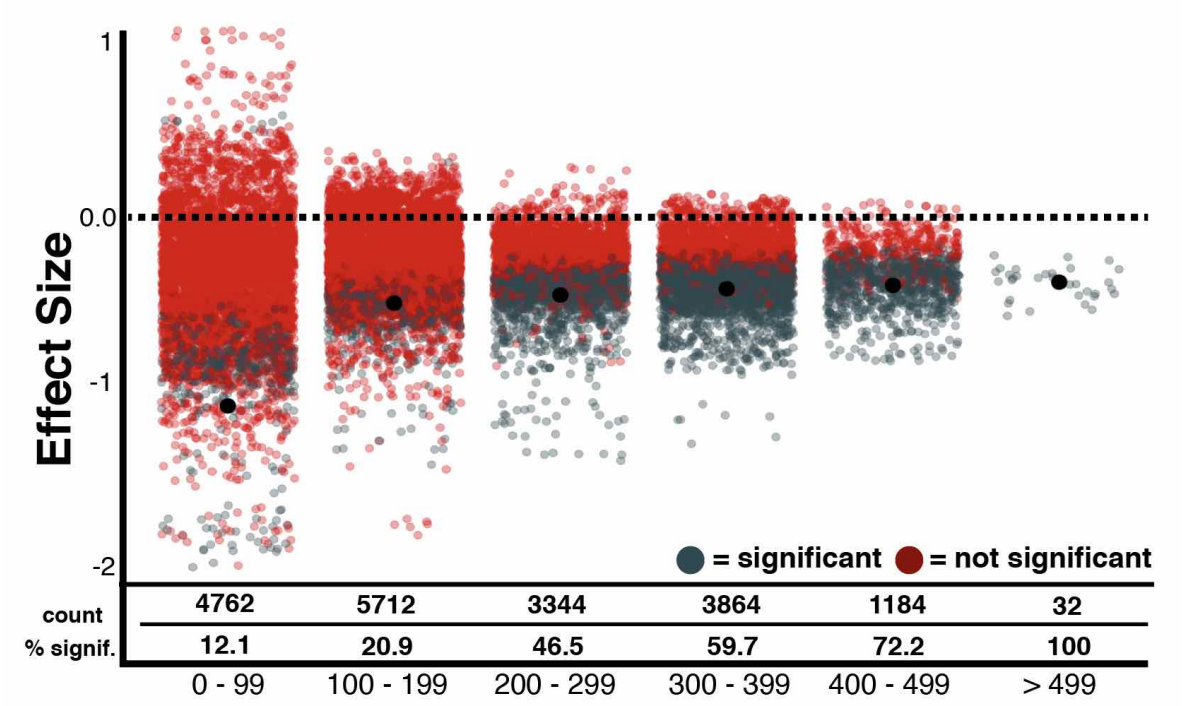


Figure 6.8: The effect sizes of each conducted comparison grouped by sample size (x-axis). Significant comparisons are presented in blue while insignificant comparisons are in red. Black dots represent the mean effect size of each group. The number of comparisons and overall percent significant results within each group are presented.

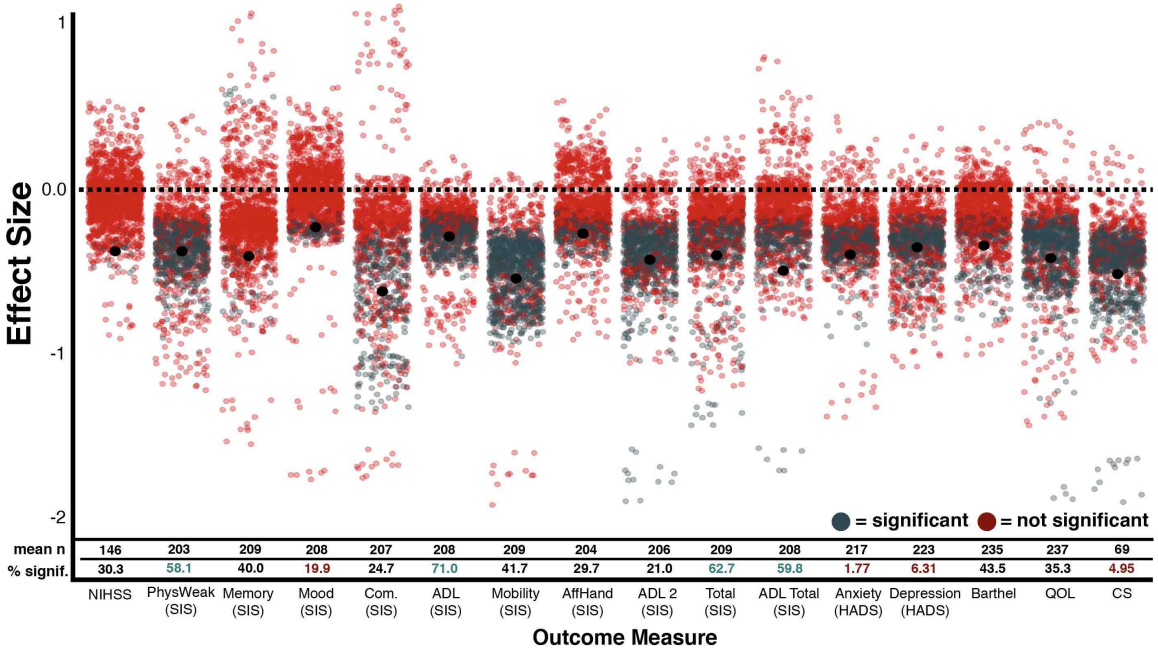


Figure 6.9: The effect sizes of each conducted comparison grouped by outcome measure (x-axis). Significant comparisons are presented in blue while insignificant comparisons are in red. Black dots represent the mean effect size of each group. The number of comparisons and overall percent significant results within each group are presented. Notably, all outcome measures resulted in an average negative effect size, indicating a robust relationship between the occurrence of acute neglect and poor functional outcome.

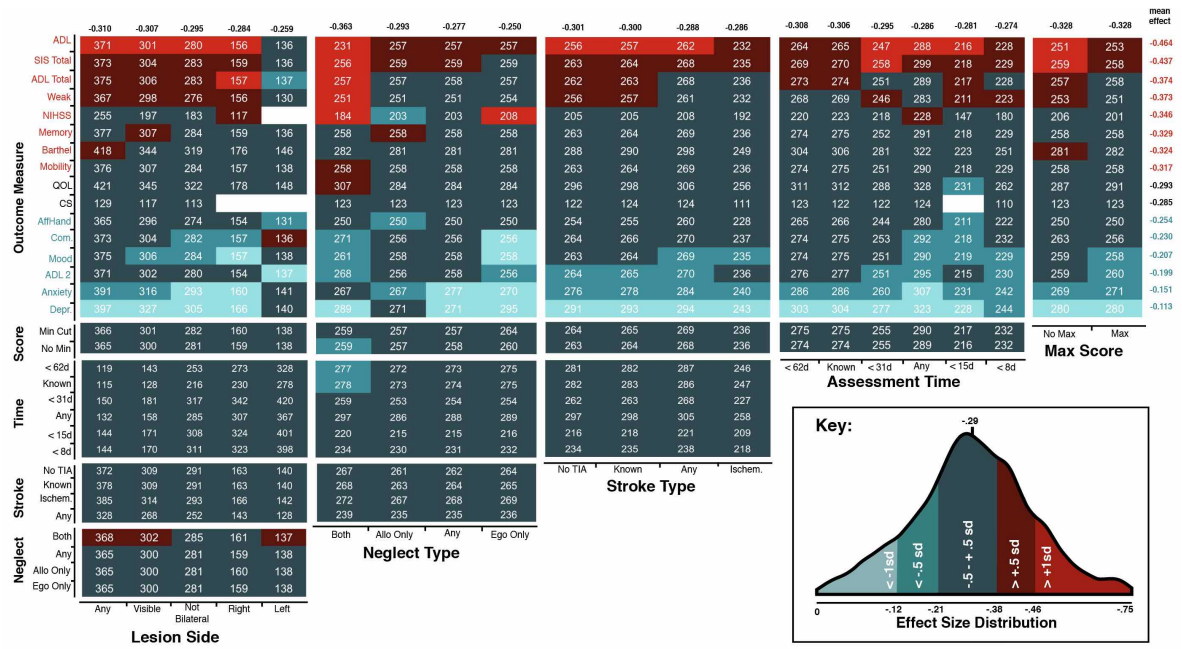


Figure 6.10: A visualisation of the impact of individual methodological choices on effect size. Each box represents the combination of two specific methodological choices listed on the x and y axes. Box colour represents the average effect size of comparisons which employed each specific combination of choices (See Key). Boxes are labelled with average sample size. The average effect size of each choice across all conducted comparisons is also reported. Red total values represent average effect sizes which are significantly higher than the overall mean effect and blue values represent average effects which are significantly lower than the mean effect as determined by t-tests. Only comparisons which are sufficiently powered to detect the average significant effect size (-0.56) are included in this figure (n > 105).

6.2.4 Discussion

The purpose of this investigation was to demonstrate the utility of multiverse analysis techniques for evaluating the strength and generalisability of effects documented within neurological populations. Overall, multiverse analysis suggests that the predictive relationship between acute visuospatial neglect and poor functional outcome is a particularly robust effect present across a range of outcome measures, patient groups, and scoring criteria. However, the strength of this effect was not constant across all comparisons.

This analysis demonstrates that it is critically important to ensure future neurological studies are adequately powered. In this investigation, comparisons employing sample sizes less than 100 were significantly less likely to detect effects which were reliably present when larger cohorts were considered. The risks associated with employing small sample sizes have been well-documented (Cohen, 1992; Maxwell, 2004; Turner et al., 2013). Conducting neurological investigations which are not powered to produce informative null results risks using valuable time and financial resources inefficiently. For example, if an underpowered study investigating a new Parkinson's Disease treatment produces a null result, it is impossible to determine whether the treatment was actually ineffective or whether the sample was simply not large enough to detect a small, but reliable effect. Additional, adequately powered studies are required to resolve this ambiguity, resulting in inefficiently used resources and significant delays in identifying feasible treatment options. It is therefore critically important to assure that future neurological investigations are adequately powered.

Methodological choices relating to outcome measure used, stroke lateralisation, neglect categorisation criteria, and scoring method created substantial variance within resultant effect sizes. Patients with neglect were found to have comparatively worse functional outcomes across each of the 16 outcome measures employed within this investigation. However, the average effect size of these comparisons varied dramatically between outcome measures. Neglect was found to have the weakest average impact on mood and communication measures and the strongest impact on measures assessing Activities of Daily Living. Interestingly, employing SIS ADL resulted in the strongest average effect sizes while employing the SIS IADL measure resulted in

one of the weakest. The SIS ADL sub-measure aims to investigate mainly self-care actives and includes questions about personal hygiene, household chores, and continence. Conversely, the SIS IADL measure assesses more participation-based metrics and includes questions pertaining to social activities, hobbies, and interpersonal relationships (Duncan et al., 1999). The results of the present investigation suggests that neglect may impact more heavily on self-care activities than on relational or participation-based activities.

Comparisons which included all patients, regardless of lesion type resulted in stronger than those which included patients with only right or left hemisphere damage. Similarly, the precise definition of neglect impairment employed within these comparisons was found to impact resultant effect sizes. Comparisons which exclusively considered egocentric neglect were found to result in weaker effect sizes than comparisons which considered allocentric neglect. Analyses including only participants exhibiting both egocentric and allocentric neglect resulted in stronger effect sizes than those which included egocentric or allocentric patients alone. These findings align with previous research suggesting that the relationship between acute neglect and poor longer term functional outcome may not be uniform across all patients with neglect, but may instead vary significantly across different subtypes of neglect (Bickerton et al., 2011). The results of this investigation indicate that it is critically important to employ a representative sample of neglect including patients with right and left lesions and egocentric and allocentric impairment. The inclusion of more representative samples will facilitate results which can be generalised to the stroke population as a whole, rather than to just a subset of patients.

These results suggest that if an investigation into the relationship between neglect and poor functional outcome is solely aiming to produce significant results, it should only include patients exhibiting both egocentric and allocentric neglect and employ an activities of daily living outcome measure. However, maximising the probability of finding significant effects does not necessarily correlate with maximising the quality and utility of information provided by a study. In order to produce clinically useful information, future neurological studies should prioritising producing findings which are generalisable over findings which are simply significant. For this reason, it is critically important for future neurological investigations to include samples which accurately represent the

variation present within the population of interest. In addition, multiverse analysis techniques should retrospectively employed to identify potential sources of bias within existing literature.

Multiverse analysis provides a novel method for evaluating the robustness of effects documented within neurological populations. This approach is particularly useful for neurological studies as it enables researchers to distinguish between large-scale drivers of phenomena and delicate, ungeneralizable effects which are dependent on the exact methodological techniques employed. Multiverse analysis enables researchers to isolate the impact of specific methodological decisions and evaluate the generalisability of their findings to wider patient populations.

Conclusion:

This section demonstrates the utility of multiverse analysis techniques within neurological research. Future investigations can aim to employ multiverse techniques to evaluate the generalisability and potential sources of bias within neurological investigations.

6.3 Chapter 3.3: Aligning formal and functional assessments of Visuospatial Neglect: a mixed methods study

6.3.1 Introduction

Existing literature has strongly suggested that visuospatial neglect in acute stroke is associated with poor functional outcome (Cherney et al., 2001; Jehkonen et al., 2000a; Katz et al., 1999; Chapter 3, Sections 1 and 2). This particularly robust effect has been documented across a wide range of functional outcome measures. However, studies have focused on identifying domain-general functional impairment rather than specific behavioural patterns in patients exhibiting neglect. For example, investigations which have employed standardised questionnaires as outcome measures have identified differences in aggregate scores rather than specific behavioural patterns which may differ between patients with and without visuospatial neglect impairment (Bickerton et al., 2011; Cherney et al., 2001; Jehkonen et al., 2000a; Katz et al., 1999). For example, Cherney et al. (2001) found that the severity of acute neglect was correlated with total, motor, and cognitive Functional Independence Measure (Oczkowski and Barreca, 1993) scores, but did not investigate whether specific items on this scale (e.g. upper body dressing, social cognition) were more common amongst patients with neglect than within patients without neglect. In order to guide therapists and care workers toward the best approach for assisting participants with neglect deficits, it is crucial to identify the specific functional impairments in activities of daily life and how they align with formal test scores on an abstract cancellation task.

This knowledge gap can be addressed by employing qualitative data from occupational therapist notes collected as a standard component of post-stroke functional assessment. (Baum et al., 2008; Mohapatra and Kulnik, 2021). In order to assess stroke survivor's suitability for discharge, occupational therapists regularly conduct structured, observational assessments to determine patient's ability to complete common daily life activities (Katz et al., 2000; Mohapatra and Kulnik, 2021). Two of the most common classes of these real-world observational assessments are kitchen-related tasks and wash and dress assessments. In a kitchen-related assessment, a therapist might ask a patient to prepare a simple meal or a hot drink in a real-world kitchen environment. Therapists then observe patients completing the assigned task, whilst taking note

of any notable behavioural patterns (Baum et al., 2008; Mohapatra and Kulnik, 2021). These behaviours of interest range from motor impairments (e.g. balance, coordination) to cognitive deficits (e.g. memory, task sequencing) and any other behaviours which might prove dangerous following discharge (e.g. forgetting to turn off a stove burner). In a wash and dress assessment, an occupational therapist observes a patient as they wash and dress themselves in a manner as similar as possible to what they would normally do at home or would expect to do following discharge (Ebrahim et al., 1985; Walker and Lincoln, 1991; Whiting and Lincoln, 1980). Therapists take note of behaviours including patients' mobility, range of movement, cognition, mood, and general independence while washing and dressing. Findings from these functional assessments are then employed to inform discharge date, destination, and level of required assistance.

Therapists' notes collected as a component of these standard assessments offer a wealth of data which can be employed to identify observed patterns of behavioural impairment associated with common post-stroke impairments. Previous research has established strong correlations between kitchen-related task performance and neuropsychological memory, language, and attention assessments (Baum et al., 2008; Katz et al., 2000). Additionally, Walker and Lincoln (1991) found that patient performance on observational wash and dress assessments was highly correlated with scores on standardized physical and cognitive assessments, including visuo-spatial abilities as reported by a neuropsychological cancellation task. However, these previous investigations largely identified associations between cognitive impairments and low overall scores, rather than determining the specific profile of behavioural impairments associated with specific cognitive deficits.

In addition to complex behavioural profiles, visuospatial neglect is not a unitary syndrome but is instead more accurately characterised as a cluster of independent spatial-attentional deficits. Additionally, previous research has suggested that egocentric and allocentric neglect may be associated with different functional outcomes. Bickerton et al. (2011) found that patients with allocentric neglect scored significantly lower on the Barthel Index activities of daily life measurement (Quinn et al., 2011) compared to patients with egocentric neglect. Patients with both allocentric and egocentric neglect also reported significantly higher levels of depression on the Hospital Anx-

iety and Depression Scale than patients with either neglect type alone (Bickerton et al., 2011). The analysis presented in Section 1 of this Chapter also found that the severity of acute allocentric, but not egocentric neglect acts as a predictor of poor, long-term Stroke Impact Scale scores. This documented differential impact of egocentric/allocentric neglect implies that it is not only important to identify the specific functional impact of the neglect syndrome as a whole, but it is also necessary to distinguish between behavioural phenotypes which are associated with egocentric and allocentric neglect impairment.

This study set out to understand in more detail how neglect subtypes and severity is associated with specific behavioural patterns. This more detailed understanding brings with it potential clinical applications: first, developing a more thorough understanding of how neglect impacts behaviour offers an avenue for improving the efficiency of observational neglect assessments. Second, it is not yet well understood how quantitative neglect severity scores translate into qualitative behavioural impairments. Gaining a better understanding of how neglect severity scales with specific functional impairments can potentially help clinician distinguish between patients who may be able to compensate for their attentional impairment, and those who will require assistance in daily tasks. Finally, establishing a detailed profile of specific behavioural impairments associated with egocentric/allocentric neglect could inform whether more tailored behaviour-based rehabilitation studies should be developed for these deficits.

This section aims to identify specific functional impairments associated with the neglect syndrome, to determine whether functional impairment profiles differ across patients with egocentric and allocentric neglect, and to investigate how neglect severity scales with functional impairments. The presented methods study employs a combination of qualitative and quantitative analysis techniques within a large, and representative sample of stroke survivors. Qualitative thematic analysis is used to identify core reference themes within occupational therapist notes. This qualitative data is then paired with quantitative neglect severity data to clarify the relationship between different neglect subtypes and specific functional impairments.

6.3.2 Methods

Participants:

This study represents a secondary analysis of existing data collected as a component of the Oxford Cognitive Screen (OCS) and OCS-Tablet studies between 2015 – 2020. These study protocols were reviewed and approved by the National Research Ethics Committee (UK) (References: 11/WM/0299 and 14/LO/0648). All participants provided informed consent in line with the Declaration of Helsinki. Participants were included if they completed the OCS Cancellation Task and had a documented, systematic wash and dress and/or kitchen occupational therapy observational assessment within the first three weeks following stroke. In total, 290 patients (average age = 73.4 (range = 18 – 94), 43.3% female, 7.6% left handed) were included in this investigation. As reported by clinical notes, this sample contained 141 ischemic stroke, 32 haemorrhagic stroke, 4 TIA, and 79 unreported stroke type patients. Stroke locations were reported as 118 right hemisphere, 84 left hemisphere, 9 bilateral, and 79 unreported.

Functional Assessment and Qualitative Analysis:

Occupational therapist notes from structured wash and dress and kitchen assessments were collected from patient clinical notes records at the John Radcliffe Hospital acute stroke unit (Oxford, UK). In kitchen assessments, patients were systematically observed whilst making a cup of tea. In wash and dress assessments, patients were systematically observed whilst showering and dressing. This data was qualitatively analysed in order to identify overarching themes. In this analysis, all occupational therapy notes were transcribed in note form and imported into NVivo v.12 (Castleberry, 2014). The notes were analysed using thematic analysis, according to the guidelines provided by Braun and Clarke (2006). This analysis involves a recursive process through a series of six stages. First, an analyst familiarised themselves with data and generated initial themes. These themes were then searched for, reviewed, and defined. Throughout this process, codes were continually reviewed with themes being created or refined when necessary. Themes which included a minimum of 20 references were included in this investigation's quantitative analyses. This threshold was established to reduce the risk of uninformative null results by

ensuring that references with very low power to detect large effects were not analysed.

Neglect Testing and Quantitative Analysis:

The OCS Cancellation Task was used to detect visuospatial neglect impairment (See Chapter 2. The centre of cancellation and allocentric proportional scoring methods described within Chapter 2 (Section Two) were employed to quantify the severity of egocentric and allocentric neglect impairment. This Cancellation Task data was then employed to complete quantitative analyses across the themes identified within this investigation's qualitative analyses. First, the occurrence and severity of neglect impairment was compared across participant groups defined by their performance on the functional assessments. For each considered reference category, patient groups were dichotomised according to presence or absence of a category reference and chi-squared analyses were performed to investigate the association between the presence and/or type of neglect across groups. Next, a series of binary linear regressions were conducted to determine the relationship between neglect severity and subtheme references.

6.3.3 Results

Qualitative Analysis Results:

In total, 142 participants completed the kitchen assessment and 234 completed the wash/dress assessment, with 113 patients having available data for both considered assessments. Performance on these two assessments was analysed separately as qualitative analysis of these assessments' data yielded different overarching themes. Six overarching themes were identified within the occupational therapist notes from kitchen assessments: Independence, Attention, Physical, Cognition, Safety, and Emotions/Cognitions (Table 6.4). Independence encompassed references to patients who were able to effectively and safely complete the kitchen assessment with no assistance. The Attention theme included reports of participants' awareness of their own bodies and space throughout the assessment. This theme's subthemes consider whether patients were able to attend to their own body, remain aware of both sides of space, reliably locate

items, and remain focused on the task. The Physical theme covered patients' ability to manoeuvre themselves around the kitchen area, maintain balance, employ fine motor skills to handle objects, and reach objects. Cognition encompassed patients' comprehension of instructions and ability to initiate, sequence, and complete steps in the correct order. These subthemes take into account the degree of guidance and prompting required to solve problems throughout the session. Safety covers whether significant safety concerns were noted in the occupational notes, especially when preparing and pouring hot liquids. Finally, the Emotions/Insight domain includes broad observations of patients' alertness, fatigue level, confidence, and insight into their ability level.

Similarly, six overarching themes emerged from qualitative analysis of wash/dress assessment data: Independence, Attention, Cognition, Dressing Assistance, Balance, and Emotions/Insight. The Independence, Attention, Cognition, and Emotions/Insight encompassed similar topics as the corresponding domains within the kitchen assessment. The Dressing Assistance theme covered patients' ability to orient their clothing correctly, employ fine motor skills to fasten buttons/zips, and employ physical/spatial attentional skills to dress both sides of the body adequately. The Balance domain included information pertaining to patients' general ability to remain steady as well as any consistently lateralised midline deviations. A total of 26 subthemes contained at least 20 references and were therefore included in this investigation's analyses.

Quantitative Analysis of Reference Frequencies:

Next, the thematic structure extracted through qualitative analysis was employed to investigate specific performance differences between patients with and without visuospatial neglect impairment. In total, 179/290 patients exhibited visuospatial neglect (age = 74, sd = 14.07) and 111 were classed as neglect controls (age = 75, sd = 12.76). Kitchen assessment data was available for 88 neglect patients (62 egocentric, 25 allocentric, 56 co-occurring egocentric and allocentric) and 54 controls. Similarly, 143 neglect patients (40 egocentric, 18 allocentric, 30 co-occurring egocentric and allocentric) and 91 controls had available Wash/Dress assessment data. First, a series of two-tailed Fisher's Exact chi-squared analyses were conducted to identify differences in reference distributions across patients with and without significant visuospatial neglect.

Table 6.4: A description of each theme and subtheme identified in qualitative analysis of occupational therapist notes. The description column contains a summary of the criteria for reference occurrence and a breakdown of subthemes which were divided into qualitative categories denoting difference in impairment type or severity is also included within the divisions column.

Kitchen Assessment Themes	**Subthemes**	**Description**	**Divisions**
Independence		Completed assessment safely without assistance	N/A
Attention			
	Body Attention	Use and attend to both hands when required without prompting	Uses Both Sides (Able, Difficulties), Lateralised Inattention
	Spatial Attention	Able to attend well to space with no sign of laterlaised inattention or non-spatial difficulty in finding items	Good Attention, Lateralised Inattention, Difficulty Finding
	Reduced General Attention	Able to remain focused on the assessment with little distraction	N/A
			N/A
Physical Aspects			
	Mobilising	Ability to move througout the kitchen environment with ease	Able, Requires Supervision, Assistance Needed
	Grip	Able to employ fine motor skills to handle items well	N/A
	Balance	Remains balanced without relying on external support	Able, Poor, Uses Countertops for Support
	Reaching	Able to access items in various locations easily	Able, Assistance Needed, Overreaching
Cognitive Aspects			
	No Difficulties	Able to plan and execute task steps in the correct order and solve problems with no prompting	N/A
	Difficulties	Required promting to plan and execute task steps in the correct order and solve problems	N/A
	Comprehension	Able to understand task instruction with minimal assistance	Good, Difficulties
	Initiating/Sequencing	Begins and Completes steps in the correct order without prompting	Able, Difficulties
	Speech	Ablility to express and understand speech	Good, Difficulties
	Problem Solving	Solves problems without prompting	Good, Difficulties
	Memory	Able to remember task instructions and progress	Good, Difficulties
	Inappropriate Use	Uses objects in the inteded manner	N/A
Saftey			
	Safe in Task	Able to complete all task aspects safely without intervention	N/A
	Unsafe in Task	Unable to complete task aspects safely without intervention.	N/A
	Liquid Pouring	Able to pour hot water safely without intervention	Able, Assistance Needed, Overfilled, Spilled, Underfilled
Emotions/Cognitions		Encompasses alertness/responsiveness, confidence, and insight into difficulties	N/A

Wash/Dress Assessment Themes	**Subthemes**	**Description**	**Divisions**
Independence			
	Minimal Assistance	Able to complete task with minimal assistance	N/A
Attention			
	Body Attention	Use and attend to both hands when required without prompting	Good, Lateralised Inattention, Upper Limbs (Coordinated, Difficulties, Unable)
	Spatial Attention	Able to attend well to space with no sign of laterlaised inattention or non-spatial difficulty in finding items	Good, Lateralised Inattention
	Reduced General Attention	Able to remain focused on the assessment with little distraction	N/A
Cognitive Aspects			
	No Difficulties	Able to plan and execute task steps in the correct order and solve problems with no prompting	N/A
	Problem Solving	Required promting to plan and execute task steps in the correct order and solve problems	Able, Difficulties
	Memory	Able to remember task instructions and progress	Good, Difficulties
	Initiation	Able to begin task steps without prompting	N/A
	Sequencing/Completion	Completes task steps in the correct order and finishes all steps	Good, Difficulties, Impulsivity
	Inappropriate Use	Uses objects in the inteded manner	N/A
	Speech	Ability to express and understand speech	Good, Dificulties
Dressing Assistance			
	Lateralised Difficulty	Exhibits lateralised difficulty due to weakness or inattention	N/A
	Orienting Clothing	Orients clothing correctly with no assistance	N/A
	Fastenings	Able to open/close clothing fastenings without assistance	N/A
Balance			
	Good Balance	Consistently maintains midline balance with little deviations or support	N/A
	Leaning to One Side	Exhibits consistently lateralised midline balance deviations	N/A
Emotions/Cognitions			
	Fatigue	Able to complete task without exhibiting significant fatigue	N/A
	Lack of Insight	Demonstrates awarness of abilities and difficulties	N/A
	Other	Other emotions and cognitions	N/A

Given than 26 individual chi-squared tests were conducted, a Bonferroni-corrected alpha level of 0.0019 was employed. All comparison proportions and chi-square statistics are reported in Table 6.5. Within the kitchen assessment, patients with neglect (regardless of type or severity) were found to be significantly more likely to have references to difficulty finding items and challenges initiating/sequencing/completing tasks than patients without neglect. Conversely patients without neglect had significantly more references to needing assistance when mobilising and pouring hot liquids, using both sides of the body well, attending well to both sides of space, and to being independent within the kitchen assessment than patients with any neglect impairment.

Within the Wash and Dress assessment, participants with neglect were found to have a significantly greater proportion of references to “challenges initiating”, “lateralised spatial inattention”, “difficulties attending to one side of the body”, and an “inability to use both upper limbs”. Patients without neglect had a significantly higher proportion of references to attending well to space, exhibiting good attention to the body, and completing the wash and dress assessment with minimal assistance than patients with neglect. Overall, participants exhibiting any visuospatial neglect deficit had a higher average proportion of references pertaining to impairments than patients without neglect (22.58% vs 17.02% respectively). Conversely, participants with no neglect had a higher average proportion of references to intact/good abilities than patients with neglect (36.48% vs 18.36% respectively).

Next, the distribution of references across participants exhibiting different neglect subtypes was investigated. No significant differences in the proportion of references made to each theme were identified between patients with pure egocentric and pure allocentric neglect (Table 6.6). Participants with both egocentric and allocentric neglect had a higher average proportion of references pertaining to impairments (n = 169 (30.7%)) than patients with pure egocentric (n = 134 (20.0%)) or pure allocentric (n = 57 (19.9%)) neglect. Conversely, participants with both egocentric and allocentric neglect had a reduced average proportion of references pertaining to good abilities (n = 102 (18.5%)) compared to patients with either pure egocentric (n = 148 (22.1%)) or allocentric (n = 63 (22.0%)) neglect. However, chi-squared analyses revealed no significant differences between patients with both neglect types, pure egocentric, and pure allocentric in specific

Table 6.5: A comparison of reference frequencies across participants with and without significant neglect impairment. See previous table for a detailed description of each reference criteria.

