COMORBIDITIES OF VISUAL SPATIAL ATTENTION DEFICITS IN ACQUIRED BRAIN LESION: THE CASE OF READING AND WORKING MEMORY

by

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ABSTRACT

Visual spatial neglect (VSN), a disordered to attentional processing, is a common neuropsychological syndrome following brain injury. Presence of VSN adversely affects recovery. The interplay of spatial and non-spatial attentional components in the syndrome has been a matter of debate. The current thesis examined the comorbidities of cognitive deficits and VSN. The working assumption is that attention ‘acts’ upon other cognitive processes, therefore the error pattern of comorbid deficits should reflect the impaired attentional components. Two cognitive comorbidities were examined: reading and working memory (WM). The relations between Reading/WM and VSN were assessed using three different methodologies: meta-analyses of the literature; analyses of two large databases of stroke patients; and experimental case studies testing the impact of saliency on spatial bias symptoms. The results suggest that patients who suffer from VSN are more likely to experience problems in reading and WM. Surprisingly, the spatial biases of VSN did not affect errors in reading or WM. Regression analyses showed non-spatial components of attention explained the comorbidity deficits better than spatial component. The experimental chapters showed that non-spatial saliency cues exasperate the spatial bias symptoms. Taken together the current thesis provide evidence supporting a non-spatial attention deficit as a core symptom of VSN.

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ABBREVIATIONS

BCoS	Birmingham Cognitive Screen
C-BCoS	Chinese Version the Birmingham Cognitive Screen
CFC	Complex Figure Copy
UK-BCoS	English Version the Birmingham Cognitive Screen
VSN	Visual Spatial Neglect
WM	Working Memory
UK	United Kingdom

CHAPTER 1: GENERAL INTRODUCTION

One-third of stroke patients are likely to experience unilateral spatial neglect, a visual spatial attentional deficit (Hepworth et al., 2016). Patients suffering from visual neglect tend to ignore stimuli presented on their contralesional side, despite intact vision. The asymmetric spatial bias observed in neglect patients is the feature that is used in common clinical assessments when diagnosing neglect (e.g., The Behavioural Inattention Test (B.I.T.), Halligan, Cockburn, & Wilson, 1991; Jehkonen et al., 1998). However, visual neglect is not a single deficit syndrome and often regarded as a heterogeneous disorder (Committeri et al., 2007; Hillis, 2005; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Neglect is frequently observed in individuals suffering from a damaged to the right parietal lobe (Karnath, Himmelbach, & Rorden, 2002; Stone et al., 1991). In line with this observation, the right parietal has been proposed to play a key role in spatial attention (Corbetta & Shulman, 2011; Posner & Petersen, 1990). Though processing in the right parietal also contributes to non-spatial attention (Corbetta & Shulman, 2011; Posner & Petersen, 1990). Accumulating evidences suggest that attention impairment of neglect patients are not confined to spatial deficits, hypothesising a role of non-spatial component deficits in persistent neglect (Beschin & Robertson, 1997; Danckert & Ferber, 2006; Husain, Shapiro, Martin, & Kennard, 1997). As attention is a core cognitive component, that governs both internal and external processing; it is not surprising that patients who suffer from unilateral spatial neglect following stroke, exhibit more severe neurological and functional symptoms; and benefit less from cognitive and physiotherapy interventions than their non-neglect counterparts (Paolucci et al., 2001). However, systematic evaluation of the impact of unilateral spatial neglect on other cognitive abilities is sparse.

Therefore, the overall aim of the present thesis is to examine comorbidities with visual attention neglect syndrome and to assess whether these relate to the spatial features of the attentional deficits. Two spatial features were considered: the asymmetric spatial processing of ipsilesional and contralesional sides, and the attentional frame of reference: egocentric and allocentric. The present thesis focused on two cognitive comorbidities: reading and working memory.

The introductory chapter started by briefly describing the clinical characteristic and prevalence of visual spatial neglect. Then, I discussed theoretical models of visual attention and how these models relate to visual neglect syndrome. After that, I briefly describe common reported comorbidities in the literature and discussed the rationale of focusing on reading and working memory as cognitive comorbidities. Finally, I outlined the structure of the current thesis. The thesis itself is divided into two parts, Part One examined comorbidity of visual neglect and reading and Part Two examined visual neglect and working memory. Theoretical consideration on the link between visual neglect and each comorbidity will be discussed in the introduction section of each part.

1.1. Visual Neglect: Characteristics and Prevalence

Visual neglect—also known as *spatial neglect, unilateral neglect, hemispatial neglect, hemi-inattention, hemisensory neglect, hemineglect* (Kerkhoff, 2001)— is a heterogeneous syndrome (Bartolomeo, 2007), and is best understood as an association of disorders of visual attention (Bartolomeo & Chokron, 2002). Classically, visual neglect disorder has been defined as a failure to report, respond, or orient towards novel or meaningful stimuli in the hemispace that is contralateral to the lesion, when this failure is not attributable to a primary sensory (i.e., hemianopia) or motor (i.e., hemiplegia) dysfunctions (see Driver & Mattingley, 1998; Halligan, Fink, Marshall, & Vallar, 2003; Heilman, Valenstein, & Watson, 1994; Parton et al., 2004a). Neglect syndrome is characterized by a reduced or complete lack of detection of information falling contralateral to the side of the brain damage, contralesional field (Vallar & Perani, 1986). Patients with visual neglect typically show difficulties in orienting spatial selective attention toward their contralesional side. At the acute stages after a stroke, patients gaze and head tend to deviate to the ipsilesional side (Barton, Behrmann, & Black, 1998; Olk & Harvey, 2002) and their exploration behaviour is also biased (Olk, Harvey, & Gilchrist, 2002).

Visual spatial deficits are more prevalent following right hemisphere damage compared to the left hemisphere (Heilman, Watson, Valenstein, & In, 2003; Chechlacz et al., 2014). Right hemisphere visual neglect is typically associated with more severe and persistent symptoms (Mesulam, 1981).

Estimated prevalence rate of neglect following stroke varies widely because it critically depends on: the types of assessment methods and measurements applied for screening, the types of inclusion criteria used, the motor and cognitive ability of the patient, and also the timing of the assessment from stroke onset (Bowen et al., 1999). Three studies report an average prevalence of neglect in stroke survivors ranging from 30–70% after right hemisphere brain damage, and ranging from 20–60% after left hemisphere brain damage (Ringman, Saver, Woolson, Clarke, & Adams, 2004; Wee & Hopman, 2008; Bickerton, Samson, Williamson, & Humphreys, 2011). Prevalence is highest when patients are tested within days following stroke. In the United Kingdom, 72% show visual neglect symptoms when tested within 2-3 days post-onset (Stone et al., 1993), and only 8% when tested 21 days post-onset (Sunderland, Wade, & Hewer, 1987). In the United States, an approximately 30 % of patients showed neglect syndrome within 24 hours post-onset but after three months, approximately 2 % of them showed severe neglect symptoms and approximately 15 % showed moderate neglect symptoms (Sunderland et al., 1987). Similarly, results of three months post-stroke onset, neglect can be detected in approximately 17% stroke patients with right-brain injury and 5% with left-brain injury (Ringman et al., 2004).

Age increases the risk of visual neglect following stroke. Approximately 69.6% of brain-damaged stroke patients above 65 years of age, showed neglect behaviour, while approximately 49.4% of patients below the age of 65 had neglect symptoms (Gottesman et al., 2008). Gender does not affect the prevalence or severity of visual neglect following stroke (Kleinman et al., 2008). Recent years have witnessed the growing concerns that when neglect persists, it can have a significant impact on the rehabilitation of the patients, delaying their progress and adversely affecting their functional outcome (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001; Parton et al., 2004a).

1.1.1. **Tasks Used to Assess Visual Spatial Neglect**

Neuropsychological diagnosis is typically done using test batteries that include number of tests (Bigler & Clement, 1997; Snyder et al., 2006). Similarly, batteries aimed at identifying visual spatial attention deficits include multiple tests. For example, the Behavioural Inattention Test (BIT), (Halligan, Cockburn, & Wilson, 1991) includes the following tests: three cancellation tasks: line crossing, letter cancellation and star cancellation; line bisection, figure and shape copying and representational drawings. The Birmingham Cognitive Screen – BCoS (Humphreys et al., 2012) includes three tasks assessing visual spatial attention deficits: an apple cancellation task, a task that requires in detecting unilateral and bilateral stimuli, and a complex figure copy task.

Most clinicians and researchers employ pen and paper assessment tasks, as these tasks are easy to carry out either in the laboratory or clinical settings. Paper and pencil tasks require that patients obtain a good control of the pen and reasonable eye-hand coordination.

Some argues that the heterogenous nature of the visual neglect syndrome is a result of the varied methods of assessing the symptoms. It is shown that different spatial attention tasks tap into different spatial attention deficits (Chechlacz et al., 2012; Verdon et al., 2010). In the current thesis, I considered only one sub-classification which related to the frame of reference (allocentric and egocentric, see 1.1.2.1), but general diagnosis of visual neglect symptoms was done using the neuropsychology diagnostic conventions –performances across multiple tasks. Next, I describe in details the tasks typically used by researchers and clinicians in identifying visual neglect symptoms. While also providing an analysis of the type of cognitive processes that is required to successfully complete these tasks.

1.1.1.1. Cancellation Tests

Cancellation tests are frequently used and are shown to be quite sensitive in detecting visual spatial neglect (Ferber & Karnath, 2001). These are pencil and paper-based assessments. A cancellation test has a stimulus page (typically A4 size) that displays multiple target items and distractors (e.g., shapes, symbols, animals, objects, or letters, lines). The stimulus page is placed on a table in front of the patient body, aligned with the midline of their body. The target and distracter items are usually pseudo-randomly arranged, to ensure equal distribution across the page along the vertical and horizontal axes. The administrator asks the patient to identify and to cancel (cross out) all the target items with a pencil and to avoid crossing non-target items. In some cases, the patients are asked to point to the corner of the page before starting the task. Usually, the administrator removes the page either after the patients specify that they have finished crossing out all the target items on the stimulus page or after the allocated time has expired. The administrator calculates an asymmetry score by counting the difference in a number of targets cancelled on right as opposed to the left side of the page. Other measures include the number of targets crossed out in various quadrants (i.e. finer resolution), re-cancellations, location of initial target cancelled, cancellation search strategy.

A cancellation task requires that orient attention along space across both hemifields. The cancellation tasks are type of a search task, tapping into selective attention. They require patients to be able to identify targets and distracters in a crowded visual field, be able to inhibit response to distracter.

Some cancellation tasks (e.g. apple cancellation task in the BCoS) include distracter that assess patients orient attention across an object (Bickerton et al., 2011), rather than the entire visual field (see 1.1.2.1)

1.1.1.2. Line Bisection Task

Line bisection task is a paper and pencil assessment test. It is regarded as a quick and effective assessment tool to diagnose visual neglect (Schenkenberg et al., 1980). Commonly, the patient is presented with a white sheet of paper, often in landscape orientation. It consists only of a black horizontal line drawn across the centre of the page. The patient is instructed to visually estimate the midpoint of the horizontal line and mark it with a small vertical line. For the scoring, the administrator precisely measures the distance between the patient’s small vertical mark and the true midpoint of the horizontal stimulus line. This distance here is a deviation from the centre or midpoint displacement. There are cases that patients are tested multiple times using a line bisection task, and an average deviation from the centre score is calculated.

This test requires that patients perceive the entire line, have a good grasp of the concept of midpoint and be able to mentally estimate it. The frame of reference is the object (the line) rather than the entire visual filed.

1.1.1.3. Figure, Representational Drawing

Drawing a common symmetrical object, like a clock, a flower is another frequent clinical measure of visual neglect (Chen & Goedert, 2012). Patients suffering from visual neglect show a marked asymmetry in the amount of details drawn on their ipsilesional (typically right) and contralesional (typically left) side of the page. Some time they omit details from the contralesional side or condense them to the ipsilesional side. Scoring is typically based on subjective evaluation by the clinician/administrator of the drawing accuracy.

This test assesses the ability to orient attention in internal space, as drawing is often based on prior knowledge of the object, but it also assesses sensitive to orienting orientation in external space, as patients processed and evaluate their drawings. The test requires ability to retrieve visual knowledge of objects. The frame of reference for orienting attention in mental and external space is the object, though within the external space spatial attention deficits at the level of the visual field may also contribute to the impairment.

1.1.1.4. Figure Copy

Patients are typically presented with a line drawing figure and are asked to copy it. The figure could vary from relatively simple (e.g. wire cube, MoCA (www.mocatest.org) to more complex figures which include multiple details like the Rey–Osterrieth complex figure test (Duley et al., 1993), or the complex figure task in the BCoS (Humphreys et al., 2012). Patients are typically scored based on the number of details included, an asymmetric score derived based on differences in drawn details between the two sides of the page.

Beyond spatial attention, these tasks heavily rely on patients' hand-eye coordination as it is a common task for assessing construal apraxia, the inability to construct, build or draw objects. Spatial attention biases are assessed primarily in relation to object space.

1.1.2. **<u>Sub-Classification of Visual Spatial Deficits</u>**

Visual neglect is characterized by several dissociable components (Halligan, Fink, Marshall, & Vallar, 2003), suggesting that different patients may experience contrasting types of impairments (Bartolomeo, 2007; Kristjánsson & Vuilleumier, 2010; Malhotra, Mannan, Driver, & Husain, 2004; Vallar, 1998). Most often visual neglect patients may suffer from combinations of various impairments, with each impairment exacerbating the others to produce the various symptoms that can be seen either in the clinical setting or in daily life activities (Driver & Husain, 2002). Here we describe the most common examples.

1.1.2.1. Allocentric and Egocentric

A sub-classification was proposed depending on the space frame of reference that is impaired, whether it is the body (egocentric) or space (allocentric). Several studies (e.g., Caramazza & Hillis, 1990; Heinke, 1998; Humphreys & Riddoch, 1995; Humphreys & Riddoch, 1994), demonstrate dissociations between patients who neglect different forms of spatial representation. For example, Walker and Young (1996) described a right-brain damage patient, three years post-stroke, who had only mild visuo-spatial neglect during reading and cancellation tasks (egocentric) but demonstrated profound neglect of the left side of objects (allocentric), when presented centrally in his visual field. Other cases of allocentric neglect were reported, with patients neglecting the left side of objects whether they appear to the centre or to the left of their body midline (Chatterjee, 1994; Savazzi et al., 2004).

In one striking example, Humphreys and Riddoch (1994, 1995) described a patient, JR. JR made left-side omissions when reading single words and nonwords (frame of reference single object: allocentric) but right-sided omissions of words on the page (frame of reference egocentric). This opposite pattern of spatial bias, according to the frame of reference, is difficult to account for when assuming a single gradient of attention across the visual field (see Driver & Pouget, 2000; Karnath, 1997). The authors argued for distinct egocentric (biased is based on where stimuli fall in relation to patient's body) and allocentric (biased is based on the contralesional side of objects irrespective of the positions of the objects relative to the patient) (Doricchi & Galati, 2000) frame of references. JR had bilateral lesions, presumably each side impaired different spatial processing, leading to opposite visual neglect pattern (see Heinke & Humphreys, 2003, for an explicit simulation).

The behavioural evidences for a dissociation between different forms of spatial processing is supported by neuroanatomical evidence. Patients showing egocentric and allocentric neglect have different sites of lesion – with egocentric neglect associated with more anterior brain regions including the inferior frontal and superior temporal gyri and allocentric neglect linked to lesions of the middle temporal and angular gyrus (Chechlaz et al., 2010); see also (Hillis, 2005; Verdon et al., 2010).

It has been assumed that cancellation task primarily reflects egocentric neglect (as asymmetry is measured relative to the body midline) while line bisection, figure drawing and copying reflect allocentric neglect (as asymmetry is measured relative to the object (Chechlacz, Rotshtein, & Humphreys, 2012).

New version of cancellation tasks was developed to differentiate between allocentric and egocentric neglect. In this task (Bickerton, Samson, Williamson, & Humphreys, 2011), distracters are defined based on asymmetric features. For example, in the apple cancellation tasks (Bickerton et. al., 2011), the targets are full-complete apples, but the distracters can be apples that miss a part in their left or right side. Allocentric neglect is diagnosed by asymmetric false detection of one-sided distracters (see 3.2.1.1. for details).

The classification of allocentric and egocentric neglect were used in the thesis as the spatial characteristics of the symptoms. I asked whether the errors pattern of reading and working memory matches the frame of reference classification of the disorder.

Caramazza and Hills (1990) (see also other more recent Marsh and Hillis (2008)) proposed a further distinction between egocentric, allocentric and 'object-centred' processing. In contrast to egocentric and allocentric neglect object centred visual neglect is informed by stored knowledge of the parts in relation to the conventional orientation of an object. In other words, while ego- and allocentric neglect are driven by attention to the sensory input (bottom up), object-based neglect is an example of a representational neglect (see 1.1.2.4.) where the deficits occur when processing active representation in working memory, after the object has been rotated. In support of this, Caramazza and Hillis (1990) reported a patient who showed neglect of the letters at the right ends of words not only when the words were upright but also when they were inverted (when the right-side letters fell on the left side of the stimulus – and so would fall on the left in both egocentric and allocentric space). The evidence for this triple dissociation is examined in the study case, reported in CHAPTER 4.

1.1.2.2. Visual Extinction and Visual Neglect

Visual extinction is a type of perceptual deficit that commonly observed following right brain injury. While patients with visual neglect may fail to attend or to respond to stimuli in contralesional space, patients with extinction can attend or report a single target presented at any location but they fail to report when items are simultaneously presented on both sides of their body, when there is no primary sensory deficit (Kerkhoff, 2001). As such, all visual neglect patients will also fail visual extinction tasks, but not vice versa.

There is a debate in the literature of whether visual extinction is a mild form of visual neglect (Kaplan et al., 1995). Function lesion mapping studies suggest that spatial neglect and extinction are dissociable (Becker & Karnath, 2007; Vossel et al., 2011). Injury to the temporo-parietal junction (TPJ) is regarded as the most reliable predictor for extinction (Chechlacz et al., 2013; Karnath, Himmelbach, & Kuker, 2003); right inferior parietal cortex (Vossel et al., 2011); while visual neglect associated with additional lesions extending to angular gyrus and superior temporal gyrus (Chechlacz et al., 2012).

However, for the purpose of the thesis, distinction was not made based on the nature of visual spatial impairment whether it is neglect (failing to detect stimulus) or extinction (failing to select objects among competing items). It is also worth noting that most clinical tests for visual neglect assesses spatial bias in the context of competing stimuli (e.g. cancellation tasks, copy figures).

1.1.2.3. Neglect Dyslexia

Neglect dyslexia (Ellis et al., 1987; Lee et al., 2009; Moore & Demeyere, 2017; Riddoch, 1990; Vallar et al., 2011) describes a sub-group of neglect patients showing an asymmetric pattern of reading errors. Neglect dyslexia patients produce reading errors in the contralesional part of single real words, non-words, sentences and text. Omissions are the most commonly reported errors, substitution next and the least common is additions (Arduino et al., 2002; Caramazza & Hillis, 1990).

It is debated whether neglect dyslexia should be viewed as a dissociated symptom of visual-spatial attention (Moore & Demeyere, 2017). It is further debated whether neglect dyslexia emerges at the perceptual level due to inability to orient and control attention in the external space, or it emerges at the mental representation space due to deficits the internal orienting system of attention (Vallar, Burani, & Arduino, 2010), therefore linked to representational neglect, see below. CHAPTER 4 presents a case of neglect-dyslexia.

1.1.2.4. Representational Neglect

Representational neglect is reported when a patient fails to report features on the contralesional side of an imagined scene (Beschin et al., 1997; Bisiach & Luzzatti, 1978; Bartolomeo et al. 1994). Historically, visual spatial neglect was argued to be caused by deficits at the representational rather than perceptual level (Bisiach and Luzzati, 1978). More recent evidences suggest that representational neglect is a sub-classification. Cases of patients with visual neglect in the absence of representational neglect are reported in the literature (see Bartolomeo, D'Erme, & Gainotti, 1994; Cantagallo & Della Sala, 1998 for details). It is estimated that 25 % of patients with visual neglect also show representational neglect (Kerkhoff, 2001).

Riddoch and Humphreys (1987) proposed that visual neglect emerges from deficits in attention to external stimuli which is distinct from spatial biases when coding of sensory information. The observation that valid cues ameliorate visual neglect symptoms shows that the deficits is at the perceptual and not representational level (Riddoch and Humphreys, 1987). Representational neglect is suggested to be a special case whereby neglect symptoms impair activation of stored internal representations and not just the more common representation of external stimuli (Bartolomeo & Chokron, 2002). Other argued that representational neglect occurred due to damage to temporary storage systems of visuo-spatial working memory, and hence does not to reflect an attentional deficit (Della Sala et al., 2004).

1.1.2.5. Motor and Tactile Neglect

Motor neglect is referred as under-use of limbs on the contralesional side without any primary strength deficits (Laplane & Degos, 1983). These patients may show lack of spontaneous or automatic limb use, but they are able to move the limbs when attention is drawn to them, for example by using a verbal command (Barbieri & De Renzi, 1989). The functional outcome of motor neglect is that patients, who may have active voluntary movement a limb, are still incapable to use the limb for functional activity, and they may need to be cued to use the limb. Similarly, tactile neglect is inability to detect tactile stimuli stimulating contralesional body parts, in the absence of motor-sensory deficits. This classification is based on motor/tactile-spatial features of the symptoms, it is irrelevant to the current thesis and will not be discussed further.

1.1.2.6. Proximity to Body

Proximity to the body (personal space) was also suggested as sub-classification of neglect patients (see Heilman, Watson, Valenstein, & Karnath, 2002; Vallar, 1998). Patients with personal neglect fail to attend to contralesional side of their body, those with peri-personal space neglect fail to attend the contralesional side within reaching distance and those with extra-personal space failed to attend contralesional side beyond the reaching space (extra-personal space) (Beschin & Robertson, 1997; Buxbaum et al., 2004). This classification is based on motor-spatial features of the symptoms, it is irrelevant to the current thesis and will not be discussed further.

1.1.3. **Comorbidities of Deficits in Visual Spatial Neglect?**

Attention is considered as a core function in cognition (Posner and Peterson, 1990, 2012). Fodor (1983) defines attention as a horizontal faculty (process), like memory, by which he means that attention is utilised independent of content and it is not a module. As modules are designed to process specific content and input (e.g. speech, reading, faces, objects). It is agreed that attention plays a key role in many cognitive operations. Hence it is not surprising that many comorbidities have been reported alongside visual-spatial neglect.

Visual neglect most often co-occurred with other clinical features such as anosognosia (denial of illness) (Hartman-Maeir et al., 2003), hemianopia (blindness in one half of the visual field of one or both eyes) (Cassidy et al., 1999), difficulty in sustained attention, phasic alerting, very slow response times and spatial memory (Husain & Rorden, 2003a). Others comorbidities were also reported like, patients who suffer from visual neglect may also show visual agnosia symptoms, the inability to recognise objects (Mattingley et al., 1998; Warrington & James, 1988); difficulty to initiate movement of contralesional limbs in the absence of hemiplegia refers to as motor-neglect (Laplane & Degos, 1983), auditory inattention symptoms (Sinnett et al., 2007) and aphasia (De Witte et al., 2008; Hreha et al., 2017)

It should be noted that the literature is inconsistent in the way other symptoms that co-occur with visual neglect are defined. Occasionally these will lead to a definition of a sub-section of neglect, especially if these deficits have an ipsilesional spatial bias characteristic: e.g. neglect dyslexia, motor dyslexia, auditory dyslexia, representational dyslexia. In these cases, it is assumed that the visual-spatial deficits cause deficits in other domains. It is often reported that presence and severity of visual neglect hinder rehabilitation. For example, this has been reported for motor functions (Chen et al., 2015), language abilities (Hallowell et al., 2004) and activities of daily living (Chen et al., 2015; Kalra et al., 1997).

In the current thesis, I choose to focus on two cognitive functions: reading and working memory. It should be noted that the prevalence of co-occurring/comorbidities of non-spatial cognitive symptoms in patients who suffer from spatial neglect is rarely reported or systematically examined. Next, I briefly describe the rationale of why I choose to focus on reading and working memory. In a nutshell, reading is a language based visual and content specific perceptual process with some embedded spatial elements. While visual working memory can be applied to different representational contents and does not have to include spatial information. Thus, these two cognitive functions offer different theoretical perspectives on potential comorbidities of visual spatial neglect.

1.1.3.1. Why Visual Neglect and Reading

Reading is the cognitive process that enables to decode meaning out of graphemes (letters that make words and sentences). It requires an ability to process linguistic information that is visually presented and become familiar with the writing system. It is a visual dedicated process to a specific content. Given that reading is a learned ability, it is debated whether we develop a module for reading (Dehaene & Brannon, 2011) or it is mastered by adjusting related processing capacities (Price & Devlin, 2003).

Reading requires some spatial processing. In phonological writing system, a word is decoded based on the relative location of individual letters. Comprehending a sentence also requires systematic scanning of the visual field. In English reading will progress from left to right (from contra to ipsilesional for right neglect patients, the preferred scanning pattern for patients). Though also in English, when reading an entire paragraph, attention needed to be shifted across both directions (within a line of text and across lines).

The neural correlates of reading are primarily identified within the left hemisphere (Martin et al., 2015). This is not surprising, as language processes are predominantly located within the left hemisphere.

The spatial processing requires for reading suggests that deficits in orienting attention in space are likely to affect reading ability (as the cases of neglect dyslexia, see 1.1.2.3). However, the laterality divergent of reading/language and attention to left and right hemisphere, respectively make the likelihood of comorbidity low.

1.1.3.2. __Why Visual Neglect and Working Memory__

Working memory is a temporary storage of information to enable further mental manipulations of it (Baddeley, 1992). Like attention it is consider a core function, horizontal process (Fodor, 1983), which is not content specific and can be applied and used in different domains. There are theories that postulates different working memory storages for different types of information, that verbal working memory involves the left hemisphere and spatial and visual working memory involves the right hemisphere (Wagner et al., 2009).

The theoretical link and clinical evidence supporting relations between working memory (especially of visual and spatial working memory) and spatial attention deficits are strong. As discussed above, the case of representational neglect (see 1.1.2.4); and below (1.3.2), where I introduce theories that postulate that visual spatial neglect symptoms emerge from deficits in processing the mental representation of information. Thus, there is a high likelihood of comorbidity of visual neglect visual and spatial working memory, but low likelihood with verbal working memory.

1.2. Theoretical framework: Peterson and Posner's Attentional Systems

The current thesis uses Posner and Petersen's (2012; 1990) theoretical framework of the attentional systems, when describing attentional deficits in visual spatial neglect. The authors introduce the neuro-cognitive attentional systems model. Their theoretical framework relied on three central assumptions: i) Different anatomical regions of the brain carry out specific cognitive operations. The attention systems are regarded as functionally and anatomically independent systems from those that are responsible for processing stimuli, making a decision and acting upon them. In another word, there is a cognitive and anatomical distinction between processing like sensory, perception, memory decision making and attention. But importantly attention interacts with all these other processing systems. ii) There are no single anatomical foci for attention processing in the brain, and attention is not a single generic function of the brain. iii) Attention consists of several interconnected neural networks (systems). Each has a specific cognitive function.

Posner and Peterson (1990, 2012) listed three distinct but interconnected neural networks of attention: 1) *the alerting network*, which includes mechanisms for alertness, vigilance, and arousal (the 'intensive' attention) including sustained attention, an ability to stay focus. The alerting system concerns with *when* stimuli happen. Strum et al. (1997) suggested that the alertness and vigilance are the most fundamental function in the hierarchy of attention. In other words, deficits in alertness will exacerbate impairments to the other attentional components. This network can be separated into phasic and tonic alertness (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Posner & Petersen, 1990). The phasic alert is triggered by an onset of a stimulus (an alert cue) which prepares the sensory systems to process incoming stimuli. Phasic alertness is the ability to increase arousal and vigilance in response, for example, to threat signal. Phasic alertness is mediated by the release of Norepinephrine (NE) from the locus coeruleus in the brain stem and thalamus, which targets areas in the dorsal fronto-parietal cortices. Behaviourally, it is measured as the ability to respond to alert cues. Tonic alertness is the ability to sustain attention over time and reflects the ability to stay focus on the task. It is associated with sleep-awake cycles and is partly mediated by the thalamus and the circadian cycles. Tonic alertness is measured using vigilance tasks. It is suggested that the right hemisphere and thalamus play a crucial role in both phasic and tonic alertness.

Neglect patients are reported to benefit from alert cue (Robertson et al., 1998), suggesting their phasic alert mechanism is intact. For example, Erez, Soroker and Katz (2018) found that phasic alerting combined with visual spatial training produced promising results in ameliorating visual spatial neglect syndrome. These results were also supported by other studies (Robertson et al., 1995, 1997, 1998). In contrast, neglect patients show impairment in tonic alertness, as measured by sustain attention tasks (Husain & Rorden, 2003; Parton, Malhotra, & Husain, 2004b). Robertson and colleagues (1995) showed that using a behavioural technique that improves sustain attention (been engaged in sorting coins and cards), attentional deficits among neglect patients can be ameliorated.

The orienting network, which involves shifts of attention in space by disengaging the focus from the first location, and re-engaging attention at another location in space (the 'selective' attention). The orienting system is concerned with *where a* stimulus is in space. Though it is suggested that orientation is not confined to sensory stimuli and can also relate to the shifting of attention in more abstract spaces (e.g. along a number axis). The orienting system is responsible for directing processing resources in space based on exogenous and endogenous cues (Posner & Petersen, 1990). For example, in the classic Posner paradigm, an arrow is used to direct attention to the correct or incorrect target location, valid or invalid cue (Posner & Cohen, 1984; Posner, 1980). Therefore, two orientation systems have been defined, both involving regions with the frontal and parietal cortices and both are more dominant in the right hemisphere. A more dorsal network supports the response to targets at expected locations (valid cues) and a second a ventral network which involve attention disengagement, or response to a target in an unexpected location (following invalid cues). The orientation system is primarily driven by the neuromodulator acetylcholine (ACH). Despite similarity in neuro-anatomical in the neuroanatomical substrates of the attention and alerting systems, the authors suggest that the two networks are dissociated based on the following evidence: i) Drugs affecting NE modulate alert but not orient responses; and drugs affecting ACH modulate orient but not alert; ii) Alert and orient responses are largely uncorrelated within and between participants. Impairment of this attentional network is the most dominant model for visual spatial neglect (see 1.3.1.).

T*he executive network* mainly exercises cognitive control. The executive function component is non-spatial: it includes the ability to monitor, to plan, to solve conflicts and to allocate attentional resources based on the observer goals while inhibiting responses to non-targets (Fernandez-Duque & Posner, 2001). This network is important as it acts as a conflict resolution between disagreeing thoughts, feelings, and responses (Petersen & Posner, 2012; Posner, 2008; Posner & Petersen, 1990). It is suggested to involve frontal regions with a potential distinct role for midline and dorsal lateral prefrontal structures. Behaviourally, the executive attention network is studied by instructing a subject to respond to one aspect of a stimulus (target) while ignoring others (distracters) (Fan et al., 2005). Neglect patients have been reported to be slow in detecting targets both on the contra and ipsilesional hemifields. The ability to ignore distractors has also been reported to be impaired in neglect patients (Mevorach et al., 2014).

According to this model, the orientation systems modulate spatial processing, as attention 'move' through space; while the non-spatial features of attention include the alertness and the control systems. It is important to note that the original model (Posner & Petersen, 1990) was guided and informed by evidence emerging from visual neglect patients and other neuropsychological cases with a disrupted visual attention mechanism. There is evidence suggesting that neglect is associated with impairments to both spatial and non-spatial components of attention. It is, therefore, possible that comorbidity of reading deficits in neglect emerge from a variety of attentional deficits.

The current thesis assesses whether cognitive deficits experienced by visual neglect patients are restricted to the orientation system – characterised by contralesional spatial bias. This was done by examining the error pattern observed in reading and memory and also by assessing non-spatial attention components in visual neglect patients.

1.3. Predictions Based on Theories of Visual-Spatial Neglect Syndrome

1.3.1. Attentional and Orientation Spatial Deficits

The most common account for visual neglect is that in these patients, the attentional orienting system (see 1.2) malfunctions. The spatial impairments associated with neglect are due to difficulties in distributing attention evenly over space (Behrmann & Geng, 2002; Kinsbourne, 1993). A spatial attention gradient bias is reported in visual neglect, whereby the ability to selectively attend and respond to stimuli decrease as one moves from ipsilesional to contralesional locations in space. The spatial bias is shown to be the most robust and reliable factors associated with the syndrome (Azouvi et al., 2002).

It is hypothesised that the spatial biases emerge due to hyper attention towards the ipsilesional side, typically the right side of the field for right brain lesions (Kinsbourne, 1987; Ladavas, 1990). Such patients can show 'a magnetic attraction' to stimuli on the right side (De Renzi et al., 1989). This is because it is assumed that each hemisphere is "responsible" for processing and representing information from the opposite visual field. Impairment to one side of the brain leads to dampening of the saliency of stimuli presented in the contralesional side, coupled by increased perceptual saliency of stimuli in the ipsilesional field due to lack of lateral competition from the damaged hemisphere.

According to Posner and Peterson's (1990, 2012) attentional systems framework (see 1.2), visual neglect emerges from impairment to the ventral attentional orientation system. Impairments to the ventral orientation system are also supported by the observation of the inability patients to shift attention away from the ipsilateral side (Losier & Klein, 2001; Posner, Walker, Friedrich, & Rafal, 1987). For example, using the classical 'spatial cueing' Posner paradigm (Posner et al., 1984) it is shown that patients with posterior parietal lesions were not impaired in detecting a stimulus in the contralesional visual field when it was preceded by a valid cue but showed marked impairment when preceded by invalid cue (cue directing attention to ipsilesional side). Other studies by the same group (Posner & Cohen, 1984; Posner et al., 1987) have noted, however, that a disengaged deficit has been observed in patients with parietal lesions without neglect or extinction, so it is unclear whether the disengagement problem is a necessary or merely contributory factor to neglect. The impact of stimulus saliency on spatial attention biases was tested in the case studies CHAPTER 2: and 7.4.

Theories that attribute visual spatial neglect symptoms to biased spatial attention, predict that any behavioural or cognitive performances that are affected by attentional deficits should show a similar spatial bias gradient. Relevant to this thesis, it was expected that reading and working memory deficits should be more pronounced in contralesional than ipsilesional side. These questions were directly addressed in the meta-analyses' chapters CHAPTER 2 and CHAPTER 6. The theories also predict that the frame of reference of the spatial bias (allocentric and egocentric) would affect the error pattern. This question is assessed by the meta-analyses and database analyses chapters.

1.3.2. **Spatial Representational Account**

A classic account proposed by Bisiach and Luzzati (1978), argued that visual neglect is a disorder of mental representation, e.g. visual short-term memory, working memory. In their topological space representational model (Bisiach & Luzzatti, 1978; Bisiach, Capitani, Luzzatti, & Perani, 1981), the authors postulated that every sensory event is coded by a mental map, this mental representation can be activated either through sensory afferents or by retrieval from memory (see Kerkhoff, 2001). In Bisiach et al.'s classic study (1981), two patients with right-sided brain damage described a scene of a familiar Italian plaza from memory. When facing the cathedral in the Plaza the patients described building on their ipsilesional side omitting buildings on the contralesional side. When asked to stand with their back to the cathedral, now describing the same scene from the opposite side of the square, they managed to describe previously ignored building, as these were now on their ipsilesional side. The authors suggested that neglects result from a disruption to internal representations of space.

Others have argued for a large overlap between mental representations in short-term visual memory, attention and perception (Kristjánsson & Vuilleumier, 2010), suggesting that these reflect similar underlining neural coding. Given that perception is likely to be the gatekeeper of visual short term memory component, it is not surprising that representational neglect is almost always present with perceptual neglect (Bartolomeo et al., 1994), though see (Kerkhoff 2001).

The question of whether neglect deficits emerge at the representational or perceptual level will be addressed in CHAPTER 2: in the case of neglect-dyslexia and also in Part Two when I specifically examine comorbidity of visual spatial neglect and working memory.

1.3.3. **Remapping Deficit Hypothesis**

Recent development of the representational theory suggests a way to merge the attentional maps and the representational account through the process of remapping (Husain et al., 2001a; Pisella & Mattingley, 2004). Remapping is the process that enables us to perceive a clear and detail environment despite sparse sampling at any given moment of sensory information. To a healthy observer, the visual perception of the environment is much clearer and detailed than the information that is sensory available. At any given moment, an only a small fraction of the environment (around the fixation point) is perceived in fine details and in focus. It is suggested that we build the rich and stable perceptual experience through integrating a snapshot of the environment extracted through multiple saccades. Remapping is the process by which any new clearer sensory input extracted by current fixation is correctly mapped to the already existing visual perceptual map. This map is located in the parietal cortices. Remapping feeds into the saliency map highlighting potentially ‘relevant’ and important locations in the environment (Pisella & Mattingley, 2004). It is argued that the process of remapping is impaired in visual neglect patients. Visual neglect patients fail to integrate information from current saccade into an existing map. This is evident by repeat re-fixation on crossed targets (Husain et al., 2001a; Wojciulik, Husain, Clarke, & Driver, 2001) during a cancellation by neglect patients relative to healthy controls. Vuilleumier and colleagues (2007) examined patients' ability to retain location information in memory for a short delay (2-3sec). Patients fixated on a target which was presented on the left or right of the screen. Once the target was identified and fixated, it was removed from the screen. In the remapping condition, during the delay period patients were asked to shift their attention to detect a letter at one corner of the screen. After a delay, a probe appeared in the same or different location as the original target. The authors show that patients’ ability to hold in memory the target location dropped from 80% during the no remapping condition to 20% when the gaze was shifted to the ipsilesional side. Taken together, previous literature suggests that visual neglect may emerge from failure to integrate and maintain information in short term visual memory based on multiple saccades.

Part Two assessed the nature of working memory impairments in visual spatial neglect. The case studies presented in CHAPTER 6, specifically addressed the remapping hypotheses.

1.3.4. **Spatial and Non-Spatial Visual Attentional Deficits**

Accumulating views argue that visual neglect reflect a combined damage to spatial and non-spatial attentional networks (Corbetta & Shulman, 2011; Priftis et al., 2013; Robertson, 2001). Corbetta and Shulman (2011) argue that visual neglect has spatial and non-spatial core components. They suggest that the high prevalence of visual neglect following right hemispheric lesion can only be account by the involvement of the non-spatial core components, which are predominantly localized to the right hemisphere. The core spatial component is associated with malfunctioning of the dorsal fronto-parietal attentional networks, leading to the bias seen in spatial and saliency maps. The non-spatial component is associated with damage to the ventral attentional systems (which is primarily in the right hemisphere). Disruption to the ventral attentional system is reflected by symptoms such as reduced arousal, inability to reorient and detect relevant events in the environment. Impairments in any of these systems primarily the ventral attention system has a knock-on effect on the ability of the other system to function.

1.4. Current Thesis Structure

The current thesis aimed to test whether visual neglect is associated with impairments to spatial and/or non-spatial attentional systems. This is done by examining deficits comorbidities and testing whether the nature of the comorbidity's deficits reflects spatial biases. I focus on two spatial bias features: the visual field (ipsilesional vs. contralesional) in egocentric space, and the frame of reference (egocentric vs. allocentric). The thesis focused on two comorbidities with visual neglect: reading (Part One) and working memory (Part Two). In each part, the prevalence and nature of the comorbidity is tested using three different methodological approaches (chapters): i) meta-analyses of previous literature, ii) analyses of existing large databases of stroke patients from the UK and China, and iii) case studies that examine specific theoretical question on the nature of the relations between the two cognitive functions.

Classification of visual neglect - across the thesis (apart from the case studies), patients were classified as suffering from visual neglect if they showed impairment in at least two tests that assess visual attention impairment (see 1.1.1.).

PART ONE: VISUAL-ATTENTION AND READING DEFICITS

Patients who suffer from visual neglect often show reading difficulties (Moore & Demeyere, 2017). This is surprising as visual neglect is typically associated with damage to the right hemisphere, while reading, as part of the language system, is typically associated with lesions to the left hemisphere. One hypothesis, associated reading deficits to the malfunctioning of the attentional systems. In line with the dominant view that neglect is primarily a deficit of the spatial orientation attentional system, it has been hypothesised that reading errors in neglect are associated with patients' spatial bias, termed neglect dyslexia (Ellis, Flude, & Young, 1987; Lee et al., 2009; Moore & Demeyere, 2017; Riddoch, 1990; Vallar, Burani, & Arduino, 2011). Posner et al. (1988) argued that spatial neglect difficulties emerge from problems to shift attention from right to left while shifting attention from left to right is normal. Given reading behaviour (at least in English or Italian languages) always begins by the left side it would be predicted that generic reading difficulty would not be expected in a visual neglect patient in these Latin-based languages.

On the other hand, accumulating evidence suggests that attention deficits of neglect patients are not confined to spatial deficits (see above). Despite decades of research into the cognition and neural mechanisms of the asymmetrical reading deficit, very little is known about the comorbid reading dyslexic deficit in visual neglect patients. Therefore, I first examined the prevalence of reading errors following acquired neglect. Second, I tested whether reading errors in neglect are associated with the nature of the spatial deficits, specifically in relation to the asymmetry in spatial attention, and attentional frame of reference. Finally, I present a case study of neglect dyslexia, where I tested the impact of non-spatial manipulation of the letters' fonts and configuration on his reading abilities and error pattern.

I. **Visual Neglect and Reading**

The dominant hypothesis associated reading deficits, made by visual neglect patients, to the malfunctioning of the orienting system. This predicts asymmetry in reading deficits (Ellis et al., 1987; Lee et al., 2009, 2009; Moore & Demeyere, 2017; J. Riddoch, 1990; Giuseppe Vallar et al., 2011), leading to a symptom called neglect dyslexia (Ellis et al., 1987; Lee et al., 2009; Moore & Demeyere, 2017; Riddoch, 1990; Vallar et al., 2011), see 1.1.2.3. In this part, the meta-analysis (CHAPTER 2) assessed whether reading deficits reported for neglect patient are driven by their spatial bias. In CHAPTER 4, I presented a case of neglect-dyslexia, where I explored in details the potential source of their reading deficits symptoms.

A few theories were proposed in an attempt to explain reading deficits in patients showing visual neglect symptoms. These theories focus on the spatial bias characteristic of the feature.

A. A Multi-Stage Model of Word Recognition (Caramazza and Hillis (1990)

Caramazza and Hillis (1990) stated that visual word recognition takes place in a number of stages, in which increasingly abstract representations of words are computed (see also Monk (1985), for an earlier account). The first stage involves retinotopic coding of the features making up the letters in the words (a retino-centric feature map). This is followed by the representation of letter shapes in a representation centred on the stimulus (a stimulus-centred, letter-shape map), and finally the derivation of a word-centred description of the graphemes in the word and their relative positions (a word-centred grapheme description).

Differences between these representations may be illustrated using an inverted word (ЯIAHƆ) presented in the left visual field (see Figure 0.1). It is assumed that the ability to group the features to letter relies on prior knowledge of letter forms this potentially also support the mental rotation process required when words are presented in mirrored orientation.

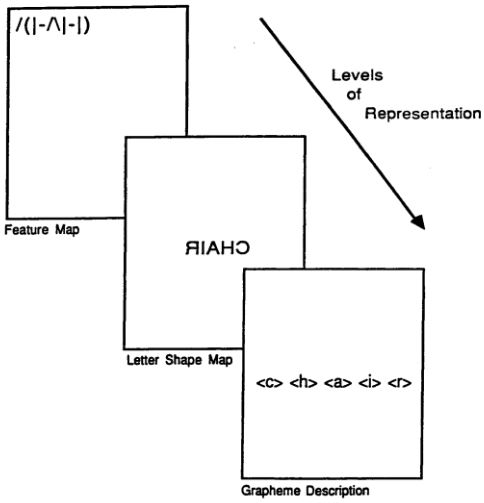

Figure 0-1. Illustration of levels of representation in visual word recognition for a mirror-reversed word, presented in the upper right quadrant of the visual field. The upper left panel is the first level of analysis (a retino-centric feature map), followed by the middle panel (a stimulus-centred letter shape map) and finally is the lower right panel (a word-centred grapheme description). (after Caramazza & Hillis, 1990).

According to this model, it can be predicted that patients who have any type of spatial biases will struggle to recognize letters and group them already the feature map stage, where features are presented using a retinotopic map. This effect maybe magnified in those with egocentric symptoms than those with allocentric; as patients with allocentric symptom may not perceive the features as part of a single object. Furthermore, Caramazza and Hillis (1990) word recognition model offer a possibility for a dissociation between stimulus and word-centred representational stages, especially when words are presented in mirrored orientation. For example, left biased attention neglect the right side would affect the beginning of the words in a stimulus-centred display (‘re’) and the end of the word (‘ing’) in a word-centre display (see Figure 0.2).

In support of the above hypothesis, Caramazza and Hillis (1990) reported patient NG left-hand dominant woman who suffered damage to the left parietal region and basal ganglia following a stroke (the uncommon type of visual neglect). She subsequently presented with neglect dyslexia failing to read the right side of words. NG generated right-side errors even when words had a vertical orientation and when they were mirror-reversed. Caramazza and Hillis attributed this deficit to spatial damage to the right-side of a word-centred graphemic representation, after the features were grouped to letters, and the letters were mentally rotated. In other words, the spatial bias affected the representation of the word rather than its perception. There are also issues about whether common representations are used in word reading and spelling. In the patient reported by Caramazza & Hillis (1990), with apparent word-level impairment, the same errors occurred when the patient read and the word and when words were spelt orally and in writing, suggesting that her errors were due to a deficit in gaining access to a common representation used for lexical input and output.

But not all patients with neglect-dyslexia show deficits at the word-centered representational level. Haywood and Colheart (2001) reported a case were neglect dyslexia was attributed to the level of the stimulus-centred letter-shape map. RR suffered infarcts in the left fronto-temporal and left temporo-parietal areas (again the les common visual neglect lesions). His errors were confined to the spatial reference frame in which the representational space is bounded by the stimulus, in other words reflect the spatial bias at the level of the visual field rather than the object space, as no errors were recorded when the words were presented vertically.

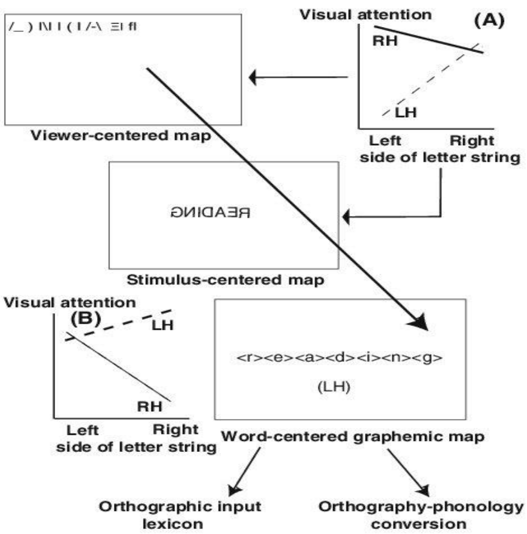

Figure 0-2. A model of neglect dyslexia consisting of three levels of Hillis & Caramazza coordinate frames (1995) and two hemispheric patterns of the lateral distribution of spatial attention/representation. LH=left hemisphere; LH=left hemisphere (adapted from (Vallar et al., 2011, p.232)

B. The Interactive Attentional System (IAS) (Humphreys & Riddoch,1993)

The interactive attention system (IAS) suggests that 'visuospatial attention' system interacts with the multilevel word recognition system. The visuospatial attention acts independently and relies on three main functional nodes: These are: internally driven selection, externally driven selection, and sustained attention (see also Corbetta & Shulman, 2002, for a related neural-level proposal). Thus, IAS suggests that reading deficits observed in patients who experience in visual spatial symptoms are not because of impairment in the word recognition process, but because core and independent attentional related processes which controls information processing are malfunctioning. This IAS therefore predicts that patients with visual neglect would show reading deficits due to impairment in their selection and sustain attention processes.

CHAPTER 5 will specifically assess whether reading impairments in patients who suffer from visual spatial neglect can be attributed to malfunction of word recognition process, or are due to impairment in attentional processes that interacts with word recognition. This will be achieved by manipulating the stimulus presentation format – which should primarily affect attention but not word recognition. The visuospatial representation is akin to the saliency map (see General Introduction), and hence guides attention to the relevant information in the scene. In the context of reading, it means that features that are visually salient can impact reading abilities, through modulation of the representational maps in words recognition model by the visuospatial maps.

II. **Attention in Developmental Dyslexia**

Similar to the IAS model (Humphreys & Riddoch,1993), attention has been hypothesised to play a key role in developmental dyslexia (Hari, Renvall, & Tanskanen, 2001). The sluggish attentional shifting (SAS) theory hypothesis that developmental reading difficulties emerge from an inability to control and shift attention (Hari et al., 2001) as well as overall slowed processing of reading materials. This hypothesis is supported by evidence showing that performances are worse when words are presented in rapid sequence (Lallier et al., 2010). Furthermore, individuals with developmental dyslexia are reported to show 'minineglect' symptoms, with slower performances for stimuli presented on the left hemifield (Hari et al., 2001) and decreased of the 'normal' biased toward the left hemifield in a line bisection task (Sireteanu et al., 2005). Thus, developmental theories predict that despite potential spatial bias in attention, reading errors would not show an asymmetric spatial pattern.

III. **Chapters Overview**

The aim of this part was to systematically assess comorbidity of visual neglect and reading deficits and to test whether these are related to the spatial bias associated with the syndrome. CHAPTER 2 is a meta-analysis of previous literature. As I have identified that previous studies were at risk of sampling and measurement bias, CHAPTER 3 examines the relation between visual neglect and reading in two large databases of sub-acute stroke patients. One cohort from the UK and a second from China. These databases were created to validate a cognitive screen test for stroke, the Birmingham Cognitive Screen (BCoS), and as such are not biased in the way stroke patients were recruited. The BCoS also provides measures of spatial and non-spatial components of attention and hence enabled me to test which attentional component best explained the reading performances. CHAPTER 4 presents a case study of a patient who showed severe neglect-dyslexia. The chapter presents a systematic test of the hypothesis that neglect dyslexia emerges from damage to the attentional system, specifically to visuo-spatial maps, aka their saliency map.

CHAPTER 2: THE META-ANALYSIS OF READING DEFICITS IN VISUAL NEGLECT

2.1. INTRODUCTION

The aim of CHAPTER 2 was to test whether reading deficits are a common feature of visual spatial neglect (Study 1). Study 2 and 3 specifically assessed whether reading deficits relate to the spatial bias typical to neglect syndrome. The current chapter used a meta-analysis approach to answer three questions. In study 1, we asked whether generic attention deficits (sluggish attention, see Part One, II) account for reading deficits in acquired neglect. To this end, we compared the number of reading errors in neglect patients relative to standardised data, matched healthy controls and neurological patients without neglect. We classified patients as suffering from neglect if they failed at least two of the neglect tasks (presented in **Error! Reference source not found.**.): cancellation task, line bisection, and copying scene tests (i.e., Halligan, Wilson, & Cockburn, 1990; Kerkhoff, Münßinger, Haaf, Eberle-Strauss, & Stögerer, 1992; Kuhn, Heywood, & Kerkhoff, 2010; Weinberg et al., 1977). In study 2, we asked whether deficits in the orienting system underlie reading errors in neglect patients, as hypothesised by the neglect dyslexia model (see 1.1.2.3). This was tested by assessing the number of errors made in each hemifield within each neglect patient. Finally, study 3 further investigated the hypothesis that reading disorder is related to the nature of the orienting deficits, by examining reading errors relative to the frame of reference (see 1.1.2.1). We first compared reading errors in neglect patients who showed reliable egocentric neglect (i.e., failed at least two cancellation neglect task) vs. those who did not show it. Next, we compared reading errors in neglect patients who showed a reliable allocentric neglect (i.e., failing in line bisection, figure copy) as opposed to those who did not show this deficit (see Driver & Mattingley, 1998; Halligan, Fink, Marshall, & Vallar, 2003; Heilman, Valenstein, & Watson, 1994; Parton et al., 2004a) We included all the data from all relevant studies reporting reading performance of visual spatial neglect patients. We considered four types of reading tests. The most common tests are reading single words and reading meaningless pronounceable letter strings, also known as non-words. Less common used in research are tasks that requires reading sentences, texts or passages of proses, even though the latter is regarded as more sensitive diagnostic tools (Siéroff, 2017) and most commonly used in the clinical assessment of visual spatial neglect (Pizzamiglio et al., 1989; Towle & Lincoln, 1991). Note that both non-words reading and sentence reading heavily relied on an ability to orient attention in space along a horizontal axis. Reading single words in proficient readers (adults), may utilise both phonological readings (phoneme at a time) or recognise the word as a whole 'object'. Hence, I predicted that in these tasks the egocentric spatial bias deficits will be most pronounced. Allocentric spatial biases should impact all the tasks in similar way.