Kitchen Assessment		**No Neglect**	**Neglect**	**Chi Value**	**P**
	Independent	48 (88.9%)	37 (42.0%)	30.5611	**<0.0001***
	Able to Use Both Sides of Body	35 (64.8%)	23 (26.1%)	20.7203	**<0.0001***
	Difficuties Using Both Sides of Body	7 (13.0%)	24 (27.3%)	4.0156	0.0451
	Good Spatial Attention	42 (77.8%)	25 (28.4%)	32.7289	**<0.0001***
	Difficulties Finding Items	1 (1.9%)	30 (34.1%)	20.3819	**<0.0001***
	Lateralised Inattention (Space)	3 (5.6%)	17 (19.3%)	5.2381	0.0221
	Sequencing/Completing (Difficulties)	1 (1.9%)	33 (37.5%)	23.3526	**<0.0001***
	Initiating/Sequencing (Able)	12 (22.2%)	27 (30.7%)	1.2022	0.2729
	Problem Solving (Able)	7 (13.0%)	14 (15.9%)	0.2305	0.6312
	Emotions	3 (5.6%)	21 (23.9%)	7.9865	0.005
	Balance (Poor)	9 (16.7%)	19 (21.6%)	0.5126	0.474
	Mobilising (Able)	35 (64.8%)	31 (35.2%)	11.7767	0.0006
	Mobilising (Assistance Needed)	35 (64.8%)	8 (9.1%)	49.2203	**<0.0001***
	Reaching (Able)	11 (20.4%)	12 (13.6%)	1.118	0.2904
	Liquid Pouring (Assistance Needed)	33 (61.1%)	16 (18.2%)	27.2894	**<0.0001***
	Liquid Pouring (Able)	14 (25.9%)	29 (33.0%)	0.376204	0.7831
	Safe in Task	15 (27.8%)	25 (28.4%)	0.0066	0.9353
Wash/Dress Assessment					
	Minimal Assistance	42 (46.2%)	25 (17.5%)	22.3716	**<0.0001***
	Dressing (Lateralised Difficulty)	1 (1.1%)	31 (21.7%)	19.9507	**<0.0001***
	Body Attention (Good)	56 (61.5%)	15 (10.5%)	68.5679	**<0.0001***
	Lateralised Inattention (Body)	1 (1.1%)	30 (21.1%)	19.1238	**<0.0001***
	Upper Limb Use (Coordinates)	10 (20.1%)	14 (10.0%)	0.1681	0.6818
	Upper Limb Use (Difficulties)	27 (29.6%)	42 (29.4%)	0.0024	0.9609
	Good Spatial Attention	46 (50.5%)	10 (7.0%)	57.9549	**<0.0001***
	Lateralised inattention (Space)	1 (1.1%)	28 (20.6%)	17.4951	**<0.0001***
	Initiating (Challenges)	0	27 (18.9%)	16.8896	**<0.0001***
	Initiating (Good)	17 (18.9%)	26 (18.2%)	0.0093	0.9234
	Fatigue	19 (20.9%)	13 (9.1%)	6.5462	0.0105
	Upper Limb Use (Unable)	2 (2.2%)	42 (29.4%)	26.8941	**<0.0001***

reference categories.

The Relationship between Neglect Severity and Impairment:

Next, a series of binary linear regressions were conducted to determine whether reference probability scaled with egocentric neglect severity within the subthemes which contained a significantly different proportion of references across patients with and without neglect (n = 15). Each regression included the absolute value of egocentric severity (centre of cancellation) as a predictor variable with reference occurrence as the binarized outcome measure. Egocentric neglect severity's contribution to predicting references survived 5% False Discovery Rate correction within the analyses considering kitchen assessment difficulty finding items ($p > 0.001$, AIC = 113.95) as well as wash/dress assessment spatial inattention ($p = 0.003$, AIC = 143.0), body inattention ($p = 0.006$, AIC = 150.46), and lack of ability to use both upper limbs well ($p = 0.009$, AIC = 180.65) (Figure 6.11). Full results and statistics for all non-significant comparisons are included within supplementary materials (Appendix IV, Figure 1).

Finally, 15 binary linear regressions were conducted to determine whether reference probability scaled with allocentric neglect severity. These regressions employed the absolute value of allocentric severity as a predictor and reference occurrence as the outcome variable. Allocentric neglect severity's contribution to predicting reference occurrence did not survive 5% False Discovery Rate correction in any of the 15 conducted regression analyses. Full statistics and visualisation of these non-significant comparisons are available within supplementary materials (Appendix IV, Figure 2).

6.3.4 Discussion

Overall, patients with neglect were found to have more references to having difficulty initiating tasks, finding items, exhibiting spatial inattention, and having difficulty using both arms than patients without neglect. The proportion of subtheme references was not found to differ significantly across patients with egocentric and allocentric neglect. However, participants with both egocentric and allocentric neglect had a higher average proportion of references pertaining to im-

Table 6.6: A comparison of reference frequencies across participants with egocentric, allocentric, and both egocentric/allocentric neglect. See Table 2.3.1 for a detailed description of each reference criteria.

Kitchen Assessment Theme		Egocentric	Allocentric	Both
Independence				
	Independent	20 (50.0%)	6 (33.3%)	11 (36.7%)
Attention (Body)				
	Uses both sides of body well	10 (25.0%)	5 (27.8%)	8 (26.7%)
	Difficulties using both sides of body	6 (15.0%)	6 (33.3%)	12 (40.0%)
Attention (Spatial)				
	Attending well to space	14 (35.0%)	4 (22.2%)	7 (23.3%)
	Dificulties finding items	14 (35.0%)	4 (22.2%)	12 (40.0%)
	Lateralised inattention (egocentric)	8 (20.0%)	1 (5.6%)	8 (26.7%)
Cognition				
	challenges initiating/sequencing/completing	13 (32.5%)	5 (27.8%)	15 (37.5%)
	good initiation/sequencing/completing	12 (30.0%)	8 (44.4%)	7 (17.5%)
	Able to solve problems	7 (17.5%)	3 (16.7%)	4 (10.0%)
Emotions/Cognitions		9 (22.5%)	4 (22.2%)	8 (26.7%)
Physical				
	balance (poor balance)	8 (20.0%)	6 (33.3%)	5 (16.7%)
	mobulising (able)	11 (27.5%)	4 (22.2%)	16 (40.0%)
	mobilising (assistance needed)	3 (7.5%)	3 (16.7%)	2 (5.0%)
	reaching (able)	6 (15.0%)	3 (16.7%)	3 (7.5%)
Safety				
	liquid assistance needed	4 (10.0%)	4 (22.2%)	8 (26.7%)
	liquid correctly filled	15 (37.5%)	3 (16.7%)	11 (36.7%)
	safe in task	13 (32.5%)	5 (27.8%)	7 (17.5%)
Wash/Dress Assessment Theme				
Independence				
	Completed with minimal assistance	11 (17.7%)	7 (28.0%)	7 (12.5%)
Assistance Needed				
	Difficulty dressing one side	9 (14.5%)	6 (24.0%)	16 (28.6%)
Attention (Body)				
	Good Attention to the body	6 (9.7%)	5 (20.0%)	4 (7.1%)
	Inattention to one side of body	9 (14.5%)	5 (20.0%)	16 (28.6%)
	Good Coordination of upper limbs	8 (12.9%)	2 (8.0%)	4 (7.1%)
	Not Full use of both upper limbs	16 (25.8%)	6 (24.0%)	20 (35.7%)
	Unable to use both upper Limbs	17 (27.4%)	6 (24.0%)	19 (33.9%)
Attention (Spatial)				
	Attending well to space	5 (8.1%)	2 (8.0%)	1 (1.8%)
	Lateralised inattention (egocentric)	11 (17.7%)	1 (4.0%)	16 (28.6%)
Cognition				
	initiating (challenges)	13 (21.0%)	3 (12.0%)	11 (19.6%)
	initiating (good)	10 (16.1%)	4 (16.0%)	12 (21.4%)
Emotions/Cognitions				
	fatigue	3 (4.8%)	1 (4.0%)	9 (16.1%)

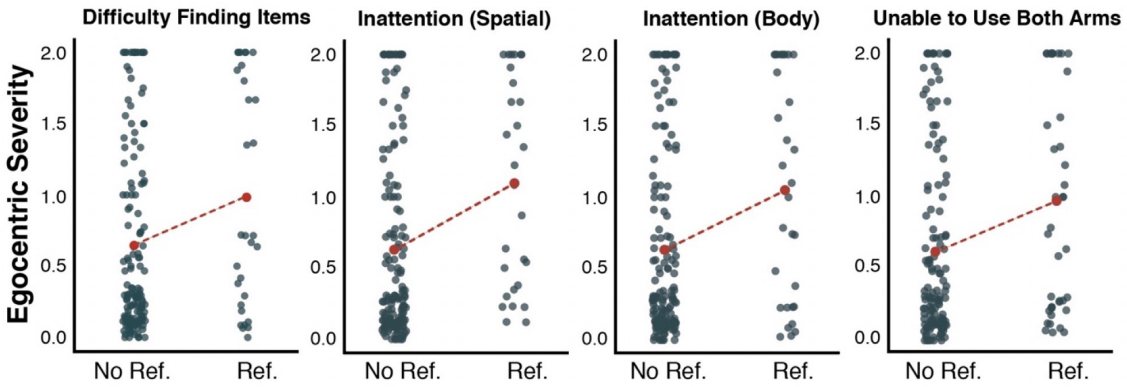


Figure 6.11: The relationship between egocentric neglect severity (y-axis) and subtheme reference (x-axis). Blue dots represent patient scores, red dots represent group means, and red lines visualise the difference in means between groups.

pairments than patients with egocentric or allocentric neglect alone. The quantitative severity of egocentric neglect impairment was found to act as a significant predictor of reference occurrence within difficulty finding items, spatial inattention, body inattention, and upper limb use subthemes. The findings of this investigation align well with previous research by demonstrating the association between the occurrence of acute neglect and reduced functional abilities in stroke survivors. This study expands on previous findings by identifying specific functional impairments which differentiate between patients with and without neglect impairment. Overall, this data provides novel insight into the impact of visuospatial neglect on functional abilities.

First, patients with neglect were found to have significantly more references to some classical behavioural symptoms of unilateral visuospatial neglect including lateralised spatial inattention, difficulties attending to one side of the body, and difficulties finding items than patients without neglect impairment. Conversely, patients without neglect had significantly more references to attending well to space and exhibiting good attention to the body than patients with neglect. Several commonly employed observational neglect assessments such as the National Institutes of Health Stroke Scale and Catherine Bergego Scale base neglect diagnosis on classic behavioural neglect symptoms such as these (Azouvi et al., 2003; Goldstein and Samsa, 1997). However, it is important to note that despite the difference in reference frequency between patients with and without neglect, only a comparatively small fraction of patients with neglect were noted to have

these behavioural impairments. Within the wash and dress assessment, only 20.6% of patients with neglect as reported by a standardised neuropsychological task were noted to exhibit signs of lateralised spatial inattention in functional assessment. Within the kitchen assessment, only 19.3% of neglect patients had references to spatial inattention with no significant difference in reference frequency from patients without neglect. These findings suggests that functional observation alone does not represent a sensitive method for diagnosing neglect impairment compared to gold-standard neuropsychological neglect assessments.

This finding is important to consider in the context of the current clinical practice for neglect diagnosis. Evald et al. (2020) conducted a large-scale survey of the methods used to detect and diagnose visuospatial neglect in clinical settings in which 90% of participating clinicians reported that they generally diagnosed neglect through observing patient behaviour. However, the results of this investigation suggest that only a small fraction of patients with neglect may exhibit overt, classical signs of spatial inattention in behavioural assessments. There are several possible explanations for this finding. First, it is possible that therapists only made note of patients exhibiting severe behavioural spatial inattention. Second, previous research has demonstrated that neglect tends to recover spontaneously within the first ten days following stroke (Stone et al., 1992).

Finally, it is possible that observational assessments do not represent a sensitive method for diagnosing neglect impairment. Previous research has found that observational assessments frequently fail to detect cases of neglect regardless of impairment severity and commonly misclassify neglect impairment as visual deficits (Puig-Pijoan et al., 2018; Chapter 2, Section 1). Gottesman et al. (2010) that adding a simple, neuropsychological cancellation task to the traditionally observational NIHSS significantly improved this scale's ability to predict stroke severity. Considered in the context of these previous studies, the results of this investigation provide additional evidence that quantitative, neuropsychological testing is needed in order to accurately detect and diagnose visuospatial neglect deficits within clinical environments.

Next, patients with neglect were found to have a significantly higher proportion of references to difficulties initiating/sequencing than patients without neglect. This finding is particularly interesting as initiating difficulties are not classically associated with visuospatial neglect behavioural

symptoms (Halligan et al., 1991). However, previous research has suggested that a subset of egocentric neglect cases may be associated with motor-intentional deficits (Husain et al., 2000; Mattingley et al., 1998). Mattingley et al. (1998) found that egocentric neglect patients with lesions impacting the right inferior parietal lobule exhibited difficulty initiating leftward movements. This impairment was not present in neglect patients with more anterior lesions (Mattingley et al., 1998). This conclusion is in line with the findings of this investigation in that initiating deficits were associated with neglect, but were not referenced in all neglect patients.

Patients with neglect were more also likely to have references to an inability to use both upper limbs than patients without neglect. This finding is likely partially accounted for the motor impairments which have been associated with the neglect syndrome. Patients with visuospatial neglect are frequently unaware of the neglected side of their body and "motor neglect" is frequently observed in patients exhibiting visuospatial neglect (Mattingley et al., 1998; Parton et al., 2004; Punt and Riddoch, 2006). Motor neglect is characterised by an underutilisation of one side win the absence of underlying strength or sensation impairments (Laplane and Degos, 1983; Punt and Riddoch, 2006). Motor neglect is behaviourally doubly dissociated from visuospatial neglect, but these syndromes do frequently co-occur (Heilman et al., 2000; Laplane and Degos, 1983). Finally, neural regions which have been strongly implicated in the neglect syndrome are anatomically proximal to the primary motor cortex. Large strokes which impact neglect correlates are therefore likely to result in lateralised motor impairments. Finally, leftward motor-intentional deficits do not selectively impact contralesional limbs, but instead impact all leftward movements (Mattingley et al., 1998). Taken together, the established association between visuospatial neglect and motor impairments may help account for the documented association between neglect and references to upper limb movement deficits.

No significant difference in subtheme reference proportion was identified between patients with egocentric and allocentric impairment. As a whole, patients with both egocentric and allocentric neglect had a higher proportion of references to impairment than patients with egocentric or allocentric neglect alone. Previous research has indicated that some degree of difference in functional outcome is present between patients with different neglect subtypes. Bickerton et al.

(2011) found that patients with allocentric neglect scored significantly lower on the Barthel Index activities of daily life measurement (Quinn et al., 2011) compared to patients with egocentric neglect. In this study, patients with both allocentric and egocentric neglect also reported significantly higher levels of depression on the Hospital Anxiety and Depression Scale than patients with either egocentric or allocentric neglect alone (Bickerton et al., 2011). It is possible that egocentric and allocentric neglect are associated with significant, but small behavioural differences which are not associated with large enough effect sizes to be apparent within occupational therapist observations. Alternatively, it is possible that allocentric and egocentric neglect differentially impact functional activities not assessed in either the wash and dress or kitchen assessment (e.g. reading). Additional research in even larger samples is likely needed to confirm whether behavioural profiles are analogous across these neglect subtypes.

The severity of egocentric neglect impairment was found to be predictive of references within four themes. Within the wash and dress assessment, the severity of egocentric neglect predicted references to both spatial inattention and body inattention. Within the kitchen assessment, egocentric severity was significantly associated with references to difficulty finding items. This finding demonstrates the external validity of the severity scores yielded by the OCS Cancellation Task, as the severity of egocentric neglect as documented by this neuropsychological test predicts the occurrence of neglect deficits within real-world, functional activities. The severity of egocentric neglect was also found to predict references to more general functional activities which are less directly related to spatial attention. Neglect severity was correlated with references to patients being unable to use both upper limbs within the wash and dress assessment. This relationship may be partially accounted for by the association between personal neglect and egocentric neglect (Committeri et al., 2018), but may also be due to the high comorbidity between hemiplegia and neglect deficits (Parton et al., 2004). This relationship between severe egocentric neglect and more general functional abilities may be partially explained by general stroke severity, as larger lesions are more likely to cause neglect than smaller ones (de Haan and Karnath, 2018). However, this potential correlation does not negate the severity of egocentric neglect's role as a prognostic indicator associated with these specific behavioural patterns.

The severity of allocentric neglect was not found to significantly predict the occurrence of references within any identified theme categories. This finding may be accounted for by the differences in expected impact between egocentric and allocentric neglect. Body-centred attention must be employed to complete many functional activities, but the role object-level attention plays in these functional activities is less well understood. It seems plausible that allocentric neglect may be more apparent when completing tasks not tested within kitchen or wash-and-dress assessments such as reading or facial recognition (Brunn and Farah, 1991; Ptak et al., 2012). Future research can endeavour to clarify the impact of allocentric neglect on a more diverse range of activities of daily life.

In line with previous research, the visuospatial neglect syndrome as a whole was found to be associated with poor functional status. Patients with neglect were found to have a higher frequency of references to impaired behaviours than patients exhibiting no neglect impairment. Conversely, patients with neglect had fewer references to intact abilities in the functional assessments than patients without significant neglect impairment. Patients without neglect were more likely to need only minimal assistance within the wash and dress assessment and were more likely to be classed as independent within the kitchen assessment than patients with neglect. This finding largely replicates similar results documented by previous investigations (Bickerton et al., 2011; Cherney et al., 2001; Jehkonen et al., 2000; Nys et al., 2006; Ten Brink et al., 2017). However, unlike previous investigations, this study documented the selective impact of neglect impairment across a range of specific behavioural references. The occurrence of neglect was not found to uniformly impact reference frequency across all subthemes, with some reference themes being equally likely to be used to describe patients with and without not neglect. This finding is important to note as it suggests that the association between neglect and poor functional outcome is not simply driven by stroke severity. Patients without neglect were found to have more references to specific impairments (e.g. needing assistance when mobilising and pouring hot liquids) than patients with neglect, suggesting that the behavioural differences observed in this study are not simply a product of difference in general stroke severity. Instead neglect seems to be associated with a more specific pattern of poor functional outcome which selectively impacts certain

functional tasks while leaving others intact.

Cumulatively, the findings of this study provide novel insight into the specific functional impairment profile associated with the visuospatial neglect syndrome. Patients with and without neglect were found to exhibit significantly different behavioural patterns within observational neglect assessments. The findings of this study are clinically relevant as they help predict the specific activities in which patients with neglect may experience comparatively higher levels of impairment. This information can be used by therapists to develop more detailed treatment plans, risk assessments, and care support networks for patients exhibiting visuospatial neglect. While observational assessments may not provide the most sensitive method for diagnosing neglect, these assessments provide undeniably critical daily life functional information which can be used to develop tailored rehabilitation strategies for patients both with and without neglect impairment.

Limitations:

This study focused on investigating functional differences between patients with egocentric and allocentric neglect. There are additional, independent subtypes of neglect which were not included in this investigation. Neglect can selectively impact additional spatial coordinates (e.g. peri-personal/extra-personal neglect (Butler et al., 2009; Ten Brink et al., 2019)) or sensory modalities (e.g. auditory neglect (Bellmann et al., 2001)). It is plausible that each of these additional neglect subtypes may be associated with distinct patterns of functional impairment. However, these specific neglect subtypes are not commonly screened for with standardised neuropsychological measurements in acute stroke settings. Therefore, the current analysis did not consider these additional neglect subtypes.

Additionally, previous research has strongly suggested that the most reliable method for detecting and diagnosing visuospatial neglect is requiring agreement between multiple, independent neuropsychological tests (Bowen et al., 1999; Huygelier et al., 2020). However, this recommendation is not commonly followed in clinical settings. For this reason, only data from a single cancellation task conducted was available in this investigation. Future research can aim to determine whether functional impairment scales with neglect type and severity as measured by a wider

range of neuropsychological metrics.

Conclusions:

The findings of this study provide novel insight into the specific functional impairment profile associated with the visuospatial neglect syndrome, aligning occupational therapist and cognitive neuropsychological assessments of neglect. In acute stroke wash and dress and kitchen assessments, patients with neglect were found to have more references to having difficulty initiating tasks, finding items, exhibiting spatial inattention, and having difficulty using both arms than patients without neglect. The proportion of subtheme references was not found to differ significantly across patients with egocentric and allocentric neglect. However, participants with both egocentric and allocentric neglect had a higher average proportion of references pertaining to impairments than patients with egocentric or allocentric neglect alone. The quantitative severity of egocentric neglect impairment acted as a significant predictor of reference occurrence within difficulty finding items, spatial inattention, body inattention, and upper limb use subthemes. Overall, this data provides novel insight into the impact of visuospatial neglect on functional abilities and provides additional evidence of the need for standardised, neuropsychological neglect testing within clinical settings.

6.4 General Conclusion

Overall, the results presented in this chapter demonstrate that acute visuospatial neglect is a strong predictor of poor overall functional outcome. While the strength of this relationship varies across different neglect subtypes, the overall effect was found to be generalisable across a wide range of patient groups and outcome measures. Additionally, the occurrence of neglect was found to be associated with a qualitatively distinct pattern of specific functional impairments within observational, activities of daily living assessments.

Section 1 presents a behavioural analysis investigating differential recovery trajectories and functional outcomes across various neglect subtypes. This section illustrates that considering the subtype and quantitative severity of visuospatial neglect provides information which can be

applied to identify patients who are more likely to end up living with chronic neglect. These findings highlight the need for standardised neuropsychological neglect assessments and for the development of allocentric-specific rehabilitation strategies.

Section 2 employs multiverse analysis techniques to demonstrate that the relationship between acute neglect and poor recovery outcomes is robust and generalisable across many outcome measures and patient groups. This analysis provides a novel demonstration of the utility of multiverse analysis techniques within neurological research.

Finally, Section 3 presents a mixed-methods analysis aiming to identify specific, real-world behavioural profiles associated with neglect impairment. Overall, this analysis provides novel insight into the impact of visuospatial neglect on functional abilities and provides additional evidence of the need for standardised, neuropsychological neglect testing within clinical settings.

7 Chapter 7.0: General Discussion

7.1 Results Summary

Overall, the data and analyses presented within this thesis aimed to investigate the underlying mechanisms and clinical utility of behavioural heterogeneity within the visuospatial neglect syndrome.

Chapter 2 presented a critical analysis of commonly employed neglect assessment methods and established the need for standardised, quantitative neuropsychological neglect testing in clinical and research environments. The results presented within Section 1 of this chapter demonstrate that one of the most commonly relied upon observational neglect assessments (National Institutes of Health Stroke Scale) demonstrates very low sensitivity compared to a simple, quantitative cancellation tasks. The findings of this study strongly suggest that observational measures of neglect overlook many cases of neglect, and that misattribution of neglect as a visual field deficit is common within clinical environment. Chapter 2, Section 2 presents complex egocentric and allocentric neglect metrics calculated using data collected from a computerised cancellation task and compares these novel metrics to more traditionally used scoring systems. Overall, this section demonstrates that centre of cancellation and allocentric proportional scoring metrics act as an effective method for detecting and quantifying the severity of neglect impairments on the OCS Cancellation Task. Together, the studies presented within Chapter 2 illustrate the clinical need for standardised quantitative, neuropsychological neglect assessments.

Chapter 3 presents and analysis of behavioural heterogeneity in neglect dyslexia and investigates the relationship between reading-related and domain-general neglect impairments. Egocentric and allocentric neglect dyslexia were found to be doubly dissociated with all cases of egocentric and allocentric neglect dyslexia occurring independently. Allocentric neglect dyslexia was dissociated from both egocentric and allocentric visuospatial neglect while egocentric neglect dyslexia was always found in the presence of domain-general visuospatial neglect. In contrast, no evidence for a dissociation between egocentric neglect dyslexia and visuospatial neglect was found. The findings of this investigation clearly demonstrate that allocentric neglect dyslexia can-

not be fully explained as a consequence of allocentric visuospatial neglect. Similarly, the analysis presented within this chapter suggests that neglect-related reading impairments may be best understood as a cluster of dissociable reading impairments rather than a unitary syndrome.

Chapter 4 presents findings from series of three case studies and a novel behavioural experiment aiming to characterise the properties of representation-level neglect in order to critically evaluate Hillis and Caramazza's (1995) three-tier model of spatial attention. Section 1 presents data from AB, a Transient Ischemic Attack patient demonstrating right representation-level neglect dyslexia in the absence of neglect. This analysis provides evidence of a behavioural dissociation between visual neglect and representational neglect dyslexia, which is not clearly predicted by Hillis and Caramazza's (1995) model. Section 2 presents data from CD, a stroke survivor exhibiting right representation-level neglect dyslexia in conjunction with right domain-general neglect deficits. The severity of CD's reading impairment was not found to be modulated by attentional factors which have been found to modulate the severity of visuospatial neglect, suggesting that CD's reading impairment may not be accurately characterised as deficit of spatial attention. Finally, Section 3 presents data from EF, an additional patient demonstration right representation-level neglect dyslexia in conjunction with right domain-general neglect deficits. EF's performance on reading, attentional, and executive function neuropsychological tasks suggests that at least some cases of representation-level neglect dyslexia should not be conceptualised as a component of the neglect syndrome, but instead represents an independent, inhibitional deficit.

Chapter 5 presents a detailed analysis of the neural correlates of various visuospatial neglect deficits. Similar to previous investigations, left egocentric and left allocentric neglect were associated with damage to distinct clusters of voxels within the posterior parietal and temporo-parietal junction areas. Unlike previous investigations, right egocentric neglect was found to most strongly associated with damage to more posterior voxels within left occipital cortical areas. Right allocentric neglect was found to be most strongly associated with damage to the anterior limb of the left internal capsule. Interestingly, the right hemisphere homologues of the areas implicated in right-lateralised neglect were not overlap with those associated with left neglect impairment. This dissociation was present across both egocentric and allocentric neglect impairment. Overall, the

analyses presented within this chapter provide novel insights into the neural correlates of spatial attention.

Finally, Chapter 6 analysed the relationship between the occurrence of acute neglect and poor long term functional outcome, demonstrating that distinguishing between different neglect subtypes may provide important prognostic and rehabilitation indicators. Section 1 of this chapter elucidates how complex neglect behavioural phenotypes predict long-term outcomes, both in terms of neglect recovery and broader functional outcomes. The findings of this section illustrate that considering the subtype and quantitative severity of visuospatial neglect provides information which can be applied to identify patients who are more likely to end up living with chronic neglect. These findings highlight the need for standardised neuropsychological neglect assessments and for the development of allocentric-specific rehabilitation strategies. Section 2 employs multiverse analysis techniques to investigate whether the relationship between neglect and poor recovery outcome is a generalisable effect. Overall, multiverse analysis suggests that the predictive relationship between acute visuospatial neglect and poor functional outcome is a particularly robust effect present across a range of outcome measures, patient groups, and scoring criteria. However, the strength of this effect was not constant across all comparisons. This section demonstrates the utility of multiverse analysis techniques within neurological research. Finally, Section 3 presents a mixed-methods analysis aiming to identify the specific profile of real-world behavioural impairments associated with neglect. Overall, patients with neglect were found to have more references to having difficulty initiating tasks, finding items, exhibiting spatial inattention, and having difficulty using both arms than patients without neglect. Participants with both egocentric and allocentric neglect had a higher average proportion of references pertaining to impairments than patients with egocentric or allocentric neglect alone. The quantitative severity of egocentric neglect impairment was found to act as a significant predictor of reference occurrence within difficulty finding items, spatial inattention, body inattention, and upper limb use subthemes. Overall, this data provides novel insight into the impact of visuospatial neglect on functional abilities.

This general discussion aims to fully analyse the wider implications of each of these individual findings in order to investigate patterns of heterogeneity within neglect, to determine this

syndrome's underlying mechanisms, and to investigate the practical utility of considering this heterogeneity within clinical settings.

First, current clinical neglect diagnosis practices are discussed in the context of this thesis' findings that observational neglect assessment methods are insufficiently sensitive compared to neuropsychological neglect tests. Second, Caramazza and Hillis' (1995) three-tier theory of neglect is critically analysed in the context of the neglect dyslexia data presented in Chapters 3-4. This accepted theories predictions are specified and evaluated versus the behavioural patterns documented in these studies in order to determine whether this model accurately characterises both domain-general neglect and neglect dyslexia. Third, the neruroanatomy of the neglect syndrome is discussed in detail and voxel-lesion symptom mapping's strengths and weaknesses within studies aiming to elucidate brain-behaviour relationships are critically evaluated. Next, the clinical implications of heterogeneity within the neglect syndrome are explored. This section discusses why considering the heterogeneity of the neglect syndrome provides clinically relevant rehabilitation and prognostic information, while clarifying the impact of different neglect subtypes on real world activities and recovery outcomes. Finally, a novel, future directions research stream building on the findings presented within this thesis is presented.

7.2 Detecting and Diagnosing Visuospatial Neglect in Clinical Environments

The findings presented in Chapter 6 illustrate the importance of accurately and reliably diagnosing neglect impairments within clinical settings. Acute neglect impairment, regardless of type, severity, or lateralisation, was found to act as a robust predictor of poor long term functional outcome in stroke survivors. First, the occurrence of neglect was associated with more severe functional impairment 6-months after stroke. Second, patients with neglect demonstrated a higher proportion of references to functional impairments than patients without neglect impairment. Third, multiverse analysis demonstrated that this association between neglect and poor long-term function outcome is not a statistical artefact of the specific methods employed in a study, but is instead a robust effect which is generalisable across many outcome measures, patient groups, and neglect definition. It is therefore important to reliably identify neglect impairment

in stroke survivors, as this information may help medical care workers identify patients who will exhibit higher levels of impairment throughout recovery.

In clinical settings, neglect is most commonly diagnosed using observational measurements such as the National Institute of Health Stroke Scale (NIHSS), Catherine Bergego Scale (CBS), or unstructured therapist observations (Rossit et al., 2019). The results of this thesis strongly suggest that these observational measures do not represent a valid method for reliably detecting neglect impairment. First, the observational National Institute of Health Stroke Scale was found to be 31.6% sensitive to neglect impairment compared to the Oxford Cognitive Screen (OCS) cancellation task. This lack of sensitivity was most likely driven by clinician expectation biases, misdiagnosing neglect as a visual problem, and a poor understanding of how allocentric neglect impacts patient behaviour. However, a portion of this lack of sensitivity may be explained by the qualitative analysis of specific behavioural impairments in neglect patients presented in Chapter 6 (Section 3).

For example, in this analysis neglect patients were generally found to exhibit qualitatively different behavioural impairment profiles than patients without neglect, but these behavioural difference were not found to be pronounced enough to facilitate sensitive impairment diagnosis on an individual scale. While patients with neglect were significantly more likely to be referenced as exhibiting spatial inattention in functional assessments than patients without neglect, only a comparatively small fraction (20.6%) of were referenced as exhibiting spatial inattention in behaviour. These impairment references were made by trained occupational therapists tasked with identifying signs of behavioural impairment within real-world activities: tea making and washing/dressing. This lack of reference sensitivity cannot be accounted for by differences in impairment severity, as the severity of egocentric and allocentric neglect were not found to significantly predict which patients exhibited clear signs of spatial inattention in behaviour. Taken together, these findings demonstrate that observational assessments alone are not able to reliably detect visuospatial neglect impairment.

There are several possible explanations for the general lack of sensitivity documented within observational neglect assessments. First, it is possible that clinician expectation biases may

strongly bias neglect diagnosis. Chapter 2 found that observational neglects were more sensitive to diagnosing left-lateralised neglect than right lateralised neglect (58.3% versus 18.7% sensitivity respectively), despite the fact that there was no significant difference in severity of these deficits. Neglect is most commonly characterised as a left-lateralised impairment which occurs following right hemisphere damage (Parton et al., 2004). Although recent research has demonstrated that neglect can occur following exclusively left hemisphere damage (Stone et al., 1992; Suchan and Karnath, 2011; Ten Brink et al., 2017), this diversity is not commonly considered in clinical practice. Second, many observational neglect assessments exclusively aim to assess egocentric-level impairment. Common observational neglect assessment including the NIHSS and Catherine Bergego Scale (CBS) exclusively include items which assesses egocentric-level attentional biases (Azouvi et al., 2003). This failure to account for allocentric-level impairment may account for a portion of the missed neglect cases. Third, neglect impairment seems to be frequently misdiagnosed as a visual impairment rather than an attentional one. Chapter 2 found that the NIHSS' Visual Field item was more sensitive to neglect than this assessment's neglect-specific item, demonstrating a common misdiagnosis of this condition. This is in line with previous findings. In a survey of 142 UK stroke clinical professionals, Colwell et al. (2021) found that visual neglect was mistakenly considered part of early visual perception by 83% of occupational therapists and 91% of orthoptists. Given the demonstrated clinical utility of providing accurate neglect diagnoses, it is important to explore additional diagnostic methods to improve the reliability of neglect detection.