2.2. <u>MATERIAL AND METHODS</u>

2.2.1. Literature Search

For the objectives of the current study, we conducted a systematic literature search to identify relevant studies that reported the reading performance and visual spatial neglect symptoms. This was done in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Moher et al., 2009) see Figure 2.1. The selection protocol was written prior to the current study.

Five electronic databases were searched: Four databases through the OVID platform: EMBASE (1974 to July 5th, 2018), MEDLINE (1946 to July 5th, 2018), PubMED (1966 to July 5th, 2018) and PsychINFO (1967 to July 5th, 2018). Another database is the ISI WEB of SCIENCE Core Collection, (1900 to July 5th, 2018). The search keywords and terms were used: (read* OR alexia* OR writ* OR agraphia* OR dyslexia*) AND (spatial neglect* OR visual inattention* OR visual extinction*) AND (patient* OR acquired brain lesion* OR brain injur*). In addition, the reference lists of relevant papers and key review papers were also searched. All citations related to reading deficit performance and visual spatial neglect were retrieved and exported to Zotero 5.056 ("Zotero.org | Your personal research assistant," n.d.), a reference manager tool, where duplicates were removed.

2.2.2. Eligibility Criteria

Inclusion criteria: (1) study participants included adults with acquired brain injury (e.g., stroke, traumatic brain injury, tumour or post-operation sequelae) above the age of 18 with a diagnosis of visual spatial neglect; (2) studies included were independent of the time of test post-stroke, (3) both chronic and sub-acute patients were included, though vast majority were chronic. (4) studies included measurements of reading performance. We excluded studies that were: (1) case studies because these do not provide data on variability which is necessary for computing an effect size, (2) review articles, (3) manuscripts that were not peer-reviewed: proceedings, conference abstracts, dissertations, editorials, commentaries, or book chapters; (4) papers that were not in English or we could not gain access to the full text. (5) studies that did not report sufficient data for calculating an effect size. In these last cases, we contacted the authors via emails for a maximum of three times during 2 months period, to request for the missing information. (6) studies that included only sample of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease or any related progressive mental deterioration disease; (7) studies which reported the same data in multiple publications. In these cases, we used the most recently published study. See Figure 2.1 for a PRISMA flowchart.

2.2.3. Data Extraction and Outcome Measures

Next, we systematically extracted the following information from each study: (1) descriptive data (first author, title, year of publication, country of origin); (2) number of subjects in each condition (experimental group and comparison groups such as healthy controls or/and brain-injured patients without neglect symptoms); (3) subjects characteristic (gender, age, and years of education); (4) condition of patient subjects (e.g., right unilateral vascular lesions, cerebrovascular ischemic stroke or right hemisphere stroke); (5) timeline of the brain lesion (i.e., acute, sub-acute or chronic; Fisher and Sullivan (2001)'s criteria); and (6) type of visual spatial neglect test.

The outcome measures extracted were the error scores in the reading tasks. The reading measurement domains included single word reading, single non-word reading, combination single word and non-word reading, sentence reading and text reading. We combined prose reading and article reading under text reading domain. For the purpose of meta-analysis, sample sizes and means and standard deviations of error scores were extracted for each study group (i.e., visual spatial neglect patients, healthy control group and brain-injured patients without neglect syndrome).

2.2.4. Quality Assessment

We used the Cochrane's core risk of bias tool in RevMan 5.3 (The Cochrane Collaboration, Oxford, UK) to assess the risk of bias for all full-text of included studies in data analysis. There were the six established risk of bias domains that were regarded to be of particular importance when assessing overall study quality: (i) selection bias (i.e., random sequence generation and allocation sequence concealment); (ii) personnel bias (i.e., blinding of participants and personnel; (iii) detection bias (i.e., blinding of outcome assessment); (iv) attrition bias (i.e.; incomplete outcome data); (v) reporting bias (i.e., selective outcome reporting); and (vi) other potential sources of bias (such as any important concerns that are not addressed in the other domains) (The Cochrane Collaboration Oxford UK, 2011). Two researchers (NS and NF) involved in this process independently and disagreements were resolved by consensus.

2.2.5. Statistical Meta-Analysis

We performed meta-analysis to assess the strength of reading deficits associated in visual spatial neglect syndrome from different published studies. We used inverse-variance-random effects models to calculate the Hedges' *g* effect sizes in RevMan 5.3 (The Cochrane Collaboration Oxford UK, 2011) for assessing differences of reading performance in each of the five reading tests (e.g. single words, single non-words). We obtained the effect size (the Hedges' *g*) by dividing the mean difference of each measure by the pooled and weighted standard deviations of the participants. In studies that did not include a control group, we computed effect size using a one-sample t-test, assuming, in line with the studies' authors, that controls are unlikely to make errors in simple reading tasks with unlimited time. An estimate effect size (*g*) of 0.2 was considered as being small, 0.5 was considered as a medium, and 0.8 was considered as being large (Zakzanis, 2001). A *P* value of less than 0.05 was considered to be statistically significant.

We assessed the presence of heterogeneity between relevant studies using the Higgins I^2 statistic. The I^2 statistic indicates whether a percentage of the total variation in the effect sizes across relevant studies is due to the heterogeneity or chance (Higgins et al., 2003; Higgins & Thompson, 2002). Higher I^2 values reflected higher levels of heterogeneity. The I^2 value of 25 % was regarded as low heterogeneous, the I^2 value of 50 % was regarded as medium heterogeneous and the I^2 value of 75 % was regarded as high heterogenous respectively. Finally, we visually assessed publication bias using funnel plots using the same software (RevMan 5.3).

2.3. GENERAL RESULTS

2.3.1. Included Studies and Study Characteristic

Figure 2.1 shows the numbers of identified studies obtained from the literature search process. Of all identified studies, 16 studies met the inclusion as specified in the eligibility criteria under the Methods section. One paper (Reinhart et al., 2011) reported the same participants on reading performance as reported in the previous study by the same authors Reinhart et at. (2010). Therefore, we excluded the earlier study. In addition, four studies were excluded after their authors fail to respond to repeated request for additional data (i.e. means and standard deviations data). Table 2.1 below illustrates the key characteristics of all the sixteen included studies in the meta-analysis. Briefly, 56 % of the included studies evaluated reading performance in visual neglect patients with right hemisphere damaged, 13 % had unilateral hemisphere damaged and the remaining 31 % was not implicitly specified.

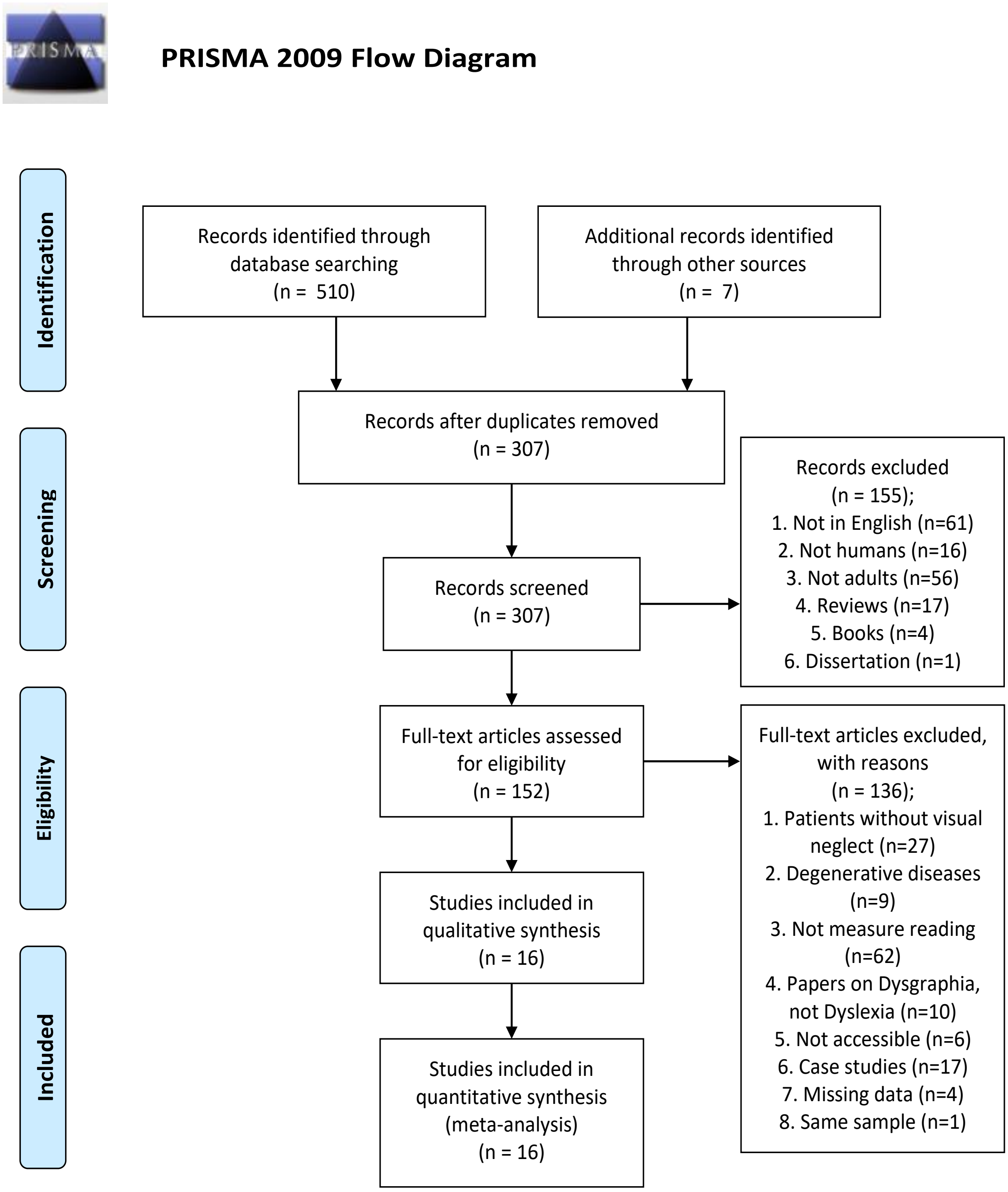

Figure 2. 1. Flowchart of the search process. n=numbers; five databases were searched, 1. MEDLINE (n=70 papers), 2. EMBASE (n=116 papers), 3. PsychINFO (n=57 papers), 4. PubMED (n=111 papers) and 5. The Web of Science (n=156 papers). Additional seven records identified were from the lists of reference of the selected papers.

Table 2. 1. Key Characteristics of Included Studies.

Study/Year/Location	Matched for	Sample					Comparative Group				
		Visual spatial neglect patients									
		Condition	**Age**	**Gender**	**Education**	**N**	**Condition**	**Age**	**Gender**	**Education**	**N**
Arduino, Burani & Vallar (2002), Italy*	No	Cerebrovascular ischaemic stroke (left hemiplegia or hemiparesis), 5 sub-acute & 1 chronic	65 (10.22)	4 M 2 F	11 (3.74)	6	Standardized normative data				
Arduino, Burani & Vallar (2003), Italy*	No	Cerebrovascular ischaemic stroke (left hemiplegia or hemiparesis), 5 sub-acute & 1 chronic	65 (10.22)	4 M 2 F	11 (3.74)	6	Standardized normative data				
Behrmann et al. (2002)	Age & Education Level	Unilateral cerebral lesion, 3 sub-acute & 6 chronic	62 (5.9)	4 F 5 M	11.3 (5.1)	9	Hemianopic patients, All chronic	53.8 (17.9)	3 M 1 F	14.67 (2.89) * (based on 3 patients, one patient not available data)	4
							Healthy controls	59.2 (3.4)	*NR*	13.1 (2.9)	5
Beschin et al. (2014), Italy	No	First stroke in the right hemisphere, Both sub-acute & chronic	62.11 (NR)	17 M 19 F	8.93 (NR)	30	Standardized normative data				
Farne' et al. (2002), Italy	No	Right unilateral vascular lesions, 5 sub-acute & 1 chronic	68 (13.08)	3 M 3 F	11.67 (4.97)	6	Standardized normative data				
Galletta et al. (2014), USA	No	An infarction or intracerebral haemorrhage in the right brain, All sub-acute	66.87 (12.97)	46 M 21 F	13.93 (3.2)	67	Standardized normative data				

Study/Year/Location	Matched for	Sample					Comparative Group				
		Visual spatial neglect patients									
		Condition	Age	Gender	Education	N	Condition	Age	Gender	Education	N
Làdavas, Umilta & Mapelli (1997), Italy	Age, Education Level & Disease Duration	Neurological patients, 7 sub-acute & 2 chronic	71 (9.27)	4 M 2 F	10.44 (4.7)	9	Right hemispheric damage without neglect, 8 sub-acute & 1 chronic	69.89 (7.91)	6 M 3 F	9.44 (4.03)	9
Lee et al. (2009), Korea	Age, Gender, Education Level & Disease Duration	Right hemisphere stroke, All sub-acute	65.07 (NR)	51 M 29 F	10.92 (NR)	80	Healthy controls	62.5 (11.9)	16 M 14 F	11.6 (4.4)	30
Marelli et al. (2013), Italy	Age & Education Level	Right hemisphere brain-damaged, 5 sub-acute & 2 chronic	47.86 (11.14)	2 M 5 F	11.29 (2.93)	7	Standardized normative data				
Martelli et al. (2010), Italy	Age & Disease Duration	Cerebrosvacular ischemic stroke, confined to right hemisphere, All sub-acute	66.33 (8.31)	5 M 1 F	9.33 (3.83)	6	Standardized normative data				
Primativo et al. (2013), Italy	Age, Gender, Education Level & Disease Duration	Cerebrosvacular ischemic stroke, All sub-acute	70.92 (7.7)	9 M 4 F	10.5 (5.3)	13	Right - hemisphere-damaged patients without neglect, All sub-acute	68.9 (10.98)	2 M 8 F	10.8 (4.54)	10
Primativo et al. (2015), Italy	Age, Education Level & Disease Duration	Right hemisphere-damaged, All sub-acute	68 (10.3)	4 M 6 F	10.5 (4.4)	10	Right brain damaged patients without neglect, All sub-acute	71.2 (7.4)	6 M 4 F	11.9 (4.2)	10

Study/Year/Location	Matched for	Sample					Comparative Group				
		Visual spatial neglect patients									
		Condition	Age	Gender	Education	N	Condition	Age	Gender	Education	N
Reinhart et al. (2011), Germany	Education Level	Right-hemispheric, vascular brain lesions, 7 sub-acute & 2 chronic	54.22 (8.7)	6 M 3 F	< 9 years (*NR*)	9	Right brain damaged patients without neglect, 5 sub-acute & 2 chronic	52.29 (12.39)	3 M 4 F	< 9 years (NR)	7
							Healthy controls	46 (33-67) [a]	6 M 3 F	< 9 years (*NR*)	9
Ronchi et al. (2016), Italy	Age & Education Level	Right hemispheric brain lesion, Both sub-acute & chronic	68.5 (14.5)	13 M 14 F	11.1 (5.1)	27	Spatial neglect patients without neglect dyslexia, Both sub-acute & chronic	66.4 (13.2)	13 M 10 F	10.8 (5.2)	23
							Healthy controls	66 (12.9)	27 M 23 F	10.9 (4.8)	50
Veronelli et al. (2014), Italy	Age, Education Level & Disease Duration	Ischemic cerebrovascular attack (right brain damaged), All sub-acute	77.4 (5.95)	2 M 6 F	8 (4.14)	8	Right brain damaged without neglect, 7 sub-acute & 1 chronic	74.6 (7.33)	6 M 2 F	9.6 (4.75)	8
Weinzierl et al. (2012), Germany	Age	Visuospatial left sided neglect, 13 sub-acute & 5 chronic	58.28 (9.08)	12 M 6 F	*NR*	18	Healthy controls	59.36 (7.93)	6 M 5 F	*NR*	11

Values provided are mean (standard deviation) unless otherwise specified. M = Male; F = Female; NR = not reported; [a] = Range. * = Arduino, Burani & Vallar (2002) & Arduino, Burani & Vallar (2003) contained the same sample subjects. Both reported the same results for words, nonwords and sentence reading. Data of the Arduino at al. (2002) was included in the words, nonwords and sentence reading domains, while data of the Arduino et al (2003) was included for the combination of word and nonword reading (refer to Table 2.2)

2.3.2. Risk of Bias of Included Studies

Figure 2.2 and Figure 2.3 present an assessment of the risk of bias for the included studies using the Cochrane Collaboration risk of bias tool. Overall, as shown in Figure 2.3, we assessed all the studies as being a high risk of bias for random sequence generation. On the other hand, all studies were deemed to have an unclear bias to allocation concealment. As it was unclear whether the patients or the researcher knew of patients reading abilities prior to the formal testing. Also, we evaluated performance bias, detection bias and reporting bias to be of least concern across all the included studies.

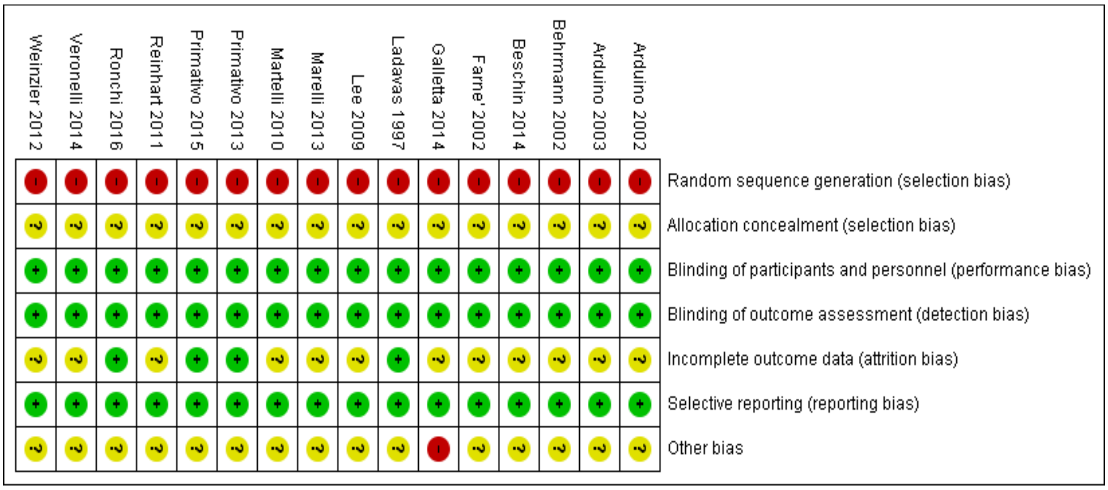

Figure 2. 2. Risk of bias summary. Our judgements about each risk of bias item for each included study.

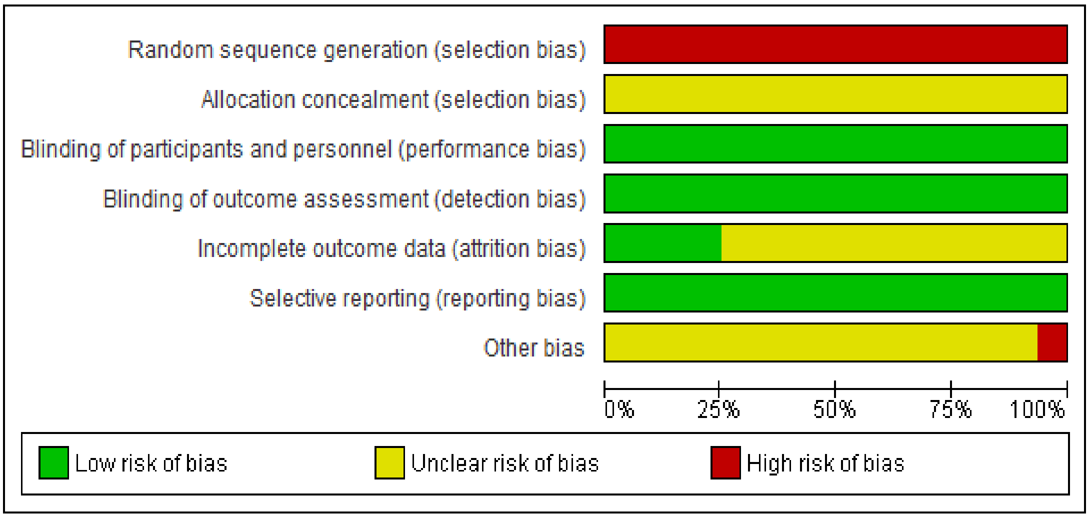

Figure 2. 3. Risk of bias graph. Each risk of bias item presented as percentages across all included studies.

2.3.3. How Reading Performance was Evaluated

Table 2.2 provides a summary of relevant studies that included for each reading domains. The most common test used was the single word reading test. The prose and article readings were put under the text reading domain because both reading materials had shared common characteristics as the reading texts which required an intense concentration (Mann, 2000) and they usually involved multiple sentences. Finally, the menu and phrase reading domains were excluded in the meta-analysis because only one study tested performances in these two domains.

Table 2. 2. Studies Included for Each Reading Domains

Reading domains	Test	Outcome	Studies that use this [Authors (Year)]
1. Words	a. Single-word reading	1. # reading errors	Arduino et al. (2002)
			Behrmann et al. (2002)
			Beschin et al. (2014)
			Galletta et al. (2014)
			Lee et al. (2009)
			Marelli et al. (2013)
			Martelli et al. (2010)
			Primativo et al. (2013)
			Reinhart et al. (2011)
			Ronchi et al. (2016)
		2. % of reading errors	Farne' et al. (2002)
			Ladavas et al. (1997)
2. Non-words	a. A single pseudoword reading test	1. # reading errors	Arduino et al. (2003)
			Marelli et al. (2013)
			Martelli et al. (2010)
			Primativo et al. (2013)
			Veronelli et al. (2014)
		2. % of reading errors	Farne' et al. (2002)
			Ladavas et al. (1997)
3. Combination words and non-words	a. Words & Non-words	1. # reading errors	Arduino et al. (2003)
	b. Combination morphologically complex words, non-words, non-derived words & non-words	2. # reading errors	Arduino et al. (2003)
4. Sentences†	a. Sentence reading	1. # reading errors	Arduino et al. (2002)
			Martelli et al. (2010)
			Primativo et al. (2013)
			Primativo et al. (2015)
			Reinhart et al. (2011)
			Veronelli et al. (2014)
5. Texts†	a. Prose reading	1. # reading errors	Beschin et al. (2014)
	b. Text reading task	2. # reading errors	Marelli et al. (2013)
			Weinzierl et al. (2012)
	c. Reading articles	3. # reading errors	Galletta et al. (2014)
6. Menu*	a. Reading menu	1. # reading errors	Galletta et al. (2014)
7. Phrase*	a. Reading two words phrases	1. # reading errors	Galletta et al. (2014)

* =excluded in the meta-analysis. We excluded both the menu and phrase domains for the meta-analysis due to only one study investigating these areas. † Prose and articles were included in the text reading domain.

2.4. CURRENT STUDIES

2.4.1. ***STUDY 1: Reading dyslexic deficit in visual spatial neglect syndrome – Analyses A, B and C***

2.4.1.1. Methods

In Study 1, we performed three separate meta-analyses. First, *Analysis A* included all the data from all relevant studies that report reading performance of visual neglect compared it with standardized normative data. *Analysis B* compared reading errors in visual neglect patients and matched healthy controls. *Analysis C* compared reading performance of acquired lesion patients with neglect versus those without neglect syndrome (Table 2.3). In a*nalyses A, B* and *C* neglect syndrome was assumed using the authors' classifications; either from one of the commonly used neglect tests or a battery of neglect measurement without applying any prior selection criteria (see the eligibility criteria).

Table 2. 3. Studies Included in The Meta-Analysis (*Analyses A, B*, and *C*)

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Reading Test Used
STUDY 1: ANALYSIS A					
1	Arduino et al. (2002)	6	Standardized normative data	*NA*	Words
2	Arduino et al. (2002)	6	Standardized normative data	*NA*	Words
3	Beschin et al. (2014)	21	Standardized normative data	*NA*	Words
4	Farne' et al. (2002)	6	Standardized normative data	*NA*	Words
5	Galletta et al. (2014)	67	Standardized normative data	*NA*	Words
6	Marelli et al. (2013)	7	Standardized normative data	*NA*	Words
7	Martelli et al. (2010)	6	Standardized normative data	*NA*	Words
8	Veronelli et al. (2014)	8	Standardized normative data	*NA*	Words
	Total	*127*			
9	Arduino et al. (2002)	6	Standardized normative data	*NA*	Nonwords
10	Arduino et al. (2002)	6	Standardized normative data	*NA*	Nonwords
11	Farne' et al. (2002)	6	Standardized normative data	*NA*	Nonwords
12	Marelli et al. (2013)	7	Standardized normative data	*NA*	Nonwords
13	Martelli et al. (2010)	6	Standardized normative data	*NA*	Nonwords
14	Veronelli et al. (2014)	8	Standardized normative data	*NA*	Nonwords
	Total	*39*			
15	Arduino et al. (2002)	6	Standardized normative data	*NA*	Sentence
16	Marelli et al. (2013)	7	Standardized normative data	*NA*	Sentence
17	Martelli et al. (2010)	6	Standardized normative data	*NA*	Sentence

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Reading Test Used
18	Primativo et al. (2013)	13	Standardized normative data	*NA*	Sentence
19	Reinhart et al. (2011)	9	Standardized normative data	*NA*	Sentence
20	Veronelli et al. (2014)	8	Standardized normative data	*NA*	Sentence
	Total	*49*			
21	Galletta et al. (2014)	67	Standardized normative data	*NA*	Articles*
22	Beschin et al. (2014)	21	Standardized normative data	*NA*	Prose*
23	Weinzierl et al. (2012)	18	Standardized normative data	*NA*	Text
	Total	*106*			
STUDY 1: ANALYSIS B					
1	Behrmann et al. (2002)	9	Healthy controls	5	Words
2	Ladavas et al. (1997)	9	Healthy controls	9	Words
3	Lee et al. (2009)	80	Healthy controls	30	Words
4	Ronchi et al. (2016)	27	Healthy controls	30	Words
5	Ronchi et al. (2016)	27	Healthy controls	30	Words
	Total	*152*		*104*	
6	Ladavas et al. (1997)	9	Healthy controls	9	Nonwords
	Total	*9*		*9*	
7	Arduino et al. (2003)	6	Healthy controls	12	Words & Nonwords
8	Arduino et al. (2003)	6	Healthy controls	12	Words & Nonwords
	Total	*12*		*24*	
9	Primativo et al. (2015)	10	Healthy controls	10	Sentence
	Total	*10*		*10*	
STUDY 1: ANALYSIS C					
1	Behrmann et al. (2002)	9	Hemianopic patients*	4	Words
2	Beschin et al. (2014)	21	Patients without neglect	9	Words
3	Primativo et al. (2013)	13	Patients without unilateral spatial neglect	10	Words
4	Veronelli et al. (2014)	8	Right brain damaged without neglect	8	Words
	Total	*51*		*31*	
5	Primativo et al. (2013)	13	Patients without unilateral spatial neglect	10	Nonwords
6	Veronelli et al. (2014)	8	Right brain damaged without neglect	8	Nonwords
	Total	*21*		*18*	
7	Primativo et al. (2013)	13	Patients without unilateral spatial neglect	10	Sentence
8	Reinhart et al. (2010)	9	Brain-damaged patients without neglect	7	Sentence
9	Veronelli et al. (2014)	8	Right brain damaged without neglect	8	Sentence
	Total	*30*		*25*	
10	Beschin et al. (2014)	21	Patients without neglect	9	Prose*
	Total	*21*		*9*	
STUDY 2: ANALYSIS D					
1	Arduino et al. (2002)	6	*NA*	*NA*	Words
2	Arduino et al. (2002)	6	*NA*	*NA*	Words
3	Behrmann et al. (2002)	9	*NA*	*NA*	Words
4	Marelli et al. (2013)	7	*NA*	*NA*	Words
5	Martelli et al. (2010)	6	*NA*	*NA*	Words
6	Primativo et al. (2013)	13	*NA*	*NA*	Words
7	Ronchi et al. (2016)	27	*NA*	*NA*	Words
8	Ronchi et al. (2016)	27	*NA*	*NA*	Words
9	Veronelli et al. (2014)	8	*NA*	*NA*	Words
	Total	*109*			
10	Arduino et al. (2002)	6	*NA*	*NA*	Nonwords
11	Arduino et al. (2002)	6	*NA*	*NA*	Nonwords
12	Marelli et al. (2013)	7	*NA*	*NA*	Nonwords
13	Martelli et al. (2010)	6	*NA*	*NA*	Nonwords
14	Primativo et al. (2013)	13	*NA*	*NA*	Nonwords

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Reading Test Used
15	Primativo et al. (2013)	13	*NA*	*NA*	Nonwords
16	Veronelli et al. (2014)	8	*NA*	*NA*	Nonwords
	Total	*59*			
17	Arduino et al. (2002)	6	*NA*	*NA*	Sentence
18	Marelli et al. (2013)	7	*NA*	*NA*	Sentence
	Total	*13*			

*Hemianopia occurs commonly after a stroke or brain injury that characterised by full vision loss in either in the left or right half of the visual field of one or both eyes **(Frassinetti et al., 2005)**

2.4.1.2. Results

Analysis A included 321 visual neglect patients from 10 relevant studies reporting scores from 25 standardised tests (i.e. word, nonword, sentence and text reading domains; see Table 2.3). Patient's error scores were compared to the standardized normative data. Significant differences were found on single words (Z=1.98, *p* =.05) and single nonwords (Z=2.52, *p*=.01) reading domains but not on sentences and text reading domains (see Figure 2.4). Additionally, the results reported high significant overall effects estimates on poor reading performance associated with visual spatial neglect symptoms (Z=3.78, *p* <.001). The data used in *Analysis A*, (I^2) was homogenous.

Analysis B included 183 visual neglect patients and 147 matched healthy controls from seven studies reporting nine experiments (e.g., word, nonword, combination word and nonword, and sentence reading domains; see Table 2.3). The results showed high significant overall effects estimates on reading deficit when compared between these two groups (Z=4.18, *p*=<.00001), though we note that I^2 values were higher than 75%, indicating large heterogeneity between studies. These effects were most pronounced when reading single-word (Z=3.58, *p*=.0003) and non-words (Z=3.95, P = .00001) (see Figure 2.5).

Analysis C included 123 visual neglect patients and 83 brain damaged patients without neglect from seven studies reporting 10 experiments (e.g., word, nonword and text reading domains; see Table 2.3). Significant differences were found on a single word (Z=2.04, p=.04), single nonword (Z=2.92, p=.003) and sentence (Z=3.22, p=0.15) reading domains but not on text reading domain due to one study reported in this area (see Figure 2.6). Together, the results showed high significant overall effects estimated on reading deficit when compared between these two groups (Z=4.26, p=<0.0001), though we note that I^2 values were 49%, indicating moderate heterogeneity between studies.

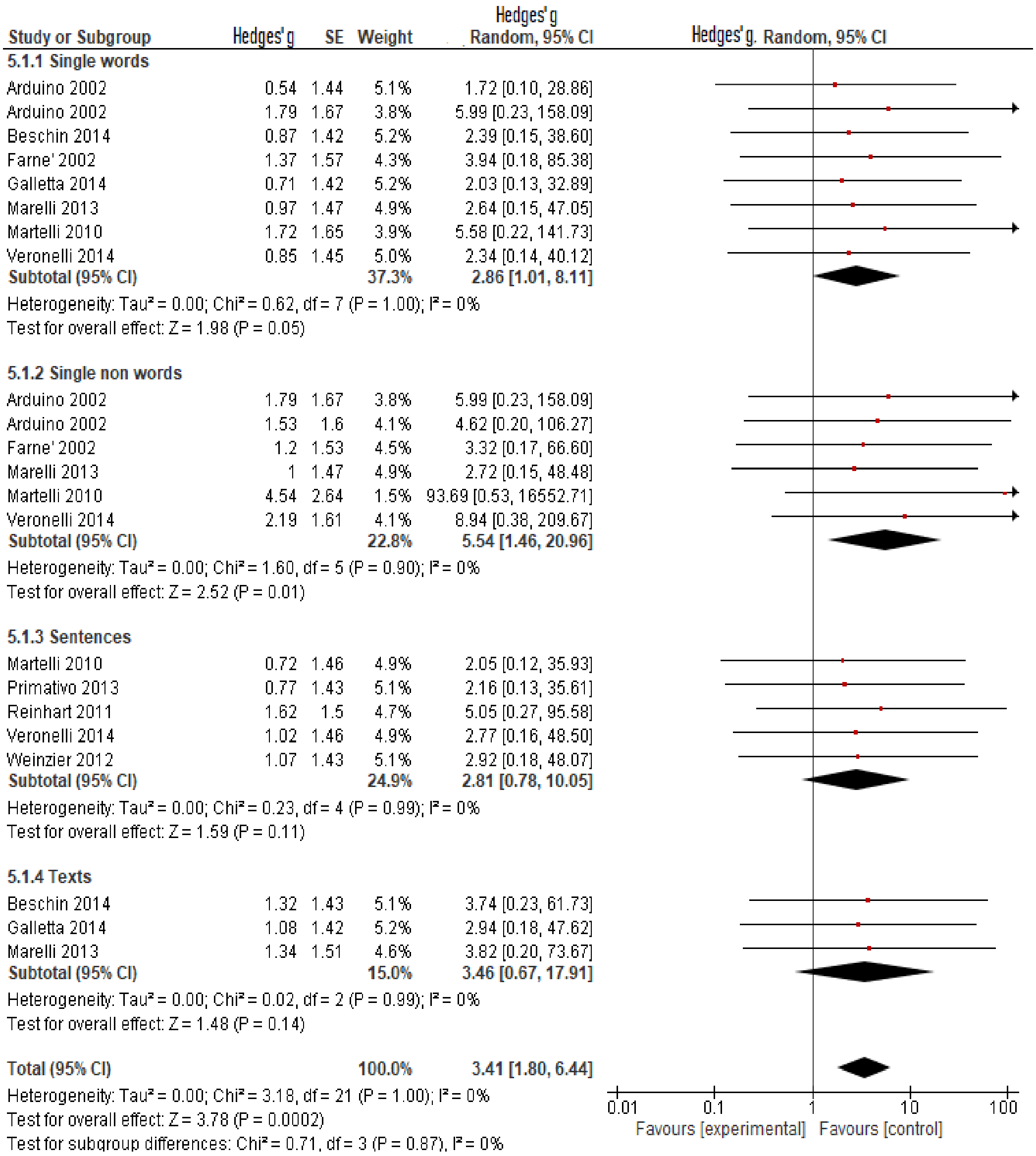

Figure 2. 4. Forest plot of outcome Analysis A: The number of error responses. Visual neglect patients compared with standardized norms.

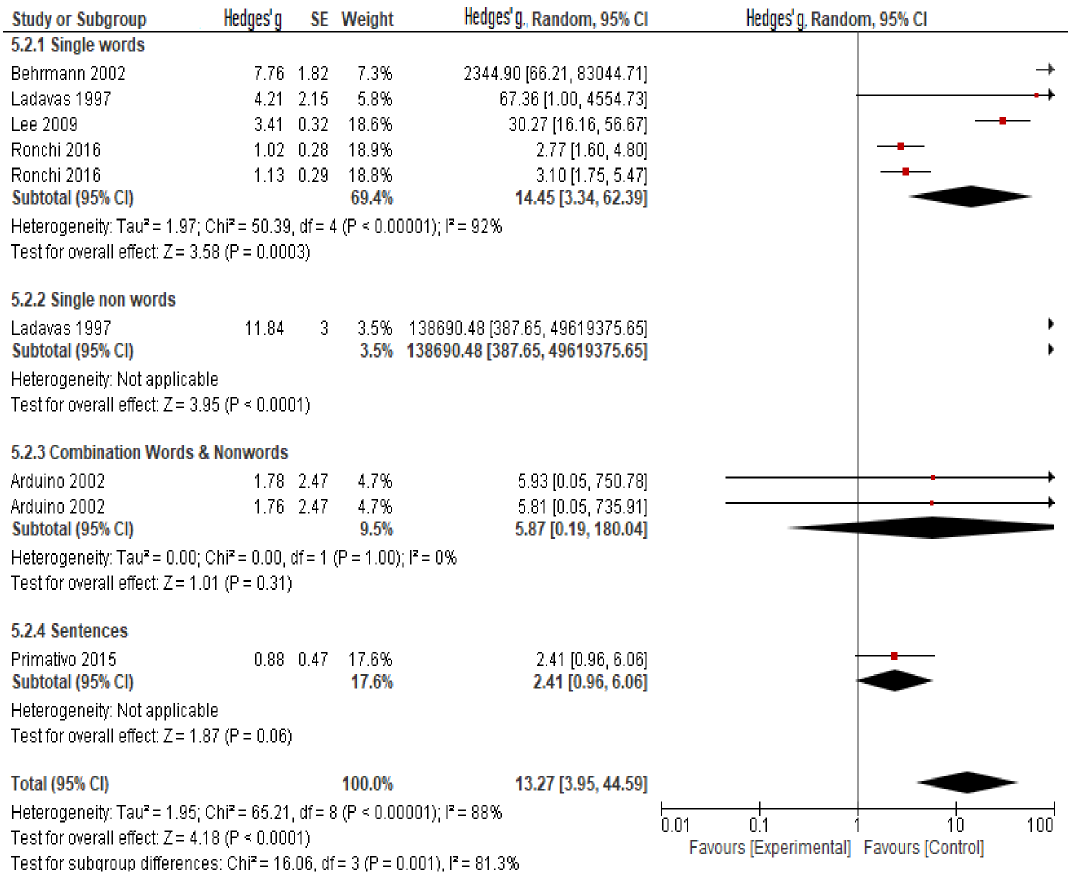

Figure 2. 5. Forest plot of outcome Analysis B: the number of error responses: Visual neglect patients compared with matched healthy controls.

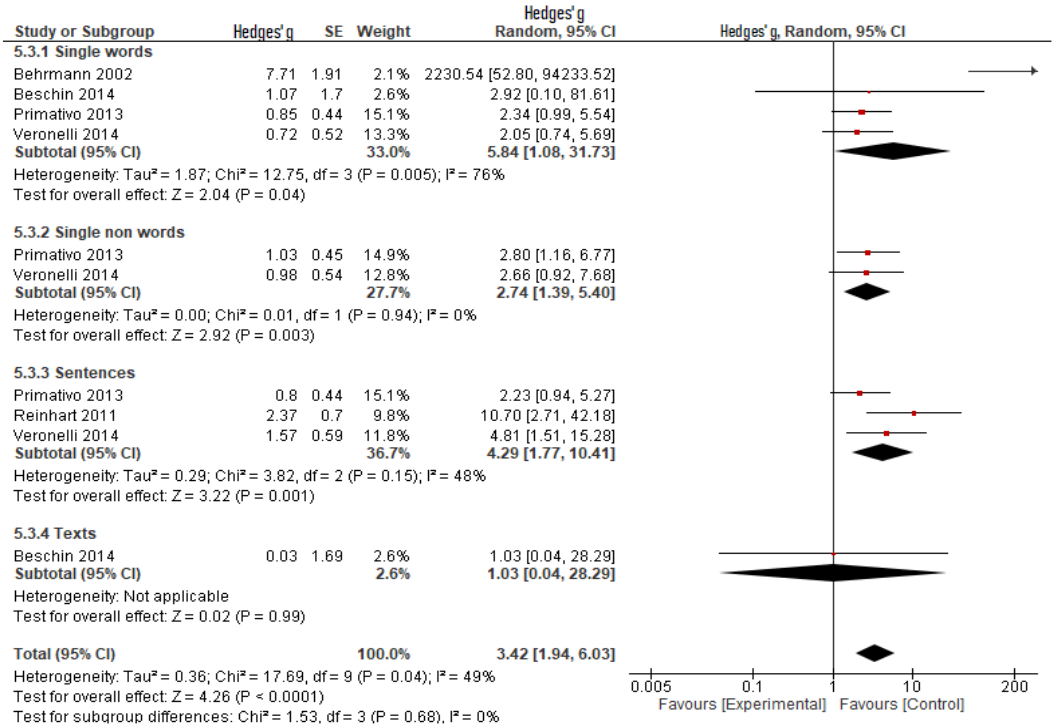

Figure 2. 6. Forest plot of outcome Analysis C: The number of error responses. Visual neglect patients compared with brain damaged controls without spatial neglect.

2.4.1.3. Discussion

The objective of the study was to examine the prevalence of reading difficulty in visual neglect patients. The meta-analysis results show that patients with acquired visual neglect have more difficulty in reading in comparison to what is expected in the normal population (standardised data, *Analysis A*), matched healthy control (*Analysis B*) and even patients with acquired lesion but with no neglect visual symptoms (*Analysis C*). This effect was most reliable in reading words and non-words tests. This is presumably because these are the most common test used to asses reading performances in the literature. Next Study 2, we ask whether reading deficits emerged due to the spatial nature for the syndrome. In another word, is neglect dyslexia can account for the generic reading deficits.

2.4.2. **STUDY 2: Effects of spatial location in reading deficit – *Analysis D***

2.4.2.1. Methods

Study 2, aimed to test whether the spatial pattern of reading errors matches the spatial deficit common in neglect. To this aim, we assumed that if reading errors are related to the spatial deficit, they should be more prevalent in the contralesional side; while showing a like-normal pattern in the ipsilesional side. To this aim, we performed one meta-analysis. *Analysis D* included only patients with neglect syndrome. In this analysis, we compared errors made on contra versus ipsilesional side (Table 2.3).

2.4.2.2. Results

We evaluated poor reading performance based on spatial location. (Contralesional and Ipsilesional sides) within visual neglect patients. *Analysis D* included 181 visual neglect patients reported in seven studies and 18 experiments (words, nonwords and sentences reading domains; see Table 2.3). Surprisingly, number of errors made on the contralesional field did not reliably differ from those made on the ipsilesional field (P= >.39) and heterogeneity between studies was minimal (see Figure 2.7). As some of the studies in this meta-analysis specifically recruited an equal number of patients suffering from neglect dyslexia and neglect without dyslexia; it is likely that by considering these two groups together any spatial pattern in errors will be cancelled out. Hence a secondary analysis only included studies which did not biased recruitment based on reading abilities. The analysis included studies that did not focus on neglect dyslexia symptoms in recruitment. We identified 3 studies reporting 46 patients, in a total of 6 experiments [Behrmann et al. (2002), Marelli et al. (2013), Veronelli et al. (2014)], (3 words reading, 2 nonwords and 1 text reading). Again we fail to observe reliable differences between number of errors made in contra and ipsilesional field: words [g=1.15 (95% CI 0.23 to

5.75), p=0.87, I²=0%], nonwords [g=0.84 (95% CI 0.12 to 6.04), p=0.86, I²=0%] and texts [g=0.58 (95% CI 0.04 to 9.61), I²=NA], overall effect estimates [g=0.92 (95% CI 0.30 to 2.89), p=0.89, I²=0%].

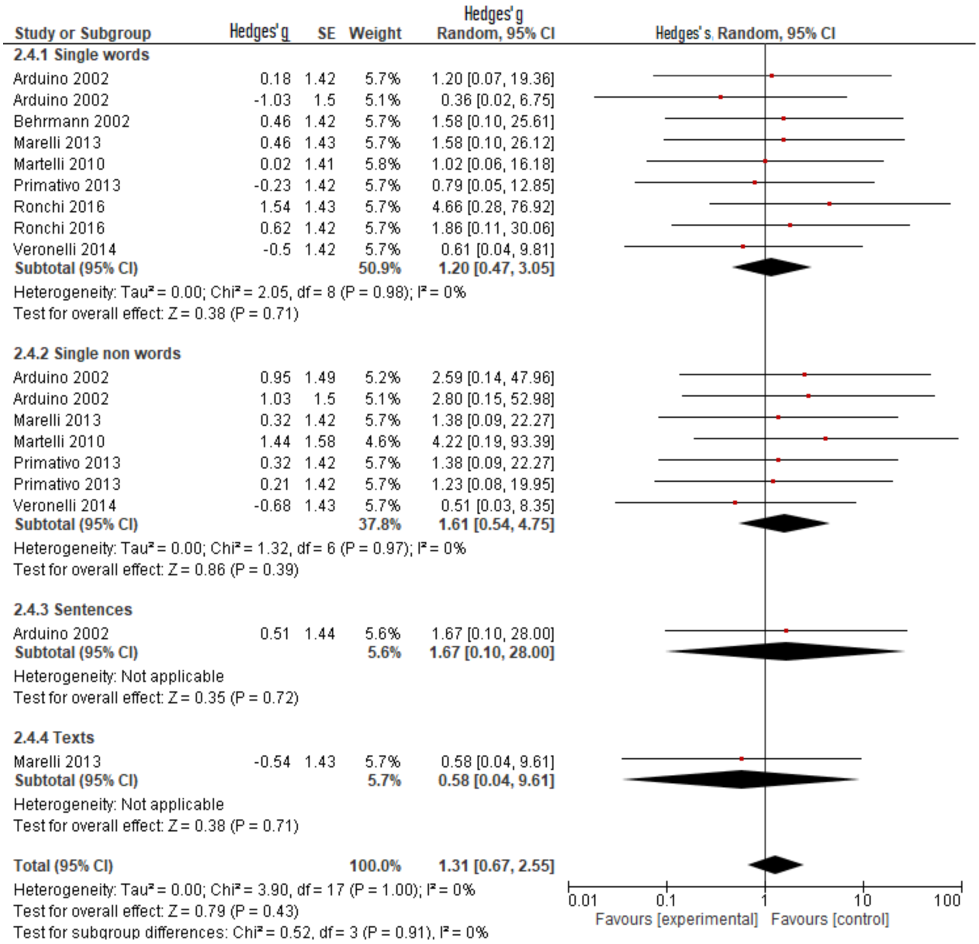

Figure 2. 7. Forest plot of outcome Analysis D: The number of error responses: Effects of contra-lesional side on reading deficit in visual neglect syndrome.

2.4.2.3. Discussion

Study 2 set out with the aim of assessing the effects of spatial nature in reading difficulty within visual neglect patients. It is somewhat surprising that the meta-analysis failed to show evidence of spatial location effects in reading difficulty in all reading domains within patients with visual neglect. This study indicates that spatial biases in attention or neglect dyslexia cannot contribute to the generic reading deficits. Next, in Study 3, we tested whether reading deficits emerged due to the neglect symptoms (egocentric versus allocentric). Is different spatial allocation can account for the generic reading deficits?

2.4.3. **STUDY 3: Effects of neglect symptoms in reading deficit – *Analysis E (Egocentric) and Analysis F (Allocentric)***

2.4.3.1. Methods

In Study 3, we examined the link of between the poor reading performance associated with impairments in allocating spatial attention either across space (using an egocentric frame of reference, *Analysis E*) or within objects (using an allocentric frame of reference, *Analysis F*). *Analysis E* included the data from the studies that employed the neglect tests that reflected symptoms on egocentric deficits such as *Line Cancellation* (Albert, 1973), *Letter Cancellation* (Diller & Weinberg, 1977), *Bells Cancellation Test*, *The Star Cancellation Task* (Halligan et al., 1990) and *Number Cancellation* (Kuhn et al., 2010) (see Table 2.4). In *Analysis F*, we included the data from the relevant studies that used neglect tests which measured allocentric deficits such as *A Clock Drawing from Memory* (Kerkhoff et al., 1992), *Figure Copying* (star, flower, cube) (Kerkhoff et al., 1992), *A Copy of Geometrical Shapes* (Arrigoni & De Renzi, 1964), *Complex Figure Drawing* (Gainotti et al., 1972) and *Line Bisection Task* (see Table 2.5).

2.4.3.2. Results

We also examined the reading deficit in relation to the patient's body or within objects (in egocentric or allocentric frames of reference). *Analysis E* included 187 neglect patients with egocentric symptoms and 51 neglect patients without egocentric symptoms from eight studies reporting 24 experiments (e.g. word, nonword, combination word and nonword, sentence and text reading domains; see Table 2.4). Number of errors made by patients with egocentric symptoms did not reliably differ from those made by without egocentric symptoms in all reading domains. However, the results showed significant overall effect estimates on poor reading performances by patients who had egocentric symptoms (failed a cancellation task) compare to those who did not (Z=2.41, p=0.02) (see Figure 2.8). The data used in *Analysis E*, (I^2) was homogenous.

Table 2. 4. Studies Included in The Meta-Analysis-*Analysis E*

No	Study ID	No. of Egocentric Patients	No. of patients without egocentric symptoms	Neglect test detecting egocentric symptoms	Reading test
ANALYSIS F					
1	Arduino et al. (2002)	5	1	Line cancellation, Letter cancellation	Words
2	Arduino et al. (2002)	5	1	Line cancellation, Letter cancellation	Words
3	Ladavas et al. (1997)	9	0	Letter cancellation, Bell cancellation	Words
4	Marelli et al. (2013)	5	2	Line cancellation, Bell cancellation	Words
5	Martelli et al. (2010)	6	0	Letter cancellation, Line cancellation	Words
6	Ronchi et al. (2016)	25	2	Star cancellation, Letter cancellation	Words
7	Ronchi et al. (2016)	25	2	Star cancellation, Letter cancellation	Words
8	Veronelli et al. (2014)	6	2	Line cancellation, Star cancellation	Words
	Total	*86*	*10*		
9	Arduino et al. (2002)	5	1	Line cancellation, Letter cancellation	Nonwords
10	Arduino et al. (2002)	5	1	Line cancellation, Letter cancellation	Nonwords
11	Ladavas et al. (1997)	9	0	Letter cancellation, Bell cancellation	Nonwords
12	Marelli et al. (2013)	5	2	Line cancellation, Bell cancellation	Nonwords
13	Martelli et al. (2010)	6	0	Letter cancellation, Line cancellation	Nonwords
14	Primativo et al. (2013)	9	4	Letter cancellation, Line cancellation	Nonwords
15	Primativo et al. (2013)	9	4	Letter cancellation, Line cancellation	Nonwords
16	Veronelli et al. (2014)	6	2	Line cancellation, Star cancellation	Nonwords
	Total	*54*	*14*		
17	Arduino et al. (2003)	5	1	Line cancellation, Letter cancellation	Words & Nonwords
18	Arduino et al. (2003)	5	1	Line cancellation, Letter cancellation	Words & Nonwords
	Total	*10*	*2*		
19	Arduino et al. (2002)	5	1	Line cancellation, Letter cancellation	Sentence
20	Marelli et al. (2013)	5	2	Line cancellation, Bell cancellation	Sentence
21	Primativo et al. (2013)	9	4	Letter cancellation, Line cancellation	Sentence
22	Primativo et al. (2015)	6	4	Letter cancellation, Line cancellation	Sentence
23	Veronelli et al. (2014)	6	2	Line cancellation, Star cancellation	Sentence
	Total	*31*	*13*		
24	Weinzierl et al. (2012)	6	12	Line Cancellation, Lettercancellation	Text
	Total	*6*	*12*		

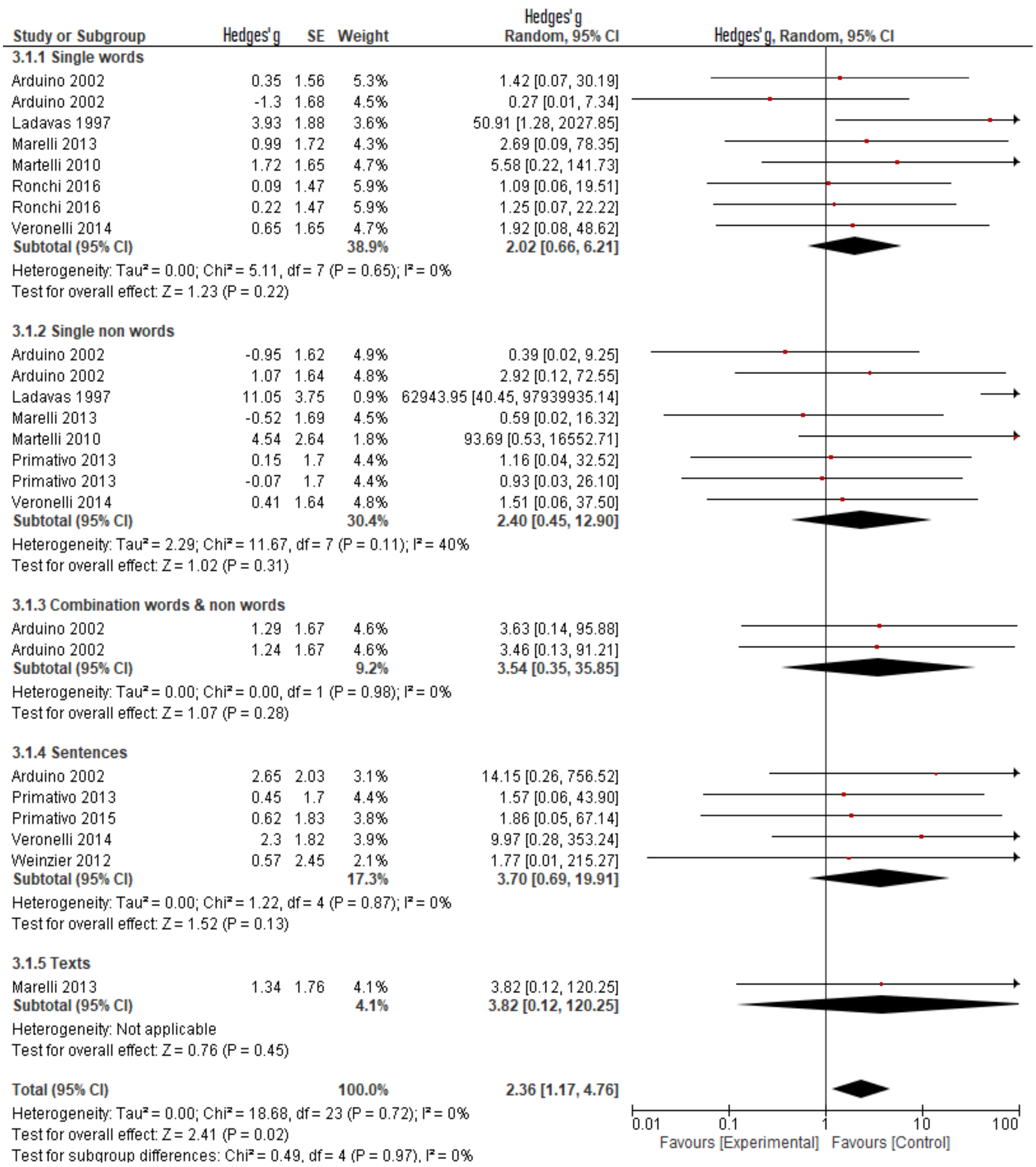

Figure 2. 8. Forest plot of outcome Analysis E: the number of error responses: Neglect patients with egocentric symptoms were compared with neglect patients without egocentric deficits.