According to an international survey of stroke professionals conducted by Checketts et al. (2020), the three most common methods employed to detect visuospatial neglect in acute stroke settings are cognitive tests, functional assessments, and neuroimaging. The data presented in this thesis demonstrates critical weaknesses within functional assessment-based neglect assessment. Specifically, observational/functional neglect assessments are insufficiently sensitive to neglect deficits, are subjective to clinician biases, and are unable to reliably distinguish between egocentric and allocentric neglect deficits. Critically analysing findings presented by existing studies reveals similarly confounding weaknesses within neuroimaging-based neglect diagnosis. Previ-

ous literature has clearly demonstrated that egocentric visuospatial neglect can result following damage to a wide range of neural correlates and likely represents a complex, disconnection syndrome rather than a localised function (Chechlacz et al., 2012; Lunven et al., 2013). Egocentric neglect most commonly occurs following damage to the right hemisphere temporo-parietal area, but has been found to result from frontal, temporal, parietal, subcortical, and cerebellar lesions within both the left and right hemisphere (Bird et al., 2006; Chechlacz et al., 2012; Kim et al., 2008; Lunven et al., 2013). This high degree of variation within egocentric neglect-causing lesions, coupled with the uncertainties associated with employing acute clinical imaging (e.g. high false positive rate) preclude valid neglect diagnoses based on imaging data alone. This thesis demonstrates that even when the areas which are most strongly related to egocentric impairment are damaged, egocentric neglect does not always occur (Chapter 5). Given these uncertainties in using clinical neuroimaging to detect egocentric neglect alone, it seems highly unlikely that this method can reliably detect egocentric neglect, let alone distinguish between egocentric and allocentric neglect impairment.

Previous research has strongly indicated that standardised neuropsychological testing is the most reliable method for detecting neglect impairments within clinical settings (Evald et al., 2020; Lyden, 2017). However, this consensus is not reflected in clinical practice. Evald et al. (2020) conducted a large-scale survey of the methods used to detect and diagnose visuospatial neglect in clinical settings which found that 90% of participants reported that neglect was diagnosed via subjective observations. Given the demonstrated clear difference in sensitivity between these tests, it is unclear whether observational neglect assessments provide any advantages over neuropsychological neglect tests.

It is possible that sensitive neuropsychological tests, such as the OCS cancellation task may produce some level of false positive neglect diagnoses. For example, Huygelier et al. (2020) conducted a binomial Monte-Carlo simulation based analysis of how the occurrence of non-spatially biases target omissions can produce false positive neglect diagnoses on cancellation tasks. This investigation found that the false positive diagnostic rate is modulated by the number of targets identified by patients, with up to 30% false positives occurring when participants had identified

less than 5 targets. However, this false positive rate can be dramatically reduced by requiring agreement between multiple tests or by employing impairment cut-offs which are adjusted for the total number of targets identified. In the real-world clinical populations employed in this investigation, only a very small number of patients identify less than ten cancellation targets (Demeyere and Gillebert, 2019) and participants who have not identified at least 5 targets are often excluded from analyses.

Any test which aims to categorise participants exhibiting a range of behavioural scores in to binary impairment groups is very likely to commit at least some false positive errors. Medical diagnostic tests are generally designed to prioritise maximising sensitivity over specificity, as false-positive diagnoses generally have less severe clinical repercussions than false negative diagnoses. For this reason, the trade-off between a potentially increased number of false positives and dramatically increasing sensitivity associated with employing neuropsychological versus observational neglect diagnosis method seems to be an overall beneficial trade-off.

Another potential disadvantage of neuropsychological test is that they take more time to complete than observational assessments. Common pen-and-paper neglect tests such as the OCS Cancellation Tasks often take up to five minutes to complete (Demeyere et al., 2015), while subjective judgement of patient visual orientation can be completed almost instantaneously. Additionally, assessments such as the NIHSS can be completed at practically any time in the treatment pathway, including when patients are verbally unresponsive and/or bed bound (Gottesman et al., 2010; Lyden, 2017). Completing a neuropsychological neglect test requires patients to have some degree of consciousness, verbal comprehension, and physical strength. These inherent prerequisites mean that not all patients are able to reliably complete neuropsychological neglect tests, but it not yet clear whether this represents a significant limitation versus observational assessments. Given the lack of sensitivity in NIHSS neglect classifications within participants who were able to complete cancellation tasks, it seems reasonable to infer that observational assessments may also be insufficiently sensitive within less able participants. This is especially probable given that observational neglect diagnoses are generally formed by watching participants interact with their environment (e.g. eat, look for items, navigate) and that these interactions are more difficult to

observe in bed bound patients.

Overall, the findings of this thesis strongly suggest that standardised, quantitative neuropsychological assessments offer the most effective method for detecting and diagnosing neglect impairments in clinical environments. This method is not currently used in many clinical environments, likely leading to a underestimation of neglect prevalence, diagnostic biases, and misdiagnosis of neglect as a visual impairment.

7.3 Re-Evaluating the Three-Tier Model of Neglect

7.3.1 Supporting Evidence

Hillis and Caramazza's (1995) three-tier model of visuospatial neglect has been well accepted since its inception. In this model, visuospatial neglect can occur within three separate frames of reference: retinocentric (L1), stimulus-centred (L2), and object-centred (L3). Within this model, retinocentric impairment is synonymous to egocentric neglect impairment, as it is characterised by perceptual errors which impact stimuli presented within one visual hemifield (Hillis and Caramazza, 1995; Parton et al., 2004). Similarly, this model's stimulus-centred model is equivalent to allocentric neglect, as it is defined by perceptual errors impacting one side of individual stimuli, regardless of where these stimuli are presented within egocentric space. In this model, level three "object-centred" errors are characterised by perceptual errors which occur with respect to stored, orientation-canonical representations of stimuli, regardless of how these stimuli are visually presented. For clarity, this discussion will refer to retinocentric level deficits as "egocentric", stimulus-centred impairment as "allocentric", and object-centred impairment as "representation-level". Perhaps the most critical assertion of this theory is the claim that this three-tier attentional system is responsible for supporting all modalities of spatial attention across different processes including reading and object recognition. This thesis provides a number of findings which can be applied to critically evaluate the claims of this well-accepted model.

First, the findings of this thesis agree well with Hillis and Caramazza (1995) claim that egocentric and allocentric-level neglect impairments represent distinct, dissociable cognitive impairments. Behavioural double dissociations between egocentric and allocentric neglect were reliably

identified throughout this thesis' analyses (Chapter 2, 3, 5, and 6). Egocentric and allocentric neglect were found to be differentially predictive of long-term functional outcome (Chapter 6). The severity of egocentric neglect was not found to be correlated with the severity of allocentric neglect (Chapter 2). Additionally, distinct neural correlates sub-serving egocentric and allocentric level spatial attention were identified (Chapter 5).

The findings of this thesis also provide limited support for the claim that egocentric and allocentric-level perceptual processes are not modality-specific. The analyses presented in Chapter 3 investigated the relationship between neglect related errors across two stimulus modalities: reading and a standardised neuropsychological test. Like egocentric and allocentric neglect, egocentric and allocentric neglect dyslexia were found to be behaviourally dissociated with 17 patients exhibiting pure allocentric and 35 patients exhibiting pure egocentric neglect dyslexia. This finding provides general support for the claim that multiple, distinct spatial reference frames are employed when reading. All patients who exhibited sentence-level (egocentric) neglect dyslexia were also found to exhibit significant domain-general perceptual deficits. Specifically, 33/35 patients exhibited similarly lateralised egocentric visuospatial neglect. Of the 2 patients without similarly lateralised egocentric neglect, 1 exhibited a similarly lateralised visual field impairment (e.g. hemianopia) that could potentially account for their reading impairment. The final egocentric neglect dyslexia patient without egocentric neglect was found to exhibit similarly lateralised allocentric neglect. These findings suggest that some cases of egocentric neglect appear to be content-unspecific, in line with the predictions of Hills and Caramazza (1995).

Some previous research has indicated that the severity of egocentric neglect deficits may be modulated by the attentional demand of the task at hand (Corbetta and Shulman, 2011; Emerson et al., 2019; Husain and Kennard, 1997). Reading aloud is a comparatively attentionally demanding task as it requires patients to conduct efficient spatial searches, recognise grapheme forms, access grapheme-phoneme correspondence rules, and give verbal responses almost simultaneously (Jackson and Coltheart, 2013). This increased attentional demand has commonly been cited as grounds for explaining cases of neglect which appear to impact reading but not less demanding, standardised neglect assessments (Riddoch, 1990; Riddoch et al., 1990). While it is

clear this theory cannot explain all cases of neglect dyslexia occurring in the absence of domain-general neglect, it may help explain the behavioural pattern observed within this single case. This observed lack of a dissociation between egocentric neglect dyslexia and egocentric neglect provides support for Hillis and Caramazza's (1995) claim that at least the first level of their three-tier attentional model is not content-specific.

However, Hillis and Caramazza's (1995) theory is not as clearly supported by this thesis' analyses pertaining to allocentric neglect dyslexia. This analysis identified a series of 17 patients exhibiting allocentric neglect dyslexia. While a portion of these cases (7/17) were found to co-occur with similarly laterlaised allocentric neglect, 8 cases of right-lateralised allocentric neglect dyslexia were found to occur independently of any domain-general egocentric or allocentric neglect. Additionally, two cases of right allocentric neglect dyslexia occurring in conjunction with left lateralised allocentric neglect were identified. While these findings may initially seem to provide evidence against Hillis and Caramazza's (1995) claim that their model is modality-unspecific, several limitations within this study must be considered.

First, Riddoch et al. (1990) has previously demonstrated that some cases of allocentric neglect dyslexia can be explained as a side-effect of the increased attentional loading associated with reading versus traditional neglect assessments. While this account cannot explain the cases of allocentric neglect dyslexia which occur alongside oppositely lateralised neglect, it could plausibly explain why some cases of allocentric neglect dyslexia were found to occur in the absence of domain-general allocentric neglect. Second, it is possible that each patient's reading errors may be caused by a comorbid non-attentional impairment. For example, patients with visual field deficits such as quadrantanopia and hemianopia may exhibit reading impairment which is completely unrelated to spatial attention deficits. De Jong et al., (2016) found that patients with early visual impairments commonly struggle to find the beginning/ends of words and lines of text and have noticeable difficulties in reading fluently. However, this account cannot explain cases of neglect dyslexia which impact the opposite side of space as co-morbid domain-general attentional and visual impairments.

Finally, the study reported in Chapter 3 did not include any behavioural measures which were

able to distinguish between allocentric neglect dyslexia and level three object-centred neglect dyslexia. While this limitation is does not impact this project's main purpose of the relationship between egocentric and allocentric neglect dyslexia, it does preclude additional assertions which equate reported cases of allocentric neglect dyslexia to impairment within Hillis and Caramazza's (1995) proposed level 2, stimulus-centred reference frame. This is due to the fact that when reading horizontally presented words, stimulus-centred and object-centred impairment would be expected to produce indistinguishable error patterns. Additional, orientation manipulations are required to reliably distinguish between stimulus-centred and object-centred neglect patterns. No orientation manipulations were included within Chapter 3, meaning that each identified case of "allocentric neglect dyslexia" could actually be caused by an impairment at either the stimulus-centred or object-centred level. It is therefore plausible that all cases of allocentric neglect which seem to be explained by domain-general neglect impairments could represent level two, stimulus-centred deficits while all cases occurring independently from neglect may be level three, object-centred impairments. For this reason, the findings of this study alone are insufficient to determine whether Hillis and Caramazza's (1995) proposed level 2, allocentric reference frame is content-specific.

7.3.2 Opposing Evidence

The neglect dyslexia case studies presented within Chapter 6 present an additional avenue to critically evaluate the content specificity of Hillis and Caramazza's (1995) three-tier model. Chapter 6 includes three, detailed case reports of patient AB, CD, and EF who each exhibited right, object-centred neglect dyslexia. Patients with right object-centred neglect dyslexia consistently misread or omit the terminal letters of individual words, regardless of how these stimuli are presented in space. Caramazza and Hillis's (1990) seminal study on this disorder concluded that object-centred neglect dyslexia was best understood as evidence that orthographic representations are spatially coded and that spatial attentional impairment could selectively impact these canonical, orientation-invariant representations. Findings from this case study eventually lead to the inclusion of the third level, object-centred spatial reference frame within the author's later

three-tier model (Hillis and Caramazza, 1995). However, very little work has been done to validate the existence and properties of this hypothesised third spatial reference frame.

A limited number of subsequent case studies have identified patients exhibiting object-centred neglect impairments. A comparatively recent review paper by Haywood and Coltheart (Haywood and Coltheart, 2000) identified four documented cases of object-centred neglect: HH (Caramazza and Hillis, 1990b), RB (Caramazza and Hillis, 1990b), NG (Caramazza and Hillis, 1990a) and ML (Hillis and Caramazza, 1995). Patients HH and NG exhibited right-lateralised neglect dyslexia whilst patients RB and ML exhibited left-lateralised reading deficits. An additional, more recent case of right representation-level neglect dyslexia has been identified by Schubert and McClosky (2013). However, these studies primarily focused on investigating evidence of spatial coding within the orthographic lexicon rather than investigating the relationship between object-centred neglect dyslexia and domain-general attentional processes. Some limited neglect testing has been conducted within these case studies. Patient ML demonstrated left neglect impairment on a scene copy and line bisection task (Hillis and Caramazza, 1995). Similarly , NG exhibited clear egocentric neglect on a clock drawing task and patient LHD (Schubert and McCloskey, 2013) exhibited no signs of egocentric neglect within a picture copy, line bisection, and a line cancellation task. However, none of these investigations included tests which could reliably detect any allocentric level impairment. Additionally, no established standardised neglect tests can reliably distinguish between participants with level two (allocentric) and level three (object-centred) neglect impairment. Therefore, there is no way to determine whether these patient's neglect dyslexia can be dissociated from domain-general spatial attentional processes. The three case studies reported in this thesis are the first to collect data regarding the relationship between object-centred neglect dyslexia and allocentric neglect.

Each of the three case studies reported in this investigation tested a representation-level neglect dyslexia patient on the OCS cancellation task. Previous research has demonstrated that this test is highly sensitive to neglect impairment and is reliably able to distinguish between egocentric and allocentric neglect impairments (Demeyere et al., 2015; Demeyere and Gillebert, 2019). Patient AB exhibited right representation-level neglect dyslexia in the absence of both egocentric and

allocentric neglect. It is important to note that a behavioural dissociation between representation-level neglect dyslexia and domain-general neglect impairments alone should not be interpreted as strong evidence that these deficits represent independent constructs. Differences in stimulus density and attentional loading can potentially explain why a neglect patient may exhibit impairment within reading, but not within more general spatial-attention tests (e.g. Husain and Kennard (1997), Riddoch et al. (1990)). However, these theories cannot account for a neglect dyslexia deficit which occurs with oppositely lateralised domain-general neglect. Patient CD exhibited right representation-level neglect dyslexia in conjunction with left allocentric neglect. Finally, Patient EF demonstrated right representation-level neglect dyslexia alongside left egocentric and allocentric neglect. These findings demonstrate that representation-level neglect dyslexia can be behaviourally dissociated from domain-general neglect impairment, both in terms of occurrence and lateralisation. This dissociation is a theoretically important finding, as it is not in line with Hillis and Caramazza's (1995) three-tier model of neglect.

Additional evidence strongly suggesting that representation-level neglect is independent from domain-general visuospatial neglect is provided by the specific error patterns documented within patients CD and EF. First, visuospatial neglect deficits are characterised by an unawareness of neglected space but both CD and EF demonstrated a preserved ability to identify stimuli which were then "neglected" whilst reading. CD and EF were both reliably able to name all individual letters within presented words, but were still found to commit neglect dyslexia errors when immediately asked to read the presented word as a whole. Second, the severity of CD and EF's reading impairment was not found to be modulated by stimulus density as would be expected in a visuospatial neglect impairment. Finally, the severity of these patient's neglect dyslexia was not found to be modulated by stimulus exposure time. Taken together, these clear violations of Hillis and Caramazza's (1995) predictions strongly suggest that representation-level neglect dyslexia does not necessarily represent a component of the neglect syndrome.

7.3.3 Alternate Explanations of Representation-Level Neglect Dyslexia

The case study evidence presented in this thesis provides novel and strong evidence suggesting that at least some cases of representation-level neglect dyslexia are not caused by a spatial attentional deficit. It is therefore critically important to generate competing hypotheses providing alternate explanations for representation-level neglect dyslexia. It is important to note that case study data is inherently better suited for determining what conditions are not rather than what conditions are. Causal generalisations pertaining to a condition as a whole should not be made based on data from any of the single patients presented in this thesis. However, the behavioural patterns presented by these patients do provide some tentative evidence which can be used to guide future research aiming to identify the underlying causes of representation-level neglect dyslexia.

The impairment patterns documented within this thesis seem to suggest that representation-level neglect dyslexia may represent a self-inhibition deficit. First, both patient CD and EF demonstrated intact serial letter form processing with impaired parallel processing of word stimuli as a whole. This performance pattern could be explained as an inhibitional deficit. The process of individually naming individual letters does not require patients to inhibit prepotent responses (Ellis and Young, 2013; Jackson and Coltheart, 2013). However, when reading words as a whole patients must serially process letters, accumulating evidence and inhibiting pre-potent responses based on incomplete data in order to give a correct response. A selective deficit impacting "reading words as whole" could be caused by an underlying inability to inhibit prepotent responses associated with the first-perceived letters, resulting in reading based on incomplete visual information.

Notably, reading in healthy controls is not generally a serial process. Instead of sequentially processing individual graphemes, healthy readers generally serially process word forms as a whole in order to efficiently match them to pre-existing orthographic representations within the lexicon (Jackson and Coltheart, 2013). However, unimpaired readers can alternatively employ a non-lexical, serial reading strategy when reading unfamiliar words (Jackson and Coltheart, 2013). In non-lexical route reading, individual graphemes are serially mapped to their corresponding

phonemes in order to be read aloud. While this route is not normally relied upon in healthy readers, a large body of existing literature that selective damage to lexical route processes can force patients to exhibit abnormal reliance on non-lexical reading strategies (Coslett and Turkeltaub, 2016; Ellis and Young, 2013). This abnormal, non-lexical reading strategy is most apparent in patients with surface dyslexia (Coslett and Turkeltaub, 2016). Patients with surface dyslexia become unable to access memorised exceptions to traditional grapheme-phoneme correspondence rules stored within the lexical route, and therefore commit phonological regularisation errors when reading irregular words (Coslett and Turkeltaub, 2016; Jackson and Coltheart, 2013). For example, a surface dyslexia patient would be expected to pronounce the word ISLANDS as “iz – lands” as a they are unable to access their stored, lexical knowledge of ISLANDS correct, non-phonetic pronunciation. EF demonstrated a pronounced inability to access representations of phonologically irregular words. Within the PALPA Regularity and Spelling subtest, EF committed a significantly higher proportion of errors when spelling phonologically irregular versus phonologically regular words (2/20 correct vs. 10/20 respectively). It therefore seems plausible that stroke patients with inhibitional dyslexia may also exhibit an abnormal reliance on non-lexical, serial grapheme processing, but future research is needed to confirm this hypothesis.

Second, patient EF’s Hayling Sentence Completion Test performance clearly demonstrated an inability to inhibit semantically pre-potent responses in the absence of visual stimuli. It seems plausible that this underlying inhibition deficit may have also modulated EF’s ability to read individual words. To read any individual word correctly, patients would need to inhibit pre-potent responses based on partial word features in order to successfully process all graphemes and match then to their appropriate phonology. For example, when serially reading the word PLANETS, after processing the first two graphemes patients would need to inhibit potentially pre-potent full-word responses such as “plant”, “place”, and “plan”. In the absence of semantic content, the most pre-potent response should be analogous to the written words which are most frequently encountered and are therefore most familiar to the patient. However, this “familiarity” cannot be precisely quantified as each patient has a unique degree of exposure to different reading materials. Similarly, it is unclear whether pre-potency would be determined based on visual familiarity

or semantic familiarity. For example, when shown the word THERE, a visual familiarity-based pre-potent response might be “THE”, while a semantic familiarity-based prep-potent response could be “THERMOSTAT” if the patient had been thinking about the temperature within the testing room. Any additional external factor that could modulate ease of word retrieval could reasonably be expected to determine what each patient’s pre-potent responses. Considered cumulatively, this complexity demonstrates that more research is needed to determine whether at least some cases of neglect dyslexia errors represent a failure to inhibit pre-potent response, as it is methodologically challenging to determine what each pre-potent response could be.

7.3.4 Updating the Three-Tier Model of Neglect

It is critically important to consider the implications of these findings within the context of Hilis and Caramazza’s (1995) three-tier model of neglect. This case study data presents clear contradictions to the predictions of this model. First, representation-level neglect dyslexia was found to be behaviourally dissociable from domain-general neglect. Second, the behavioural phenotype associated with representation-level neglect dyslexia was found to be clearly distinct from that of a spatial-attention deficit. Finally, patient EF’s reading impairment can more neatly be accounted for as a side effect of self-inhibition impairments rather than a component of the neglect syndrome. These documented violations of Hillis and Caramazza (1995) model’s predictions suggest that the three-tier model of neglect should be revisited and revised.

First, the data presented in this thesis does provide strong evidence in support of the idea that egocentric and allocentric-level neglect impairment represent dissociable, and content-unspecific impairment. These findings align well with Hillis and Caramazza’s (1995) theory, suggesting that the theorised first and second neglect reference frames of neglect do in fact align with experimental observation. However, it is unclear whether the hypothesised “third level” of neglect actually exists. Given that the results of this thesis demonstrate that at least a portion of representation-level neglect dyslexia deficits do not align with the predictions of Hillis and Caramazza’s (1995) model, it is critically important for future research to identify additional evidence of neglect deficits impacting representation-level reference frames. The strongest evidence in

support of this error pattern would be provided if representation-level neglect errors could be documented within non-orthographic stimuli, but this error pattern has yet to be clearly identified. Future research should aim to identify evidence of representational neglect errors using paradigms similar to those proposed within Chapter 5 of this thesis. Specifically, these investigations should be conducted within patients exhibition representation-level neglect like impairment in reading. If these patients are not found to also exhibit similar error patterns within non-orthographic stimuli, this would demonstrate an additional clear violation of Hillis and Caramazza's (1995) claim that the third-tier spatial reference frame is content-unspecific. If apparent representation-level errors cannot be reliably identified in non-orthographic stimuli, this provides strong evidence that Hillis and Caramazza's (1995) model should be amended to include only two, rather than three neglect reference frames. If this is the case, apparent representation-level neglect dyslexia should instead likely be re-termed "inhibitional dyslexia" and considered as being completely independent of spatial attention impairment.

Overall, the data presented within this thesis demonstrates that at least some cases of neglect dyslexia cannot be explained within the framework proposed by Hillis and Caramazza (1995). Additional research is needed to confirm the cognitive mechanisms subserving these unexplained cases in order to determine whether representation-level neglect dyslexia can be accurately conceptualised as an inhibitional, rather than a spatial attentional deficit.

7.4 The Neuroanatomy of Spatial Attention

7.4.1 The Neural Correlates of Egocentric and Allocentric Neglect

It is currently well established that the right hemisphere plays a dominant role in distributing attention across space (Connine et al., 1990; Tanaka-Ishii and Terada, 2011). According to this idea, right hemisphere temporo-parietal areas are involved in distributing attention across ipsilesional as well as contralesional space while anatomical homologues within the left hemisphere are responsible for attending to only contralesional space (Corbetta and Shulman, 2011; Ptak and Schnider, 2011; de Schotten et al., 2011a). This hemisphere dominance is thought to account for why neglect is more frequent and severe following damage to the right hemisphere, and

is largely responsible for the incorrect assumption that neglect only occurs follows right hemisphere lesions (Demeyere and Gillebert, 2019; Stone et al., 1992; Stone et al., 1993; Suchan and Karnath, 2011; Ten Brink et al., 2017). Taken together, previous research investigating the anatomy of spatial attention has indicated that spatial-attentional impairments are best understood as disconnection syndromes rather than deficits sub-served by any single neural correlate (see introduction) (Bartolomeo et al., 2007; Chechlacz et al., 2010; de Schotten et al., 2008). It is important to acknowledge the anatomical heterogeneity of visuospatial neglect when using this disorder to investigate the neural correlates of human spatial attention.

In this thesis, the identified anatomical correlates of left egocentric neglect agree well with those identified in previous studies. Chechlacz et al. (2012) conducted an anatomical likelihood estimate (ALE) meta-analysis of the neural correlates of left egocentric and allocentric neglect concluding that egocentric impairment was associated with damage to voxels within the pre- and post-central gyri, supramarginal gyrus, and superior temporal gyrus and white matter pathways including the thalamic radiation, corona radiata, superior longitudinal, inferior-fronto-occipital fasciculi. This thesis found that left egocentric neglect was found to be associated with a large cluster of significant voxels extending throughout the right hemisphere supramarginal gyrus, and planum temporale, lateral occipital cortex (superior division). Signifcant voxels were also present within sub-cortical white matter tracts including the internal capsule (posterior and retrolenticular parts), tapetum, and posterior corona radiata were also significantly associated with left egocentric neglect impairment. This analysis also identified significant voxels within other established egocentric neglect-related cortical ROIs including the insula (Carson et al., 2019; Chechlacz et al., 2010; Gandola et al., 2013; Karnath et al., 2002, 2004, 2009, 2011; Kenzie et al., 2015; Machner et al., 2018) and angular gyrus (Pedrazzini and Ptak, 2020; Ten Brink et al., 2019; de Schotten et al., 2014; Toba et al., 2017; Vossel et al., 2011; Wiesen et al., 2019).

Similarly, the anatomical correlates of left allocentric neglect identified within this thesis' VLSM analysis agree well with those identified in past literature. Chechlacz et al's (2013) meta-analysis concluded that left allocentric neglect was primarily associated with more posterior lesions primarily impacting the angular, middle temporal, and middle occipital gyri. This study also

identified multiple white matter tracts involved in allocentric-level deficits including the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and thalamic radiation. This thesis identified two distinct clusters associated with left allocentric neglect impairment. The posterior cluster impacted occipital cortical areas including the intercalcarine cortex, lingual gyrus, and supracalcarine cortex. Voxels within the left posterior thalamic radiation and corpus callosum (splenium) were also significantly associated with right egocentric neglect impairment. The more anterior cluster impacted subcortical areas underlying the left insular cortex, primarily the anterior putamen. These results demonstrate a reasonable amount of variance from Chechlacz et al's findings, especially given the reliance on diverse clinical samples within these studies. Considered cumulatively, the results of these analyses agree well with the results of previous literature in that they conclude that allocentric neglect is associated with damage to more posterior areas than egocentric neglect.

As in previous studies, left egocentric and allocentric neglect were associated with distinct but overlapping voxel clusters. Overall, 6.45% of significant voxels were associated with both left egocentric and left allocentric neglect. These overlapping voxels were centred within the lateral occipital cortex (superior division) and planum temporale. These results suggest that the common co-occurrence of egocentric and allocentric neglect is likely due to their neural correlates' anatomical proximity rather than being indicative of a common underlying mechanism. The voxels most strongly associated with egocentric and allocentric neglect impairment both fall within the right, Middle Cerebral Artery (MCA) territory. A medium to large stroke within this commonly impacted territory would therefore be likely to impact both areas (Ng et al., 2007).

However, the neural correlates of right egocentric neglect identified in this investigation do not as neatly agree with those identified in past studies. In the analyses presented within Chapter 5, right egocentric neglect was found to be associated with two distinct significant voxel clusters. The posterior cluster impacted occipital cortical areas including the intercalcarine cortex, lingual gyrus, and supracalcarine cortex. Voxels within the left posterior thalamic radiation and corpus callosum (splenium) were also significantly associated with right egocentric neglect impairment. The more anterior cluster impacted subcortical areas underlying the left insular cortex, primarily

the anterior putamen. Only one voxel of overlap was present between the voxels associated with left egocentric neglect and the right hemisphere homologues of voxels associated with right egocentric neglect impairment. This voxel was centred near the inferior medial border of the lateral occipital cortex (superior division).

This finding conflicts with previous study's assertions that the correlates of right egocentric neglect are best understood as the left-hemisphere homologues of the right hemisphere areas implicated in left egocentric neglect. Most notably, Suchan and Karnarth (2011) conducted a study including 11 patients with right neglect following left hemisphere lesions which concluded that right neglect is caused by damage to left hemisphere anatomical homologues of traditional right hemisphere attentional areas including the superior and middle temporal gyri, inferior parietal lobule, and insular cortex. Given the very small number of neglect patients included in this investigation, larger scale studies are needed to confirm this hypothesis. However, none of the areas identified as subserving right neglect in Suchan and Karnarth's (2011) study contained significant voxels within this thesis.

Given this analysis' use of highly conservative Bonferroni corrections, the results presented in Chapter 5 are extremely unlikely to be false positives. Bonferroni corrections are widely regarded to be too conservative for general VLSM analyses because of the large number of comparisons conducted in voxel-wise VLSM analyses (Bates et al., 2003; Mirman et al., 2018). Permutation-based and family-wise error rate corrections are more commonly employed in VLSM analyses (de Haan and Karnath, 2018; Mirman et al., 2018). However, the present investigation opted to rely on Bonferroni corrections in order to ensure that only a limited number of voxels with strong associations with neglect impairment survived statistical correction. These highly conservative VLSM parameters suggest that the significant voxel cluster identified in this investigation's VLSM analysis of right egocentric neglect does not represent a false positive finding.

There are several possible explanations for why this thesis' findings differ from those of previous investigations aiming to identify anatomy implicated in right egocentric neglect. First, this study included a large and representative sample of stroke survivors which contained substantially more patients exhibiting right egocentric neglect than previous investigations (n= 38 versus n =

11 (Suchan and Karnath, 2011) and n = 21 (Beume et al., 2017)). This improved statistical power may help account for why this investigation identified correlates which remained insignificant in previous studies. Next, the present investigation employed behaviour-based patient groupings rather than lesion-location based groups. For example, any patient exhibiting right egocentric neglect was included as impaired in the right egocentric VLSM analysis, regardless of whether their lesion was in the left or right hemisphere. This approach contrasts with previous studies which have required patients to exhibit both right egocentric neglect and left hemisphere lesions. This approach allowed this thesis to include a more representative sample of right egocentric patients who were not pre-selected based on lesion type. Finally, this thesis employed whole-brain VLSM analyses rather than analyses which are restricted to voxels within a single hemisphere. This analysis structure enabled whole-brain VLSM analyses with the potential to detect and compare implicated anatomy across hemispheres.

One of the key methodological differences between the analyses presented in Chapter 5 and previous neglect VLSM investigations is the inclusion of patients demonstrating ipsilesional neglect. Previous investigations have suggested that a portion of egocentric neglect cases may involve ipsilesional impairments (Agrell et al., 1997; Kim et al., 1999; Kwon et al., 2012; Weintraub and Mesulam, 1987; Williamson et al., 2018). Kim et al. (1999) assessed 30 right hemisphere stroke survivors on a line bisection task and identified 5 patients exhibiting ipsilesional (right) egocentric neglect deficits. Agrell et al (1997) identified a single patient who exhibited consistent right, ipsilesional neglect across five standard neuropsychological measures. Similalrly, Kwon et al. (2012) who exhibited ipsilesional right neglect impairment within a line bisection and midline identification task. It has been posited that apparent right-laterlaised neglect may occur as a consequence of compensatory strategies learned to ameliorate the impact of left egocentric neglect (Williamson et al., 2018). For example, a patient who is aware that they struggle to perceive objects on their left may learn to take extra care to attend to this side of space, creating apparent attentional deficits on the opposite (right) side of space. There are several potential weaknesses in this hypothesis. First, many patients with neglect exhibit anosognosia, or an unawareness of their attentional impairments (Vossel et al., 2013; Vossel et al., 2012). Before learning compen-

satory strategies, it is necessary that patients are aware of their deficits. However, not all patients with neglect exhibit anosognosia. More convincing evidence against the characterisation of right neglect as a compensatory strategy comes from the findings of Kim et al. (1999). If right neglect develops as a compensatory strategy for left neglect, it follows that patients who exhibit right neglect would be expected to exhibit left neglect deficits immediately following stroke and develop right neglect deficits over time. However, the patients assessed by Kim et al. (1999) completed repeated neglect assessments throughout the course of recovery and were never found to exhibit signs of left lateralised neglect impairment. This study concluded that ipsilesional neglect could not be explained as a compensatory strategy, as patients did not initially present with contralesional neglect impairment (Kim et al., 1999). Taken together, both the existing literature and the present investigation suggests that at least a portion of right egocentric neglect cases represent ipsilesional defects.

This thesis' anatomical identified correlates of right egocentric neglect is in line with the theory that the right hemisphere is involved in distributing attention across ipsilesional as well as contralesional space (Corbetta and Shulman, 2011; de Schotten et al., 2011a; Weintraub and Mesulam, 1987). However, it is clear that not all cases of right or left egocentric neglect documented were ipsilesional (See Chapter 5, Table 1). Previous research has also identified contralesional neural correlates predicting right egocentric neglect impairment (Beume et al., 2017; Suchan and Karnath, 2011). This heterogeneity suggests that right visuospatial neglect may be best conceptualised as a common behavioural symptom with multiple underlying causes. It is plausible that neither the right hemisphere ipsilesional attentional system nor the non-dominant left-hemisphere attention network are fully responsible for attending to right hemispace. This lack of complete redundancy would mean that neither the left nor right hemisphere is initially able to fully compensate for damage to the opposite hemisphere. This possibility could also help account why right egocentric neglect consistently presents as less severe and tends to recovers more completely than left lateralised egocentric neglect (Demeyere and Gillebert, 2019; Stone et al., 1992; Ten Brink et al., 2017). However, the findings of the present study provide only tenuous support for this potential conclusion. Additional, more focused, research is needed to confirm

the degree of collaboration between right and left hemisphere attentional systems in attending to egocentric space.

Notably, this thesis is the first study to successfully identify the neural correlates of right allocentric neglect. Beume et al. (2017) initially aimed to identify the neural correlates identified with allocentric errors, but failed to identify any patients exhibiting allocentric neglect following left hemisphere lesions. In this thesis' VLSM analysis, 39 patients with right allocentric neglect were identified. Right allocentric neglect was found to be significantly associated with a small cluster of voxels centred within the external capsule and internal capsule (anterior limb). Inferior temporo-frontal cortical regions have been consistently associated with object-level perceptual processes and is a key anatomical component of the ventral visual processing stream (Borowsky et al., 2007; Grill-Spector, 2003; Quiroga et al., 2005). It is plausible that damage to the external and internal capsule white matter tracts disrupts communication with these areas, resulting in allocentric neglect impairment. However, there was no overlap between the neural correlates of left and right allocentric neglect. This suggests that the allocentric level spatial-attentional system is not homologous across hemispheres. Additional research is therefore needed to provide a more detailed characterisation of the neural correlates of allocentric-level visual attention in order to better understand the exact mechanisms which underly this condition

The results of this thesis also strongly suggest that right egocentric neglect cannot be accurately characterised as an anatomical homologue of left egocentric neglect. Suchan and Karnath (2011) proposed that right neglect occurs after damage to left-hemisphere evolutionary relicts of traditional right hemisphere attentional areas. However, this assertion was based off of an analysis conducted within a restricted sample of 11 neglect patients considering only left hemisphere voxels. This thesis provides strong evidence that this theory does not generalise to a larger, more representative sample of stroke survivors. First, this investigation identified cases of right egocentric neglect occurring following right and left hemisphere lesions. This qualitative finding alone demonstrates that not all cases of right egocentric neglect are associated with damage to the left-hemisphere. Third, previously proposed left hemisphere attentional homologues such as the left superior/ middle temporal gyri, inferior parietal lobule, temporal pole, frontal operculum, and

insular cortex were not found to contain any voxels which significantly predicted the occurrence of right egocentric neglect (Beume et al., 2017; Suchan and Karnath, 2011). These findings would not be expected if right/left neglect could be explained as consequences of damage to opposite hemisphere homologues. Instead, the findings of this investigation strongly suggest that right egocentric neglect is a complex entity which generally results from damage to more posterior left hemisphere areas.

Considered cumulatively, the results of the present investigation support the characterisation of visuospatial neglect as a heterogenous cluster of impairments rather than a unitary syndrome. Similarly, the consistent involvement of damage to white matter tracts in egocentric/allocentric neglect supports previous assertions that neglect represents a disconnection syndrome in which neglect symptoms with distinct cortical correlates may be linked back to common white matter damage. Future investigations need to account for this heterogeneity. Studies which do not account for differences between left/right or egocentric/allocentric neglect deficits may risk producing overgeneralised results confounded by considering distinct behavioural deficits as a single, unitary impairment. The inclusion of large, representative patient samples assessed for both egocentric and allocentric level neglect impairment is critical in order to facilitate valid conclusions about the neglect syndrome as a whole.

The findings of this investigation provide novel insight into the distinct neural correlates of right and left visuospatial neglect deficits in a large, representative sample of stroke survivors. The findings pertaining to left egocentric/allocentric neglect align with and replicate findings from existing literature. With regards to the critical neuro-anatomy underlying right-lateralised visuospatial neglect, where little research exists, we found right egocentric neglect to be most strongly predicted by damage to voxels within the posterior occipital cortex. Importantly, right neglect should not be characterised as a consequence of damage to left-hemisphere homologues of the right hemisphere attentional systems, but instead may represent a common behavioural consequence of multiple underlying causes. Notably, this is the first study to identify the neural correlates of right allocentric neglect in the left internal/external capsule white matter. Cumulatively, these findings provide novel insight into the neural correlates of spatial attention.

7.4.2 Lesion Symptom Mapping Methodology in Neglect

However, these findings are not without limitations. VLSM is commonly employed to investigate the neural correlates of neglect, but it remains unclear whether this analysis technique represents the most effective method for elucidating the neural correlates of neglect. At its core, VLSM is designed to identify specific voxels that when damaged are associated with behavioural impairment (Bates et al., 2003; de Haan and Karnath, 2018). VLSM sequentially tests each voxel independently, binarily classifying each voxel in order to group all patients with damage into the impaired group and all patients without damage into the intact analysis group. However, the brain is not a 3D matrix of functionally independent pixels but instead represents a complex network of components interacting across various spatial scales (Sporns, 2010; Thiebaut de Schotten et al., 2008). Each individual cortical area must both receive input and send output to and from anatomically distant areas in order to effectively function as a component of this network (Sporns, 2010). Traditional VLSM does not take this complexity into account (Bates et al., 2003). The VLSM analyses conducted in this investigation attempted to account for patterns of connectivity within the human brain by considering white matter ROIs as well as cortical ROIs within anatomical analyses. However, this control alone is not entirely sufficient to eliminate potentially confounding variance due to functional connectivity.

These potential issues can be best illustrated by considering VLSM analysis in the context of neural functions which involve collaboration across a wide range of cortical and subcortical areas. For example, it is well established that low-level visual perception relies on a number of processes sub-served by anatomically distinct locations. Light is first transduced to electrical stimuli by photoreceptors located within the retina (Bear et al., 2020). This information is compiled by ganglion cells and sent out of the eye through the optic nerve. This tract crosses the optic chiasm and passes through thalamus's lateral geniculate nucleus before arriving at the primary visual cortex (V1) in the intercalcarine sulcus (Bear et al., 2020). Damage to many different points of this pathway could potentially result in identical behavioural deficits. A left visual field deficit could be caused by selective damage to the right hemisphere primary visual cortex, the thalamocortical fibres connecting the thalamus to V1, the optic nerve within the left hemisphere

(prior to the optic chiasm), or the left eye's retina.

When a single V1 voxel is considered in VLSM analysis, patients with visual deficits due to damage within other areas of this pathway are grouped into the "intact" group. This can then reduce the difference in behavioural scores between the lesioned and intact group, lowering the effect size associated with the analysed voxel. This "moving reference group" problem results in VLSM tending to flag only the voxels with the largest effect sizes as being significant whilst ignoring the contributions of less pronounced, but equally critical regions. This issue is most prominent when analysing functions with bilateral neural correlates. Clinical data is notoriously heterogeneous and it is exceptionally rare for studies to include equal numbers of patients with damage to each hemisphere. Even if patient groups are equal in number, differences in individual lesion patterns will result in unequal distributions of patients across voxels considered in VLSM. This variance can produce confounding bias. For example, a VLSM investigating the correlates of motor function includes an unequal number of patients with damage to critical voxels within the left and right basal ganglia would be biased towards reporting voxels in the more frequently damaged hemisphere as being significant while ignoring the contributions of the opposite hemisphere (see Jacob Levenstien, PhD Thesis).

The inherent structure of VLSM can also produce inaccuracies when more proximal critical correlates are analysed. If a function is sub-served by two distinct, but nearby correlates, VLSM analysis will be biased to report the intermediate (non-critical) location as being significant whilst ignoring the contributions of the two actual correlates. This problem can be illustrate by considering a simplified model of aphasia. Previous research has demonstrated that patients can exhibit aphasia deficits after damage to either Broca's or Wernicke's area (Ellis and Young, 2013; Hickok, 2000). Broca's area is located within the pars opercularis and triangularis of the left hemisphere inferior frontal gyrus while Wernicke's area is located more posteriorly within the lateral superior temporal gyrus (Bear et al., 2020; Ellis and Young, 2013). When analysing a voxel within Broca's area, a VLSM analysis would place all patients with damage to Wernicke's are in the intact group, lowering the difference between these groups. However, a lesion impacting both Broca's and Wernicke's area would include all aphasic patients within the impaired group. Given that lesions

impacting both areas are more likely to be centred on a voxel in between rather than in these areas, this VLSM analysis would be likely to report an intermediate voxel in a non-critical location such as the primary motor cortex to be the neural correlate of aphasiac impairment.

Finally, VLSM struggles to identify critical white matter structures. For example, previous studies have found that the inferior fronto-occipital fasciculus plays a key role in semantic processing (Fang et al., 2018). This white mater tract covers a particularly large area spanning from the frontal lobe to the posterior portion of the inferior occipital gyrus (Fang et al., 2018; Schmahmann et al., 2008). A lesion selectively impacting the most posterior or most anterior portion of this fasciculus would be expected to yield the same behavioural impairment. However, this spatial separation yet common underlying function cannot be reliably identified by voxel-wise VLSM analyses. This specific issue can be addressed by conducting VLSM on an ROI rather than a voxel-wise basis (de Haan and Karnath, 2018). In ROI-based VLSM, the brain is segmented into anatomically distinct regions of interest and these regions are analysed as a whole. This approach has several advantages as it is able to consider white matter tracts as a whole, therefore compensating for issues due to damage at different locations along these tracts. ROI-based VLSM also reduces the need for very conservative multiple comparison corrections, as fewer individual statistical tests are conducted in these analyses (de Haan and Karnath, 2018; Mirman et al., 2018). However, these advantages of ROI-based VLSM are coupled with equally critical disadvantages. ROI-based VLSM makes the critical assumption that each considered ROI is functionally homogenous. For example, ROI-based VLSM would not distinguish between functional specificity within an area such as the postcentral gyrus, but would instead consider this area as a functionally uniform whole. Previous research has strongly suggested that the postcentral gyrus is not functionally homogenous, but instead is composed of a large number of spatially segregated areas sub-serving movement within a range of anatomically distinct areas (Bear et al., 2020; Ellis and Young, 2013). ROI-based VLSM which considers the precentral gyrus as whole would be unable to distinguish between the different coordinates associated with upper limb and lower limb impairment. Studies can aim to employ fine-grained, function specific ROI atlases, but these area definitions would be inherently defined based on our incomplete knowledge of brain

function. These methodological issues imply that the utility of both voxel-wise and ROI-based VLSM is limited, especially in cases where cognitive functions involving collaboration between multiple, distinct regions are considered.

Importantly, VLSM's limitations do not nullify this thesis' findings pertaining to the anatomy of neglect. Instead, these limitations restrict the generalisations which can be made based on these findings. Previous research has strongly suggested that visuospatial neglect is a disconnection syndrome (Bartolomeo et al., 2007; Chechlacz et al., 2010; Lunven et al., 2013). This suggests that the analyses conducted within this investigation may be biased towards reporting only the most significant voxel clusters whilst ignoring the contributions of additional critical areas. This potential issue is most clearly illustrated by the cases of right egocentric neglect considered within this thesis. VLSM analysis reported that right egocentric neglect was associated with damage within the left lateral occipital cortex, but the behavioural data observed in this investigation clearly demonstrates that additional critical sites must be involved. A subset of 8 patients exhibited right egocentric neglect following lesions selectively impacting right hemisphere areas (Table 5.1, Figure 5.3). The contributions of these areas to neglect impairment was likely statistically underestimated due to the right hemisphere, ipsilesional patients being included in the intact group during VLSM analysis of left-hemisphere voxels. This limitation means that these findings are not absolute evidence, but should instead be interpreted as preliminary evidence suggesting that right egocentric neglect is an anatomically heterogenous condition which, to some extent, involves ipsilesional neural correlates. The limitations of VLSM also imply that the results presented in Chapter 5 may represent an "average location" of the correlates involved in neglect rather than the actual areas underlying these deficits. Again, this limitation does not nullify the findings reported. If only the "average location" of left egocentric neglect was found to be anatomically distinct from only the "average location" of left allocentric neglect, this finding would still provide strong evidence that these impairments represent anatomically dissociable deficits. Additional research is needed to investigate whether the anatomical correlates of neglect identified within this thesis are components of a wider, more anatomically distributed functional network.

Several lesion-mapping techniques which account for patterns of functional connectivity

within the human brain have been proposed. First, de Schotten et al., (2014) employed a probabilistic diffusion tensor imaging based atlas to run an analysis of the subcortical white matter pathways involved in visuospatial neglect. In this analysis, binarized lesion masks were compared to white mater anatomy. When lesion masks impacted voxels which had at least a 50% probability of being within a given tract, the relevant tract was considered to be "disconnected" within the patient. A series of regressions were then conducted to identify specific tracts that, when lesioned produced neglect deficits. Each regression included lesion volume. This hodological lesion-mapping analysis concluded that damage to the second branch of the superior longitudinal fasciculus was the strongest single predictor of neglect impairment. Despite this analysis style's consideration of connectivity patterns, it suffers from many of the same limitations of ROI-based VLSM. This analysis technique relies on an existing DTI atlas which assumes functional homogeneity within its defined ROIs. Additionally, the relevant atlas was constructed from a sample of healthy, young subjects between the ages of 18 and 22 (Catani and de Schotten, 2008; de Schotten et al., 2014) . It is not quite clear whether this atlas can be neatly generalised to older adults. Older subjects commonly experience some degree of white matter degeneration during ageing (de Groot et al., 2015, 2016; Salat et al., 2005). This variance is particularly problematic within clinical datasets as stroke is highly comorbid with white matter degeneration-related conditions including small vessel disease and dementia (Alistair, 2002; Jeerakathil et al., 2004). However, this potential methodological limitation can be avoided by employing age-matched white matter templates in future research.

For example, Hearne et al. (Under Review) controlled for age-related white matter variance in their demonstration of a novel lesion-connectivity mapping technique which aims to link specific patterns of dysconnectivity to multiple, co-varying cognitive outcomes. Instead of using DTI atlases based on group data, this analysis created age and sex-matched normative structural connectomes for each patient based on a publicly available normative connectome data base (Horn and Blankenburg, 2016) (https://www.nitrc.org/). This analysis identified a single, underlying lesion-behavioural pattern linking disconnection damage to cognitive impairment in stroke survivors with a left-right hemispheric bias for language and attention functions, respectively. Net-

work analysis of these results identified a set of neural regions which when damaged, yield a disproportionate impact on global processing due to their comparatively high network centrality (Hearne et al., Under Review). Future research should aim to employ this technique could be applied to clarify how patterns of structural connectivity (and dysconnectivity) are implicated in the anatomy of visuospatial neglect.

Additional alternative VLSM methodologies which do not rely on hodological atlases have been proposed. Toba et al. (2017) employed multi-pertuberation Shapley value Analysis to infer causal neural region contributions to specific post-stroke behavioural deficits. Shapely Value Analysis aims to identify the relative importance of various predictor variables in a linear regression style analysis (Winter, 2002). This technique is generally used to account for moderate to high correlation within predictor variables, which can confound traditional linear regression analyses (Fox, 1997; Winter, 2002). Toba et al's (2017) analysis used coalitional game theory to establish causal contributions and interactions between various pre-defined anatomical "nodes" within the right hemisphere attentional network. Subsequent studies have also relied on support vector regression VLSM analyses, which employ supervised machine learning algorithms to create a model based on training data which best describes a continuous relationship between lesion location and behaviour (Sperber et al., 2019; Wiesen et al., 2019; Zhang et al., 2014). Wiesen et al. (2019) found that support vector regression lesion-mapping produces similar results to traditional univariate VLSM when used to investigate the neural correlates of visuospatial neglect. However, Sperber et al. (2019) conducted a critical evaluation of support vector lesion mapping approaches which concluded that this technique is only appropriate for large patient samples (>100). Additionally, this analysis concluded that support vector lesion mapping is susceptible to misplacement of statistical topographies along the brain's vasculature to a similar extent as traditional VLSM analyses (Sperber et al., 2019). In other words, this technique cannot distinguish between critical and non-critical voxels which are commonly damaged together due to their proximity and inherent likelihood to be impacted by the same stroke event. For example, MCA strokes commonly impact voxels within the insular ribbon (Rabinstein and Resnick, 2009). If a given deficit is sub-served by a proximal correlate within the basal ganglia, but is only damaged within patients who have

MCA strokes also impacting the insula, this analysis technique would not be able to distinguish between the contributions of these paired voxels. Additional research is needed to further establish the utility of these alternative lesion-mapping methodologies and to apply these approaches to better understand the neuroanatomy of human spatial attention.

Considered cumulatively, the data presented in this thesis provides a novel illustration of the anatomical heterogeneity of the neglect syndrome. Future research can aim to expand upon these findings by employing network-based VLSM techniques to account for complex patterns of distributed functional contributions that seem to underlie human spatial attention.

7.5 Clinical Implications of Heterogeneity in Neglect

7.5.1 The Relationship between Egocentric and Allocentric Neglect

There is a degree of debate surrounding whether or not egocentric and allocentric neglect should be characterised as dissociated cognitive impairments. On one side, Driver and Pouget (2000) claim that allocentric neglect is best understood as a form of relative egocentric neglect rather than in independent impairment. For example, Karnath and Rorden (2012) propose that unilateral visuospatial neglect is characterised by a core inability to distribute attention evenly throughout space and that this core deficit results in a series of lateralised spatial and attentional deficits, including syndromes such as allocentric neglect, visual extinction, and neglect errors in reading. This model of unilateral visuospatial neglect asserts that neglect-related cognitive deficits are best understood as satellite components of a unitary syndrome, each resulting from a shared core impairment. Theories which assume a common cause underlying both egocentric and allocentric neglect make several key predictions about how visuospatial neglect deficits should appear within the stroke patient population. First, allocentric neglect should always co-occur with egocentric neglect. Second, allocentric neglect should always impact the same lateralisation as egocentric neglect. Third, egocentric and allocentric neglect should be associated with damage to identical neural correlates. Fourth, within patients with neglect, the probability of committing an allocentric-level neglect error should be modulated by each stimulus' location within egocentric space. The results presented within this thesis clearly demonstrate that these predictions do not

align with experimental observation.

With regards to the first assumption, allocentric neglect was consistently found to occur in the absence of egocentric neglect deficits. Conversely, egocentric neglect was also documented in a large number of patients who did not also exhibit allocentric neglect deficits. In Chapter 6 (Section 1) 41 patients exhibiting allocentric neglect in the absence of egocentric neglect and 71 patients demonstrating egocentric neglect without allocentric neglect were identified. In Chapter 2 (Section 2) the severity of egocentric and allocentric neglect were not found to be significant. Similarly, the lesion-mapping analyses presented within Chapter 5 concluded that the neural correlates of egocentric and allocentric neglect are largely distinct. These findings demonstrate a classic, behavioural double dissociation between egocentric and allocentric neglect which is broadly considered as strong evidence that these conditions represent independent impairments (Fama and Sullivan, 2014). The double dissociation model represents the gold standard neuropsychological approach for determining whether two cognitive processes can occur independently of one another (Katz and Sevush, 1989). According to this model's logic, if two cognitive impairments can occur independently of one another, they cannot be dependent on the exact same underlying cognitive process (Katz and Sevush, 1989). It follows that if allocentric and egocentric are doubly dissociated, allocentric neglect cannot be fully explained as a side-effect of egocentric neglect deficits. However, in some specific cases it is possible for two conditions to be causally related and apparently doubly dissociated. It has been proposed that allocentric neglect represents a form of "stimulus-density sensitive" egocentric neglect (Moore and Demeyere, 2017; Riddoch et al., 1990). This argument is based on findings that increasing stimulus density increases the severity of egocentric neglect, meaning that some patients only commit neglect errors when examining more visually demanding stimuli (Riddoch et al., 1990). This modulation could potentially explain some cases of allocentric neglect which appear to occur in the absence of egocentric neglect. For example, a patient could exhibit an underlying egocentric spatial bias which is only apparent when processing more complex stimuli (e.g. words). In this case, a patient could appear unimpaired on some classic tests of egocentric spatial bias (e.g. line cancellation) whilst appearing impaired on more demanding tests aiming to identify object-centred attentional problems (e.g. reading).

However, this potentially illusory dissociation would be strictly task dependent and it seems unlikely that such a false dissociation would impact performance on the standardised neglect test employed in this investigation.

Alternatively, it is possible that patients are able to learn to compensate for egocentric biases over broad, but not narrow areas of space. Previous research has illustrated that lateralised attentional cueing or training patients to employ organised spatial search patterns can help ameliorate egocentric visuospatial symptoms (Chechlacz et al., 2012). However, it is unclear whether these compensation strategies would have any impact on allocentric-level neglect deficits. This implies that a subset of patients might still exhibit residual allocentric symptoms whilst compensating for an underlying egocentric spatial bias. Additional, strong evidence against these alternative explanations is provided by examining the second assumption of theories which assert allocentric neglect is caused by egocentric neglect.

If allocentric neglect represents a side-effect of egocentric neglect, these deficits should always co-occur within the same lateralisation (Driver and Pouget, 2000). However, both the results of this thesis and the existing body of literature strongly suggest that it is possible for egocentric and allocentric neglect to co-occur in opposite lateralisations within the same patient. In Chapter 2 (Section 1), 7 patients were identified exhibiting this impairment conjunction. In Chapter 3, 8 cases of allocentric (stimulus-centred) neglect dyslexia were identified in the absence of egocentric spatial biases. Both Driver and Pouget's (2000) attentional gradient model and Riddoch et al.'s (1990) stimulus density model struggle to provide an adequate explanation of how egocentric and allocentric neglect could co-occur in opposite lateralisations. It is not clear how a single, uniform attentional gradient could produce attentional deficits within different reference frames which impact opposite sides of space (Driver and Pouget, 2000). Similarly, it is not clear how stimulus density modulation could produce allocentric error impacting the opposite side of space.

Additional evidence suggesting that egocentric and allocentric neglect represent distinct conditions is provided by the anatomical analyses conducted within this thesis. If allocentric neglect was a consequence of egocentric neglect, these two impairments should be associated with dam-

age to the same regions (Chechlacz et al., 2012; Sullivan and Pfefferbaum, 2014). The associated lesions can be expected to vary slightly in size and exact location due to random noise within lesion data, but should ultimately be centred around the same area. The results of this thesis clearly demonstrate that this is not the case. Notably, this analysis was conducted in a large, diverse, and representative clinical sample employing strict statistical corrections and whole-brain, voxel-wise (theory-blind) analyses. Left egocentric and allocentric visuospatial neglect were found to be associated with damage to neighbouring, yet distinct clusters of voxels within the temporo-parietal junction area and posterior parietal cortex. Specifically, left egocentric neglect was most strongly associated to damage to voxels within the parietal operculum whilst left allocentric neglect was most strongly associated with more posterior lateral occipital cortex (superior division) damage. This finding is in line with existing literature (Chechlacz et al., 2010; Chechlacz et al., 2012). Similarly, right egocentric neglect was associated with damage to the left occipital fusiform gyrus whilst right allocentric neglect was associated with a more anterior, distinct voxel cluster within the left internal capsule (anterior limb). This clear anatomical dissociation provides additional evidence that allocentric neglect cannot be accurately characterised as a side-effect of egocentric neglect impairment, but instead represents a distinct, independent cognitive impairment.

Finally, if egocentric neglect causes allocentric neglect, patients with egocentric neglect would be expected to commit a higher portion of allocentric errors within the neglected egocentric hemifield. This prediction is based off the characterisation of hemispatial neglect as an attentional gradient slanting from full attention in the attended field to inattention within the opposite side of space (Driver and Pouget, 2000). If allocentric neglect can be characterised as a form of "relative" egocentric neglect rather than an independent condition, neglect patients should make more allocentric errors when targets are presented nearer to the unattended hemifield (Driver and Pouget, 2000). The data presented within Chapters 2 (Section 2) of this thesis demonstrate that this prediction does not align with empirical observation. Chapter 2 (Section 2) demonstrates that there is no significant difference in the average location of allocentric errors between patients exhibiting left and right egocentric neglect. This thesis demonstrates that many egocentric patients commit no allocentric neglect errors, regardless of stimulus location. Taken together, these

findings strongly suggest that allocentric neglect cannot be accurately characterised as a side-effect of egocentric neglect, but instead represents an independent, behaviourally dissociated impairment.

7.5.2 Neglect Heterogeneity in Rehabilitation and Recovery

Importantly, the dissociation between egocentric and allocentric is not only of theoretical interest, but also has clear clinical implications. If egocentric and allocentric neglect are dissociated conditions, patients exhibiting these impairments should not be assumed to be behaviourally or prognostically similar. The data presented within Chapter 6 (Section 1) of this thesis illustrates that egocentric and allocentric neglect differentially impact stroke survivors. Egocentric neglect exhibited proportional recovery with the severity of acute impairment predicting the severity of chronic impairment. However, allocentric neglect was not found to recover proportionally with a subset of patients remaining unchanged or getting worse over time, regardless of initial severity. In proportional recovery, the amount of improved function is proportional to the initial degree of function loss (Hope et al., 2019; Marchi et al., 2017). In the context of neglect, this suggests that patients with the most severe egocentric deficits would be the least likely to spontaneously recover over time. This information can be harnessed by clinicians who can aim to develop targeted rehabilitation strategies focusing on the subset of neglect patients who are least likely to recover without intervention. However, this guidance does not seem to be generalisable to patients exhibiting allocentric neglect impairment.

Patients with allocentric neglect were found to follow a non-proportional, non-fixed recovery pattern. Initial severity of allocentric impairment was not found to significantly distinguish between allocentric patients who had and had not recovered before follow-up assessment. This novel finding suggests several directions for future research to pursue before effective allocentric neglect-specific rehabilitation programmes can be designed. First, it is important to investigate whether additional factors may help distinguish between allocentric neglect patients who will and will not recover without clinician intervention. The analyses included within Chapter 6 were only able to include a comparatively small number of allocentric neglect patients within each recovery

group analysis. Additionally, this patient set had comparatively limited non-cognitive clinical data meaning that additional potentially significant recovery predictors such as stroke severity, lesion size, and comorbidities could not be considered in this analysis. Future research could aim to collect this more general stroke data in order to explore alternate methods for distinguishing between allocentric neglect patients who do and do not spontaneously recover.

For example, it is possible that allocentric neglect recovery could be reliably predicted based on lesion anatomy. Chechlacz et al. (2012) found that allocentric neglect which persisted into the chronic stage of stroke recovery was specifically associated with damage to the angular gyrus, temporo-parietal junction, and superior longitudinal fasciculus. Allocentric neglect which occurred following other lesion patterns was found to be more likely to spontaneously recover (Chechlacz et al., 2012). Importantly, this study also found that lesion size acted as a predictor of allocentric neglect recovery with patients with smaller lesions being more likely to recovery over time. These results suggest that although the neglect syndrome is associated with a wide range of lesions, only a subset of these lesion profiles act as significant predictors of poor recovery outcomes (Chechlacz et al., 2012). However, there are several potential issues involved with applying these findings within clinical settings.

First, in order to be useful within the acute stage, these anatomical classifications would have to be made based on comparatively poor-quality clinical imaging. While acute stroke CT scans are reliably able to identify differential lesion patterns within large patient groups (Moore et al., Under Review – Appendix I), these scans are less useful on the individual level. Acute CT scans have a high false negative rate (Khan et al., 2013; Rabinstein and Resnick, 2009). Lesion topographies change dramatically throughout recovery with lesion boundaries becoming more clearly visible as cells die off and are replaced with cerebrospinal fluid (de Haan and Karnath, 2018; Rabinstein and Resnick, 2009). The imaging data employed within Chechlacz et al.'s (2012) study was collected at a sub-acute timepoint, meaning that it is not clear whether these results will neatly generalise to acute imaging data. Second, exact lesion anatomy quantification is a technically challenging and time consuming process. In order to precisely determine impacted anatomy, scans must be manually delineated, reoriented, normalised, and compared

to standardised neurological atlases (de Haan and Karnath, 2018). This procedure is necessary to produce accurate lesion size and anatomy data, but it is not generally performed in clinical settings (de Haan and Karnath, 2018). Instead, lesion anatomy classifications are more regularly made based on qualitative, subjective impressions of affected anatomy. Given that Chechlacz et al.'s (2012) study employed quantitative lesion mask data rather than qualitative clinician judgments of lesion anatomy, it is not clear whether this information can reasonably be expected to be applied in clinical settings. Future studies aiming to enable clinicians to make neglect prognosis assumptions based on neuroimaging data must either investigate predictions based on less fine-grained, subjective anatomy judgments or adjust lesion quantification protocols to be feasible within clinical settings. For example, studies could ask trained clinicians to describe lesion anatomy then investigate whether these classifications can be applied to identify patients who are less likely to spontaneously recover from acute neglect. Alternatively, researchers could aim to develop automated methods for quantifying lesion anatomy in order to instantly provide detailed and quantitative anatomical statistics for patients within acute clinical settings.