Analysis F, included 121 neglect patients with allocentric symptoms and five neglect patients without allocentric symptoms from five relevant studies reporting 10 experiments (e.g., word, non-word and sentence reading domains; see Table 2.5) to assess the effects of allocentric neglect on poor reading performance. Number of errors made by patients with allocentric symptoms did not reliably differ from those made by without allocentric symptoms in all reading domains. Like the egocentric neglect, the results showed significant overall effect estimates on poor reading performances by those with allocentric symptoms (failed the line bisection and drawing tasks) compared with those with not (Z=2.47, p=0.01) (see Figure 2.9). The data used in *Analysis F*, (I^2) was homogenous.

Table 2. 5. Studies Included in The Meta-Analysis-*Analysis F*

No.	**Study**	**No. of Allocentric Patients**	**No. of patients without allocentric symptoms**	**Neglect test detecting allocentric symptoms**	**Reading test**
ANALYSIS G					
1	Marelli et al. (2013)	7	0	Clock drawing, Copy of geometrical shapes	Words
2	Reinhart et al. (2010)	8	1	Clock drawing, Figure copy	Words
3	Ronchi et al. (2016)	25	2	Line bisection, Figure copy	Words
4	Ronchi et al. (2016)	25	2	Line bisection, Figure copy	Words
5	Veronelli et al. (2014)	8	0	Complex figure drawing, Line bisection	Words
	Total	*73*	*5*		
6	Marelli et al. (2013)	7	0	Clock drawing, Copy of geometrical shapes	Nonwords
7	Veronelli et al. (2014)	8	0	Complex figure drawing, Line bisection	Nonwords
	Total	*15*	*0*		
8	Marelli et al. (2013)	7	0	Clock drawing, Copy of geometrical shapes	Sentence
9	Veronelli et al. (2014)	8	0	Complex figure drawing, Line bisection	Sentence
	Total	*15*	*0*		
10	Weinzierl et al. (2012)	18	0	Line bisection, clock drawing	Text
	Total	*18*	*0*		

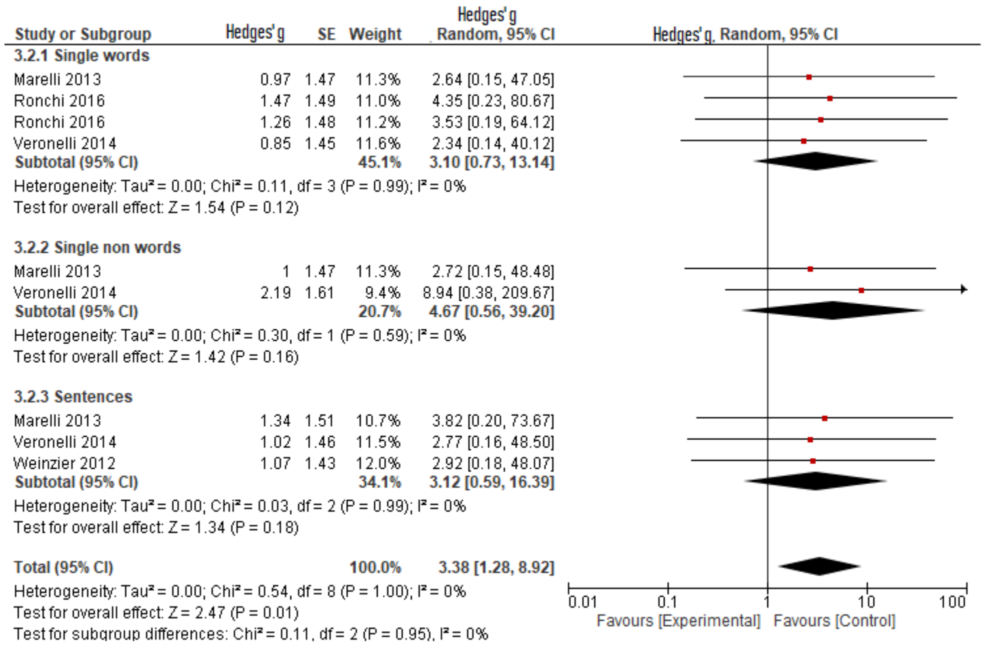

Figure 2. 9. Forest plot of outcome Analysis F: the number of error responses: Neglect patients with allocentric symptoms were compared with neglect patients without allocentric symptoms.

2.4.3.3. Discussion

The number of patients who showed only egocentric (N=65) or allocentric (N=41) symptoms was very small. Thus, with small sample sizes, caution must be applied, as the findings might not represent the population accurately. In addition, there was a large overlap between the two groups.

This meta-analysis sought to determine whether neglect symptoms (egocentric and allocentric reference of frame) associated with reading difficulty in spatial neglect patients. The meta-analysis results show that neglect patients with egocentric symptoms have more difficulty in reading in comparison to neglect patients without egocentric symptoms. Similarly, visual neglect patients with allocentric symptoms have poor reading performance in comparison to neglect patients without allocentric symptoms.

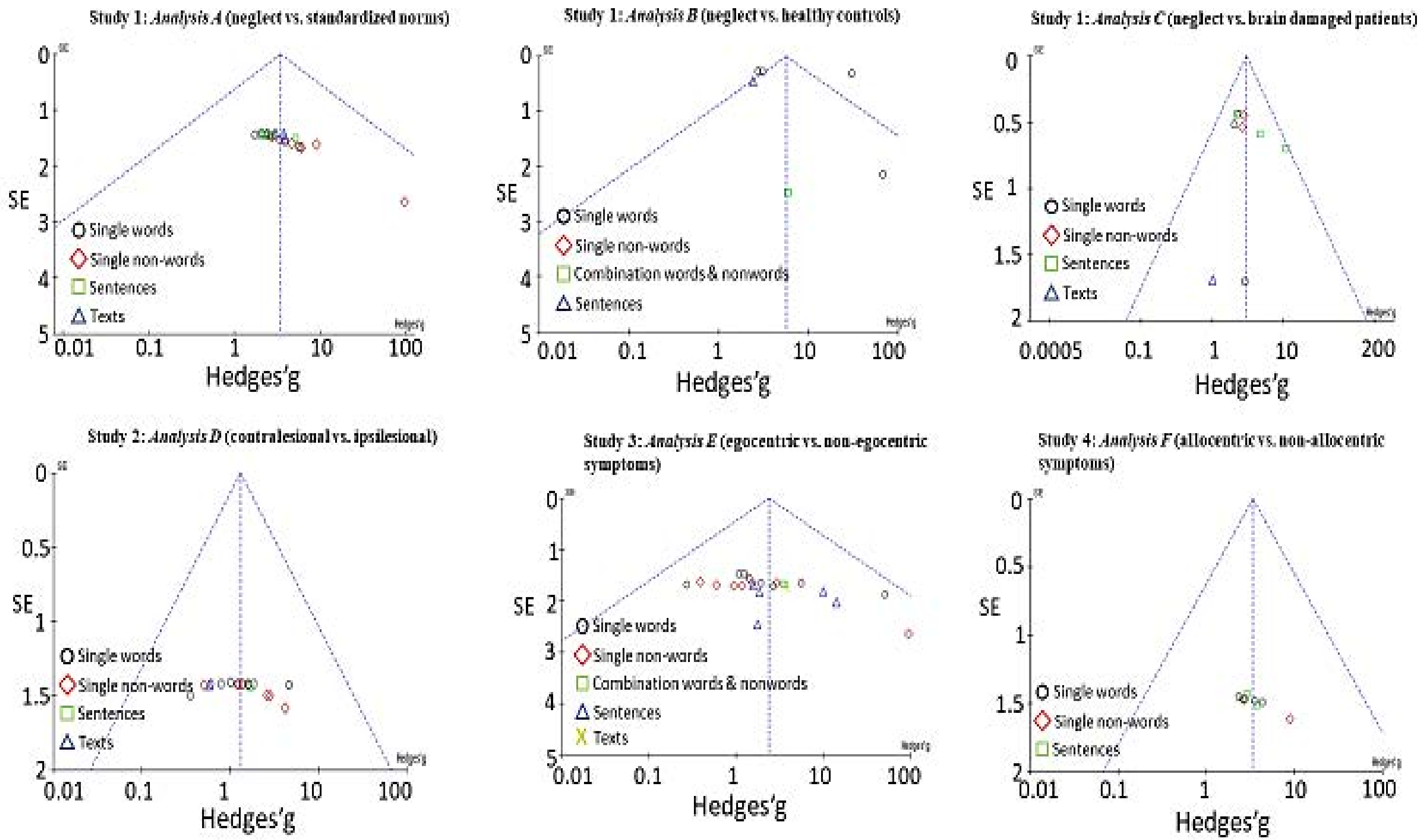

Figure 2-10. Funnel plot of the standard error of hedges' g. Study 1 consists of Analysis A (compared reading errors in neglect patients with standardized normative data); Analysis B (compared reading errors in neglect patients with healthy controls); Analysis C (compared reading errors

in neglect patients with acquired brain damaged patients). Study 2 includes Analysis D (compared poor reading performance within neglect patients based on spatial location). Study 3 includes Analysis E (compared reading errors within egocentric neglect patients with non-egocentric neglect patients) and Analysis F (compared reading errors within allocentric neglect patients with non-allocentric neglect patients).

2.4.4. **Publication Bias**

We generated a funnel plot depicting the standard error of Hedges' *g* to visually inspect for asymmetry of the potential for publication bias for each meta-analysis. Some biases are present (see Figure 2.10).

2.5. GENERAL DISCUSSION AND CONCLUSION

To my knowledge, this is the first qualitative meta-analysis study of generic reading deficits in unilateral spatial neglect. The meta-analyses revealed that visual neglect patients are more likely to experience reading impairments than expected by standardized normative data, when compared with matched controls and even when compared with brain injury patients who do not suffer from visual neglect symptoms. Surprisingly, these reading impairments were not clearly associated with the spatial deficits that characterise the syndrome. No reliable difference was observed between errors on contra and ipsilesional fields. In the case of neglect symptoms, both egocentric and allocentric may exacerbate generic reading impairments, though within the analysed studies' sample there was a large overlap of patients showing both egocentric and allocentric symptoms, with less than a handful showing deficits only in one frame of reference.

The presence of clinical visual neglect symptoms predicted reading impairment across all tasks but it was most pronounced and robust in single word reading, and specifically in non-words. This may suggest that reading ability may be affected by the familiarity of the items (words versus non-words). It is assumed that reading nonwords (like exceptional words) requires more spatial attentional resources (Siéroff, 2017). Specifically, in phonological writing systems (representing all studies in the meta-analysis) reading nonwords requires an ability to shift attention along horizontal axes, as each phoneme needs to be read. An alternative explanation is that the deficits may relate to the impairment in non-spatial attentional systems, as reading non-familiar words is a more demanding task and may require higher vigilance or executive functions.

The theoretical implication of these findings will be discussed in length at the discussion of CHAPTER 3 below. As these two chapters address similar questions; while providing complementary methodological approaches.

2.5.1. **Limitations**

The type of included studies; only studies published in the English language were included and non-English language studies may influence the overall findings here. Therefore, CHAPTER 3 will include data from China, where reading was based on a completely different writing system, logographic rather than alphabetic-phonological.

The meta-analyses did not include unpublished studies. Therefore, the results should be interpreted with caution, as positive results are more likely to be published and have a higher chance to be cited than negative results (Cooper et al., 2009; Greco et al., 2013).

Others concern is that studies lacked large enough sample sizes that required to match for multiple comparisons across visual neglect patients with different symptoms (e.g., Study 3).

Finally, and most importantly all studies had severe biases in the way the participants were recruited and the data was collected. All studies were prospective case-control studies, both the researchers and participants aware of their conditions. This limits the ability to generalise the findings. In CHAPTER 3, I will analyse data of two large unbiased samples of stroke survivors.

2.5.2. **Future research**

Majority of the included studies have predominantly been conducted in the same location, such as Italy. Future research should aim to evaluate neglect patients globally to attain a more generalised result. Moreover, many of the papers on neglect patients mainly examined single word or sentence reading as a measure of reading, and very few studies have examined prose reading. It is also pertinent to examine neglect patients reading deficits in all kinds of domains in order to identify their reading disorder and help implement effective treatment strategies to unilateral neglect patients.

2.5.3. **Conclusion**

This chapter presents a systematic evaluation of existing reading performance literature in visual neglect. Based on the examined literature, patients suffering from visual neglect are likely to show generic reading deficits. These deficits were not driven by the asymmetric spatial attention bias that characterises the syndrome.

CHAPTER 3: VISUAL ATTENTION AND READING DEFICITS: BCoS AND C-BCoS

3.1. INTRODUCTION

The meta-analysis chapter showed that patients who have visual neglect symptoms are more likely to make errors while reading. Surprisingly the reading errors were not associated with the spatial bias deficits when compared across the egocentric space or in relation to the frame of reference (allocentric and egocentric). However, one limitation of the meta-analyses was the high risk of generalizability due to selection bias in all studies (*Figure 2.3*). As mentioned above, all studies explicitly recruited visual neglect patients and control groups. The researchers and the participants were not blind to their conditions at the time of testing. It is therefore likely that the high observed comorbidity may relate to the biased sampling. Therefore, this chapter will assess a similar question in a non-biased sample of stroke survivors. Two databases of stroke patients were analysed one from the UK and one from China. Both databases were created as part of a validation test of a cognitive screen developed to assess cognition following stroke – the Birmingham Cognitive Screen (BCoS).

The Birmingham Cognitive Screen (BCoS) was developed to screen individuals for cognitive problems following stroke. It provides a cognitive profile across five cognitive domains (Attention and Executive Function; Language; Memory; Number Skills; and Praxis) (see Bickerton et al., 2015; Humphreys, Bikerton, Samson, & Riddoch, 2012). The instrument is specifically designed to be "aphasia friendly", for example, by using mostly short and high-frequency words. When language is not directly assessed, it forced-choice response options, so aphasic patients can point even when they cannot make a verbal response. Importantly, the screening instruments are spatially designed as “neglect friendly”. When spatial attention deficits are not assessed stimuli are presented along the vertical mid-line, and multimodal exposures are used. The Chinese Birmingham Cognitive Screen (C-BCoS) has two versions: Cantonese and Mandarin. The Cantonese version was validated with stroke patients in China (see Pan et al., 2015 for details). The C-BCoS included four specific cultural modification, picture naming, sentence and non-word reading, gesture production and gesture recognition and word writing.

Both databases were designed to be as inclusive as possible. All patients who had a diagnosed stroke and had good chances of survival for at least 12 months were considered for recruitment. In the UK, the sample included all type of stroke (e.g., ischemic, haemorrhagic) patients within 3 months of the stroke. In China recruitment was limited to ischemic stroke with 1 month of the stroke. Exclusion criteria included the inability to concentrate for at least 30 minutes, the inability to comprehend the instruction as assessed by the orientation questions. Thus, importantly examiners were blind to the patients’ cognitive symptoms at the time of recruitment.

In this chapter, we analysed a large unbiased sample of patients using the existing UK-BCoS (United Kingdom) and C-BCoS (China) databases to answer whether reading deficits relate to the spatial bias common to neglect syndrome. Similar to the approach taken in the meta-analysis, we classified patients as suffering from neglect if they failed at least two of the spatial-visual attention tasks that are available in UK-BCoS and C-BCos databases: Key Cancellation Test, Apple Cancellation Test, Visual Extinction Test and Figure Copy Test. We asked whether reading errors in neglect patients across the UK and China are common in patients who show visual-spatial attention deficits and whether these deficits relate to their spatial bias in term of frame of reference.

A number of correct reading words in visual-neglect patients were compared relative to neurological patients without neglect from the same database. We considered two types of reading test: single words: Non-Word Reading Test (UK) / exceptional words (China) and Sentence Reading Test. Based on CHAPTER 2, it was predicted that readings errors will be more prevalent in patients suffering from visual neglect and that allocentric and egocentric attention would not have a differential effect on reading error patterns (similar effects when reading words and sentences). The BCoS also include cognitive measures that assess the function of the alert attentional system; assessing the ability to sustain attention and of the executive control attentional system, assessing the ability to ignore distracters. We assess whether patients suffering from visual neglect also showed more impairment in those non-spatial based measures. Finally, we evaluated what predicted error readings better, the severity of spatial attentional symptoms or non-spatial symptoms.

3.2. METHODS

3.2.1. **Participants**

The UK:

The BCoS database (Bickerton et al., 2012) includes eight hundred and seventy-two brain injury patients (478 males and 394 females) (Birmingham University Cognitive Screen, http://www.bucs.bham.ac.uk), recruited from stroke units across the West Midlands area (United Kingdom). The mean age within the group was 70.04 years old, with ages ranging from 18 to 95 years old. From the total number of patients, 39 % showed visual neglect syndrome. Clinical and demographic data were obtained from the patients' clinical files. See Table 3.1 for full clinical and demographic data. All participants provided written informed consent in agreement with ethics protocols.

China:

Three hundred first ischemic stroke patients included in the C-BCoS database. They were all recruited from the Neurological Department of Guangzhou First People’s Hospital in China, within a month of their stroke. The age ranged from 50 to 94 years old. Out of the total number of patients, 15 % showed visual neglect syndrome. Clinical and demographic data were obtained from the patients' clinical files. See Table 3.1 for full clinical and demographic data

Table 3-1. Patients' details: Clinical and demographic data.

	Brain Damaged Patients with Visual Neglect		Brain Damaged Patients without Visual Neglect	
	UK	**China**	**UK**	**China**
	(*n*=243)	(*n*=45)	(*n*=629)	(*n*=255)
Age in years-mean (*SD*)	71.41 (13.05)	69.77 (13.05)	69.51 (13.90)	69.54 (11.11)
Sex (Male/Female)	133/110	25/20	345/284	125/120
Aetiology (I/H/N.A)	143/11/89	45/0/0	378/32/219	255/0/0
Handedness (R/L/B/N.A)	217/18/7/1	39/6/0/0	557/61/27/2	235/20/0/0
Stroke days (acute/sub-acute/chronic/N.A)	36/188/4/6	8 (4.3)	157/447/3	10.87 (10.34)
Education in years-mean (*SD*)	10.87 (2.58)	7.22 (3.01)	10.59 (2.68)	10.89 (3.35)
Visual Neglect tests				
Key cancellation test				
Left/Right egocentric neglect #patients	63/46	Not Tested	-	-
Asymmetry score mean *(SD)*	2.88 (7.55)	Not Tested	0.14 (1.93)	Not Tested
Apple cancellation test				
Left/Right egocentric neglect #patients	142/57	29/13	-	-
Asymmetry score mean (*SD*)	3.84 (7.7)	2.62 (7.628)	0.29 (2.60)	0.45 (3.21)
Left/Right allocentric neglect #patients	36/119	23/1	-	
Asymmetry score mean (*SD*)	3.57 (7.5)	2.83 (4.21)	0.08 (1.68)	0 .70 (4.43)
Visual extinction test (4 unilateral, 8 bilateral)				
Left/Right egocentric unilateral neglect #patients	63/41	14/9	-	-
Asymmetry score mean (*SD*)	.3 (1.95)	0.266 (2.4)	0 (0.65)	-0.007 (0.23)
Left/Right egocentric bilateral neglect #patients	113/49	20/12	-	-
Asymmetry score mean (*SD*)	1.72 (4.56)	1.31 (5.53)	-0.02 (1.43)	0.16 (1.24)

	Brain Damaged Patients with Visual Neglect		Brain Damaged Patients without Visual Neglect	
	UK	**China**	**UK**	**China**
Figure copy test (57 features)				
Right / Left neglect #patients	40/91	19/14		
Asymmetry score mean (*SD*)	-1.95 (4.59)	1.2 (5.45)	0.21(1.45)	-0.064 (1.7)
Sustain attention tests				
Auditory sustain attention score (54 trials)-mean (*SD*)	37.83 (16.1)	39.26 (15.13)	43.73 (13.48)	42.73 (14.74)
Auditory sustain attention omissions-mean (*SD*)	4.28 (4.75)	4.51 (5.22)	3.72 (4.83)	3.57 (4.38)
Overall correct responses – Key cancelation task (50 targets)-mean (*SD*)	33.75 (14.26)	Not tested	47 (7.23)	Not tested
Overall correct responses Apple Cancelation (50 targets)-mean (*SD*)	26.68(14.78)	29.22 (16.04)	44.32 (8.73)	43.41 (10.79)
Overall correct - Complex figure copy (47 features)-mean (*SD*)	26.09 (11.57)	25.35 (12.85)	37.01(10.57)	36.96 (10.8)
Executive and attention control tests - ability to ignore distracters				
Auditory attention - false alarm -mean (*SD*)	4.5 (5.54)	4.4 (5.16)	2.88 (4.66)	2.91 (4.4)
Key cancelation – false alarm-mean (*SD*)	0.89 (2.18)	Not tested	0.32 (3.53)	Not tested
Apple cancelation false alarms -mean (*SD*)	9.01 (14.76)	7.68 (14.1)	1.56 (8.16)	2.69 (10.28)

H=Haemorrhage; I=Ischemic; *n*=Total number; N.A=non-available; *SD*=standard deviation. Asymmetric egocentric scores were computed by subtracting number of correct responses on the right minus those on the left (not including the centre), a positive value means more right bias (left neglect) and negative more left bias (right neglect).

3.2.2. **Tasks Descriptions**

3.2.2.1. Assessment of Visual Neglect

Patients were classified as suffering from visual spatial attention deficits if they performed below the standardised cut-offs for at least two of the below tasks, independent of the spatial bias direction they presented in individual tests. Not all patients completed all tasks, for example only a minority of patients in the UK completed the key cancellation task and no patient in China completed this task. Patients sometimes did not complete a task because they refused, were tired or the examiner decided to skip the task from various reasons. Only completed tasks were included in the analyses. Hence the degree of freedoms may change between analyses.

The presence of visual neglect was assessed by these tests:

i. Key Cancellation Test

The key cancellation is a search array with a line drawing of targets (keys) and distracters (phones and airplanes). One-third of the distracters are of double size. The page is divided into five vertical columns. Within each column, there are 10 keys (targets), 10 airplanes (distracters) and 10 phones (distracters) which are equally distributed along the vertical line. In total there are 50 targets and 100 distracters. Patients get 5 minutes to complete the task. Patients were classified as having a clinical deficit on key cancellation task that based on cut-offs drawn from the BCoS, see Table 3.2. The key cancellation task was not included in the C-BCoS and was only tested with 280 patients from the UK-BCoS.

Table 3-2. BCoS and C-BCoS cut off scores for visual neglect assessments based on 5th/95th percentile.

		*BCoS cut off points (impairment=less than given scores, unless specified			†C-BCoS cut off points	
		≤64 (N=34)	≤64 - 74 (N=34)	≥75 (N=34)	50-69 (N=94)	≥70 (N=39)
Key Cancellation Test	Key cancellation – total 48 47 47	48	47	47	NA	NA
	Key cancellation – false +ve	>0	>0	>0	NA	NA
	Key cancellation – asymmetry	<0 or >1	<-1 or >1	<-1 or >1	NA	NA
Apple Cancellation Test	Apple cancellation -total	42	42	42	42	39
	Apple asymmetry - full	< -2 or >2	<-2 or >3	<-2 or >3	0,1	-2,1
	Apple asymmetry - incomplete	<-1 or >1	<-1 or >1	<-1 or >1	-3,3	-3,4
Visual Extinction	Left visual neglect	4	4	4	4	4
	Right visual neglect	4	4	4	4	4
	Left visual bilateral	8	7	7	8	8
	Right visual bilateral	8	8	8	8	7.97
Complex Figure Copy	Figure copy	42	41	37	37	34

NA=not available; *= The UK BCoS cut off scores for visual neglect were derived from performance of a group of 100 control participants age-matched to the stroke population (see Bickerton et al., 2015 for details); †=China-BCoS cut off scores for visual neglect were derived from performance of a group of 133 healthy control participants age matched to the stroke population (see Pan et al., 2015) for details).

ii. Apple Cancellation Test

The Apple Cancellation test is designed to measure both egocentric and allocentric neglect (Bickerton et. al., 2011; Chechlacz, at. al.,2010) and it is similar to the Ota's et. al.'s Gap Detection Task (2001). The test consisted of 150 apples, 30 large and 120 smalls. The sizes of large apples were 50% bigger than the small apples. The apples were presented in an upright orientation on a page of A4 paper in landscape orientation. Out of 150 apples, 100 were distractor items (50 apples with an opening on the left side and 50 apples with an opening on the right side) and 50 were target items (full apples). Target and distracter items were equally distributed across the page which was divided using a 2(rows) x 5(column) invisible grid. Each cell of the grid include 15 apples: 3 large apples (one without opening, one with an opening on the right side, and one with an opening on the left side) and 12 small apples (four without openings, four with an opening on the right side, and four with an opening on the left side). The midline of the page was placed at the midline of the participant.