Data presented within Chapter 6 of this thesis suggests that egocentric and allocentric neglect may differ slightly in their relationship with poor long-term functional outcome in neglect. First, allocentric, but not egocentric severity was found to act as a predictor of poor long term functional outcome as quantified by Stroke Impact Scale (Duncan et al., 1999) total scores. Second, in the multiverse analysis analyses which considered allocentric neglect yielded larger average effect sizes than comparisons exclusively considering egocentric neglect. These findings indicate that egocentric and allocentric neglect are differentially associated with functional outcome. Specifically, allocentric impairment seems to be a stronger predictor of poor long term functional than egocentric neglect. Interestingly, egocentric and allocentric neglect were not found to result in specific differences in functional impairment as reported by occupational therapist observations. Previous research has indicated that some degree of difference in functional outcome is present between patients with different neglect subtypes. Bickerton et al. (2011) found that patients with allocentric neglect scored significantly lower on the Barthel Index activities of daily life measurement (Quinn et al., 2011) compared to patients with egocentric neglect. In this study, patients

with both allocentric and egocentric neglect also reported significantly higher levels of depression on the Hospital Anxiety and Depression Scale than patients with either egocentric or allocentric neglect alone (Bickerton et al., 2011). It is possible that egocentric and allocentric neglect are associated with significant, but small behavioural differences which are not associated with large enough effect sizes to be apparent on the relatively subjective occupational therapy observations of functional activities of daily living. Alternatively, it is possible that allocentric and egocentric neglect differentially impact functional activities not assessed in either the wash and dress or kitchen assessment (e.g. reading). Additional research is likely needed to confirm whether behavioural profiles are analogous across these neglect subtypes.

It is also important to consider the dissociation between egocentric and allocentric neglect in the context of current neglect rehabilitation practices. A wide range of neglect rehabilitation therapies have been proposed (Bowen and Lincoln, 2007; Bowen and Wenman, 2002; Cumming et al., 2013), but these rehab strategies have only considered egocentric-level neglect deficits. For example, Prism Adaptation Therapy is a popular neglect rehabilitation strategy in which patients wear prism glasses which shift their gaze towards the neglected visual hemifield (Chaudhari and Barrett, 2015; Ten Brink, Visser-Meily, et al., 2017). More recent investigations have aimed to develop virtual reality neglect rehabilitation programmes. For example, Fordell et al. (2016) developed a reality programme for neglect in which patients complete various visual scanning training in a 3D virtual reality environment (RehAtt). A sample of 15 chronic left egocentric neglect were found to exhibit significant improvement on multiple neuropsychological neglect tests versus baseline assessment following 15 hours of RehAtt training (Fordell et al., 2016). The efficacy of these therapies have never been studied in allocentric neglect patients. Given that these therapies aims to ameliorate egocentric-level biases, it is unclear whether they could be expected to have any effect on allocentric attentional biases.

Therapies which aim to improve non-spatial attentional biases underlying visuospatial neglect may offer a more appropriate method for treating allocentric neglect. Approaches based on phasic alerting (Robertson et al., 1998), vestibular stimulation (Agrell et al., 2013), neck muscle vibration (Johannsen et al., 2003), or motor feedback training (Rossit et al., 2019) seem poten-

tially appropriate for ameliorating allocentric neglect symptoms. For example, Right hemisphere lesions which cause neglect deficits have also been linked to impairments in maintaining alertness or arousal (Parton et al., 2004; Robertson et al., 1998; Thimm et al., 2006). Robertson et al., (1998) found that egocentric neglect deficits could be reduced by increasing tonic alertness through auditory, phasic alerting. Similarly, previous research has demonstrated that egocentric neglect can be improved through non-spatial sustained attention training protocols (Robertson et al., 1995). Given that egocentric and allocentric neglect are thought to be sub-served by similar attentional biases, it seems feasible that these non-spatial attention focused therapies might help ameliorate neglect deficits within multiple reference frames. However, additional research is needed to investigate this possibility.

Additionally, Rossit et al's (2019) proposed behavioural, visuo-motor feedback neglect rehabilitation approach could plausible target both egocentric and allocentric spatial biases. In this approach, patients are presented with a wooden rod and a series of marked locations on a table. Patients are asked to pick up the rod at its centre point, and place the centre on the marked location. If neglect biases cause patients to misjudge the rod's centre, the rod is unbalanced providing immediate visuo-motor feedback prompting them to correct their perceptual error (Rossit et al., 2019). In order to successfully complete this task, patients must employ allocentric spatial attention to identify the midpoint of objects (e.g. the rod) and egocentric spatial attention to place them at the correct location on the table (Rossit et al., 2019). However, the impact of this rehabilitation therapy on allocentric-level attentional biases has not yet been adequately investigated in large and representative samples of neglect patients.

Overall, the analyses presented within this thesis demonstrate the clinical utility of detecting and differentiating between egocentric and allocentric neglect, clarify the long-term recovery trajectories of different neglect subtypes, and identify the specific behavioural profiles associated with different kinds of neglect impairment. These findings can be employed to optimise current neglect rehabilitation practices.

7.6 Future Directions

One of the key current knowledge gaps in neglect research is the lack of understanding of the exact computational mechanisms underlying the neglect syndrome as a whole. Existing theories which conceptualise neglect as a lateralised bias in spatial attention can explain some, but not all of the symptoms (e.g. spatial working memory errors) associated with neglect. Additionally, it is not clear exactly how spatial attention biases cause neglect. There are many different functions which must all successfully collaborate to facilitate normal spatial-attentional processes. For example, input from top-down and bottom-up sources must be balanced to both voluntarily direct attention and to allow attention to be attracted by salient aspects of the environment (Chikkerur et al., 2010; Corbetta and Shulman, 2011; de Schotten et al., 2011b). It is not clear whether neglect impacts one or all of these attentional functions, meaning that the exact computational mechanisms underlying spatial-attentional biases in neglect is not yet understood.

It is critically important to understand the cognitive deficits underlying visuospatial neglect following cerebral stroke, as a better fundamental understanding of the disorder will help optimise rehabilitation practices. A 2013 Cochrane systematic review by Bowen et al. (Bowen et al., 2013) concluded that no existing neglect rehabilitation approach can be supported based on existing randomised control trial findings. Behavioural and corresponding anatomical diversity poses a key challenge in developing neglect rehabilitation programmes, as it is likely that therapies which target specific behavioural profiles would not be effective across a more diverse range of neglect subtypes (Luauté et al., 2006). Therapies such as prism adaptation, for example, may improve a single behavioural symptom of neglect (egocentric attentional biases), but it is not clear whether this approach would ameliorate other, often comorbid, behavioural symptoms including visual localisation errors, alertness deficits or allocentric biases (Parton et al., 2004). For this reason, it is crucial to identify the core cognitive mechanisms underlying neglect to facilitate the development of rehabilitation strategies targeting the syndrome's underlying causes rather than its variable behavioural symptoms.

Conceptualising neglect within a Bayesian framework may help provide a cohesive explanation for the diverse behavioural impairments present in the syndrome. Bayesian approaches to

understanding brain function characterise perception as a dynamic neural process of integrating top-down, predictive ("prior") information about the external environment with bottom-up, saliency ("likelihood") information (O'Reilly et al., 2012). For example, when searching a scene for cars, prior information focuses attention on flat, drivable surfaces while likelihood information guides attention towards red, speeding sports cars. Prior and likelihood information are encoded within distinct human brain regions which, when damaged, are associated with neglect (Chechlacz et al., 2012; Vilares et al., 2012). In neglect, attention can be drawn into the neglected hemifield by likelihood cueing, but is not spontaneously directed there voluntarily by patients themselves, implying a spatial bias in attentional priors (Riddoch and Humphreys, 1983). It is critical to establish whether neglect deficits can be accurately conceptualised within this framework to clarify the specific computational mechanisms underlying the syndrome as a whole.

Eye-tracking provides a useful methodology for investigating how the reliability of prior and likelihood information influences naturalistic searches in neglect (Cox and Davies, 2020). However, neglect eye tracking data have not yet been examined within a Bayesian framework (Bays et al., 2010). Additionally, visual search has been conceptualised as "attentional foraging" in which attention is sequentially used to resolve perceptual uncertainty and compare expected value (Manohar and Husain, 2013). In this model, prior and likelihood information can be applied to improve the efficacy of both search phases. For example, if a patient knows that the most valuable target is likely to be presented in a specific location, both stages are spatially focused. It is therefore plausible that neglect may differentially impact how prior/likelihood information is used at the uncertainty-resolution or value-comparison phase of search. Quantifying the impact of neglect deficits on visual search patterns is a critical precursor to understanding exactly how the syndrome's underlying cognitive impairments result in such striking behavioural abnormalities.

There is also a need to further understand the mechanisms underlying neglect-related spatial working memory deficits. Neglect patients often have difficulty remembering previously-identified locations (Malhotra et al., 2004, 2005). Although this impairment is most commonly characterised as a memory deficit, research has suggested that it may be caused by saccadic re-mapping errors (Vuilleumier et al., 2007). Visual information is topographically arranged on

the retina, but retinotopic maps are overwritten with each new fixation, meaning that higher-level processing is required to maintain a stable representation of the visual environment (Pisella and Mattingley, 2004). Previous research has demonstrated that patients with neglect exhibit behavioural deficits characteristic of a saccadic-remapping impairment, but the relative contribution of this deficit to localisation errors has not been explicitly quantified in naturalistic visual searches (Vuilleumier et al., 2007). This question is particularly relevant in the clinic because if localisation errors are caused by a remapping deficit, previously proposed memory-based neglect interventions are unlikely to be effective (Striemer et al., 2013). Overall, there is a clear clinical need to develop a more thorough understanding of the specific cognitive deficits underlying the neglect syndrome. Future research can aim to apply a novel, Bayesian conceptualisation of neglect to elucidate the syndrome's underlying causes.

Chikkerur et al. (2010) propose a computational, Bayesian model of visual attention in which distinct prior and likelihood information is employed for location- and feature-based attentional processes. In this model, location information helps identify where targets will be, whereas feature information helps determine what objects are. This model has been influential in the field of computer vision (Viciana-Abad et al., 2014), but has not yet been validated in humans. No study has investigated how feature and location priors modulate human visual search, or investigated whether a Bayesian model can account for neuropsychological perceptual impairments. Future research can aim to first document how location and feature priors and likelihoods modulate perception in healthy adults, and second, to investigate whether deficits within this framework may be causally related to the neglect syndrome.

Figure 7.1 presents two novel behavioural paradigms which can be used to address this knowledge gap. Each experiment employs a 2x2 design in which the reliability of information provided by priors and likelihoods is systematically manipulated. In these tasks, cues will provide information about how likely a given target location (A) or feature (B) is (priors) whilst stimulus saliency will determine the likelihood. These data can be analysed to determine how response time is modulated by prior/likelihood probability information in controls, facilitating the detection of abnormal response patterns in patients with neglect. For example, 2x2 ANOVA analyses will be

employed to investigate whether reaction time in patients with neglect is a function of both prior and likelihood information (as expected in controls) and how the relative reliance on these sources of information is different between left- and right-side targets. Additionally, data from this paradigm can be analysed to determine whether egocentric and allocentric neglect can be conceptualised as selective deficits in employing location and feature priors, respectively.

This basic set of experiments can also be extended to answer several key neuroanatomical questions. For example, Vilares et al. (2012) established that prior and uncertainty information are encoded within distinct brain regions, but this analysis did not investigate how location versus feature prior/uncertainty information might be differentially represented. This behavioural paradigm can be paired with lesion-mapping analyses to address this issue.

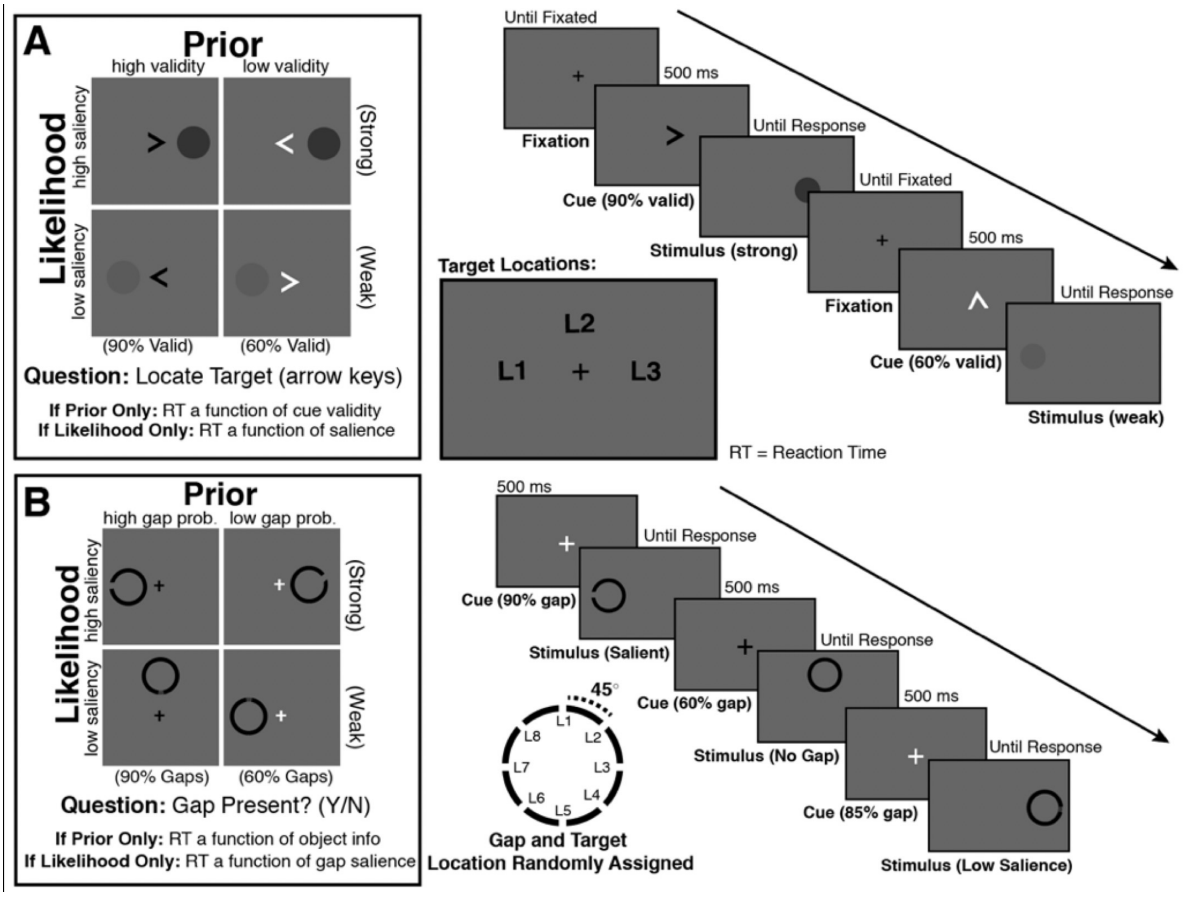


Figure 7.1: A visualisation of the novel behavioural paradigms aiming to determine the degree to which location and feature based priors modulate spatial attention. Prior cues will be followed by stimuli of varying likelihoods. Participants will be asked to report the stimulus location (A) or the presence of gaps (B).

Figure 7.2 presents an additional behavioural paradigm which can be employed to characterise how prior and likelihood information modulate visual search, and therefore help elucidate which specific factors drive spatial-attentional biases in neglect. Specifically, this paradigm can employ eye-tracking to clarify how different sources of attentional information are used to forage visual environments and how this process is disrupted in neglect.

The paradigm employs a 2x2 design in which participants are asked to identify the brightest target in a search display (Fig 2). To complete this task efficiently, participants must conduct thorough visual searches, encode the locations of potential targets, and conduct efficient stimulus comparisons. Eye-tracking data from this task can therefore be analysed to clarify the competition between resolving perceptual and value uncertainty, identify the factors driving re-fixation patterns, and to investigate how prior/likelihood manipulations modulate the fine-grained dynamics of visual search. Additionally, this paradigm provides a novel method for investigating whether Manohar and Husain's (Manohar and Husain, 2013) characterisation of visual search as "attentional foraging", as described above, can be validated within neuropsychological populations. Behavioural data from this paradigm can be combined with functional or structural neuroimaging data to elucidate the correlates of specific search properties (re-fixations, lateralised biases). The number of target/distractor stimuli can be manipulated, and display luminance can be graded to determine the impact of providing competing bottom-up cues (e.g. (Bays et al., 2010)). This paradigm can also be adapted for use with naturalistic scene searches to investigate whether findings generalise to complex, real-world environments.

Finally, Figure 7.3 presents a novel search-disruption paradigm which employs differences in temporal information decay to differentiate between working memory and remapping impairments. In this experiment, patients perform a spatial 1-back test, reporting whether sequential displays are identical following variable "search disruption" intervals while eye movements are recorded. Critically, information stored in working memory follows a predictable temporal decay trajectory, whereas mapping information is overwritten with each new fixation. Therefore, if localisation errors are a working memory impairment, the frequency of these errors should increase as disruption time increases. Alternatively, if localisation errors are caused by remapping deficits,

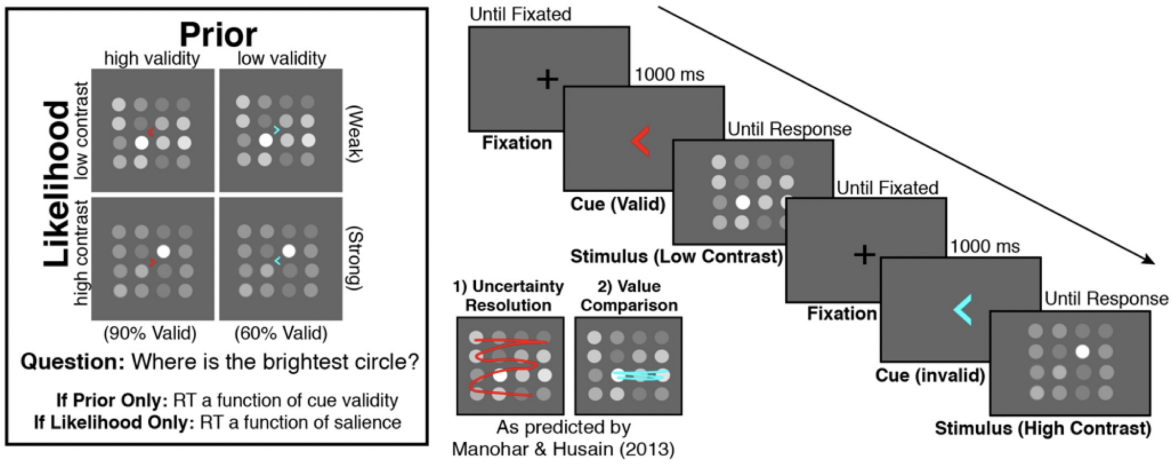


Figure 7.2: A novel behavioural experiment employing eye-tracking data to determine how different sources of prior and likelihood information interact to modulate visual search.

the occurrence of errors should be predicted by fixation changes. Data from this paradigm can be analysed to determine how saccade direction relates to localisation errors (e.g. Vuilleumier et al., 2007). Additionally, these data can be used to determine whether similar patterns of localisation errors occur in non-self-centred neglect subtypes (e.g. allocentric neglect). This basic paradigm can be expanded to address additional research questions. For example, saccade direction and attentional focus could be controlled via required fixation points (e.g. Saj et al., 2020; Vuilleumier et al., 2007), or the impact of including salient distractor stimuli (e.g. Bays et al., 2010)) could be investigated.

Together, these proposed behavioural paradigms aim to provide novel insight into the mechanisms underlying stroke-induced deficits in spatial cognition. It is fundamentally important to establish a firm understanding of the neglect syndrome in order to design treatment programmes which efficiently promote recovery. This research will further our understanding of what causes a common and debilitating neuropsychological disorder that commonly occurs after stroke. This knowledge will help optimise neglect rehabilitation practices to reduce reliance on approaches which target symptoms rather than underlying causes, thereby preventing unnecessary or inefficient health resource usage. In terms of theoretical gain, the proposed research will test the validity of several recent computational models of spatial attention and visual search. This knowledge gain will extend our understanding of how humans perceive and interact with spatial envi-

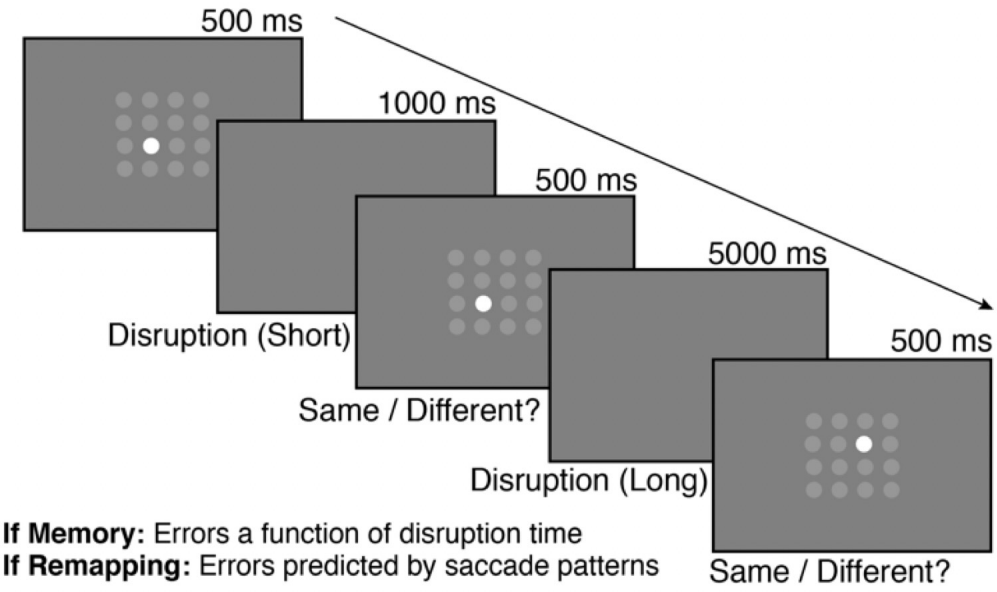


Figure 7.3: A novel behavioural experiment aiming to determine whether spatial localisation errors in neglect are best understood as consequences of spatial working memory or retinal remapping impairments. Patients will be asksed to report whether subsequent displays are identical.

ronments, a topic which has significance across multiple scientific disciplines from neuroscience to computer vision and artificial intelligence.

7.7 General Conclusion

This thesis presents a range of novel findings which add to current knowledge pertaining to visuospatial neglect's behavioural heterogeneity, underlying mechanisms, and prognostic utility. Chapter 2 presents a demonstration of the utility of quantitative neuropsychological neglect tests versus traditional observational assessments. Section 1 presents the first analysis of how clinician expectation biases may result in poor sensitivity within observational assessments and a novel allocentric neglect severity metric. Additionally, Section 2 presents and validated a novel allocentric neglect severity metric which is used throughout this thesis.

Chapter 3 provides the first empirical demonstration of a behavioural double dissociation between domain-general allocentric neglect and allocentric neglect dyslexia. This finding is particularly clinically relevant, as it suggests that allocentric neglect dyslexia patients may not benefit from commonly employed scanning-based and egocentric neglect focused reading therapies. Chapter

Four presents three case studies of representation-level neglect dyslexia and novel evidence that this deficit may be better characterised as inhibitional dyslexia rather than a component of the neglect syndrome. This significant theoretical advancement furthers fundamental understanding of representation-level neglect dyslexia.]par Chapter Five employs Voxel-Lesion Sympotm Mapping techniques to explore the neural correlates of left and right egocentric and allocentric visuospatial neglect. This study is the largest lesion-mapping study of neglect, is the first to identify the neural correlates of right allocentric neglect, and provides novel insight into the neuroanatomy of spatial attention. Chapter Six presents a detailed analysis of recovery trajectories and associated functional outcomes in neglect. Notably, this chapter includes the first use of multiverse analysis to investigate how patient selection criteria impact experimental outcomes as well as the first investigation of specific behavioural phenotypes within both egocentric and allocentric neglect.

Taken together, these findings provide novel insight into heterogeneity within neglect, neglect's underlying mechanisms, and the practical utility of considering this heterogeneity within clinical settings.

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9 Appendix I: Chapter 1 Supplementary Materials

Contents: This Appendix contains the manuscript Moore and Demeyere (Under Review), which is referenced and discussed within Chapter 1. This project is currently under review at Human Brain Mapping.

Lesion Symptom Mapping of Domain-Specific Cognitive Impairments using Routine Imaging in Stroke

Margaret Jane Moore and Nele Demeyere

9.1 Abstract:

Background and Purpose: This large-scale lesion-symptom mapping study aimed to investigate the necessary neuro-anatomical substrates of 5 cognitive domains frequently affected post stroke: Language, Attention, Praxis, Number, and Memory. This study aims to demonstrate the validity of using routine clinical brain imaging from a large, real-world patient cohort for lesion-symptom mapping.

Methods: Behavioural cognitive screening data from the Oxford Cognitive Screen and routine clinical neuroimaging from 573 acute patients was used in voxel-based lesion-symptom mapping analyses. Patients were classed as impaired or not on each of the subtests within 5 cognitive domains.

Results: Distinct patterns of lesion damage were associated with different domains. Language functions were associated with damage to left hemisphere fronto-temporal areas. Visuo-spatial functions were associated with damage to posterior occipital areas (Visual Field) and the right temporo-parietal region (Visual Neglect). Different memory impairments were linked to distinct voxel clusters within the left insular and opercular cortices. Deficits which were not associated with localised voxels (e.g. praxis, executive function) represent distributed functions.

Conclusion: The standardised, brief Oxford Cognitive Screen was able to reliably differentiate distinct neural correlates critically involved in supporting domain-specific cognitive abilities. By demonstrating and replicating known brain anatomy correlates within real-life clinical cohorts using routine CT scans, we open up VLSM techniques to a wealth of clinically relevant studies which can capitalise on using existing clinical brain imaging.

9.2 Introduction:

Decades of neuropsychological, neurological, and neurophysiological research has indicated that some degree of functional specialisation exists within the human brain. From early single case evidence to modern neuroimaging studies, previous investigations have reliably identified localised, task-specific neural correlates. Within neurosciences, studies investigating the neural underpinnings of cognition within animal models have provided a basic understanding of the necessary neural substrates of many low-level functions (Garcia and Buffalo, 2020). However, the generalisability of animal models is limited by small samples, non-naturalistic procedures, and an inherent inability to create adequate proxies of higher-order cognition (Jucker, 2010). In contrast, functional imaging struggles to discriminate between activity which is minimally sufficient versus strictly necessary for cognitive functions. Similarly, transcranial magnetic simulation studies are limited by a comparatively incomplete understanding of this technique's physiological effect and poor spatial resolution (Sack and Linden, 2003). However, naturally occurring lesions from acquired brain injuries, including stroke, provide an opportunity to reliably identify the neuroanatomy which is causally related to and strictly necessary for specific higher-order cognitive functions (Vaidya et al., 2019).

Though many textbooks refer to behavioural consequences of particular stroke locations, the evidence for these relationships often relies on single cases and has not been demonstrated in a single overarching study of acute stroke (Cumming et al., 2013). The majority of previous stroke lesion-mapping studies have aimed to identify the correlates of impairment within a single, specific test (e.g. trail-making (Varjacic et al., 2018)) rather than providing a representative overview of multiple stroke-related deficits. Conversely, studies which have analysed correlates of a range of deficits have been limited by language-dependent assessments[9,10]. For example, Zhao et al. (2018) conducted a large-scale analysis (N=410) using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA requires verbal responses for 25/30 possible points, including those assessing non-language domains (Demeyere et al., 2016, 2019). This language-dependence confound was confirmed in Zhao et al. (2018), as left hemisphere language areas were found to be associated within all investigated functions including attention,

which is well-established to be a right-hemisphere function (Bartolomeo and Seidel Malkinson, 2019; Chechlacz et al., 2012; Corbetta and Shulman, 2011). Further research is needed to identify correlates of domain-specific post-stroke cognitive impairments using assessments unconfounded by language demands.

The present investigation aims to demonstrate the relationship between stroke locations and specific cognitive impairments as measured through a brief domain- and stroke-specific screen (Demeyere et al., 2015), in the largest anatomical study of acute post-stroke cognitive impairment. Voxel-Based Lesion Symptom Mapping (VLSM) provides an effective methodology for identifying the necessary correlates supporting cognitive function (de Haan and Karnath, 2018) . However, the inferential power of VLSM is limited by the quality of data considered. Ideally, VLSM analyses should include high-quality neuroimaging and behavioural data from representative acute samples (de Haan and Karnath, 2018). Unfortunately, it is often impossible to obtain high-quality imaging for acute patients as many have MR contra-indications or are unable to lie still (Singer et al., 2004). Additionally, the higher costs of MR mean that CT is generally the standard pathway (Khan et al., 2013). With respect to timing, neuropsychological studies often require lengthy testing and stroke survivors do not often partake in research until later in recovery. During this recruitment delay, cortical re-organisation and recovery occurs, weakening brain-behaviour relationships (de Haan and Karnath, 2018). Previous research has strongly suggested that VLSM analyses that do not include acute neuroimaging and behavioural data may be unable to precisely identify correlates (de Haan and Karnath, 2018). Additionally, many VLSM studies include small samples, restricted to patients exhibiting specific stroke types or locations, or specific milder impairments linked to smaller lesions. This frequent reliance on non-representative samples greatly limits the generalisability of many VLSM findings. Given these limitations, new avenues for improving VLSM studies are needed.

UK Clinical Stroke Guidelines (Royal College of Physicians, 2016) require each suspected stroke patient to complete acute diagnostic CTs and bedside cognitive assessment. This data facilitates investigation of the validity of using routine CT for VLSM of domain-specific cognitive impairments. Clinical CT scans are low-resolution and often have incomplete visualisation of

damage due to the presence of irreversibly damaged tissue that has not yet been replaced by cerebrospinal fluid (Urbach et al., 2000). This temporal development may lead to underestimations of damage extent, which is generally cited as grounds for avoiding CT in VLSM. However, it also follows that analyses involving acute CTs are extremely unlikely to yield false positives. Therefore, if the feasibility of using these scans for research is established, any positive results yielded by employing clinical CT would provide strong evidence in identifying necessary correlates.

VLSM has the potential to enhance conclusions on the necessity of functional neuroanatomy from neuroimaging, behavioural, and animal-lesion hypotheses via this human lesion approach. The present study investigates the validity of using routinely collected clinical neuroimaging to identify the necessary anatomy supporting well-known, domain-specific cognitive impairments. This question is particularly important as large-scale lesion mapping approaches capitalising on clinical imaging could significantly expand both the power of future lesion mapping, as well as improving representativeness of samples. This would facilitate more ecologically valid conclusions in a patient group that is characterised by often co-occurring changes in structural integrity (Raz, 2004).

9.3 Methods:

9.3.1 Participants:

This investigation presents a retrospective analysis of data collected within previous OCS studies (references:14/LO/0648,18/SC/0550,12/WM/00335). These studies recruited consecutive stroke survivors during acute hospitalisation, regardless of lesion location or behavioural pathology with minimal exclusion criteria. The studies include participants with communication difficulties and severe cognitive impairments, augmenting representativeness. All participants with available OCS data and clinical neuroimaging were considered. Patients with no visible lesions or clear evidence of multiple, temporally distinct lesions were excluded. /par 573 patients (age=72(sd=13.2), 43.8% female, 9.7% left-handed) met inclusion criteria. This sample included ischemic (n=455) and haemorrhagic (n=118) patients (282R, 233L, 58 Bilateral) ranging from

lacunar strokes to large lesions (average volume=39.2cm^3(SD=56.2), range=0.015-444.3cm^3). The sample size of each conducted comparison varied (n=499-568), due to different numbers completing each subtest.

9.3.2 Neuroimaging Data:

Routine post-stroke imaging (497 CT,67 T2,2 T1,7 FLAIR) was employed. Lesions were manually delineated in native space by investigators blind to behaviour. Lesion masks were smoothed at 5mm full-width at half maximum in the z-direction (de Haan and Karnath, 2018), binarized(0.5 threshold), reoriented, warped into 1×1×1mm stereotaxic space using Statistical Parametric Mapping (Ashburner et al., 2016), and were visually inspected for quality.

9.3.3 Behavioural Data:

Routine OCS (Demeyere et al., 2015) post-stroke cognitive assessment data was employed to identify impairments in 5 core cognitive domains. The OCS is a standardised, stroke-specific clinical screen assessing language, attention, memory, praxis, and number processing. Each subtest assesses cognitive functions independently, explicitly minimising language-related and visuo-spatial confounds present in many other screens (Demeyere et al., 2016). OCS is currently the standard in >1100 settings and is recommended in clinical guidelines (Royal College of Physicians, 2016). Behavioural impairment was binarized using standardised thresholds. Language domain subtests include expressive language (Picture Naming), receptive language (Semantics) and Reading (Sentence Reading). The Number domain includes Number Writing and Calculation Tasks. The memory domain contains long-term memory (Orientation), prompted verbal recall(Recall), and unprompted episodic recognition (Recognition) subtests. Visuo-spatial abilities are measured in terms of visual perception (Visual Field Task) and visuo-spatial attention (Cancellation Task), with right and left-lateralised deficits separated. Finally, Praxis is measured through meaningless gestures imitation and non-verbal trail-making assessed Executive Function.

9.3.4 VLSM Statistics:

VLSM was conducted to determine the correlates of impairment within each behavioural comparison group. Theory-blind voxel-wise analyses were conducted using NiiStat (https://github.com/neurolabusc/N (overlap >5). Non-parametric Leibermeister measures were used to evaluate significance. Results were adjusted for multiple comparisons using highly conservative Bonferroni corrections (alpha=0.05). Z-statistic significance cut-offs are reported, with negative z-scores representing association with impairment. Lesion anatomy was evaluated versus the Harvard-Oxford Cortical (Desikan et al., 2006) and John's Hopkins University White Matter atlases (Mori et al., 2005).

9.3.5 Data Availability:

All anonymised data, code, and analysis output associated with this project has been made openly available on the Open Science Framework (https://osf.io/dc7ay/).

9.4 Results:

Figures 1 and 2 illustrate lesion overlays for all 573 participants and for impaired patients in each comparison group. Maximum overlap (n=88) was within MCA territory with lesser affected territories still containing sufficient overlap (overlap=5-31). Comparison z-statistics, significance thresholds, and detailed anatomy are reported in Tables 1 and 2.

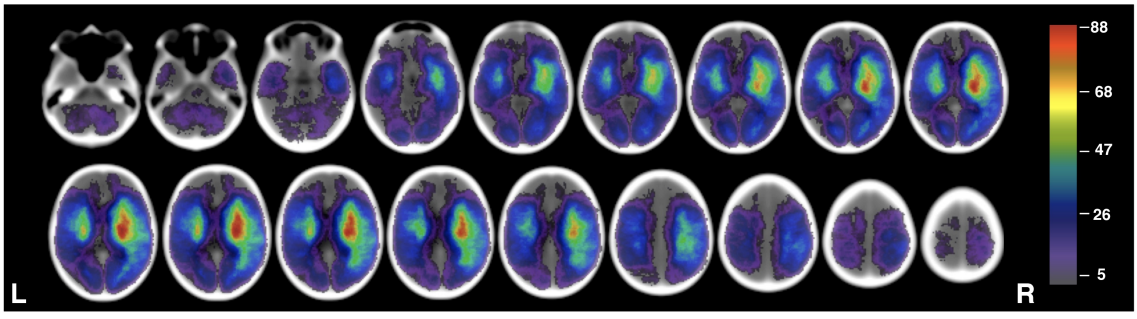


Figure 9.1: Lesion overlay for all 573 patients in this investigation. Colour represents number of lesions overlapping. Only regions with >5 lesions are visualised. Slices within the MNI z-coordinates -44 to +66 are visualised.

Within the language domain, *Picture Naming* results indicated that language production impairment was most strongly associated with left central operculum cortex damage. Additional significant clusters impacted the left frontal operculum cortex and planum polare. Receptive language impairment (*Semantics*) was most associated with left frontal operculum cortex voxels, extending into the neighbouring insular and central opercular cortices. Finally, Sentence Reading impairment was most strongly associated with damage to the left precentral gyrus and superior longitudinal fasciculus. This cluster extended into the left central operculum cortex and inferior frontal gyrus (pars opercularis and triangularis).

Within the number domain, *Number Writing* impairment was significantly associated with left frontal-temporal voxels extending throughout the frontal/central operculum, insula, Heschl's gyrus and internal capsule white matter. This comparison's peak z-values were located within the left central operculum. Alternatively, *Calculation* impairment was most strongly associated with left parietal operculum cortex voxels with additional significant clusters within Heschl's gyrus, planum temporale, and external capsule.

In Memory, *Orientation* impairment was associated with peak z-value voxels within the left parietal operculum. Additional significant voxel clusters were present within the frontal/central opercular and insular cortices. Impairment within the *Verbal Recall* task was associated with voxel clusters within the insular and central/frontal opercular cortices. The peak z-coordinates corresponded to the left anterior putamen. Alternatively, *Episodic Recognition* impairment was most strongly associated with damage to left insular cortex with additional clusters within the central operculum and planum polare cortices. Within the Visuo-Spatial domain, analysis of *Left Visual Field* impairment yielded a large cluster of significant voxels extending throughout the right occipital and posterior/superior parietal areas and underlying white matter. This cluster primarily impacted the right parietal operculum cortex, intracalcarine cortex, and angular gyrus. Damage to the right lateral occipital cortex (superior division) was found to be most strongly associated with impairment. Conversely, *Right Visual Field* impairment was found to be associated with peak z-values within the posterior left temporal fusiform gyrus. Additional significant voxel clusters were located within the posterior division of the left occipital fusiform gyrus, temporal-occipital fusiform

cortex, and lingual gyrus.

In comparison, analysis of left-lateralised *Cancellation* impairment resulted in a large cluster of significant voxels extending throughout the right temporal/parietal cortices and underlying white matter. Specifically, these clusters primarily impacted the right parietal operculum, Heschl's gyrus, planum temporale, and insular cortex. White matter tracts including the external capsule, internal capsule (retolenticular and posterior limb), and superior longitudinal fasciculus were also significantly impacted. Damage to voxels within the right parietal operculum cortex was found to be most strongly associated with left-lateralised neglect impairment. Conversely, right neglect *Cancellation* impairment was found to be most strongly associated with damage within the left lingual cortex.

Within the executive domain, analysis of *Trail Making* data yielded no significant voxels. Finally, *Praxis* impairment was associated with a very small (4 voxel) cluster centred in the left intercalcarine cortex.

Table 9.1: VLSM results for each subtest analysis conducted. MNI coordinates (X,Y,Z) are provided for each analysis' peak z-value. Z-cut denotes the z-score cut-off representing significance. This value represents a highly conservative Bonferroni correction in which the alpha level is determined by the number of voxels (N Voxels) considered in each individual analysis. Z-range represents the full range of z-values associated with all voxels analysed. N represents number of patients included and Impaired reports the number impaired in each group.

Test	N	Impaired	Voxels Sig.	Peak Z-Value Location	
Picture Naming	543	178 (32.7%)	1748	L	Central Opercular Cortex
Semantics	565	54 (9.7%)	15370	L	Insular Cortex
Sentence Reading	532	123 (23.1%)	10,345	L	Precentral Gyrus
Number Writing	568	155 (27.3%)	48,588	L	Central Opercular Cortex
Calculation	564	105 (18.6%)	1433	L	Parietal Operculum
Orientation	566	121 (21.4%)	3173	L	Parietal Operculum
Verbal Recall	552	168 (30.4%)	2883	L	Insular Cortex
Episodic Recognition	559	141 (25.2%)	730	L	Insular Cortex
Left Visual Field Deficit	557	56 (10.1%)	137,250	R	Lateral Occipital Cortex (Superior Division)
Right Visual Field Deficit	557	34 (6.1%)	43,879	L	Temporal Fusiform Cortex (Posterior Division)
Left Neglect	499	142 (28.5%)	70,242	R	Parietal Operculum
Right Neglect	499	85 (17.0%)	98		Lingual Gyrus
Praxis	560	154 (27.5%)	4	L	Intracalcarine Cortex
Executive	510	121 (23.7%)	0		N/A

Table 9.2: Detailed anatomical descriptions of significant voxel clusters identified in each individual analysis. Starred ROIs contain the peak z-values for each test. Only voxel clusters containing >50 voxels are reported. If a test was found to be associated with more than 5 ROIs, only ROIs containing at least 5% significant voxels are reported. Smaller clusters are included if they contained peak z-values for each test. Full anatomical descriptions for each voxel cluster are available on the Open Science Framework. Fraction represents the proportion of each ROI covered by each significant z-statistic map. All anatomical areas are defined based on the Harvard-Oxford Cortical Atlas (HAROX) and the Johns Hopkins University White Matter Atlas (JHU). Hem = hemisphere (Left/Right).

Domain	Test	Anatomical Label	Hem	Nsig	Fraction	Atlas
Language:						
	Picture Naming					
		Central Opercular Cortex*	L	973	10.4%	HAROX
		Frontal Operculum Cortex	L	185	4.6%	HAROX
		Planum Polare	L	59	1.4%	HAROX
		Insular Cortex	L	122	1.0%	HAROX
		Inferior Frontal Gyrus pars opercularis	L	78	1.0%	HAROX
	Semantics					
		Frontal Operculum Cortex	L	2514	62.1%	HAROX
		Insular Cortex*	L	5580	46.8%	HAROX
		Central Opercular Cortex	L	1808	19.3%	HAROX
		External capsule	L	1464	18.2%	JHU
		Superior longitudinal fasciculus	L	748	7.9%	JHU
		Anterior corona adiata	L	515	5.9%	JHU
		Planum Polare	L	222	5.1%	HAROX
	Sentence Reading					
		Central Opercular Cortex	L	1677	17.9%	HAROX
		Inferior Frontal Gyrus pars opercularis	L	1149	14.4%	HAROX
		Inferior Frontal Gyrus pars triangularis	L	728	8.1%	HAROX
		Precentral Gyrus *	L	3457	7.6%	HAROX
		Superior Longitudinal fasciculus *	L	722	7.6%	JHU
		Parietal Operculum Cortex	L	294	5.1%	HAROX
Number:						
	Number Writing					
		Insular Cortex	L	8801	73.9%	HAROX
		Central Opercular Cortex *	L	6765	72.3%	HAROX
		Parietal Operculum Cortex	L	4166	72.2%	HAROX
		Heschl's Gyrus	L	1356	40.9%	HAROX
		Planum Temporale	L	2412	39.0%	HAROX
		Frontal Operculum Cortex	L	1551	38.3%	HAROX
		External capsule	L	3008	37.3%	JHU
		Planum Polare	L	1441	33.2%	HAROX
		Superior ongitudinal fasciculus	L	3090	32.5%	JHU
		Supramarginal Gyrus posterior division	L	2312	17.3%	HAROX
		Supramarginal Gyrus anterior division	L	1679	16.6%	HAROX
		Precentral Gyrus	L	4482	9.9%	HAROX
		Superior corona adiata	L	829	9.1%	JHU
		Retrolenticular part of internal capsule	L	184	5.7%	JHU
		Temporal Pole	L	1362	5.6%	HAROX
	Calculation					
		Parietal Operculum Cortex *	L	982	17.0%	HAROX
		Angular Gyrus	L	132	1.1%	HAROX
		Supramarginal Gyrus posterior division	L	100	0.7%	HAROX
		Central Opercular Cortex	L	57	0.6%	HAROX
		Superior ongitudinal fasciculus	L	55	0.6%	JHU
Memory:						
	Orientation					
		Parietal Operculum Cortex*	L	1120	19.4%	HAROX
		Central Opercular Cortex	L	426	4.6%	HAROX
		Insular Cortex	L	527	4.4%	HAROX
		Frontal Operculum Cortex	L	123	3.0%	HAROX
		Planum Temporale	L	141	2.3%	HAROX
		Superior Longitudinal Fasciculus	L	118	1.2%	JHU
		Precentral Gyrus	L	438	1.0%	HAROX
		Frontal Orbital Cortex	L	80	0.5%	HAROX
	Verbal Recall					
		Insular Cortex	L	654	5.5%	HAROX
		Central Opercular Cortex	L	208	2.2%	HAROX
		Frontal Operculum Cortex	L	72	1.8%	HAROX
	Episodic Recall					
		Planum Polare	L	245	5.6%	HAROX
		Central Opercular Cortex	L	234	2.5%	HAROX
		Insular Cortex *	L	62	0.5%	HAROX

Domain	Test	Anatomical Label	Hem	Nsig	Fraction	Atlas
Visuo-Spatial:						
	Left Visual Field Deficit					
		Parietal Operculum Cortex	R	4880	90.1%	HAROX
		Intracalcarine Cortex	R	6656	81.1%	HAROX
		Angular Gyrus	R	11408	78.8%	HAROX
		Supramarginal Gyrus posterior division	R	10957	73.4%	HAROX
		Supramarginal Gyrus anterior division	R	5499	69.3%	HAROX
		Middle Temporal Gyrus temporooccipital part	R	7811	68.3%	HAROX
		Planum Temporale	R	3624	68.1%	HAROX
		Posterior thalamic adiation	R	3403	65.5%	JHU
		Lateral Occipital Cortex superior division *	R	24511	52.1%	HAROX
		Heschl's Gyrus	R	1641	50.4%	HAROX
		Lingual Gyrus	R	8485	47.5%	HAROX
		Occipital Fusiform Gyrus	R	5309	46.3%	HAROX
		Sagittal stratum	R	1300	39.7%	JHU
		Superior Temporal Gyrus posterior division	R	4012	39.6%	HAROX
		Temporal Occipital Fusiform Cortex	R	3321	39.2%	HAROX
		Superior longitudinal fasciculus	R	3487	36.8%	JHU
		Lateral Occipital Cortex inferior division	R	7429	35.3%	HAROX
		Supracalcarine Cortex	R	866	30.1%	HAROX
		Cuneal Cortex	R	1722	25.5%	HAROX
		Tapetum	R	196	22.3%	JHU
		Temporal Fusiform Cortex, posterior division	R	1751	22.0%	HAROX
		Middle Temporal Gyrus posterior division	R	2289	18.0%	HAROX
		Superior Parietal Lobule	R	2558	16.1%	HAROX
		Inferior Temporal Gyrus temporooccipital part	R	1113	13.0%	HAROX
		Retrolenticular part of internal capsule	R	410	12.5%	JHU
		Occipital Pole	R	2983	10.3%	HAROX
		Parahippocampal Gyrus posterior division	R	417	10.2%	HAROX
		Posterior corona adiata	R	363	7.2%	JHU
		Precuneous Cortex	R	1523	5.8%	HAROX
	Right Visual Field Deficit					
		Occipital Fusiform Gyrus	L	9351	75.5%	HAROX
		Temporal Occipital Fusiform Cortex	L	4911	67.9%	HAROX
		Lingual Gyrus	L	9642	61.1%	HAROX
		Temporal Fusiform Cortex posterior division *	L	3546	41.9%	HAROX
		Parahippocampal Gyrus posterior division	L	2292	40.2%	HAROX
		Intracalcarine Cortex	L	2158	31.2%	HAROX
		Cingulum (hippocampus)	L	485	24.7%	JHU
		Occipital Pole	L	5390	18.0%	HAROX
		Posterior thalamic adiation	L	907	16.9%	JHU
		Supracalcarine Cortex	L	552	16.6%	HAROX
		Sagittal stratum	L	369	11.2%	JHU
	Cancellation (Left Neglect)					
		Parietal Operculum Cortex *	R	5289	97.6%	HAROX
		Heschl's Gyrus	R	2700	83.0%	HAROX
		Planum Temporale	R	3989	75.0%	HAROX
		External capsule	R	5925	73.3%	JHU
		Insular Cortex	R	7803	67.8%	HAROX
		Retrolenticular part of internal capsule	R	2086	63.5%	JHU
		Posterior limb of internal capsule	R	2898	62.3%	JHU
		Central Opercular Cortex	R	4146	48.9%	HAROX
		Planum Polare	R	2008	46.0%	HAROX
		Superior longitudinal fasciculus	R	4298	45.3%	JHU
		Uncinate fasciculus	R	246	39.9%	JHU
		Supramarginal Gyrus anterior division	R	3046	38.4%	HAROX
		Supramarginal Gyrus posterior division	R	5659	37.9%	HAROX
		Posterior corona adiata	R	1231	24.3%	JHU
		Angular Gyrus	R	3356	23.2%	HAROX
		Superior Temporal Gyrus posterior division	R	1868	18.4%	HAROX
		Superior corona adiata	R	1427	15.6%	JHU
		Fornix (cres) Stria terminalis	R	244	12.9%	JHU
		Sagittal stratum	R	383	11.7%	JHU
		Posterior thalamic radiation	R	537	10.3%	JHU
		Superior fronto-occipital fasciculus	R	69	10.3%	JHU
		Lateral Occipital Cortex superior division	R	4712	10.0%	HAROX
		Frontal Operculum Cortex	R	342	8.5%	HAROX
		Middle Temporal Gyrus temporooccipital part	R	601	5.3%	HAROX
	Cancellation (Right Neglect)					
		Lingual Gyrus *	L	67	0.4%	HAROX

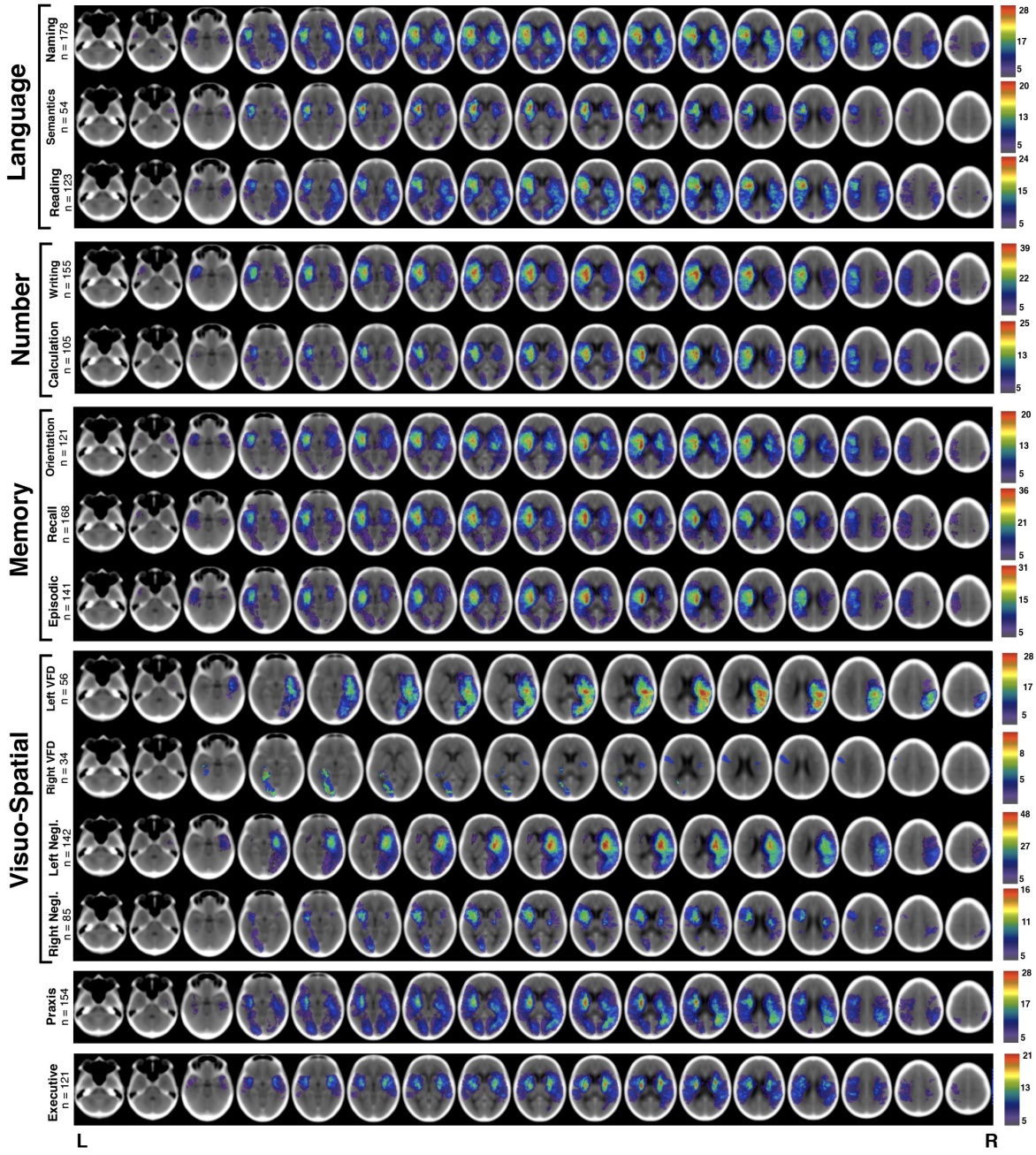


Figure 9.2: Lesion overlays for each OCS subtest. Only lesions from impaired patients are presented, with n representing the number of impaired patients. Colour indicates number of lesion overlaps within each region. Slices within the MNI z coordinates -44 to +66 are visualised

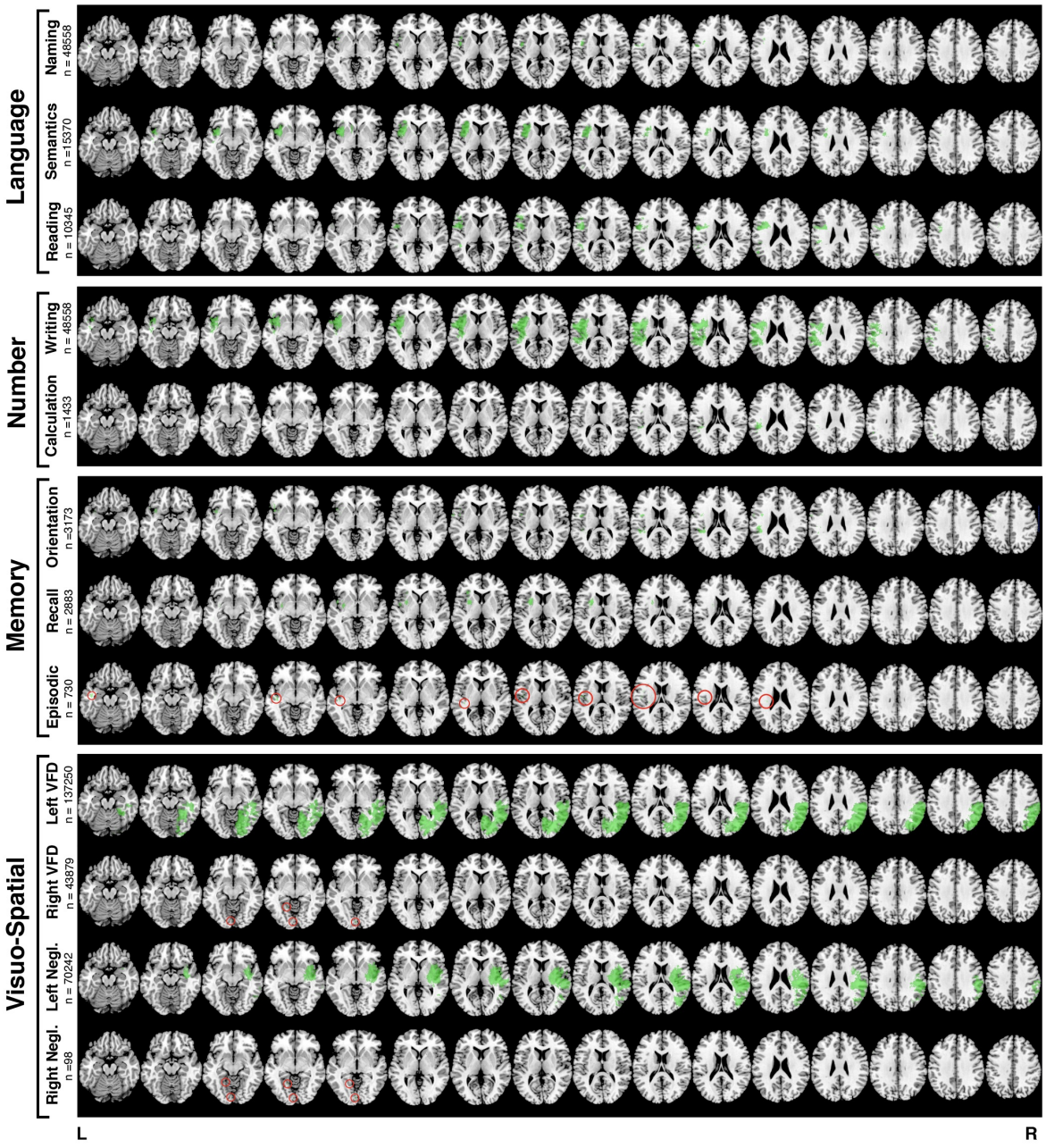


Figure 9.3: A visualisation of the voxels surviving correction for each subtest. N denotes number of significant voxels for each comparison. Small voxel clusters are highlighted in red.

9.5 Discussion:

These results provide a comprehensive validation of VLSM using routinely acquired clinical scans, through the demonstration of functional specialisation within the human brain. The study further extends this evidence base with an acute, clinically representative sample in the single largest cohort of domain-specific cognitive VLSM to date. VLSM analyses of focal post-stroke cognitive impairments strongly suggests that distinct impairments are related to separable correlates with necessary rather than simply correlational contributions. The correlates identified in this study generally agree well with those found in previous investigations, validating the use of acute CT scans. This finding is critically important, as employing clinical data can dramatically increase the scope of future analyses. This study also highlights important strengths and limitations of VLSM.

The correlates identified in this investigation agree well with past literature. Language functions were most strongly associated with damage to left frontal/temporal areas, agreeing well with previous research. Walker et al. (2011) found that damage to the left anterior temporal lobe and middle temporal gyrus was the best predictor of aphasic semantic error production. This investigation similarly found that anterior temporal damage including the frontal operculum and insula predicted semantics test impairment. Baldo et al. (2013) concluded that picture naming errors were subserved by a large, left peri-sylvian network including the middle temporal gyrus. Although our results did not specifically link middle temporal gyrus to naming errors, damage to nearby peri-sylvian cortical and white matter significantly predicted impairment. Finally, Baldo et al. (2018) found an association between reading impairment and damage to left inferior temporo-occipital areas including the middle/superior temporal gyri and the supramarginal gyrus. These findings were replicated. In sum, the present study employing brief screening measures and routine clinical scans closely matches previous findings with equivalent language tasks. In this investigation, visual field deficits were associated with damage to posterior occipital areas including the intracalcarine sulcus. This finding is in line with primary visual field perception being localised within this region (Zhang et al., 2006). The involvement of additional occipital regions (e.g. lingual gyrus) can be explained by the strong association between PCA strokes and visual field deficits (Kas et al.,

2011). Similarly, findings outside the occipital cortex (e.g. parietal operculum) can be accounted for by neglect resulting in confrontation task deficits, as severe neglect is often misdiagnosed as visual impairment (Moore et al., 2019).

Left visuospatial neglect was most associated with damage to voxels centred within the right temporo-parietal region (Chechlacz et al., 2012). Previous research has associated left visuospatial neglect deficits with damage to the right temporoparietal junction and superior temporal gyrus, the angular gyrus and parahippocampal region, as well as the white matter tracts underlying these cortical areas (superior/inferior longitudinal fasiculi and inferior fronto-occipital fasciculi) (Chechlacz et al., 2012). A similar degree of heterogeneity was present within the regions found to be associated with left visuospatial neglect in this study. This variation is accounted for by characterising visuospatial neglect as a disconnection syndrome, rather than a deficit subserved by any single neural correlate (Bartolomeo et al., 2007).

Conversely, right visuospatial neglect was found to be associated with the left lingual gyrus. This finding contrasts with previous VLSM studies which have identified neural correlates for right visuospatial neglect within more anterior left hemisphere areas. Suchan and Karnath (2011) found that right visuospatial neglect was subserved by the left superior/middle temporal gyri, inferior parietal lobule, and insula. Similarly, Beume et al. (2017) found that damage to the left superior and middle temporal gyrus, temporal pole, frontal operculum, and insula were the strongest predictors of right neglect. However, previous research has identified a wide range of cortical and subcortical right hemisphere regions which are associated with left neglect (Molenberghs et al., 2012). It is highly plausible that similar variance exists within the left hemisphere areas responsible for distributing attention across space. Additional research is needed to further characterise the left hemisphere cortical areas involved in spatial neglect.