The accuracy score was the total number of targets selected (maximum = 50, for each test). The asymmetry score for egocentric neglect was the difference between the number of targets selected on the right side and the number targets selected on the left side (excluding the middle column) (maximum = 20, for each test). Positive values mean more targets were selected on the right than the left side (left neglect) and negative values mean more targets were selected on the left side than the right side (right neglect). While for the asymmetry score for allocentric neglect was the difference between the total number of distractor items cancelled with a left opening and the total number of distractor items cancelled with a right opening. Positive values mean right neglect and negative values mean left neglect. The cut off scores were based on the 100 control participants, Table 3.2 (see Bickerton et al., 2010 for details). Patients get 5 minutes to complete the task. The apple cancellation was tested with 707 patients from the UK-BCoS and with all the C-BCoS patients.

iii. Visual Extinction

Visual extinction test comprises of four unilateral left visual stimuli (fingers wiggle by the examiner), four unilateral right and eight bilateral items. The scores of performances were basically based on whether unilateral stimuli are missed (indicates a measure of neglect or a field defect), and based on whether there is a spatially selective drop in detection on one side when two stimuli relative to one stimulus are presented (indicates a measure of extinction). Patients were categorized as having a clinical deficit on visual extinction task that based on cut-offs drawn from the BCoS, see Table 3.2.

iv. Complex Figure Copy

Complex figure copy task contains a figure to copy that has a middle structure and additional structures to the left and right sides. The numbers of elements to the left and right sides are equated to balance the probability of left or right neglect. Patients can be awarded 47 points according to presence, accuracy, placement, and fragmentation. See Table 3.2 for cut off scores.

3.2.2.2. Assessment of Non-Spatial Deficits

Non-spatial deficits can be divided into two types: sustain attention reflecting the alertness attentional system, and the ability to ignore distracters which reflect the executive control attentional system.

i. Assessing Sustain Attention:

Apple and key cancellation tasks - we used the total number of correct hit responses (cancelling a target). Similarly, the total number of correct responses in the complex figure copy task was used as a measurement ability to sustain attention and focus on the task requirement.

The auditory attention task was specifically designed to measure sustained attention. In this task, participants listen to 54 words which are read at an average paste of 1 word every 3 seconds, with variable inter trail interval of 2-4 seconds. Participants are given 3 high-frequency words as targets, they need to tap with their finger every time they hear the target, the task also has three high-frequency distracter words which are semantically related. Half of the trails are the target and half are the non-target. For the measure of sustain attention, we extracted the overall number of correct responses and the number of omissions (failing to detect a target word).

ii. Assessing Executive Control:

The number of false alarms was used as a measure of the function of the executive control attentional system, specifically as a measure of the ability to inhibit the response to distracter. These were the number of distracters crossed in the cancellation tasks, and number of tapping to a distracter in the auditory attentional tasks.

3.2.2.3. Assessment of Reading Abilities

i. Reading Non-Words

UK-BCoS:

The nonword reading stimulus consists of six items, presented each five or six-letter words. The items were presented three at a time. The test assessed both the ability to use phonological procedures in reading and the ability to use lexical procedures when reading non-words.

C-BCoS:

In the Cantonese/Mandarin written words, irregular characters were regarded as similar to exceptional words or nonwords (see Pan et al., 2015 for details). This because in logographic writing system non-word cannot be created, as graphemes always have a meaning.

ii. Reading Sentence

UK-BCoS:

The stimulus set comprised of two sentences that allowing the examiner to access a patient's ability to read different word classes such as verbs, nouns, pronouns, adjectives, adverbs and prepositions. The sentences consisted of both regular and exception words, as well as suffixed and prefixed words. These sentences presented across three lines; for the first sentence and five lines for the second sentence. The sentences are presented in centred alignment on the stimulus page.

C-BCoS:

The C-BCoS version included regular characters in their reading sentence tests (see Pan et al., 2015 for details).

3.2.3. **Data Analysis**

Missing data were not replaced; hence analysis slightly differ in the number of participants included depending on the available data.

Visual spatial neglect was defined based on standardised BCoS and C-BCoS cut-off scores that derived from performance of a group of healthy controls, age and culture-matched to the stroke population (see 3.2.2.1) The data for the UK and China were analysed separately in order to provide internal replications across cohorts.

Independent two-sample *t*-tests were used to compare the demographic and performances of patients, who suffer from visual neglect and those who did not. In all *t*-tests, the variance was assumed to be unequal, given the large difference in size between the group with visual neglect symptoms and those with non-neglect symptoms. Note that this correction has affected the degrees of freedom and *t*-statistics in the tables. Holme-Bonferroni correction was used to correct for multiple comparisons, such number of comparisons was reduced for each Bonferroni corrected reliable effect. In addition, for each statistical test, the Hedges' *g* effect size is provided, to adhere to the same procedures as in the meta-analysis chapters. Finally, we computed stepwise regression analyses to assess whether the severity of spatial bias (absolute asymmetric scores) or of non-spatial symptoms explains the reading impairment better. The regression included all the tasks/measures presented in Table 3-3 as predictor with the dependent variable being the accuracy of the reading sentence, or reading single words.

To answer the second question of whether the spatial features of visual neglect were associated with the type of reading errors. It was expected that egocentric would be associated with errors in sentence readings, while allocentric with errors in single words/non-words reading. Here only data from the cancellation tasks was used to classify patients to one of four groups: a) patients showing allocentric and egocentric symptoms, b) patients showing only egocentric, c) patients showing only allocentric and d) patients showing impairment in neither. One-way ANOVA followed by Bonferroni post-hoc *t*-test was used to compute the impact of frame of reference on reading different types of text.

3.3. RESULTS

In both databases (the UK & China), neglect and non-neglect patients did not differ in age, years spent in education, time from stroke to cognitive test, handedness, and sex distribution. In comparison to patients with no spatial neglect symptoms, patients who suffered from visual neglect showed larger impairment in sustain attention, cancelled fewer targets, drew fewer features in the complex figure copy task and the UK sample also had difficulty in sustaining attention to auditory stimuli. Patients with visual neglect symptoms also showed larger impairment in executive control attention, as they responded more to distracters, compared with their counterparts who did not show spatial neglect symptoms. Though all the effect sizes were relatively small.

Table 3-3. Visual neglect, sustain attention and executive controls.

A. UK

Sustain Attention	**Group**	***N***	***M***	***SD***	***t***	***df***	***p***	**Hedges'*g* effect size**
Apple Cancellation #Hit	Neglect	210	26.68	14.78	-16.14	272.53	.000	-1.45
	No neglect	497	44.31	8.72				
Auditory Attention #Correct	Neglect	210	37.82	16.1	-4.72	325.87	.000	-0.39
	No neglect	555	43.72	13.47				
Auditory Attention #Omission	Neglect	210	4.28	4.75	1.44	381.98	.150	0.11
	No neglect	555	3.72	4.82				
CFC #Correct	Neglect	216	26.09	11.56	12.00	364.228	.000	-0.98
	No neglect	548	37.01	10.56				
Executive Controls								
Apple Cancellation #FA	Neglect	210	3.42	7.24	4.64	278.195	.000	0.42
	No neglect	496	0.92	4.45				
Auditory Attention #FA	Neglect	210	4.49	5.54	3.73	327.102	.000	0.31
	No neglect	554	2.88	4.66				

B. CHINA

Sustain Attention	**Group**	***N***	***M***	***SD***	***t***	***df***	***p***	**Hedges'*g* effect size**
Apple Cancellation #Hit	Neglect	41	29.22	16.04	-5.45	46.58	.000	-1.04
	No neglect	233	43.41	10.79				
Auditory Attention #Correct	Neglect	43	39.26	15.15	-1.40	56.47	.168	-0.23
	No neglect	251	42.73	14.74				
Auditory Attention #Omission	Neglect	43	4.51	5.23	1.11	52.61	.271	0.19
	No neglect	251	3.57	4.38				
CFC #Correct	Neglect	44	25.89	12.64	-5.50	54.19	.000	-0.94
	No neglect	265	36.98	10.92				
Executive Controls								
Apple Cancellation #FA	Neglect	41	7.68	14.1	2.17	47.77	.035	0.40
	No neglect	233	2.69	10.28				
Auditory Attention #FA	Neglect	43	4.4	5.17	1.78	52.98	.047	0.31
	No neglect	251	2.91	4.41				

#=numbers; CFC=complex figure copy; *df*=degree of freedom; FA=false alarm; M=mean; *N*=total; p=P-value; t= t-test; *SD*=standard deviation.

More importantly for the current thesis, patients who suffer from visual neglect showed more deficits when reading sentences and when reading single words (non-words in English or exceptional words in simplified Chinese). Visual neglect patients also took longer to read. The difference was more reliable in the UK database, this is potential as the UK sample was much larger. However similar effects sizes were observed in China and the UK cohorts.

Table 3-4. Visual neglect and reading.

A. UK

Reading Tests	**Group**	***N***	***M***	***SD***	***t***	***df***	***p***	**Hedges' *g* effect size**
Sentence Reading #Correct	Neglect patients	221	32.8	12.57	-6.04	298.18	.000	-0.52
	No neglect patients	586	38.32	8.45				
Sentence Reading Time	Neglect patients	215	47.73	64.91	3.93	246.52	.000	0.36
	No neglect patients	573	29.68	28.91				
Nonwords Reading #Correct	Neglect patients	222	3.81	2.18	-3.72	369.72	.000	-0.30
	No neglect patients	580	4.43	1.99				
Nonwords Reading Time	Neglect patients	210	27.76	30.7	4.06	278.30	.000	0.36
	No neglect patients	565	18.49	20.1				

B. China

Reading Tests	**Group**	***N***	***M***	***SD***	***t***	***df***	***p***	**Hedges' *g* effect size**
Sentence Reading #Correct	Neglect patients	40	30.93	13.64	-3.35	43.20	.002	-0.66
	No neglect patients	257	38.34	7.95				
Sentence Reading Time	Neglect patients	38	50.51	42.41	3.1	43.20	.003	0.61
	Healthy controls	253	27.88	30.85				
Nonwords Reading #Correct	Neglect patients	40	4.03	2.28	-1.96	47.48	.056	-0.36
	No neglect patients	255	4.77	1.86				
Nonwords Reading Time	Neglect patients	36	31.47	33.37	2.34	40.10	.024	0.47
	Healthy controls	251	18.01	23.42				

#=numbers; *df*=degree of freedom; M=mean; *N*=total; p=P-value; t= t-test; *SD*=standard deviation.

We next tested whether the spatial bias associated with a specific frame of reference led to a different pattern of errors. To this end, the patients were divided into four groups: patients with no visual neglect symptoms, those with only allocentric neglect, only egocentric neglect, or both neglect types. One-way ANOVA was computed for each reading measurement independently (see Figure 3.1.). All ANOVAs in the UK cohort show a strong and reliable effect of group: reading sentence accurately $F(3,803) = 13.8$, $p = .000$; reading sentence time $F(3,784) = 8.9$, $p = .000$; reading non-words $F(3,798) = 4.1$, $p = .007$; reading non-word time $F(3,774) = 6.3$, $p = .000$. Bonferroni corrected post-hoc showed that the effect primarily emerged from the difference between the non-visual neglect patients and those who show egocentric neglect. The performances on patients with allocentric neglect only did not differ from the non-visual neglect group on any of the measures. The group factor had no reliable effect on any of the reading task in the Chinese cohort (all Ps > .5), this is potential because of lack of power and the very small number of patients showing allocentric neglect symptoms.

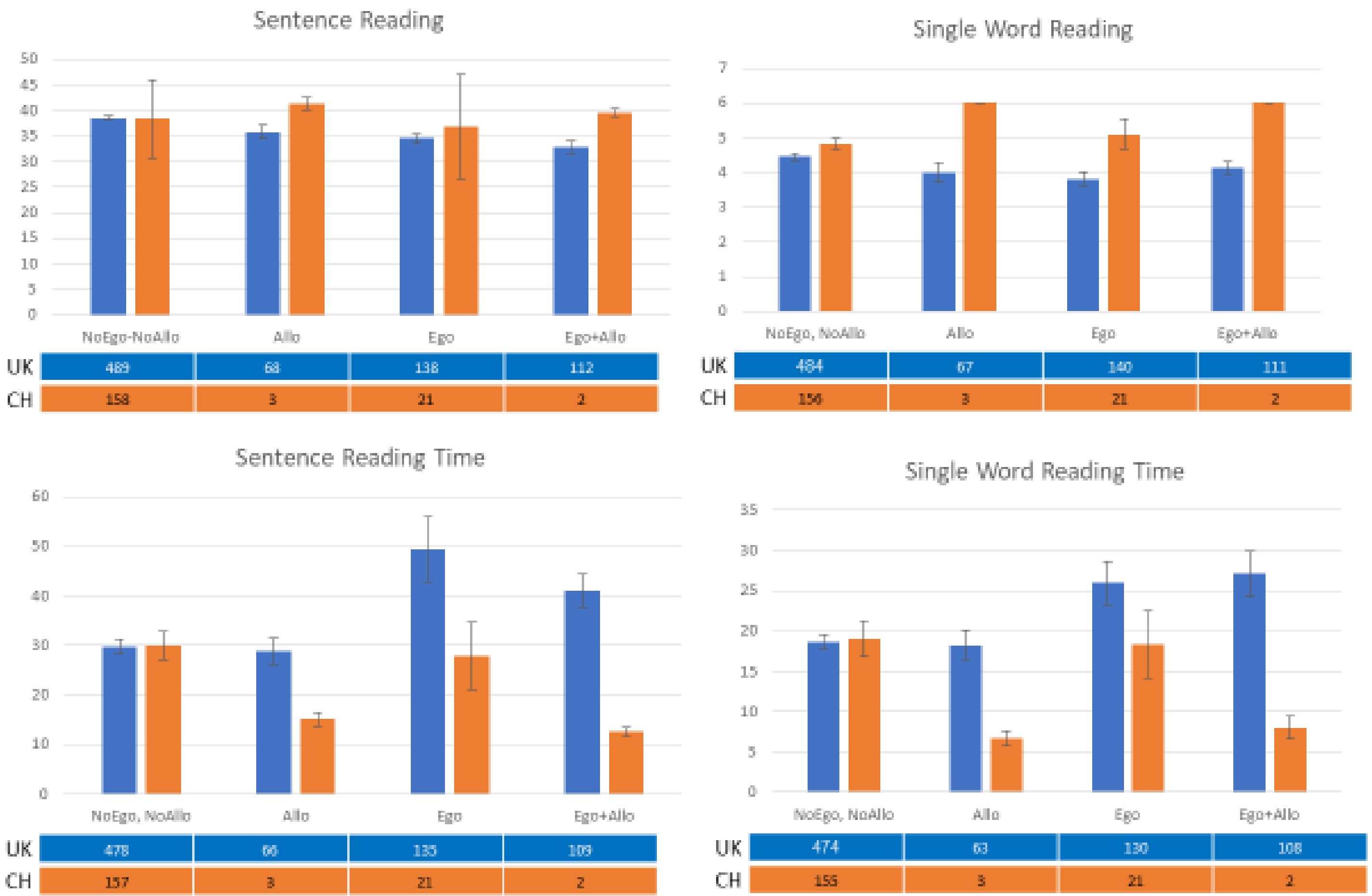

Figure 3-1. Reading and allocentric and egocentric neglect The figure shows the average performance of each group on each of the reading measures. The top charts represent reading accuracy (number of correct words read), the bottom reading time in seconds. how long it took to complete the task. The number of patients in each group is presented below the charts.

Finally, a stepwise linear regression analysis was used to determine the attentional components that best predicts reading impairment. A separate regression was performed for each reading task and each cohort. Continues data was used. *Spatial attention* was modelled using the size of the allocentric and egocentric asymmetric bias (absolute score) from the apple cancellation task and CFC. *Non-spatial components* include the *sustain attention*: number of hits in the apple cancellation task, correct response in the auditory attention, number of omission in the auditory attention task, and number of correct responses in the CFC; *executive control attention* was modelled using the false alarm responses in the apple cancellation task and the auditory attention task. Altogether there were 9 potential predictors. Table 3-5 presents the predictors that were included in the final model for each task and cohort. The final models were highly reliable across all tasks across both cohorts.

As can be seen across all four tasks, the measurements of sustain attention were the best predictors of reading abilities. These included the auditory attention task and the number of correctly cancelled targets, the number of correctly copied features in the complex figure task also predicted sentence reading and single-word reading in Chinese. In the Chinese cohort, spatial biases of allocentric and egocentric neglect were also a good predictor for sentence reading difficulty.

Table 3-5. Stepwise linear regression.

Sentence reading	**Standardized Beta**	***t*-statistic**	***p***
China: *F*(5,254) = 25.9, *p*=.000			
Apple cancellation #HITS	0.485	7.846	.000
Auditory Attention #Correct	0.211	3.966	.000
Egocentric Asymmetry	0.128	2.127	.034
CFC Asymmetry	-0.163	-2.815	.005
Allocentric Asymmetry	0.118	2.111	.036
UK: *F*(3,590) = 58, *p*=.000			
Auditory Attention #Correct	0.283	7.333	.000
Apple Cancellation #HITS	0.193	3.929	.000
CFC #Correct	0.139	2.744	.006

Single non-words reading*	**Standardized Beta**	***t*-statistic**	***p***
China: *F*(2,251) = 18.7, *p*=.000			
Auditory Attention #Correct	0.296	4.907	.000
Apple cancellation HITS	0.155	2.566	.011
UK *F*(3,381) = 43.38, *p*=.000			
Auditory Attention #Correct	0.355	7.060	.000
CFC Asymmetry	-1.950	-4.000	.000
Auditory Attention #Omission	-1.320	-2.950	.003

*In C-BCoS, the single words were exceptional words, while in UK-BCoS these were pronounceable non-words.

3.4. <u>DISCUSSION</u>

Similar to the results reported in the meta-analyses (CHAPTER 2), the analysis of the unbiased sample databases of stroke survivors that reading deficits were more prevalent in stroke patients who suffer from spatial attention deficits than their counterparts who do not. This was shown for both the accuracy and speed of reading sentence and single words; it was also shown in the UK sample and a sample from China. The type of spatial neglect (as reflected by the impaired attentional frame of reference) did not affect the error pattern. Finally, stepwise regression analysis showed that the most reliable predictors for sentence and words reading performances were measurement associated with sustain attention; though spatial bias measures were also reliable predictors for sentence reading tasks.

CHAPTER 2 and CHAPTER 3 results showed that generic reading difficulty was greater for neglect patients than other control groups and surprisingly reading performance within neglect patients was much worse than other brain damaged patients. In terms of Posner and Peterson's Attentional model (1990), the data suggests that the non-spatial component, specifically of the alert attentional network may be impaired in spatial neglect patients and contribute to their reading deficits. These errors pattern may also be understood in terms of difficulties to control and shift attention as proposed by the sluggish attentional shifting (SAS) account (Hari et al., 2001).

Visual neglect patients have been shown to be slow in processing rapid sequences of stimuli relative to non-neglect patients (Husain et al., 1997). Husain et al. (1997) reported that patients with right hemisphere lesion neglect may likely to have up to four times longer attentional blink compared to healthy individuals. These prolongations were also observed in developmental dyslexic readers (Hari, Valta, & Uutela, 1999). Developmental dyslexic readers had significantly prolonged attentional blink up to 30 % longer than it does in normal healthy controls. Therefore, poor reading performance in neglect patients could emerge from sluggish attention shifting, as experienced by developmental dyslexic readers that are slower in disengaging their attention from the previous target. This is commonly attributed to malfunctioning of the posterior parietal lobe (Posner & Raichle, 1994). Thus, attentional dysfunctions of the parietal lobe, may contribute to the generic reading impairment we observed in neglect patients.

The high prevalence of reading errors observed in visual neglect patients can be explained using the ‘stimulus density-sensitive’ hypothesis of unilateral visuospatial (Riddoch, 1990; Trojana, Grossi, & Flash, 2009; Husain & Kennard, 1997). This hypothesis puts forward the idea that unilateral visuospatial neglect patients frequently show a more severe deficit in tasks that require high cognitive demands (Trojana, Grossi, & Flash, 2009; Husain & Kennard, 1997), especially when the visual field is crowded with information, such as the case when needing to perceive/process single items presented in compound format (letter in words, and words in sentences). The increase in reading times of visual neglect patient, observed especially in the UK sample, support the idea that reading required more attentional resources in those patients than in the non-neglect patients. It has been shown that neglect patients who are impaired when completing a complex task tend to show a good performance on simpler, less cognitively demanding (less crowded display) tasks (Trojano, Grossi, & Flash; Husain & Kennard, 1997). An example of this can be shown by Bonato, Prifits and Umilta (2013) who found that ten stroke patients showed no neglect when performing a simple line cancellation task but had a worse performance when they were confronted with a complex display in a computerised task. These results support the idea that crowded displays may be at the root of the reading impairments. Riddoch, Humphreys, Cleton & Fery (1990) demonstrated that the attentional demand may also cause an increase in errors in neglect dyslexia patients.

In contrast to my hypothesis, the current data indicated that reading impairment was not associated with the spatial deficits that characterise the syndrome. One possible explanation is that reading impairment emerge from the non-spatial deficit hypothesis of visual neglect (Corbetta and Shulman, 2011). It is shown that visual neglect patients have reduced arousal (Heilman, 1979; Storrie-Baker, 1997). Chatterjee et al. (1992) described a left-sided neglect patient who alternately cancelled targets on the right and left side of an array. Using this procedure, this patient was able to eliminate her right-sided bias, but she did not cancel more targets. Instead, she now neglected in the centre of the stimuli. The authors suggested that her inattention deficits emerged from loss of vigilance.

The data also showed that the spatial frame of reference did not affect reading abilities or reading errors. It was hypothesised that allocentric (object-centred) would show larger impairment when reading single words compared with ego centric (field based) neglect. As single words are typically presented at fixation and are perceived as a single object. However, the data (CHAPTER 3) especially suggested the opposite, patients showing only allocentric neglect were slightly better at reading both sentences and single words than those who showed only egocentric symptoms. The meta-analysis data showed that cases of dissociated ego and allocentric neglect are rare, but this could be because of selection bias favouring ego-centric neglect, which is the most pronounce symptom, or because the standard tests are not optimise to dissociate between the two type of spatial biases.

Comparison across different writing systems, the data suggested that visual neglect patients from the UK and China showed more impairment in reading than patients who did not show neglect symptoms. This suggests that independent of the writing system in visual neglect have negative impacts on reading.

3.4.1. **Reading Deficits in Visual Neglect - Attentional Systems Framework**

I explored the rule of different attentional systems in reading using regression analyses. The model included regressors that estimated: 1) *the alertness and vigilance system* (overall accuracy in cancelation, the auditory sustain attention and complex figure copy tasks), 2) *the spatial orientation system* (egocentric and allocentric spatial asymmetry scores in the cancelation task and complex figure task) and 3) *the executive control system* (ability to ignore distracter, measures of false alarm in the cancelation task and auditory attention task). Across both reading tasks (single non-words, sentence reading) and both cohorts (UK, China), impairment in the alertness and vigilance system was most reliable predictor of reading impairment. Here, the best predictors of the regression analysis demonstrated that independent of writing system, non-spatial attention deficits, experienced by visual neglect patients best explains reading impairments. Deficits in the orientation systems as indicated by the asymmetric scores, predicted sentence reading impairment in the China database and single word reading deficits in the UK data. Regressors associated with executive control function, and especially the ability to ignore distracter were not associated with reading impairment in neither of the models.

3.4.2. **Limitations and Future Direction**

Assessing spatial biases in reading. Reading in Latin based writing systems (studies contributing to meta-analysis and the UK database) requires attentional shift in the direction that is easier to most visual neglect patients: left-to-right - contralesional-ipsilesional. Hence it is possible that the observation that reading is not related to the spatial biases may emerge from the fact there is little data and fewer cases of patients who show spatial bias toward the left hemifield in an opposite direction to the reading scanning path. CHAPTER 4 will focus on a single case that shows the non-common spatial bias (right visual neglect), following a left parietal lesion. Furthermore, CHAPTER 3, did not analyse the spatial distribution of errors reading made by participants. Given the unbiased sample, and the use of two different writing systems, it will be important in the future to test whether the spatial distribution of the reading errors support the results obtained in the meta-analysis - lack of spatial biases effects.

Comorbidities of reading and attention deficits in acquired lesions can be argued to emerge because stroke affect neuro-anatomical areas based on the structure of neurovascular system rather than the architecture of neurocognitive function. In other words, it is possible that comorbidities emerge because regions that process word recognition and control for attention rely on the same blood artery and are located in the spatial proximity, but the two are not functionally connected. This will accord with Caramazza and Hills (1990) proposal, that neglect deficits directly affect the word recognition process; which contrast with Humphreys and Riddoch (1993) proposal that the impairment in readings deficits are mediated by malfunctioning of core attentional processing. CHAPTER 5 attempted to tests this contrasting models.

3.4.3. **Conclusion**

CHAPTER 2 and CHAPTER 3 showed that deficits in sustain attention and the ability to keep vigilant are the core problem that hinder ability to read in patients suffering from visual neglect. While deficits to the orientation systems, may also exasperate the deficits, but less consistently. This conclusion emerged using two very different methods and data.

CHAPTER 4: AN ANALYSIS OF HIGH-LEVEL NEGLECT DYSLEXIA: A CASE STUDY

4.1. INTRODUCTION

In the previous chapters, I showed that reading deficits are common in patients who suffer from neglect. Though unlike neglect-dyslexia, as a group the errors pattern produces by visual neglect patients did not reflect their spatial deficits. In this chapter, I will focus on a single case of a patient who showed a clear neglect-dyslexia, i.e. the error pattern matches the spatial bias observed in their visual attention. The current case study presents patient UB12, who showed high-level neglect- type impairment in reading characterised by affecting the ending (right) of words across a variety of transformations. Note that the reading deficits of UB12 matches their attentional spatial bias, favouring the left over the right hemifield (the less common spatial biased). UB12 spatial attention deficits are also similar to those reported by Caramazza and Hills (1990) and Haywood and Colheart (2001), all representing the less common left-biased visual neglect symptoms.

The current study aimed to provide a better understanding of the interplay between spatial attention and reading, specifically whether attention hinder perception or the representation of objects. It uses Caramazza and Hills model for word recognition as a theoretical framework. It critically asked whether reading deficits observed in some patients with visual neglect symptoms are due to malfunctioning of the word recognition process, or are due to the malfunctioning of the core attentional systems, as predicted by the IAS model (see above).

The multilevel word recognition (Caramazza and Hills, 1990) and IAS accounts for the comorbidity observed between spatial attention and reading deficits (Humphreys & Riddoch,1993) propose differing set of predictions regarding the impact of visually based manipulations (i.e. change of fonts). The multilevel word recognition predicts that deficits are specific to the damage level of the word representation. Thus, font manipulation would only affect the stimulus-centre level but not the word-centre stage, where words are presented in an abstract way. In contrast, if neglect dyslexia emerge from deficits in independent attentional orienting systems (visuospatial representation) manipulation of visual features of words would affect processing at the highest level of representation (word grapheme, word-centre). In such a case, a spatial deficit arises following damage to the visuospatial attention system and the problem manifests as a consequence of the typical pattern of integration of spatial attention and the word recognition system. Thus, damaged visuospatial function thought to be irrelevant to the word-centre level that could alter the word grapheme representation of the stimulus.

The impact of altering visual information on word recognition has been examined by manipulating letter case (e.g. Braet & Humphreys, 2006; Mayall, Humphreys, & Olson, 1997). Braet and Humphreys (2006) showed that impaired function in parietal cortex was associated with reduced reading ability for mixed case stimuli but not a reduced ability to discriminate words with lower visual contrast. Here attentional functions, in the parietal cortex, are needed when words present with an unusual shape, but not merely when they are degraded. These demands appeared to arise after the feature-level of coding and to reflect attentional involvement at higher levels of the word representation.

4.1.1. **Dyslexia-Neglect and Recognition of Words and Objects**

A related but separate issue concerns the similarity between the ‘word’ object proposed by Caramazza and Hillis (1990) and the more common non-verbal object which is typically studied within the object recognition literature (Vuilleumier, 2002). Central to this is the veridical left and right quality of an object. Object representation is by nature a conceptual, spatially invariant representation, and the quality of having left- and right-side is unusual for such a representation. It would seem words as ‘objects’ may be one of the few exceptions since the left-right scanning order of the letters in English words is critical to word identification.

To test the possibility that non-verbal objects might be neglected in a canonical left-right fashion similarly to words, Savazzi et al. (2004) asked to neglect patients to bisect a picture of a dog with the head always present at one end and the tail at the other. On a critical final trial, the image of the dog was left-right reversed and patients once again performed a bisection task. A subset of the patients showed a reversal of their bisection responses indicating a similar response to that for word reversal. The same researchers (Savazzi et al., 2009) also taught neglect patients a canonical left and right of a novel stimulus, and similar results were obtained to the earlier study (Savazzi et al., 2004). Savazzi et al. propose that high-level canonical representation exists for objects as well as words, and that neglect can affect both – indeed, if this level of representation is common to objects and words then the same pattern of error in reading and object recognition would be expected in a patient with a high-level representational deficit.

Taken together, if Patient UB12 shows similar deficits in processing non-verbal and verbal objects following feature saliency manipulation, I can conclude that their deficit likely due to malfunctioning of their attentional systems.

4.1.2. **Current study**

In this study, I present a patient with profound lateralised reading impairment. The main aim was to explore the nature of his deficit, with particular emphasis on the level of representation involved. To test the effects of varying the visual input, we examined the influence of mixed case on letters in the words – would CaSe MiXiNg combine additively or interactively with the spatial reading deficit in the patient? We were also interested in the degree of similarity in the patient's processing of word and non-verbal stimuli. If there is a high-level deficit in word representation, would this be evident also in object recognition?

I first investigated UB12's general reading ability. This included data on the effects of word frequency, regularity and imageability. Following this, I conducted a series of experiments (Experiments 1-6) to explore the nature of his deficit, partially replicating Caramazza and Hills (1990) paradigms. In Experiment 7, I presented a novel manipulation investigating the effect of mixed upper and lower text formats on UB12's word recognition (Braet & Humphreys, 2006; Braet & Humphreys, 2007). In the next experiment (Experiment 8), I presented data on the effect of derived words and completed words on UB12's reading performance. In the final experiments (Experiment 9 and 10) I explored the nature of 'object' processing and the similarity between word and non- verbal objects, I examined the way UB12's unilateral neglect affects his processing of non-verbal objects.

4.2. CASE REPORT

4.2.1. **Clinical Details and Cognitive Profile**

UB12 was a 77-year-old (date of birth 29th October 1933) male at the time of testing, with ten years' formal education and training as a plumber. UB12 is left-handed, has a corrected-to-normal vision with glasses, and continues to live on his own and performs most activities independently, such as shopping, cooking, cleaning, and driving his car. UB12 suffered his first stroke in 1986 at age 53 and a second stroke in December 1999 at age 66. An MRI scan (Figure 4.1) shows damage in the left hemisphere over the left temporal lobe and inferior parietal lobe, not affecting his dominant (left) hand. UB12 was assessed using the BCoS (Humphreys et al., 2012) twice when he was 72 (2004) and 74 (2006), see Table 4.1. He presented with number of neuropsychological deficits and overall, his cognition deteriorated. On the language tasks, he showed severe deficits on language and number tasks he presented with severe extinction, failing to detect any right (contralesional) visual stimuli when presented with a left stimulation. His ability to detect right stimulation deteriorated across the two years. He also showed severe impairment in sustain attention. Surprisingly he showed no impairment in the key cancellation task or the complex figure copy, see Table 4.1. UB12's other neuropsychological assessments were presented in Table 4.2.

4.2.2. **Test of Visuo-Spatial Ability**

No errors were detected in the standard line bisection or star cancellation tasks (from the Behavioural Inattention Test (BIT)) (Halligan et al., 1991). UB12 then completed 33 apple cancellation sheets (Bickerton et al., 2011), which demonstrated no spatial field deficit but did show significant object-based neglect with objects neglected on their right-hand side (average number of objects neglected per sheet = 2; $t(32)=5.08$, $p<0.001$). This showed that UB12 suffered from allocentric but not egocentric spatial biased.

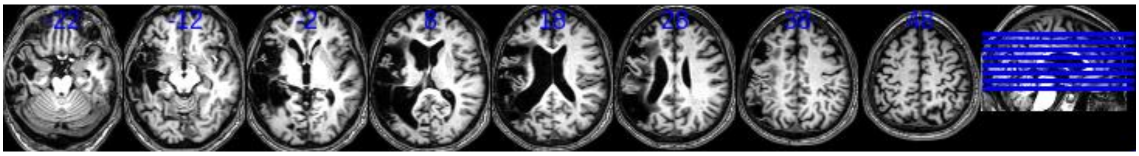

Figure 4-1. UB12's T1-weighted MRI brain scan.

Table 4-1. Cognitive profile UB12, BCoS.

	Year of Test	**2004**	**2006**
	Age of Test	**72**	**74**
Language	Picture naming (14)	11	8
	Sentence construction (8)	3	7
	Sentence Reading (42)	24	16
	Sentence reading (Time, sec)	59.52	152
	Nonwords readings (5)	0	0
	Nonwords reading (Time, sec)	NR	NR
	Words + nonwords writing (5)	NT	0
Number	Number Reading (9)	NT	4
	Number writing (5)	NT	0
	Calculation (4)	NT	0
Praxis	Multistep object use (12)	12	10
	Gesture production (12)	12	8
	Gesture recognition (6)	5	6
	Gesture immitation (12)	10	9
	Complex figure copy (47)	NT	44
Memory	Orientation personal (8)	8	7
	Orientation Time and space (6)	4	5
	Orientation Time and space FC (6)	6	NR
	Immediate Story recall (15)	6	3
	Immediate Story recognition (15)	13	11
	Delay Story recall (15)	9	3
	Delay Story recognition (15)	14	12

	Year of Test	2004	2006
	Age of Test	**72**	**74**
Attention	Key cancelation (50)	50	46
	Key Cancelation (FA)	0	0
	Key Cancelation asymmetry	0	1
	Visual Left Unilateral (4)	4	4
	Visual Right Unilateral (4)	3	0
	Visual Left Bilateral (8)	8	8
	Visual Right Bilateral (8)	0	0
	Tactile Left Unilateral (4)	4	4
	Tactile Right Unilateral (4)	4	4
	Tactile Left Bilateral (8)	8	8
	Tactile Right Bilateral (8)	8	8
	Birmingham Rule Finding accuracy (18)	1	1
	Auditory attention corrects (54)	9	NR
	Auditory attention false positive (27)	0	NR
	Auditory attention omissions (27)	9	NR
	Auditory attention memory of target words (3)	2	NR

The table presents performances of UB12 on two test occasions separated by 2 years. Each task is presented line with a bracket indicating the maximum scores that can be achieved. Tasks highlighted in grey represented impaired ability relative to age match controls. Lighted grey represents impaired but borderline performances; NR=not reported; NT=not tested.

Table 4-2. UB12's neuropsychological assessment.

Other neurocognitive tests:	**Assessed in 2007**
Test of verbal intelligence:	
a. National Adult Reading Test (NART)	49/50
b. Full Scale Intelligence Quotient (FSIQ)	70
c. Verbal Intelligence Quotient (VIQ)	72
Non-verbal intelligence:	
a. WAIS-R block design, corrected scale score	9
***Speed of information testing* was within the normal range**	
a. Speed of comprehension test, SCOLP	23/26=>5%
b. The non-verbal test WAIS-R, digit symbol: age-corrected	SS=7
***Memory testing*: (profound deficit in the verbal component)**	
a. (WMS-R, Logical memory I (LM I)	Raw=6/50, %=2
b. WMS-R, Logical memory II (LM II)	Raw=4/50, %=9
Non-verbal memory showed less impairment a. WMS-R, Visual Reproductions I (VR I)	raw = 23/41; % = 34
b. WMS-R, Visual Reproductions II (VR II)	raw = 16/41; %=25
Attention testing showed high normal scores	
a. the Behavioural Inattention Test	144/146, WNL

Other neurocognitive tests:	**Assessed in 2007**
Verbal short-term memory showed a striking impairment	
a. WAIS-R, Digits forward and backwards: age-corrected	SS=6; F raw =0/14, %=<5
	B raw=1/14, 1/14, %=<1
Non-verbal testing of attention demonstrated impairment	
a. Tests of everyday attention: Map search	1 min raw = 5, SS=<1
	2 min raw = 15, SS=<10
Executive function testing on verbal fluency was impaired	
a. Controlled oral word association test	FAS = 2, % = < 10; mean = 35.6 (12.1)
b. Animals	=7, % = <10; mean = 17.6 (4.7)
Some Non-verbal tests were impaired	
a. Trails A	A = 83 secs; % = <10, m=35.8 (11.9)
b. Trails B	B = 286 secs; % = <10, m=81.2 (38.5)
Picture naming on the Birmingham Object Recognition Battery (BORB)	
a. Picture naming (short) was reasonable	12/15
Measures of depression (HADS)	normal range
Activities of daily living (Nottingham ADL)	normal

4.3. PRELIMINARY INVESTIGATIONS

To explore how well the model explicates UB12's deficit I quantified his reading ability with a variety of tasks: word/non-word reading; letter naming and letter colour identification; changes in the topography of the word including inverted and mirror-reversed word reading, word position in the visual field and full-page text reading. In addition, I tested UB12's spelling and copying abilities. For these analyses, I recorded UB12's errors on whole words and letters in words, each incorrectly read letter or misplaced letter within a word was consider as an error (e.g. 'legs' was read as 'lengs', scored 0 0 1 0 0) or the transposing of two letters, such as 'maps' reads as 'masp', then 2 errors point was allocated response (e.g.

‘masp’ would be scored as 0-0-1-1). To examine the effects across letter position in words the data were assessed using chi-square tests and hierarchical log linear analyses.

4.3.1. **BASIC READING**

4.3.1.1. Reading Words and Non-Words

To test general reading ability and more specifically the effect of lexicality and the position of the letter in the word, UB12 read 40 4-letter words and non-words. See (Appendix B). Table 4.3 shows the number of errors for words and non-words at each position. Hierarchical log-linear analyses showed significant differences in reading that were contingent on lexical quality (words/non-words) ($\chi^2(1)=6.08$, $p<0.014$) and the position of the letter in the word ($\chi^2(3)=39.29$, $p<0.001$).

Table 4-3. Number of words and non-words read correctly and reading errors according to letter position.

		Number of Errors			
	Number correct words	**Position 1**	**Position 2**	**Position 3**	**Position 4**
Words	17/40	6	8	13	20
Non-words	2/40	6	10	21	37

Table 4-4. Examples of UB's reading errors.

Target words	Responses	Target non-words	Responses
BOND	BORE	DILD	DUCE
CARE	CAB	FUDE	FUNNY
DEEP	DEAR	HART	PAT
DRAW	DRIVE	HULY	HUT
EASY	ATE	KIPE	KILL
GAIN	GAPE	JOPY	JOB

Word frequency is considered a key factor in the speed of lexical processing (Behrmann, Plaut, & Nelson, 1998; Monsell, Doyle, & Haggard, 1989) and imageability is indicative of semantic processes. These tests measure the state of preservation of UB12's word system function

4.3.1.2. Imageability

UB12 read 4-letter strings presented horizontally in normal left-to-right orientation. Words were selected from the MRC Psycholinguistic Database (*UWA Psychology: MRC Psycholinguistic Database (Dict Interface)*, n.d.). Appendix B. He read 22/60 words and 4/59 non-words correctly. The psycholinguistic assessment of language processing in adult-acquired aphasia (PALPA) tool was used to assess the effect of imageability on reading. To test the effect of imageability as a function of the frequency, UB12 read words varying in both imageability (high and low) and frequency (high and low) (see Table 4.5). Backward elimination using hierarchical log-linear analysis showed a main effect of imageability ($p<0.001$) but no effect of the frequency of words. Thus, top-down processes associated with the imageability of a word may be one mechanism through which UB12 assists impaired lower-level operations. The absence of a strong word frequency effect, however, suggests that any top-down mediation is semantically- rather than lexically-based.

Table 4-5. Number of correctly read words varying in imageability and frequency.

		Frequency		
		Low	**High**	
Imageability	**Low**	3/20	2/20	5/40
	High	9/20	14/20	23/40
		12/40	16/40	28/80

4.3.1.3. Spelling Sound Regularity and Reading

PALPA (task 35) was used to examine the influence of spelling-sound regularity on reading. Words (N=60) split evenly between regular and exception words. UB12 read 29% for regular and 35% for exception words respectively. There was no effect of spelling-sound regularity on reading.

4.3.1.4. Copying Letters

UB12 was instructed to copy four-letter words either from left-to-right (Table 4.6) or right-to-left (Table 4.7). After backward elimination, a hierarchical log-linear analysis revealed reliable effects of position within a word (1 to 4) and instruction (left-to-right versus right-to-left), the instruction by position within word interaction was also reliable ($p<0.001$). When writing from left-to-right UB12 made errors at the right ends of the words. When writing from right-to-left, he made errors at the left ends of words. This result is instructive since it suggests that UB12's spatial errors in copying were not based on a high-level representation that is constant irrespective of whether the words are written from left-to-right or right-to-left.

Table 4-6. Number of words and letters written from left-to-right.

	Number Correct Letters	Number Correct Words	Number of errors relative to position in word			
			Position 1	Position 2	Position 3	Position 4
Words	17/80	13/20	0	0	4	6
Non-Words	66/76	12/19	1	0	3	6

Table 4-7. Number of Words and letters written from right to left

	Number Correct Letters	Number Correct Words	Number of errors relative to position in word			
			Position 1	Position 2	Position 3	Position 4
Words	59/76	9/19	6	4	5	2
Non-Words	66/76	11/19	4	4	1	1

4.3.2. **INTERIM SUMMARY**

These findings indicate that UB12 is much better at reading words than nonwords. This suggests that he struggle when reading relies on his ability to shift attention from left-to-right, which is mostly pronounced when each phoneme must be identified. Real words may rely on a compensatory mechanism, where serial phonological reading route that can be bypassed using eh semantic route. Nevertheless, both when reading words and non-words, his spatial bias is pronounced, and he mostly misses letters on his neglected side. As expected less imaginable words and less familiar words, both magnify his reading impairment. Copying letter, which requires a serial spatial shift of attention is impaired both for words and non-words. UB12 makes right-end errors in reading and in copying left-to-right but make the reverse when copying right-to-left. This may suggest that beyond spatial bias, his very limited sustain attention capacity hinders his performances.

4.4. <u>EXPERIMENTAL INVESTIGATIONS</u>

Following these initial tests, a series of experiments was conducted in order to tie-down the nature of UB12's reading deficit in more detail. This included comparing word reading with letter reading and reading non-linguistic material placed in the same positions (Experiments 1-3), examining the effects of position in field and position in word on reading (Experiment 4), the effects of word topography (e.g., whether or not words were inverted, (Experiment 5), delayed copying and spelling of words (Experiment 6) and reading words in different formats (mixed case and handwritten, Experiment 7).

4.4.1. <u>**Experiment 1-3: Reading words, Reading Letters and Letter Colour Description**</u>

4.4.1.1. Experiment 1

4.4.1.1.1 **Methods**

UB12 was presented with 80 4-letter words, all mid-frequency in English (Kucera & Francis, 1967, word frequencies >10 and <50) and 80 4-letter nonwords created by changing one letter in the words. Appendix B. The words were chosen without regard to spelling-sound regularity as UB12 showed no effect of this variable. The nonwords were all pronounceable.

The stimuli were presented in times New Roman typography size 14 on an A4 sheet. Each letter was a different colour and the colours of individual letters were selected at random from a set of 8 colours that UB12 could name (red, blue, pink, yellow, green, orange, purple, brown). The viewing time was unlimited.

4.4.1.1.2 **Results**

UB12 read 28/80 words (35%) correctly. Errors in reading whole words showed a significant change across letter position ($\chi^2(3) = 25.59$, $p < 0.001$). The data showed neglect of the right side of the word, as a greater number of errors occurred on the final letters (87%) of the words in comparison with initial letters (13%) (Figure 4.2). In total, UB12 read 5% (4/80) of non-words correctly. Reading non-words showed a significant change across letter position ($\chi^2(3) = 21.02$, $p < 0.001$). The data showed neglect of the right side of the non-word, as a greater number of errors occurred on the final letters (94%) of the words in comparison with the initial letters (48%).

4.4.1.2. Experiment 2 & 3: Naming the Letters and Naming Their Colours

4.4.1.2.1 **Methods**

UB12 was asked to name each letter in the words and nonwords (Experiment 2) and then to name the colours of the letters (Experiment 3).

4.4.1.2.2 **Results**

In total, UB12 named 79% (63/80) of the letters correctly. Letter identification showed no significant change across letter position ($\chi^2 < 0.2$) (Figure 4.2). Overall UB12, accurately described 90% (72/80) of the letter colours correctly. Colour description of letters demonstrated no significant change across letter position ($\chi^2 < 0.8$) (Figure 4.2).

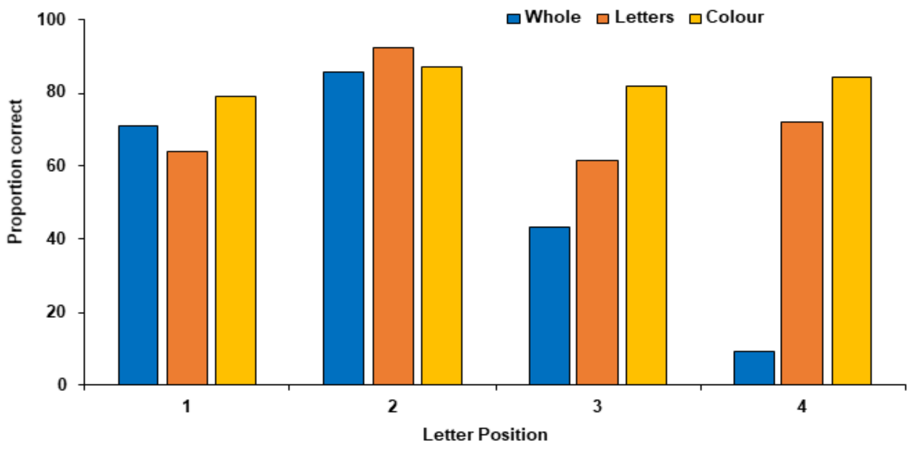

Figure 4-2. Mean per cent correct responses for reading whole words/non-words, reading letters and identifying letter colours.

A Comparison of Letter Positions Across Whole Word Reading, Letter and Colour Identification

A hierarchical log-linear analysis comparing the reading of whole words and letters across letter position was significant for all factors (word vs. letter identification, position and the interaction) ($\chi^2(9)=66.11$, $p<0.001$). In Figure 4.2, the main difference was on the right-hand side of the word (letter positions 3 and 4) where the accuracy for reading whole words was lower than letter identification. Similarly, a comparison of whole words and colour identification revealed a significant effect of all factors ($\chi^2(9)=172.56$, $p<0.001$). Again, there was a drop in reading accuracy at the final letters of the word was the main difference between these groups (Figure 4.2).

4.4.1.3. Summary

UB12 read the left half of words and neglected the right-side letters. This was not a purely perceptual deficit because the letters and their colours could be accurately identified.

4.4.2. **<u>Experiment 4: Position in Field and Text Error Detection</u>**

4.4.2.1. Methods

We want to examine the extent of UB12's retino-centric spatial deficit may associate with reading. He was asked to perform two tasks. First, he read 4-letter words (a subset of items from *Experiment 1*) presented in four different locations in the visual field. Words were randomly presented so that fixation fell at letter positions 1-4. In the second task, UB12 was given a passage containing errors with different parts of the text and also within different parts of the words within the text (stimuli were taken from Humphreys & Heinke, 1998). Error detection was assessed as a function of the position of the word in the text (left, middle or right side) and the letter within the words, allowing measurement of page-based (egocentric) and stimulus-based (allocentric) neglect.

The words were presented in black against a white background on a computer using e-prime software. Each trial had a fixation cross and when UB12 reported fixating, the word was presented for 200ms. The letters each subtended 0.5 degrees of visual angle and appeared in Times New Roman font. There were 40 trials at each fixation and words were repeated across the different fixation positions.

4.4.2.2. Results

Overall, UB12 correctly read 39/160 (24%) of the words presented at different positions in his visual field. The reading showed a significant change as a function of the position of the items in the field ($\chi^2(3)=17.73$, $p<0.001$). The correct reading of words occurred more frequently in the left-field (fixation position 4) (43%) than in the right field (fixation position1) (5%) (see Figure 4.3). For text reading, there was no significant difference in the number of correctly detected errors on the left (20%), middle (33%) and right (9%) of the page. Though these results suggest weaker detection to the right side of the page. UB12 more frequently detected errors to the left of a word (43%) than errors which occurred to the right (14%) of a word. Together, these findings suggest some effect of retino-centric positioning and consistent right-sided neglect of individual objects.

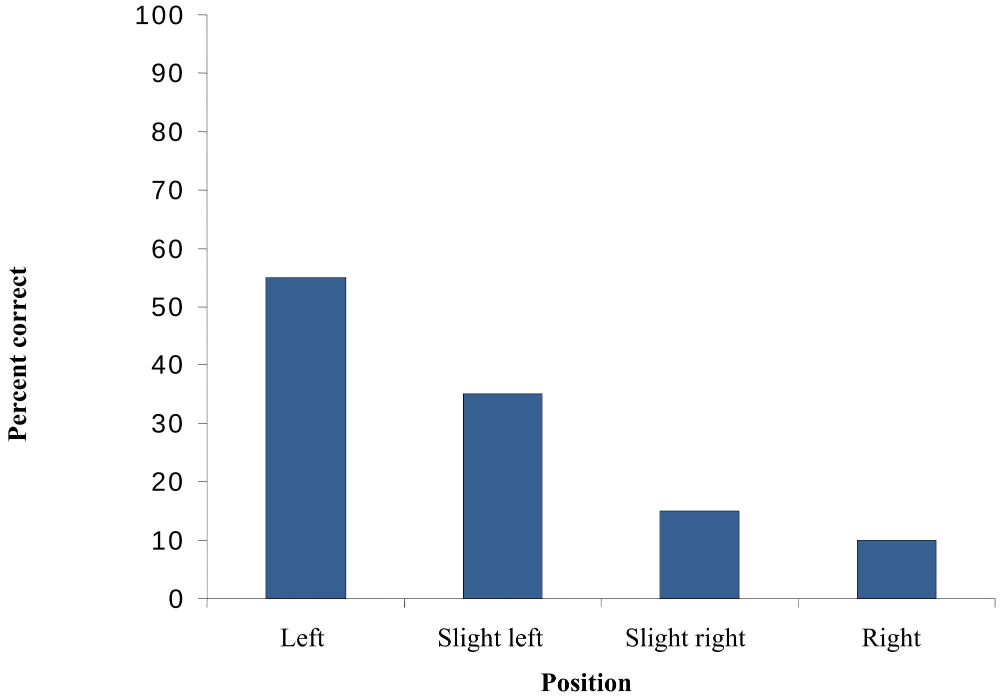

Figure 4-3. Mean percent correct responses for reading whole words in different locations in the visual field.

4.4.3. <u>**Experiment 5: Word Topography**</u>

For a direct comparison with patient NG (Caramazza & Hillis, 1990) and in order to examine the autonomy of word representation for UB12, we examined the effect of topographical changes on early word recognition.

4.4.3.1. Methods

UB12 was first presented with 276 4-letter words and 80 4-letter nonwords, with the words drawn from a similar frequency range as the items used in Experiment 1. The nonwords were formed by changing one letter in the words while leaving the strings still pronounceable. The stimuli were presented in size 14 Times New Roman font on single cards with the letters set out in a vertical orientation. The exposure duration was unlimited. In a second session, he was presented with a subset of 80 of the words which were showed inverted (so the first letter of the word now fell on the right).

4.4.3.2. Results

In total, UB12 correctly read 26% (71/276) vertical whole words and 5% (4/80) of the vertical non-words. Word reading showed a significant change across letter position ($\chi^2(3)=15.09$, $p<0.002$). There was neglect of the canonical right end letters in the words (lower part of the vertical word) (97% of these letters were misidentified or omitted) of the words compared to initial letters (32%) (Figure 4.4).

Overall, UB12 correctly read 25% (20/80) inverted words. The reading showed a significant change across letter position ($\chi^2(3)=22.11$, $p<0.001$). There neglect of the canonical end of the word (which was presented towards the left of UB12), as a greater number of errors were made on the final letters (78%) of the words in comparison to the initial letters (25%) (Figure 4.4).