Not all cognitive deficits included in this investigation were found to be associated with significant clusters of localised voxels. While VLSM analysis of praxis impairment did yield a cluster of four significant voxels within the left intracalcarine cortex, this voxel cluster was not large enough to be included within this investigation's analysis. Previous research has strongly suggested that praxis functions are not subserved by a single, localised neural correlate but instead represent dif-

fuse, network-based cognitive functions (Hoeren et al., 2014). For example, Hoeren et al. (2014) found that gesture imitations were associated with damage to the left lateral occipito-temporal, posterior inferior parietal lobule, posterior intraparietal sulcus, intraparietal sulcus, and superior parietal lobule. However, in order to successfully imitate gestures participants must first accurately perceive the presented stimulus. This reliance on visual information suggests that visual perception areas also play a critical role in supporting praxis abilities. Visual examination of the lesion overlays of participants with praxis impairment demonstrates a clear, bilateral damage pattern associated with this disorder. Given that VLSM is less well suited to identifying the neural correlates of bilateral functions (de Haan and Karnath, 2018), additional analyses are needed to more thoroughly understand the neural correlates of praxis impairment.

Similarly, impairment on the OCS executive function task was not found to be significantly associated with damage to any voxels in VLSM analysis. While executive functions such as response inhibition, goal-directed behaviour, and self-monitoring are classically linked to damage within the left or right pre-frontal cortex (Muir et al., 2015), various components of executive function have been associated with damage to a wide range of neural correlates. For example, Varjačić et al. (2018) found that the left insula plays a critical role in subserving executive set switching. Similarly, specific executive function components, such as inhibition, have been found to be associated with distinct neural regions even within the prefrontal cortex (Cipolotti et al., 2016). This diversity is clearly illustrated within this study's lesion overlay of patients exhibiting executive function impairment, as bilateral lesions involving a range of primarily the white matter underlying temporo-parietal regions was found to be impacted. In sum, the existing literature strongly suggests that executive function, like praxis, is best understood as a diffuse function subserved by multiple, interconnected neural correlates.

VLSM is designed to identify localised neural correlates and is a less appropriate method for identifying the underlying mechanisms of diffuse functions or disconnection syndromes (de Haan and Karnath, 2018). When any single voxel is analysed in VLSM, the behavioural scores of all patients with lesions to the relevant voxel are compared to all patients without damage at that voxel, regardless of behavioural phenotype. If a specific deficit is supported by multiple or bilateral

correlates, this approach can lead to the impact of lesions at different critical sites cancelling each other out, leaving only a single significant correlate (de Haan and Karnath, 2018). This implies that this study's failure to identify the neural correlates of praxis and executive function is not indicative of insufficient data, but rather illustrates one of the established weaknesses within VLSM methodology. Alternative, network-based lesion mapping techniques are more appropriate for investigating the neural correlates of disconnection syndrome cognitive deficits such as executive function.

The inclusion of routine imaging rather than research-specific scans offers an exceptionally valuable resource for improving the scope and quality of research aiming to identify the neural correlates of behaviour. These results demonstrate the utility of standardised post-stroke cognitive assessment for detecting and differentiating between distinct patterns of cognitive impairments. The OCS assessment alone was able to reliably identify post-stroke cognitive deficits, teasing apart distinct patterns of underlying damage (Demeyere et al., 2016, 2019). These findings further validate the OCS as an effective method for identifying domain-specific rather than domain-general deficits (Demeyere et al., 2016). The consistent involvement of classical language areas across the number and memory domains does imply that these tasks, though inclusive for patients with language impairments, tend to involve a degree of language dependency. Nevertheless, the analyses demonstrated that cognitive functions such as verbal recall and episodic recognition, were related to distinct neural correlates within the memory domain. Similarly, the present analysis was able to distinguish neural correlates of distinct functions which often present similarly in behaviour. For example, left visual neglect and left visual field deficits were found to be associated with distinct impairment patterns. Even so, when visuo-spatial neglect is severe, the attentional orientation to the neglected field can be so severely affected that patients fail a confrontation test designed to detect a perceptual deficit. This was apparent also in the lesion correlates for the confrontation visual field task which showed involvement of more anterior (non-visual) temporo-parietal areas. This is in line with previous findings that severe visuospatial neglect is commonly misdiagnosed as a visual impairment (Moore et al., 2019).

The results of this investigation also highlight inherent limitations in VLSM. First, regardless

of the scan quality, there will inevitably be measurement error associated with creating quantitative lesion masks from uncertain clinical data. Investigations including low numbers may produce results skewed by this noise. Future VLSM analyses must therefore aim to include large, representative samples with sufficient lesion coverage to detect generalisable effects. These large group analyses do require strict corrections for multiple comparisons VLSM. Second, while VLSM effectively identifies localised functions, this technique is not designed to identify networks of distributed cognitive abilities. Researchers should use extreme caution when using VLSM to investigate potential disconnection syndromes.

9.5.1 Study Limitations:

Ideally, cognitive impairments should be diagnosed based on agreement between independent assessments (Demeyere et al., 2016), but it was not possible to include additional tests in this retrospective analysis. Additionally, different underlying problems can result in impairment on any single task. However, this investigation's large sample size likely prevented this inherent noise from significantly impacting results.

While this study's results indicate that separable lesion patterns are associated with different cognitive profiles, any potential clinical utility of using neuroimaging-based diagnosis of cognitive difficulties is extremely limited. First, clinical CT has a high-false negative rate (Urbach et al., 2000). Second, lesions outside identified critical sites can cause a specific cognitive impairment, as apparent in disconnection syndromes. Finally, standardised neuropsychological testing represents a simpler and more reliable cognitive impairment diagnostic method (Demeyere et al., 2015). The findings presented in this investigation are meant to illustrate large-scale patterns of functional specialisation based on routinely collected data, not to guide diagnosis of cognitive impairments in clinical settings.

9.5.2 Conclusions:

We demonstrated the validity of using routinely collected clinical neuroimaging data and cognitive screening data for VLSM analysis. A domain-specific bedside assessment alone was able

to reliably differentiate post-stroke cognitive deficits, teasing apart distinct patterns of underlying damage, confirming findings of focal stroke lesions selectively impacting cognitive functioning post stroke. The present demonstration opens up VLSM techniques to a wealth of clinically relevant lesion mapping studies to capitalise on existing clinical neuroimaging.

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10 Appendix II: Chapter 2 Supplementary Materials

Contents: This Appendix contains the published, letter version of the project reported in Chapter 2, Section 1 (Moore et al., 2019).

When Neglect Is Neglected: NIHSS observational measure lacks sensitivity in identifying post-stroke unilateral neglect.

Margaret Jane Moore, Kathleen Vancleef, Nir Shalev, Masud Husain, and Nele Demeyere

10.1 Introduction:

Unilateral visual neglect is characterised by lateralised spatial-attentional deficits, resulting in dramatic behavioural impairments [1]. Neglect negatively impacts functional outcome and needs to be successfully detected in order to inform neglect-specific as well as general post-stroke rehabilitation goals and strategies. It is therefore critically important to evaluate current clinical methods for detecting and measuring the extent of this syndrome.

Observational neurological assessments, such as the National Institutes of Health Stroke Scale (NIHSS), rely predominantly on subjective impression of impairment levels rather than objective measurements [2]. Although the NIHSS was not designed as an individual diagnostic tool, it is frequently employed as one. However, previous research has suggested that observational assessments may not be sufficiently sensitive to visual neglect [2–4]. The purpose of this study was to evaluate the diagnostic sensitivity of the NIHSS' visual neglect item compared to a brief neuropsychological cancellation test and to identify factors which modulate this sensitivity.

10.2 Methods:

428 acute stroke patients (mean age=71,SD=12.8, mean time post-stroke=7.3 days, SD=7.4) completed the NIHSS and OCS Cancellation Task (mean interval=1.2 days). 63.1% of patients completed both tests on the same day and the NIHSS was administered first in 33.9% of cases. The NIHSS Extinction/Inattention and Visual Field items were considered in this investigation, with Extinction/Inattention scores of 0 (none), 1 (mild) or 2 (profound) and Visual Field scores of 0 (normal), 1 (partial) or 2 (complete).

The OCS is a brief stroke-specific cognitive screen which includes a highly sensitive Cancellation Task [5]. This test was therefore used as the comparison standard for NIHSS sensitivity

calculations. In this Cancellation Task, patients are instructed to search for and mark complete heart outlines while ignoring incomplete hearts. Egocentric neglect was scored by subtracting the number of targets identified on the left and right side of the page while allocentric neglect was scored by subtracting the number of right-gap and left-gap hearts identified. Egocentric asymmetries larger than 3 and allocentric asymmetries greater than 1 represent significant impairment [5].

10.3 Results:

First, the sensitivity of the NIHSS to neglect was evaluated. 83/428 (19.4%) and 199/428 (46.5%) patients exhibited neglect as reported by the NIHSS and OCS respectively. In comparison to the OCS, the NIHSS exhibited a high neglect specificity (91.2%), though a low sensitivity (31.6%). Interestingly, the Extinction/Inattention Item was not found to be significantly more sensitive to neglect than the Visual Field Item (sensitivity=28.1%, McNemar's, X2=0.735, p=0.39). Next, the relationship between NIHSS sensitivity and neglect severity was investigated (Figure 1). A regression analysis demonstrated that patients with milder neglect on the OCS cancellation were significantly less likely to be identified by the NIHSS than patients with more severe neglect (R2=0.107, F(1,42)=5.016, p=0.030, beta=-0.327). Similarly, there was a significant difference in cancellation total for neglect patients with different Extinction/Inattention Item scores (F(2,169)=4.777, p=0.010). However, there was large individual variability in all NIHSS item severity categories and the NIHSS was still found to have a low sensitivity (38.1%) when only the most severe neglect patients (cancellation totals <10/50) were considered.

Finally, the relationship between neglect subtypes and NIHSS sensitivity was investigated. The NIHSS was found to be more likely to detect left-lateralised (sensitivity=58.3%, N=111) than right-lateralised neglect (sensitivity=18.7%, N=75). This substantial difference in sensitivity occurred despite the fact that there was no significant difference in the severity of cases of right and left neglect in this sample; t(157)=1.767, p=0.079. Finally, the NIHSS was found to be more sensitive to co-occurring egocentric and allocentric neglect (sensitivity=68.8%, N=54) than pure egocentric (28.8%, N=118) or allocentric (25.9%, N=27) neglect cases.

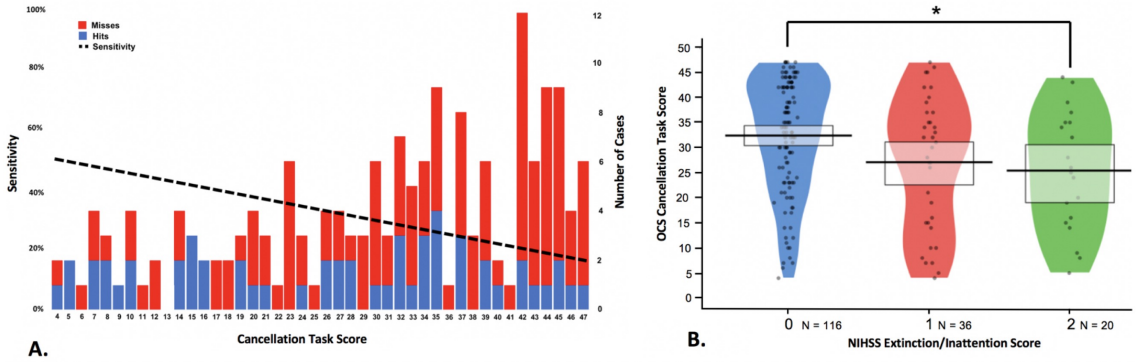


*Figure 10.1: Panel A provides an illustration of the relationship between cancellation score and NIHSS sensitivity. The number of neglect cases of each severity level is denoted by bar height (right y-axis). Cases which were successfully identified by the NIHSS are blue and missed cases are red. The sensitivity linear regression line is plotted as the dashed line. Panel B illustrates the relationship between NIHSS inattention/Extinction Score and OCS Cancellation Task Score in egocentric neglect patients. Score distribution is represented by plot width, points represent individual cases, and rectangles represent upper and lower quartiles. Lower cancellation scores represent more severe neglect. * = p <0.05*

10.4 Discussion:

The NIHSS was found to have poor sensitivity compared to the Cancellation Task. While the NIHSS was more likely to successfully identify severe versus mild cases of neglect, it frequently failed to detect even the most severe cases, demonstrated by the large spread of the neglect severity data in each NIHSS inattention item scoring category. Visual Field Item sensitivity to neglect was not found to differ from that of the Extinction/Inattention Item suggesting that the frequent failure of clinical observation alone to detect neglect may also be associated with a misattribution of neglect impairments to visual field deficits (e.g. hemianopia). Additionally, the NIHSS did not reliably detect less common subtypes of visual neglect, such as right-sided and allocentric neglect. These results indicate that reliable detection of post-stroke neglect requires, at the minimum, the inclusion of a simple cancellation task.

These findings have important implications when considered in the context of post-stroke care. First, relying solely on observational assessments like the NIHSS will lead to an underestimation of neglect prevalence. Failure to detect neglect might alter perceived clinical prognosis or lead to a lack of necessary care packages being put into place. Second, the failure of clinical ob-

servation to detect neglect may be associated with a general misunderstanding of visual neglect. This investigation demonstrates that observational assessments are more likely to detect leftward than rightward neglect, regardless of the severity of these deficits. This could potentially be explained by expectation bias, as visual neglect is commonly mischaracterised as an exclusively leftward deficit. Finally, with regards to the heterogeneity of neglect, observational assessment was shown to be more sensitive to the more broadly understood egocentric than to allocentric neglect. While the fractionation of neglect may appear only theoretically relevant, previous research has contradicted this by demonstrating that allocentric neglect is associated with poorer long term functional outcomes than egocentric neglect [4]. A portion of this egocentric/allocentric sensitivity difference might result from a lack of clinician awareness of the fractionation of neglect. NIHSS training protocols could be improved to promote a more thorough understanding of neglect as a syndrome and to include a simple neuropsychological assessment to help detect less common neglect subtypes.

In conclusion, the inclusion of an objective, brief standard cancellation task in post-stroke screening is necessary to reliably identify visual neglect, differentiate neglect from visual field impairments, and eliminate subjective biases.

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11 Appendix III: Chapter 4 Supplementary Materials

Contents: This Appendix contains the behavioural reading data summarised in Chapter 4, Sections 1-3. Additional reading audio recordings of error types of interest are available on the Open Science Framework.

Scoring Acronyms:

? - Unclassified

A – Letter Addition Error

DK - Don't Know

LBL – Letter-by-letter Reading Error

ND – Neglect Dyslexia

NR – Not Read / No Response

O – Letter Omission Error

R – Regularisation Error

S – Letter Substitution Error

SC – Self-Corrected

V – General Visual Error

11.1 Section One: AB's Reading Responses

Table 11.1: A complete list of all normally-presented real word stimuli (Experiment One). Each stimuli's frequency, AB's responses, and corresponding error categorisations are also provided. All stimuli in this table and in subsequent tables listed in the order of presentation.

Experiment One: Normally Presented Words

Stimulus	Freq.	Response	Error Type	Stimulus	Freq.	Response	Error Type	Stimulus	Freq.	Response	Error Type	Stimulus	Freq.	Response	Error Type
LET	159	Correct		**EVENT**	525	Correct		**RELATED**	3414	"relate"	Omission	**BOOKSHELF**	11458	Correct	
GOT	39	Correct		**HEART**	460	Correct		**EXCITED**	3449	"exorcists"	Substitution	**BEWITCHED**	34753	Correct	
ART	346	Correct		**ALLOW**	339	Correct		**ONESELF**	7731	Correct		**BARTENDER**	8027	"don't know"	Not Read
CAP	2320	Correct		**EVERY**	172	"even"	Substitution	**BROTHER**	614	Correct		**FORGOTTEN**	10116	Correct	
POD	8536	Correct		**PITCH**	3177	Correct		**EXAMINE**	1166	Correct		**ADAPTABLE**	15365	Correct	
RAT	6243	Correct		**PLANE**	1151	Correct		**TOTALLY**	1921	"total"	Omission	**UNDEFINED**	21989	"undefinable"	Substitution
TAN	9850	Correct		**PLANT**	623	Correct		**FORTUNE**	2719	Correct		**ADDRESSES**	1029	Correct	
RAW	2800	Correct		**GROWN**	16251	Correct		**FOUNDER**	2817	Correct		**ONLOOKING**	13292	Correct	
SAT	268	Correct		**GLOBE**	4779	Correct		**DEVOTED**	5186	Correct		**APPEALING**	7141	Correct	
HUB	6659	Correct		**WOMAN**	111	Correct		**STUDIED**	16649	"study"	Substitution	**OFFSPRING**	6604	Correct	
BIN	2512	Correct		**SHOWN**	177	"show"	Omission	**KNOWING**	12972	Correct		**BILLBOARD**	7257	Correct	
PAT	4580	Correct		**IDEAL**	2832	Correct		**WORKING**	2836	Correct		**THRASHING**	25323	Correct	
YES	258	Correct		**PEACE**	934	Correct		**REMOVED**	38021	"removable"	Substitution	**OURSELVES**	1776	Correct	
WAR	349	Correct		**LOWER**	2063	Correct		**TOWARDS**	2014	Correct		**LIMESTONE**	9393	Correct	
PAN	2495	Correct		**GRANT**	1917	Correct		**UPSTAGED**	21301	Correct		**MISTAKEN**	13103	"mistake"	Omission
MAN	94	Correct		**THERE**	53	Correct		**UPDATED**	10969	Correct		**HANDSTAND**	38122	Correct	
NUN	5759	Correct		**POWER**	271	Correct		**MESSAGE**	807	"messenger"	Substitution	**ENCOUNTER**	2728	Correct	
LAD	9567	Correct		**COVER**	560	Correct		**THOUGHT**	760	Correct		**BACKSTAGE**	11202	Correct	
RAM	12402	Correct		**HUMAN**	399	Correct		**EXAMPLE**	853	Correct		**DELIVERED**	41561	"delivery"	Substitution
SAP	15197	Correct		**LABEL**	2635	Correct		**LEARNED**	11115	"leaner"	Substitution	**MILESTONE**	9228	Correct	
RIB	4611	Correct		**SPARE**	4629	Correct		**MISSING**	3523	Correct		**BEEKEEPER**	23680	Correct	
WET	2487	Correct		**START**	173	Correct		**READING**	1586	Correct		**OBSESSION**	10784	"obsessed"	Substitution
WED	758	"win"	Substitution	**BLAME**	1807	Correct		**HERSELF**	792	Correct		**SPIRITUAL**	22108	Correct	
HOW	76	Correct		**TABLE**	539	Correct		**PASSAGE**	2224	"passenger"	Substitution				
JOG	8489	Correct													

Table 11.2: AB's responses and corresponding error categorisations for Experiment Two's vertically presented stimuli.

Experiment Two, Block One: Vertically Presented Stimuli

Stimulus	Response	Error Type	Stimulus	Response	Error Type	Stimulus	Response	Error Type
Block One: Words			**ADDRESSES**	"address"	Omission	**DRONEWS**	"downwest"	Regularisation
HUB	Correct		**BEEKEEPER**	Correct		**RANDEMORT**	Correct	
YES	Correct		**HANDSTAND**	Correct		**GLOPFLARN**	"glopflanded"	Addition
GOT	Correct		**THRASHING**	Correct		**FOSTEREND**	"foreagain"	Visual
MAN	Correct					**PLOMBITED**	"plomibi"	Omission
ART	Correct		**Block Two: Pseudowords**			**CROPSDORT**	"rope"	Uncategorisable
PAN	Correct		**KED**	Correct		**BOAKSMARK**	Correct	
WED	Correct		**ROP**	"rope"	Addition	**TRONRADAM**	Correct	
WAR	Correct		**HUD**	Correct		**BRONSHOVE**	"bokshova"	Visual
GLOBE	"global"	Substitution	**YOT**	Correct				
COVER	Correct		**VIT**	"vint"	Visual	**Block Three: Numbers**		
PITCH	Correct		**FOM**	"foam"	Regularisation	**696**	Correct	
GRANT	Correct		**TEG**	"get"	Visual	**625**	Correct	
TABLE	Correct		**MOMAR**	"momaray"	Addition	**321**	Correct	
BLAME	Correct		**ANTOW**	"ant"	Omission	**313**	Correct	
SHOWN	"show"	Omission	**HATOP**	"hat-top"	Visual	**215**	Correct	
SPARE	Correct		**PANOW**	"pantow"	Visual	**872**	Correct	
MISSING	Correct		**NOTAD**	Correct		**697**	Correct	
RELATED	Correct		**PARAP**	Correct		**231**	Correct	
ONESELF	"oneselfish"	Addition	**HUBEN**	Correct		**34204**	Correct	
FORTUNE	Correct		**RATUG**	"rat"	Omission	**65697**	Correct	
THOUGHT	"don't know"	Not Read	**SRAPIDATE**	Correct		**37121**	Correct	
STUDIED	"study"	Substitution	**RAREACH**	"racha"	Visual	**2194**	Correct	
EXCITED	"exit"	Omission	**SANDACE**	Correct		**53310**	Correct	
SPIRITUAL	Correct		**PASTAMP**	"pasts"	Substitution	**23379**	Correct	
ONLOOKING	Correct		**BUSHORT**	"bushnot"	Visual	**21332**	Correct	
ADAPTABLE	"table"	Omission	**SIDEALS**	"sideless"	Substitution	**39142**	Correct	
BARTENDER	"don't know"	Not Read	**PUREACH**	Correct				

Table 11.3: AB's responses and error categories for Experiment Two's mirror-reflected words.

Experiment Two, Block Three: Reflected Words

Stimulus	Response	Error Type	Stimulus	Response	Error Type
CAP	Correct		**REMOVED**	Not Read	Not Read
LAP	Correct		**READOMG**	Correct	
BIN	Correct		**UPSTAGED**	Not Read	Not Read
JOG	Correct		**TOWARDS**	Not Read	Not Read
POD	Correct		**UPDATED**	Correct	
LAB	Correct		**KNOWING**	Correct	
RIB	Correct		**LEARNED**	Correct	
SAP	Correct		**BEWITCHED**	Correct	
GROWN	"grow"	Omission	**OBSESSION**	"obsess"	Omission
WOMAN	Correct		**MILESTONE**	Correct	
EVERY	Correct		**LIMESTONE**	Correct	
POWER	Correct		**REMISSION**	"reminiscence"	Substitution
THERE	"the"	Omission	**OURSELVES**	Not Read	Not Read
START	Correct		**UNDEFINED**	Not Read	Not Read
FORMAT	"formed"	Substitution	**ENCOUNTER**	Not Read	Not Read
FOUNDER	Correct				

Table 11.4: AB's responses and error categorisations for Experiment Two's mirror-reflected numbers.

Experiment Two, Block Four: Reflected Numbers

Stimulus	Response	Error Type	Stimulus	Response	Error Type
305	Correct		**52634**	Correct	
276	Correct		**15475**	"75427"	Visual
925	"952"	Visual	**93467**	Correct	
563	Correct		**18549**	"78246"	Visual
259	"526"	Visual	**42662**	Not Read	Not Read
224	Correct		**56212**	Not Read	Not Read
477	Correct		**61832**	Correct	
934	Correct		**22791**	Not Read	Not Read

Table 11.5: AB's responses and error categorisations for Experiment Two's mirror-reflected pseudo-words.

Experiment Two, Block Five: Reflected Words

Stimulus	Response	Error Type	Stimulus	Response	Error Type
NAD	"dan"	Visual	**LASTANK**	"nastener"	Uncategorisable
GOM	"got"	Substitution	**POSTAND**	"posited"	Regularisation
FUB	"nup"	Uncategorisable	**GAVENGE**	"gavelgen"	Visual
HET	"helt"	Visual	**NAMEND**	"nomedend"	Visual
TAL	"jadge"	Uncategorisable	**DROVEND**	"divorced"	Regularisation
CAX	"cat"	Substitution	**RABESTS**	"rabested"	Substitution
TRA	"tart"	Regularisation	**GRAMEND**	"gamedend"	Visual
NEB	Correct		**HALFELL**	"halefen"	Visual
LOWAY	"lower"	Regularisation	**VEANPLIMP**	Not Read	Not Read
GALAB	"gallable"	Visual	**DORPMOTAN**	"doropmand"	Visual
CONIP	"conipip"	Addition	**FLUBERTON**	Correct	
NORAD	"noraday"	Addition	**ARDORMALY**	Not Read	Not Read
CAMAX	"cama"	Omission	**PLANERMAT**	"planement"	Regularisation
SIMAP	Correct		**PLOPERMANT**	Correct	
TANUP	Correct		**TRANSHOULD**	"tart"	Regularisation
DADIN	Correct		**HARSHAND**	Correct	

Table 11.6: A complete list of Experiment Three's normally presented numbers.

Experiment Three: Normally Presented Pseudowords and Numbers

Stimulus	Response	Error Type	Stimulus	Response	Error Type
Block One: Pseudowords			**FRINPLONE**	Correct	
POG	Correct		**POGFALROP**	Correct	
WID	"wind"	Regularisation	**FUEDARTH**	Correct	
BEM	"bream"	Visual	**TAINLANET**	Correct	
ARD	"don't know"	Not Read	**SCRANWITCH**	Correct	
ZAM	Correct		**DISCRAMET**	"don't know"	Not Read
MAB	"mad"	Substitution/Regularisation	**FEAMFLOMS**	"feamfomems"	Visual
MOX	Correct		**GALENDANT**	Correct	
FAW	"flaw"	Regularisation			
DIBET	Correct		**Block Two: Numbers**		
CABOG	"bogabog"	Uncategorisable	**932**	Correct	
GUNOD	"gunded"	Visual	**272**	Correct	
WEDAW	"wendrew"	Visual	**592**	Correct	
FEWIN	Correct		**147**	Correct	
VANET	Correct		**915**	Correct	
TOPAR	Correct		**645**	Correct	
GASAW	Correct		**409**	Correct	
CODEDAM	Correct		**367**	Correct	
LANDAWN	Correct		**87820**	Correct	
BESTAMP	Correct		**72552**	Correct	
MORALOT	Correct		**98847**	Correct	
WAVENTS	Correct		**36591**	Correct	
SOMEVEN	Correct		**77102**	Correct	
DOWNOG	Correct		**25410**	Correct	
PRIMEAT	Correct		**98254**	Correct	
			10940	Correct	

11.2 Section Two: CD's Reading Responses

Table 11.7: CD's responses for all horizontal words presented under unlimited exposure conditions.

Horizontal Conditon Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
adaptable	NR	NR		milestone	millstone	V	
addresses	address	O	R	missing	Correct		
allow	Correct			mistaken	mistake	O	R
appealing	Correct			nun	Correct		
art	Correct			obsession	DK - named all letters	NR	
backstage	Correct			offspring	Correct		
bartender	NR	NR		oneself	Correct		
beekeeper	Correct			onlooking	looking	O	L
bewitched	Correct			ourselves	ourself	S	R
billboard	Correct			pan	Correct		
bin	Correct			passage	Correct		
blame	Correct			pat	Correct		
bookshelf	Correct			peace	Correct		
brother	Correct			pitch	Correct		
cap	Correct			plane	plan	O	R
classes	Correct			plant	Correct		
cover	Correct			pod	Correct		
delivered	Correct			power	Correct		
devoted	d-e-v-o-t-e "devote"	O	R	ram	Correct		
encounter	e-n-c-o-u-n "entrance"	S	R	raw	Correct		
event	Correct			reading	Correct		
every	ever	O	R	related	?	?	
examine	exminister	S	R	remission	r-e-m-o- "remiss"	O	R
example	excise	S	R	removed	remove	O	R
excited	extent	S	R	rib	Correct		
forgotten	Correct			sap	snap	V	
format	Correct			sat	Correct		
fortune	Correct			shown	show	O	R
founder	Correct			spare	space	S	R
globe	Correct			spiritual	NR	NR	
got	Correct			start	Correct		
grant	Correct			studied	Correct		
grown	growl	S	R	table	Correct		
handstand	Correct			tan	Correct		
heart	Correct			there	Correct		
herself	self	O	L	think	Correct		
how	Correct			thought	NR	NR	
hub	Correct			thrashing	thrasher	S	R
human	Correct			totally	Correct		
ideal	Correct			towards	Correct		
impartial	impala	S	R	undefined	Correct		
jog	Correct			updated	update	O	R
knowing	Correct			upstage	Correct		
lad	Correct			vow	Correct		
learned	l-e-a-r-n-e-d "legend"	S	R	war	Correct		
let	Correct			wed	Correct		
limestone	Correct			wet	Correct		
lower	Correct			woman	Correct		
man	Correct			working	Correct		
message	massage	V		yes	Correct		

Table 11.8: CD's responses for all words presented vertically under unlimited exposure conditions.

Vertical Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
adapatable	NR	NR		noted	Correct		
addresses	NR	NR		obsession	NR	NR	
agreement	?	?		pad	Correct		
applicate	apply	S	R	pan	Correct		
assembler	assembled	S	R	plane	plant	S	R
avenged	avent	O	R	remands	remember	S	R
begun	begin	V		remission	Correct		
boarded	barber	S	R	removed	remove	O	R
can	Correct			replicate	?	?	
cap	Correct			reporters	report	O	R
chart	char	O	R	requester	request	O	R
clashed	?	?		resembled	remember	S	R
continuer	con- contour	S	R	resigns	NR	NR	
cot	Correct			respire	?	?	
coven	cover	S	R	respite	recipt	S	R
crowned	crow	O	R	rib	Correct		
delivered	deliver	O	R	rid	Correct		
despite	desperate	S	R	sap	snap	V	
dim	Correct			scare	scale	S	R
disagrees	?	?		sequester	NR	NR	
downs	down	A	R	sew	swoon	S	R
drowned	drown	O	R	shown	show	O	R
event	Correct			slashes	slash	O	R
every	event	S	R	smasher	smash	O	R
excited	extend	S	R	spark	spade	S	R
fable	apple	?		studied	s-t-u-d-i-e-d Correct		
growl	Correct			supported	support	O	R
grown	grow	O	R	tad	Correct		
hag	Correct			tan	Correct		
ham	Correct			there	Correct		
hands	hand	O	R	tin	Correct		
immatured	NR	NR		totally	Correct		
impartial	impart	O	R	unaltered	NR	NR	
lad	Correct			updated	update	O	R
lands	l-a-n-d-s land	O	R	usage	?	?	
learned	l-e-a-r-n- NR	O	R	wed	Correct		
mar	Correct			whose	hows	?	
may	Correct						

Table 11.9: CD's responses in the reflected word reading condition (unlimited exposure).

Reflected Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
appeals	apple	S	R	moved	m-o-v-e-d "move"	O	R
bar	Correct			muttons	m-u-t-t-o-n "mutton"	O	R
begin	Correct			nip	Correct		
blessed	b-l-e-s-s-e-d "bleed"	S	R	pan	Correct		
brokers	broker	O	R	peg	Correct		
bug	gub	V		pew	pupe	S	R
buttons	Correct			plane	Correct		
cap	Correct			plans	plant	S	R
carts	c-a-r-t-s "cast"	S	R	rad	Correct		
charged	c-h-a-r-g-e-d "catch"	S	R	removed	r-e-m-o-v-e-d "revolved"		
clovers	c-l-o-v-e-r "cloves"	S	R	reveals	r-e-v-e-a-l-s	LBL	
dew	DK d-e-w	LBL		rib	Correct		
dressed	d-r-e-s-s-e-d "drose"	S	R	rod	Correct		
event	Correct			rub	Correct		
every	e-v-e-r-y "even"	S	R	sap	spam	S	R
excited	excrement	S	R	shown	shoe	S	R
faction	f-a-c-t-o-n "fact"	O	R	slate	s-l-a-t-e "slat"	O	R
fog	Correct			sower	s-o-w-e-r "snog"	S	R
gable	g-a-b-l-e "grab"	S	R	steamer	s-t-e-a-m-e-r "stash"	S	R
get	Correct			studied	s-t-u-d-i-e-d "study"	S	R
grown	growl	S	R	there	t-h-e-r-e "??	LBL	
hedge	head	O	R	those	t-h-o-s-e "touche"	S	R
kin	Correct			totally	t-o-t-a-ll-y "tolow"	S	R
lad	Correct			toted	t-o-t-e-d "tot"	O	R
lag	Correct			transfix	t-r-a-n-s-f- "NR"	LBL	
lanes	l-a-n-e-s "lans"	V	R	updated	u-p-d-a-t-e-d "update"	O	R
learned	l-e-a-r-n-e-d "DK"	LBL		voter	v-o-t-e-r "vote"	O	R
ledge	l-e-d-g-e "leg"	S	R	wed	Correct		

Table 11.10: CD's reading performance within the reduced exposure reading condition (exposure time = 500 ms).

Reduced Exposure Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
allow	Correct			passage	passenger	S	R
art	Correct			pat	rat	S	L
bin	Correct			peace	peach	S	R
blame	Correct			pitch	Correct		
brother	Correct			plane	plan	O	R
cap	Correct			plant	Correct		
classes	Correct			pod	Correct		
cover	growl	?		power	Correct		
devoted	NR	NR		ram	Correct		
event	even	O	R	raw	Correct		
every	ever	O	R	reading	NR	NR	
examine	NR	NR		related	NR	NR	
example	NR	NR		removed	remove	O	R
excited	extend	S	R	rib	Correct		
format	NR	NR		sap	snap	V	
founder	NR	NR		sat	NR	NR	
globe	NR	NR		shown	show	O	R
got	Correct			spare	spat	O	R
grant	Correct			start	Correct		
grown	growl	O	R	studied	stud	O	R
heart	Correct			table	Correct		
herself	heart	S	R	tan	Correct		
how	Correct			there	Correct		
hub	Correct			think	Correct		
human	Correct			thought	throat	S	R
ideal	NR	NR		totally	trolley	S	L
jog	Correct			towards	tower	S	R
knowing	Correct			updated	update	O	R
lad	Correct			upstage	upstand	S	R
learned	NR	NR		vow	Correct		
let	Correct			war	Correct		
lower	Correct			wed	Correct		
man	Correct			wet	Correct		
missing	Correct			woman	Correct		
nun	Correct			working	Correct		
oneself	NR	NR		yes	Correct		
pan	pay	S	R				

Table 11.11: CD's responses within the pseudoword reading condition (unlimited exposure).

Pseudoword Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
antow	Correct			loway	Correct		
bem	Correct			mab	Correct		
bestamp	bedstamp	V		momar	m-o-r-a-r DK Morrow	S	R
bushort	DK b-u-s-h-o-r-t	LBL		nad	Correct		
cabog	c-a-b-o-g cab	O	R	namend	Correct		
dat	Correct			neb	Correct		
downog	Correct			notad	Correct		
drovend	Correct			panow	Correct		
fabests	f-a-b-e-s-t-s past	V		pogfalrop	pongrop	V	
faw	f-a-w	LBL		postand	Correct		
fewin	f-e-w-i-n finwin	V		pureach	preach	V	
fluberton	f-l-u-b-e-r-t-o-n "DK"	LBL		rop	Correct		
fom	from	V		san	Correct		
frinplone	f-r-i-n-p-l-o-n-e	LBL		sideals	sideal	O	R
gad	Correct			someven	s-o-m-e-v-e-n somevent	S	R
galendant	grandel	V		topar	Correct		
gasaw	gasway	S	R	transhould	t-r-a-n-s-h-o-u-l-d tranhouse	S	R
habey	hankrail	S	R	vanet	Correct		
halfell	h-a-l-f-e-l-l something feel	V		vit	Correct		
haton	Correct			wavents	wave- something wasted	S	R
hud	Correct			wedew	wedded	S	R
landawn	Correct			zam	sab	V	

Table 11.12: CD's performance in the location manipulation condition.

Location Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
about	Correct			hotel	Correct		
abuse	Correct			input	Correct		
admin	admit	S	R	issue	Correct		
admit	Correct			legal	legend	S	R
adopt	a-d-o-p	O	R	links	Correct		
agent	Correct			mango	Correct		
allow	Correct			manor	Correct		
asset	Correct			maybe	Correct		
bacon	Correct			meant	meat	V	L
bagel	???	?		minor	Correct		
baton	Correct			noted	Correct		
beast	Correct			paint	Correct		
begin	Correct			pants	Correct		
begun	Correct			peach	Correct		
below	bowel	V		pearl	Correct		
bingo	Correct			pilot	Correct		
black	Correct			pinup	Correct		
blame	Correct			plate	Correct		
bones	boner	S	R	robin	Correct		
bored	Correct			robot	Correct		
brace	Correct			sales	sale	O	R
braid	NR	NR		scare	NR	NR	
brain	Correct			scary	scar	O	R
brake	Correct			shelf	Correct		
brand	Correct			shell	Correct		
brave	Correct			shoes	shole	S	R
brown	Correct			shoot	shot	V	
cabin	Correct			slope	Correct		
cable	Correct			space	spade	S	R
cargo	Correct			spare	span	S	R
chart	Correct			spark	Correct		
chips	Correct			sport	Correct		
cobra	NR	NR		stage	stag	O	R
coven	cover	O	R	state	Correct		
crash	car	V		sunup	Correct		
crown	crow	O	R	super	support	S	R
dealt	dental	ND	R	table	Correct		
dount	Correct			taken	Correct		
dozen	doze	O	R	tango	Correct		
drugs	Correct			taxes	tax	O	R
fable	NR	NR		their	Correct		
fired	fire	O	R	think	Correct		
forgot	Correct			tired	t-i-r-e	O	R
forum	forrun	S	R	today	Correct		
gable	gamble	V		twins	twist	S	R
grade	grand	S	R	upend	Correct		
grand	Correct			upset	Correct		
growl	Correct			usage	?	?	
hands	hand	O	R	wedge	Correct		
heart	Correct			whose	hoe	V	

Table 11.13: CD's performance in the spaced word condition (unlimited exposure).

Spaced Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
accused	access	S	R	ongoing	Correct		
adverse	advance	S	R	parking	Correct		
airline	Correct			passion	Correct		
another	Correct			passive	p-a-s-s-i-v-e "passage"	S	R
banking	Correct			passive	p-a-s-s-i-v-e "passage"	S	R
barking	Correct			patrols	patrol	O	R
battery	Correct			pension	Correct		
billing	Correct			plastic	Correct		
billion	Correct			prepare	Correct		
brought	b-r-o-u-g-h-t "DK"	LBL		prevent	Correct		
burning	Correct			privacy	p-r-i-v-a-c- "privat"	S	R
capable	cable	V		private	preview	S	R
capital	Correct			protein	p-r-o-t-e-i-n "probably"	S	R
capitan	Correct			protest	poster	S	R
capture	Correct			protest	poster	S	R
ceiling	calling	V		qualify	Correct		
clawing	Correct			quality	q-u-a-l-i-t-y "quiet"	S	R
contest	Correct			radians	r-a-d-i-a-n-s "raddish"	S	R
control	Correct			radical	Correct		
develop	Correct			rapture	Correct		
display	Correct			reacher	research	S	R
drastic	Correct			reeling	relign	S	R
drawing	Correct			removal	r-e-m-o-v-a-l "revow"	S	R
driving	reviewing	S	R	removed	remove	O	R
dynamic	d-y... "domestic"	S	R	replace	r-e-p-l-a- ... "DK"	LBL	
envelop	envelope	A	R	reprove	improve	S	L
esquire	square	V		require	request	S	R
expires	express	S	R	retires	r-e-t-i-r-e-s "retire"	O	R
federal	f-e-d-e-r-al "DK"	LBL		revenue	renew	S	R
forward	Correct			reverse	r-e-v-e-r-s-e "DK"	LBL	
general	Correct			rewards	reward	O	R
imagine	Correct			session	s-e-s-s-i-o-n "DK" "assension"	S	L
imaging	orgasm???	?		smitten	smitt	O	R
improve	Correct			student	studied	S	R
journal	Correct			succede	s-u-c-c-e-d-e "sucess"	S	R
journey	Correct			success	Correct		
keeping	Correct			support	Correct		
killing	Correct			suppose	s-u-p-p-o-s-e "supposed"	A	R
kissing	Correct			sustain	s-u-s-t-a-i-n "Euston"	LBL	
leading	Correct			teacher	Correct		
logical	l-o-g-i-c-a-l "local"	V		telecom	Correct		
massive	Correct			tension	Correct		
million	Correct			thought	Correct		
mineral	minirail	V		towards	Correct		
minimal	m-i-n-m-a-l "minual"	S	R	turning	Correct		
missing	Correct			warning	Correct		
mission	Correct			weeping	keeping	S	L
morning	Correct			welcome	Correct		
network	Correct			welfare	Correct		
nowhere	Correct			written	Correct		

Table 11.14: CD's responses in the letter string condition (unlimited exposure time).

Letter String Condition Performance							
Target	**Response**	**Error Type**	**Error Side**	**Target**	**Response**	**Error Type**	**Error Side**
gjx	Correct			armxt	S	L	
brt	Correct			Correct			
crh	Correct			Correct			
cwrmh	Correct			Correct			
cxrwn	Correct			Correct			
dsb	Correct			Correct			
fdp	Correct			Correct			
fmp	rnt	V		rf	V		
frdhc	Correct			Correct			
gbv	Correct			Correct			
gsnfp	Correct			Correct			
hjwln	Correct			Correct			
hkn	Correct			Correct			
hrwdx	Correct			Correct			
jlfcx	Correct			Correct			
jpm	Correct			Correct			
jrdhm	Correct			Correct			
klr	Correct			xip	V		
krljx	Correct			Correct			
krs	Correct			Correct			
krwzx	Correct			Correct			
lgk	Correct						

11.3 Section Three: EF's Reading Responses

Table 11.15: EF's responses for all horizontally presented word stimuli.

Horizontal Condition Performance							
Target	**Response**	**Type**	**Side**	**Target**	**Response**	**Type**	**Side**
war	war			example	explain	S	R
hub	hub			removed	mover	V	
cap	cap			studied	stupid	S	R
raw	raw			examine	examine		
nun	nun			knowing	knowing		
jog	jog			upstage	upstaged	A	R
rib	rip	S	R	towards	tower	S	R
pod	pod			message	message		
lad	lad			thought	thought		
how	how			brother	brother		
vow	vow			founder	founder		
yes	yes			excited	excitement	S	R
sat	sat			missing	missing		
ram	ram			related	related		
art	art			herself	herself		
wed	went	S	R	devoted	devoted		
bin	bin			classes	classic	S	R
got	got			oneself	oneself		
sap	sap			learned	?		
wet	wet			updated	update	O	R
pat	pat			totally	total	O	R
let	let			passage	passenger	S	R
tan	tan			working	working		
man	man			reading	reading		
pan	pan			fortune	fortune		
globe	globe			thrashing	thrashing		
pitch	pitch			mistaken	mistaken		
grown	ground	S	R	milestone	milestone		
heart	heart			ourselves	ourselves		
every	ever	O	R	addresses	address	O	R
spare	spanner	S	R	appealing	applying	S	R
grant	grant			encounter	encounting	S	
lower	power	S	R	undefined	NR		
plant	plant			adaptable	applied	S	R
cover	cover			beekeeper	beekeeper		
plane	plane			impartial	impatient	S	R
table	table			spiritual	NR		
start	start			bartender	NR		
there	there			obsession	obsessed	S	R
event	event			bookshelf	bookshelf		
ideal	ideal			limestone	limestone		
format	format			remission	remissed	S	R
think	think			billboard	billboard		
blame	blame			backstage	backstage		
woman	woman			handstand	handstand		
allow	all well	?		forgotten	forgotten		
power	power			offspring	offspring		
shown	show			bewitched	bewitched		
human	human			delivered	delivery	S	R
peace	peace			onlooking	onlooking		

Table 11.16: EF's responses for all reduced exposure condition words (exposure time = 500ms).

Reduced Exposure Condition Performance							
Target	**Response**	**Type**	**Side**	**Target**	**Response**	**Type**	**Side**
war	war			example	example		
hub	hub			removed	remove	O	R
cap	cap			studied	NR	NR	
raw	raw			examine	example	S	R
nun	run	S	L	knowing	NR	NR	
jog	jog			upstage	?		
rib	rip	S	R	towards	toward	O	R
pod	pod			message	message		
lad	laid	V		thought	through	S	R
how	how			brother	brother		
vow	vowed	A	R	founder	founder		
yes	yes			excited	excitement	S	R
sat	sat			missing	NR	NR	
ram	NR	NR		related	NR	NR	
art	art			herself	NR	NR	
wed	went	S	R	devoted	NR	NR	
bin	bin			classes	NR	NR	
got	got			oneself	NR	NR	
sap	sap			learned	learn	O	R
wet	wet			updated	update	O	R
pat	pat			totally	total	O	R
let	let			passage	passage		
tan	tan			working	working		
man	man			reading	reading		
pan	pan			fortune	fortunes	A	R
globe	globe			thrashing	thrashing		
pitch	pitch			mistaken	mistaken		
grown	?			milestone	milestone		
heart	heart			ourselves	ourselves		
every	every			addresses	Address	O	R
spare	spare			appealing	appalling	V	
grant	grant			encounter	?		
lower	lower			undefined	defend	S	L
plant	plant			adaptable	adapt	O	R
cover	cover			beekeeper	beeper	V	
plane	plane			impartial	impartial		
table	NR	NR		spiritual	spiritual		
start	NR	NR		bartender	NR	NR	
there	NR	NR		obsession	obsessed	O	R
event	event			bookshelf	?self	O	L
ideal	deal	O	L	limestone	milestone	S	L
format	NR	NR		remission	remiss	O	R
think	think			billboard	board something	V	
blame	blame			backstage	backstage		
woman	woman			handstand	handstand		
allow	allow			forgotten	forgotten		
power	power			offspring	offspring		
shown	show	O	R	bewitched	bewitched		
human	human			delivered	delivered		
peace	peace			onlooking	onlook	O	R

Table 11.17: EF's responses for all reflected words.

Reflected Condition Performance							
Target	**Response**	**Type**	**Side**	**Target**	**Response**	**Type**	**Side**
wed	NR	NR		steamer	NR		
peg	NR	NR		excited	exciting	S	R
rib	rip	S	R	learned	learning	S	R
bar	band	S	R	blessed	blesses	S	R
fog	fog			muttons	monitor	S	R
pew	NR	NR		faction	fantasy	S	R
kin	kin			removed	remove	O	R
cap	cad	S	R	charged	NR		
pan	NR	NR		dressed	dresser	S	R
dew	NR			reveals	revent	O	R
rub	rub			updated	NR		
get	gend	S	R	transfix	NR		
lad	lad			clovers	convent	?	
lag	lad	S	R	appeals	NT	NT	
nip	nip			buttons	buttons		
bug	bug			brokers	NR	NR	
rod	rod			studied	study	S	R
rad	rad			totally	total	O	R
sap	sad	S	R	scavenges	circumvent	V	
every	even	S	R	tractions	NR		
lanes	NR			redactors	recent	S	R
carts	NR	NR		misguides	NR		
those	thought	S	R	decievers	division	S	R
there	tight	S	R	misspends	mispronounce	S	R
slate	spirit	V		remission	NR		
moved	movie	S	R	distended	distend	P	R
sower	NR			adaptable	NR	NR	
ledge	ledge			represent	NT		
plans	plan	O	R	bleachers	NR	NR	
begin	beginning	A	R	detracted	NT		
voter	voter			impartial	NT		
gable	NR	NR		reaffirms	NT		
plane	plane			delivered	NT		
grown	ground	S	R	revenges	NT		
hedge	hedge			addressed	NR	NR	
toted	tote	O	R	obsession	NT		
shown	showed	S	R	presented	NT		
event	event						

Table 11.18: EF's responses for all letter sting condition stimuli.

String Condition Performance							
Target	**Response**	**Type**	**Side**	**Target**	**Response**	**Type**	**Side**
plw	plw			krwzx	krwzx		
_gjx	_gjx			cxrwn	cxrwn		
krs	krs			hrwdx	hrwdx		
jpm	jpm			jrdhm	jrdhm		
gbv	gbv			jlfcx	jlfcx		
vmz	vmz			bmntf	bmntf		
lgk	lgk			cwrmh	cwrmh		
str	str			lrmxt	lrmxt		
trl	trl			hjwln	hjwln		
fdp	fdp			wnjkl	wnjkl		
sdq	sdq			sntmb	sntmb		
xdp	xdp			gsnfp	gsnfp		
ygc	ygc			rwnvxzq	rwnvxzo		
fmp	fmp			mstnbrp	mstnbrp		
mcn	mcn			dtgnjlm	dtgnjlm		
dsb	dsb			kntwfds	kntwfds		
brt	brt			knjtrmw	knjtrmw		
klr	klr			xvtpmn	xvtpmn		
crh	crh			fntmpsr	fntmpsr		
hkn	hkn			grnczst	grnczst		
rwm	rwm			ntvxdgz	ntvxdgz		
mjb	mjb			krtnwsx	krtnwsx		
zqf	zqf			ljkwntz	Jkwntz		
ync	ync			fwmxzpl	fwmxzpl		
rjf	rjf			lntrdgh	lntrdgh		
qnryc	qnryc			drwqcbp	drwqcbp		
tvbms	tvbms			yqtnzdl	yqtnzdl		
prxtz	prxtz			xljgnwt	xljgnwt		
jrmnv	jrmnv			mkpyrw	mkpyrw		
pytfg	pytfg			xnrwqpm	xnrwqpm		
qprwt	qprwt			gfrnmtw	gfrnmtw		
lhbvc	lhbvc			hkgjplx	hkgjplx		
krljx	krljx			klnstdc	klnstdc		
rvntk	rvntk			swntkhg	swntkhg		
frdhc	frdhc			rtyplnk	rtyplnk		
bvngw	bvngw			sqxnfgp	sqxnfgp		
stfgn	stfgn			cqzrnts	cqzrnts		
qvtgh	qvtgh						

Table 11.19: EF's responsees for all vertically presented words.

Vertical Condition Performance							
Target	**Response**	**Type**	**Side**	**Target**	**Response**	**Type**	**Side**
wed	wen	S	R	whose	NR		
rib	rip	S	R	event	event		
sew	NR			lands	lands		
can	can			every	event	S	R
hag	hag			fable	fabulous	S	R
rid	rid			usage	NR		
lad	lad			plane	planer	A	R
cot	cod	S	R	coven	convent	A	R
pan	pan			slashes	NR		
dim	NR			learned	NR		
tan	tan			removed	remote	S	R
ham	ham			boarded	border	S	R
mar	mar			resigns	resting	S	R
may	may			remands	remain	S	R
pad	pad			respire	NR		
cap	cad	S	R	despite	NR		
tad	tad			excited	excitement	S	R
sap	sap			respite	respect	S	R
tin	tin			updated	upperdating	S	R
downs	downs			totally	totally		
growl	growl			drowned	NR		
chart	NR			avenged	adventure	S	R
there	NR			crowned	NR		
spark	spark			clashed	clasher	S	R
scare	scar	O	R	smasher	smashing	S	R
hands	hands			studied	?		
shown	shown			supported	NR		
grown	growing	S	R	unaltered	NR		
noted	knowing	?		reporters	reposession	S	R
begun	beginning	S	R	immatured	immature	O	R

Table 11.20: EF's responses for all location condition words.

Location Condition Performance									
Target	**Response**	**Type**	**Side**	**Location**	**Target**	**Response**	**Type**	**Side**	**Locaton**
stage	stage			right	admin	admit	S	R	left
forum	forming	A	R	left	links	links			right
chart	NR	NR		left	shoot	shoot			right
baton	baton			right	abuse	abus	O	R	right
issue	issue			right	upset	NR	NR		right
tired	tired			right	drugs	NR	NR		left
hotel	hotel			right	crown	NR	NR		left
shell	shell			right	dealt	NR	NR		left
legal	legal			right	agent	NR	NR		left
robin	NR	NR		left	spare	spare			left
mango	NR	NR		left	peach	peach			left
below	below			left	braid	NR	NR		right
super	super			right	space	spaced	A	R	right
brace	brace			left	noted	NR	NR		right
robot	NR	NR		left	allow	allow			left
bones	bones			left	blame	blame			right
minor	mirror	V		left	input	input			right
sunup	sup	V		left	cable	cable			left
grade	NR	NR		left	growl	grow	O	R	right
sales	yes	S	L	left	brand	NR	NR		left
fable	clable	S	L	right	bored	boring	S	r	left
cargo	cargo			left	meant	?			right
taken	take (SC)	O	R	right	today	today			left
admit	admit			left	chips	chips			right
bingo	NR	NR		right	brake	brake			right
twins	NR	NR		left	begun	NR	NR		right
spark	spark			left	pearl	pearl			right
cabin	cabin			right	shelf	shelf			right
black	black			right	dozen	dozen			left
taxes	tax	O	R	right	maybe	maybe			right
bacon	bacon			left	manor	mirror	V		left
table	table			left	plate	plant	S	R	right
scare	scare			left	scary	scared	S	R	left
asset	set	O	L	right	dount	NR	NR		right
shoes	NR	NR		right	beast	beast			right
slope	slope			left	forgot	forgot			left
wedge	wedge			right	brown	brown			right
upend	upended	A	R	left	brave	brave			left
sport	NR	NR		left	crash	NR	NR		right
pinup	NR	NR		left	begin	begin			left
pilot	pilot			right	think	think			right
heart	heart			right	usage	?			left
coven	oven	O	L	right	their	NR	NR		left
adopt	NR	NR		right	about	about			left
tango	NR	NR		left	pants	painted	S	R	right
gable	gable			left	grand	grand			right
brain	NR	NR		right	whose	?			right
cobra	NR	NR		right	state	NR	NR		left
hands	hands			left	bagel	NR	NR		left
paint	paint			right					

12 Appendix IV: Chapter 6 Supplementary Materials

Contents: This Appendix contains full statistics and visualisation for the binary regressions reported in Chapter 6, Section 3.

Table 12.1: Full Statistics for the series of binary regressions conducted to investigate the relationship between egocentric (top table) and allocentric (bottom table) neglect severity and reference category.

Egocentric Neglect Severity

Test	Reference	df	Null Deviance	Residual Deviance	AIC	P
Kitchen	Good Spatial Attention	102	114.72	113.34	117.34	0.262
Kitchen	**Difficulty Finding Items***	**102**	**124.96**	**109.95**	**113.95**	**0.0002**
Kitchen	Uses Both Sides Well	102	104.64	104.64	108.64	0.979
Kitchen	Difficulty Initiating	102	116.97	113.16	117.16	0.0489
Kitchen	Independence	102	135.4	131.75	135.75	0.0716
Kitchen	Mobility (Able)	102	116.97	116.96	120.96	0.97499
Kitchen	Liquid (Assistance Needed)	102	78.368	78.36	82.36	0.926
Wash/Dress	Difficulty Dressing One Side	157	156.88	154.62	158.62	0.129
Wash/Dress	Good Spatial Attention	157	74.684	68.841	72.841	0.0698
Wash/Dress	**Spatial Inattention***	**157**	**148.01**	**139**	**143**	**0.00285**
Wash/Dress	Good Body Attention	157	99.364	96.369	100.37	0.118
Wash/Dress	**Body Inattention***	**157**	**154.01**	**146.46**	**150.46**	**0.00605**
Wash/Dress	**Unable to Use Both Upper Limbs***	**157**	**183.6**	**176.65**	**180.65**	**0.00852**
Wash/Dress	Difficulty Initiating	157	144.88	144.6	148.6	0.594
Wash/Dress	Minimal Assistance Needed	157	138.36	136.57	140.57	0.202

Allocentric Neglect Severity

Test	Reference	df	Null Deviance	Residual Deviance	AIC	P
Kitchen	Good Spatial Attention	102	114.72	114.67	118.67	0.826
Kitchen	Difficulty Finding Items	102	124.96	124.7	128.7	0.602
Kitchen	Uses Both Sides Well	102	104.64	103.83	107.83	0.416
Kitchen	Difficulty Initiating	102	116.97	113.86	117.86	0.0847
Kitchen	Independence	102	135.4	133.79	137.79	0.2467
Kitchen	Mobility (Able)	102	116.97	113.84	117.84	0.0835
Kitchen	Liquid (Assistance Needed)	102	78.368	77.992	81.992	0.519
Wash/Dress	Difficulty Dressing One Side	157	156.88	153.2	157.2	0.0516
Wash/Dress	Good Spatial Attention	157	74.684	74.506	78.5	0.688
Wash/Dress	Spatial Inattention	157	148.01	146.57	150.57	0.217
Wash/Dress	Good Body Attention	157	99.364	99.363	103.36	0.977
Wash/Dress	Body Inattention	157	154.01	149.51	153.51	0.0323
Wash/Dress	Unable to Use Both Upper Limbs	157	183.6	182.32	186.32	0.251
Wash/Dress	Difficulty Initiating	157	144.88	143.38	147.38	0.261
Wash/Dress	Minimal Assistance Needed	157	138.35	136.51	140.51	0.221

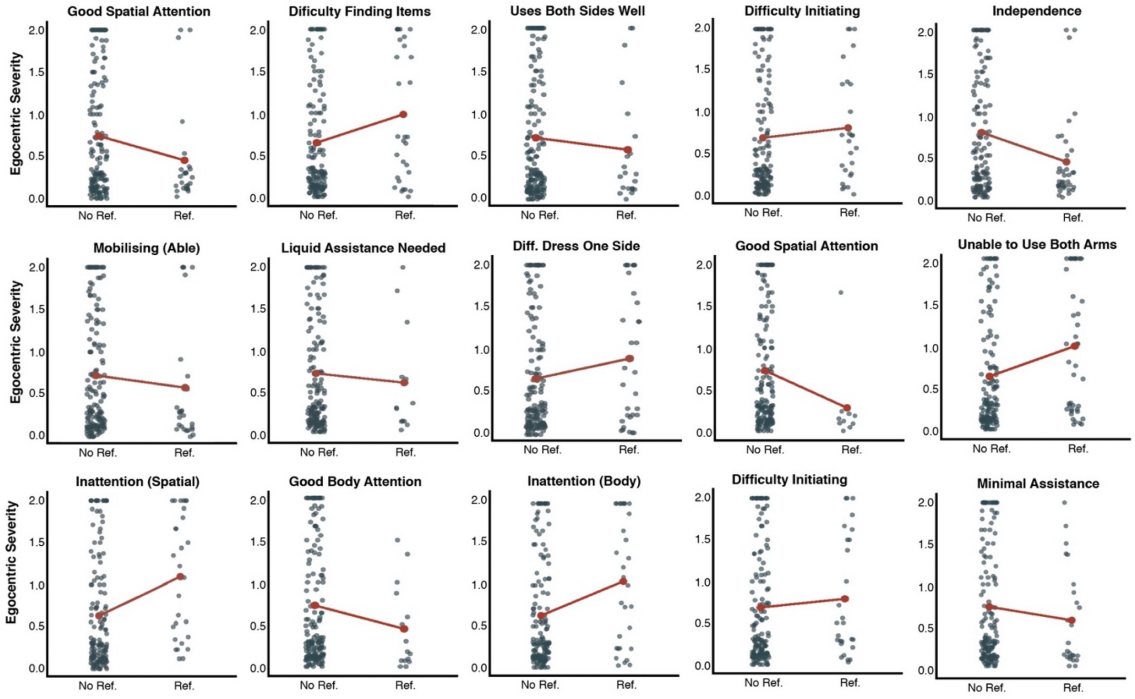


Figure 12.1: A visualisation of the binary linear regressions conducted to determine the relationship between egocentric neglect severity (y-axis) and reference outcome (x-axis) across different reference categories. Blue points visualise individual patients, red dots represent group means, and red lines highlight the difference in means between comparison groups.

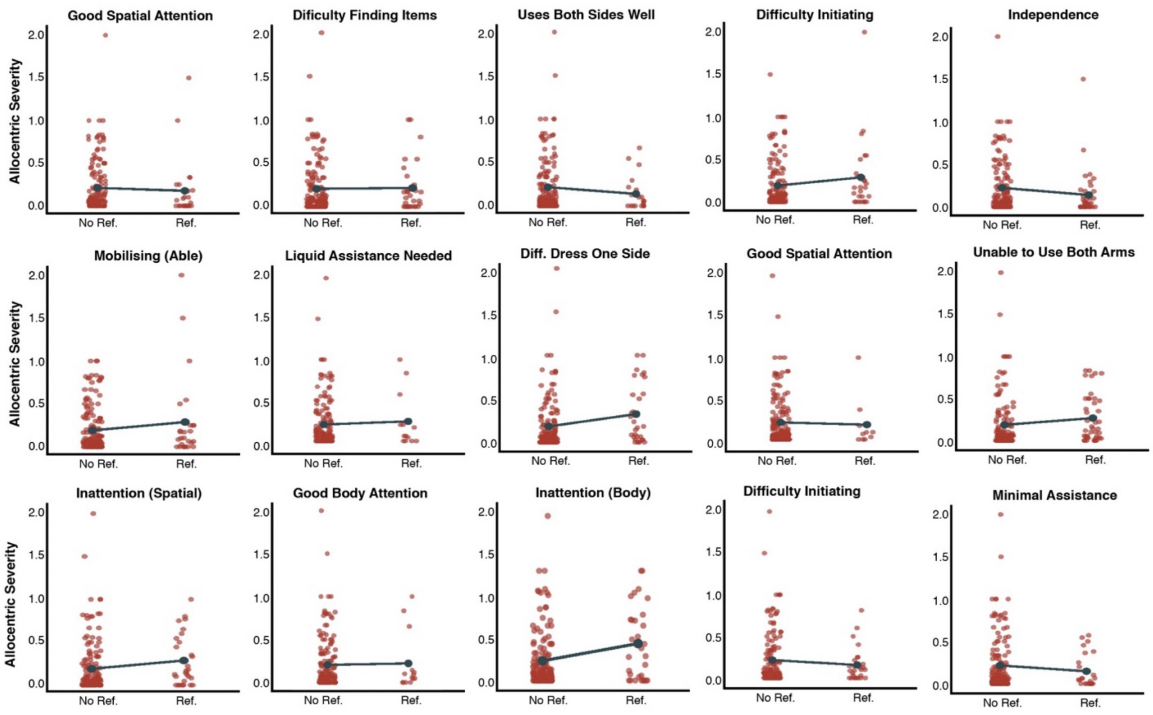


Figure 12.2: A visualisation of the binary linear regressions conducted to determine the relationship between allocentric neglect severity (y-axis) and reference outcome (x-axis) across different reference categories. Red points visualise individual patients, blue dots represent group means, and blue lines highlight the difference in means between comparison groups.