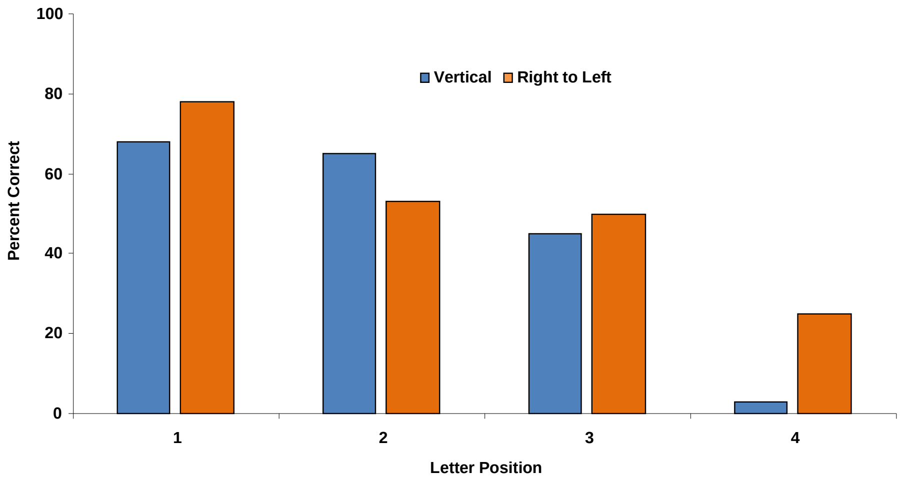

Figure 4-4. Mean percent correct responses for reading each letter position in vertical and right-to-left oriented words.

4.4.3.3. Discussions

Here, UB12 showed a pattern of neglect dyslexia and as before he neglected letters at the ends of the words and nonwords. The interesting result is that this occurred even though the words were written vertically or they were inverted. The data are consistent with UB12 neglecting a canonical word-centred representation, similarly to patient NG (Caramazza & Hillis, 1990). If this is a central representation used for output as well as input, we expect to see a similar pattern in copying and spelling – especially when copying must be done from memory so that it by-passes any early representation that may be used to support direct letter transcription (as in the initial tests; see above).

4.4.4. <u>**Experiment 6: Copying and Spelling**</u>

4.4.4.1. Methods

UB12 was asked to copy 20 4-letter medium frequency words, all presented in size 14 Times New Roman typeface, each on an A4 sheet of paper. Immediately after copying the letter, the stimulus was withdrawn and UB12 was asked to copy the word again from memory. On a second test occasion, he was given the same words again verbally and asked to orally spell out the letters in the words.

4.4.4.2. Results

Overall, UB12 correctly copied 100% (20/20) of the written words immediately, 35% (7/20) of the words following a delay and he verbally spelt just 5% (1/20) words correctly. Immediate copying showed no significant change across letter position. Delayed copying and verbal spelling showed neglect of the right of the word, and a greater number of errors were made on the final letters (78%) of the words in comparison to the initial letters (25%) (Figure 4.5). Delayed copying was also better than oral spelling. Summing across delayed copying and oral spelling there was a significant effect of position on letter report ($\chi^2(3)=13.34$, $p<0.004$)

4.4.4.3. Discussion

Similar to his reading, UB12 showed right neglect of words when asked to write the letters after a delay and when asked to spell words orally. The poor delayed copying occurred even though he perceived the letters correctly in the first place, shown by his intact immediate copying performance.

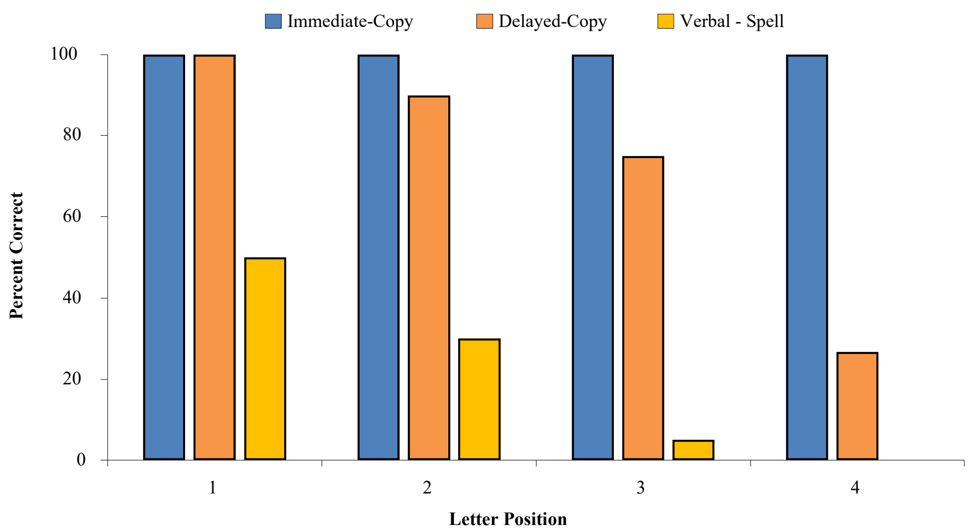

Figure 4-5. Mean percent correct responses for copying words immediately, with a delay and oral spelling.

4.4.5. <u>**Experiment 7: Format Effects**</u>

To test the effect of case mixing on word recognition, UB12 read words with mixed upper- and lower-case letters, and handwritten words.

4.4.5.1. Methods

UB12 was presented with 20 medium frequency 5-letter words, once in a single case (half in upper and half in lower case) and once in mixed case (half starting with an upper-case letter and half with a lower-case letter). (Appendix B) On a second occasion, he was also asked to read the same items presented in Lucida handwriting script. The stimuli were presented in Times New Roman type font size 14 on single A4 sheets.

4.4.5.2. Results

Overall, UB12 correctly read 5% (1/20) mixed-case words and 50% (10/20) single case words. Reading single case words reproduced an earlier finding with a significant change across letter position ($\chi^2(4)=20.95$, $p<0.001$). Reading mixed case words too showed a significant change across letter position ($\chi^2(4)=47.67$, $p<0.001$). The data showed neglect of the right side of the word, as a greater number of errors occurred on the final letters (95%) of the words in comparison to the initial letters (5%). Hierarchical log-linear analysis of mixed and single case words showed a significant interaction of word type and position ($\chi^2(4)=9.68$, $p<0.046$) (Figure 4.6). Mixed case words showed a stronger effect of letter position than single case words.

Overall, UB12 correctly read 23% (9/40) handwritten words. Reading handwritten words showed a significant change across letter position ($\chi^2(4)=22.11$, $p<0.001$). The data showed neglect of the right side of the word, as a greater number of errors occurred on the final letters (75%) of the words in comparison to the initial letters (27%).

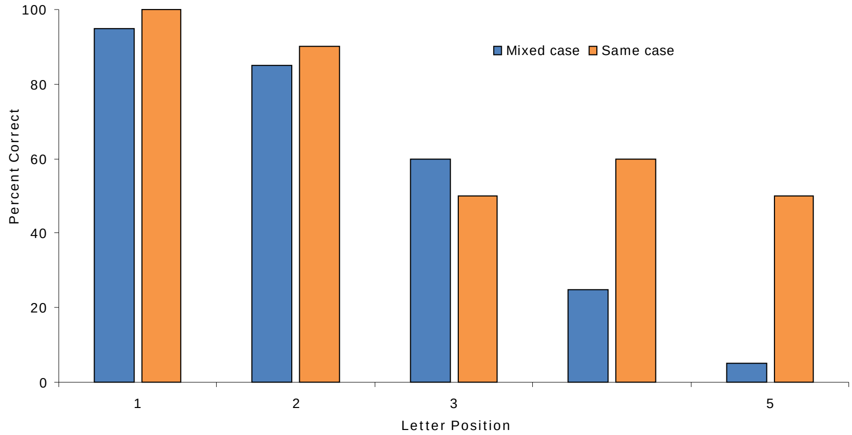

Figure 4-6. UB12's percent correct responses for mixed and single case words across five letter positions.

4.4.6. **Experiment 8: Reading Derived Words Versus Completed Words**

We further interested to know the effects of morphologically suffixed words (derived words) on UB12's reading performance. If the word representation being coded is morphologically decomposed, then there may be neglect further into the word for derived stimuli relative to completed words – since the third letter of the derived word would be coded as the end letter in a decomposed, word-level representation. (Appendix B).

4.4.6.1. Methods

The experimental stimuli consisted of 30 completed words such as WARD (20 x 4 letters long and 10 x 5 letter longs) and 30 derived words such as WARS (20 x 4 letters long and 10 x 5 letters long). All words were derived from completed words. The derived words were comparable to the completed words in length but differed in morphological endings (i.e., CUBE – CUBS). Completed and derived words were shown in uppercase. The stimuli were presented on a screen computer, using ePrime psychology software. These words were presented randomly to reduce the likelihood that UB12 would notice patterns in word endings.

Each trial was initiated once UB12 was ready and focused on the screen. Each display started with the presentation of the fixation cross that appeared for 400ms. Then the stimuli were presented in the centre of the computer screen in white against a black background. The duration was 1000ms and the font size was 28 New Courier. The experiment was preceded by a 10-trial practice block. UB12 was first advised that he would see a series of words in the centre of the screen. He was asked to respond by reading aloud and I pressed the corresponding key on the keyboard ('Z' for a correct response and 'M' for an incorrect response). After that, UB12's responses were written on a sheet of paper.

4.4.6.2. Results

Overall, UB12's accuracy in the reading task was minimal, as only 3 out of 60 trials (5 %) were correct. UB12 made errors in response to 27 out of 30 trials (90 %) completed words and to 30 out of 30 trials (100 %) with derived words. UB12 correctly read 2 out of 10 (20 %) 5-letter-completed words and 1 out of 20 (5 %) 4-letter-completed words. (Figure 4.7).

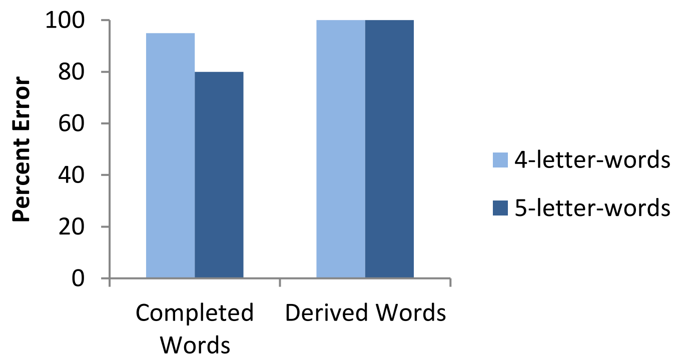

Figure 4-7. UB12's per cent error responses by types of words and length of words.

Reading 4-letter completed words showed significant change across letter position ($\chi^2(3)=14.87$, $p=0.002$). A greater number of errors occurred in the final letters (95%) of the words in comparison to the initial letters (15%). Reading 4-letter derived words too showed significant change across letter position ($\chi^2(3)=16.35$, $p=0.001$). A greater number of errors occurred in the final letters (100%) of the words in comparison to the initial letters (30%). (Figure 4.8).

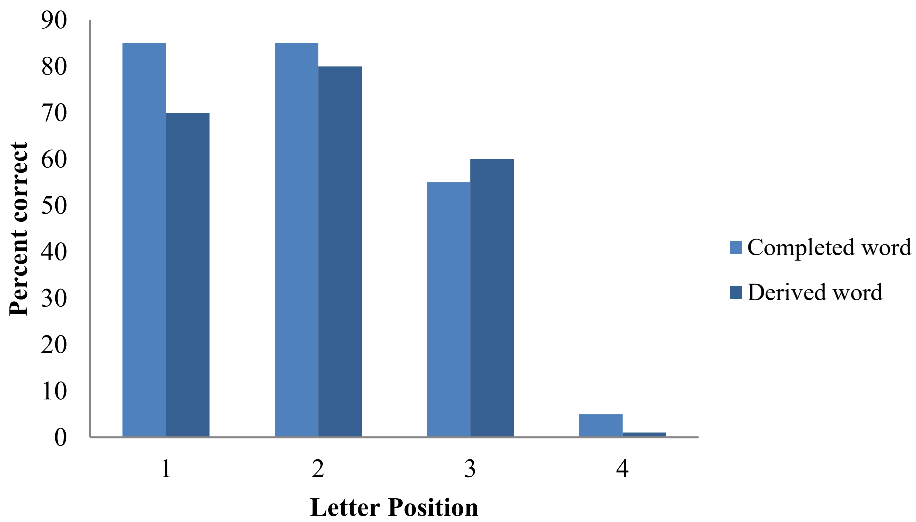

Figure 4-8. Percent correct responses for reading 4-letter completed words and 4-letter derived words.

Reading 5-letter completed words showed no significant change across letter position (Figure 4.9). Reading 5-letter derived words showed significant across letter position ($\chi^2(4)=13.304$, $p=0.01$). A greater number of errors occurred in the final letters (100%) of the words in comparison to the initial letters (10%).

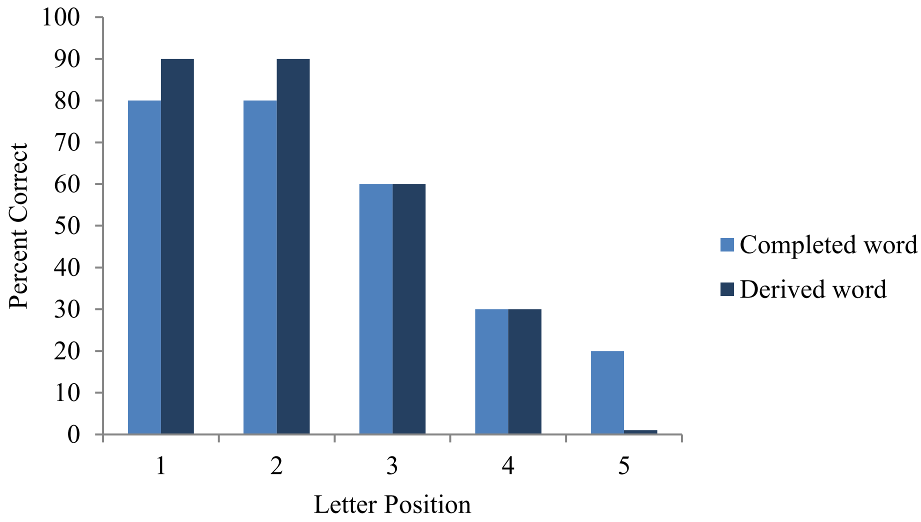

Figure 4-9. Percent correct responses for reading 5-letter completed words and 5-letter derived words.

There was little evidence that UB12's reading differed for morphologically derived and complete words and the two-word types did not vary greatly across the letter positions. In particular, there was no evidence that UB12's neglect began earlier in derived than complete words. There was no evidence here that UB12's neglect occurred after a stage of morphological decomposition of the words.

4.4.6.3. Discussion

UB12 made more errors on letter on the right end of the words, and in words that were on the right visual field. He made errors at the right ends of words and nonwords even when the stimuli were written vertically or were inverted. Similarly, right-end errors occurred in delayed copying and oral spelling, though immediate copying was intact.

Case mixing and handwriting greatly interfered with UB12's reading performance and the spatial errors were more pronounced with mixed case items. There was no evidence that the reading errors arose after an initial morphological decomposition of the words, and both complete and morphologically derived words showed similar drop-offs in letter identification as a function of the serial position of the letter.

In the final experiment, we set out to assess whether UB12's problems with the right sides of words extended also to the right sides of objects. To what extent do words and objects share common spatial processing mechanisms?

4.4.7. **Experiment 9: Chimeric Object Identification**

4.4.7.1. Methods

To test the similarity between word and non-word objects, UB12 was asked to identify stimuli with differing left and right sides to measure lateralised aspects of object processing. In Experiment 9, this involved attempting to identify the left and right sides of chimeric face stimuli (see (Humphreys & Heinke, 1998;Young, Hellawell, & Welch, 1992). The stimuli were also show upright and inverted. Is there a deficit in identifying the right side of a chimeric object, and does the problem in identifying the right part still occur when the stimulus is inverted (so the right of the object appears on the left on the retina)?

4.4.7.2. Results

Figure 4.10 shows the frequencies for identification of the right and left sides of chimeric objects positioned the right-way-up, as well as the frequencies for the canonical right and left sides of the chimeric objects' upside down. There were no significant differences between right-way-up and upside-down orientations. Figure 4.10 demonstrates a trend for less frequent identification of the right side of objects compared with the left side of objects regardless of object orientation.

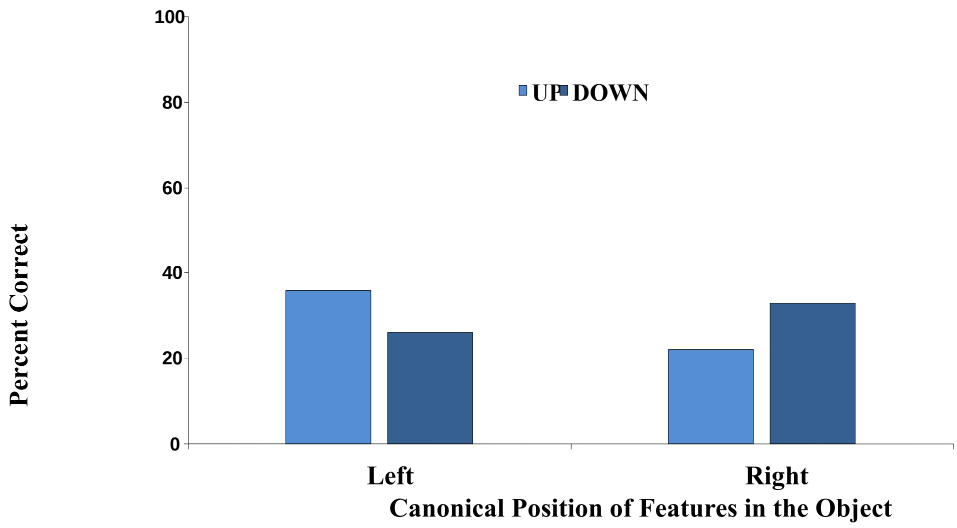

Figure 4-10. Percent of responses for the identification of chimeric objects presented right-way-up and up-side-down.

4.4.8. <u>Experiment 10: Judging the Handedness of Objects</u>

A final experiment (Experiment 10) assessed whether UB12 was able to identify the left-right locations of features in objects, or whether he had a similar problem to that influencing his reading (poor identification of right ends).

4.4.8.1. Methods

A figure of a girl was presented, one per A4 sheet of paper, wearing a bracelet on either her left or right hand or not at all. The view of the girl figure was randomly varied between facing either the front (face visible) or back (back of head visible) (see Figure 4.11). The task was to state whether the girl was wearing a bracelet and on which hand she was wearing it. UB12 completed 55 sheets of right-way-up and 55 inverted sheets (where the figure was presented up-side-down). The stimuli had unlimited presentation times.

4.4.8.2. Results

UB12's responses were scored immediately to reflect whether the absence or presence of the bracelet was correctly identified in every trial and for identification of the correct hand (i.e., canonical left or right hand). UB12 made only a single error on the right-way-up sheets (54/55 correct trials) and no errors in the inverted sheets (55/55 correct trials), demonstrating that his spatial impairment did not affect his ability to perform this task.

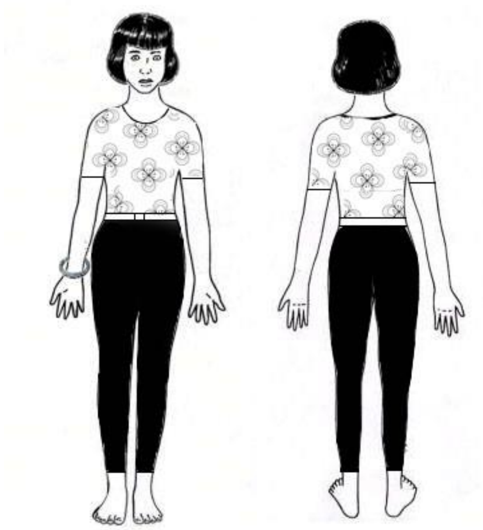

Figure 4-11. Examples of Manikin stimuli.

4.5. GENERAL DISCUSSION

In this chapter, I have presented evidence on reading and object recognition in a patient UB12 who presented with right neglect dyslexia. Similar to the influential patient NG (Caramazza & Hillis, 1990), UB12's right side errors were maintained even when words were presented in formats where the letters no longer fell spatially in the right visual field (e.g., with vertically arranged letters and inverted words). Caramazza and Hillis have interpreted such results as indicating damage to a high-level word representation, which is derived irrespective of how the word is presented. These authors also argued that the representation was common across input (reading) and output (spelling) tasks. Consistent with this, UB12 also made right-sided errors in delayed copying and spelling.

On the other hand, UB12's reading was affected by the position of the words in the visual field – more errors when he fixated to the left rather than the right of the words. This does not fit with the idea that his deficits are at the higher level of word recognition (word-centred) representation.

Similarly, neglect dyslexia were more pronounced for the mixed case than single case words. This last result is interesting because, within a high-level, stimulus-independent word representation (word-centred), the letter should be coded independent of their case and hence case mixing should have a combine additive effect on performance which is not affected by the letter serial positioning. This was not the case.

Does UB12 have deficits in word-centred representations, like NG? As the UB12 showed a spatial bias across both input and output tasks. However, representation in the word-centred does not include the particular retinal locations of the words or letter and also do not include the features representing the letter fonts. The effects of case mixing should, therefore, be independent of any high-level neglect at the word-centred representation. The fact that this was not the case suggests either of two things.

One proposal is that there is a deficit not only at the word-centred but also at an earlier at the stimulus-centred representation (Figure 4.4). Such intermediate representations may be more difficult to code when words are in mixed case and they may be sensitive to the mapping of letters from particular letter positions into the stimulus- centred representation (see Heinke & Humphreys (2003), for a simulation). One interesting prediction from this two-deficits account is that the two deficits may cancel each other out to some degree when words are inverted. In this case, the word level impairment should produce right-end errors still (from left-side retinal positions) while the stimulus-centred deficit should produce a poor report of left end (right visual field) letters. It follows that the gradient of lateralised impairment should reduce compared with when the two deficits align (as with normal text). However, there was little evidence for this in the data. Both when reading words in their standard topography and when they were inverted, there was a drop of around 60% in the identification of the first to the last letters (e.g., Figures 4.2 and 4.4).

An alternative view is that UB12's deficit is not within a word representation system but in attentional operations that are recruited to code letters in reading, as predicted by the IAS (Humphreys and Riddoch, 1993). Mixed case words relative to same case words, appear to be attention-demanding (Braet & Humphreys, 2006) and patients with an impaired attentional system struggle more in reading these mixed-case words. This then leads to a more lateralised deficit as there are fewer attentional resources available when the word is in an unfamiliar format.

Note that UB12 showed strong 'top-down' effects in reading – there was a substantial effect of lexicality, familiarity (frequency) and also imageability. Such results suggest that UB12's lexical system, far from being impaired, was, in fact, being recruited to support poor ability to use phonological reading where attention is serially controlled. Impoverish attentional resources also affected UB12's performance when words had to be copied after a delay or when words were orally spelt. Thus, it is likely that attention was required to maintain a buffer representation common across the tasks. Finally, the effects found with reading vertical and inverted words may result from mental transformation and the transcription of letters into the common buffer representation, rather than a deficit in a high-level word representation – as argued by Farah et al. (1988).

There was also a contrast between UB12's object processing and his reading. UB12 tended to identify the left rather than the right sides of chimeric figures, but this changed when the figures were inverted, when the left sides of the chimeric (now in the right visual field) tended to suffer. This shift in performance goes against the idea that a common high-level object representation mediated identification for words and objects alike and suggests instead that UB12 was using a retinotopically or stimulus-based encoding of objects. This might be because UB12 can use such a representation directly to identify the individual chimeric if their visual representations were sufficiently distinct. In contrast, for word identification UB12 may have to rotate a retinotopic representation of the stimulus in order to facilitate identification of the specific word, and the right-end errors that then occur reflect the use of the same retinotopic/stimulus centred representation both when the words are upright and when they are inverted (Farah et al., 1988; Costello et. al., 1987).

The most parsimonious argument is that UB12 has impaired attentional operations which are recruited during the retinotopic or stimulus-centred representation in order to sustain activation across the representation as words are identified. The demands on these operations are increased when the word formats are unfamiliar (with mixed relative to same case words), the stimuli themselves are unfamiliar (e.g., nonwords relative to words, low frequency words) and abstract (as opposed to highly imageable). The attentional operations are applied not only on-line, as stimuli are identified, but also off-line – for example when items are imagined or when words are spelt aloud from memory.–. when common representations (perhaps again retinotopic/stimulus centred) are recruited. Words written in unusual formats (vertically or inverted) may be rotated into this retinotopic/stimulus-centred form to enable words to be individually identified, and hence similar lateralised errors can arise as to when the words are presented upright. With objects, however, which may have more individually distinct parts (as with the chimeric here), then an identification may proceed from the retinotopic/stimulus-centred representation directly – without rotation – in which case the predominant side of the errors will shift when the stimuli are upright and when they are inverted.

This argument for UB12 having a general attentional impairment fits with other results from his performance. For example, Kitadono and Humphreys (2007) reported that UB12 had a general pattern of right-side visual extinction (poor report of contralesional stimuli when ipsilesional items compete for attention) that affected not an only letter but also colour identification. This same attentional limitation may apply particularly strongly when a multi-item representation must be maintained for identification – e.g., as in word reading. It is particularly noteworthy in this regard that UB12 was able to identify and copy single letters perfectly – tasks that required him to scan his attention systematically across the letters present. This indicates that he did not have an impairment on attentional scanning – and indeed he did not present with neglect in standard clinical measures of search and cancellation, which are dependent on the voluntary control and scanning of visual attention. The problem was more selective and emerged when multi-items had to be processed in parallel for identification. It is possible that this requires a distinct aspect of attention. Corbetta and Shulman (2002), for example, have argued that there is a distinction between a dorsal attentional system which controls voluntary shifts of attention, and a more ventral system involved in calling attention to a stimulus in a bottom-up manner. In addition to this, the present results indicate that there may be a third form of attention involved in distributing resources across multiple stimuli which are being processed in parallel. It is this process that is specifically disrupted in UB12.

4.5.1. **Limitations and future direction**

The present chapter presents a single case study. While UB12 was subjected to intensive testing and tasks, it should be acknowledged that he is a single case. He has multiple cognitive deficits, beyond the allocentric spatial attention deficit, his overall cognition was deteriorating and his formal education was limited. His working memory capacity was very limited, as well as his ability to sustain attention. Hence it is possible that when words were unfamiliar or the task was requiring to many cognitive resources, he just drifted out when he reached the end of the word, which in English language happens to be on the right side.

As with all single cases inference on general cognitive architecture should be done with cautious. UB12, like NG present rare symptoms, hence it is possible that they present a unique cognitive mechanism to support reading, which is not share by all humans.

CHAPTER 5: DISCUSSION OF PART ONE: VISUAL-SPATIAL DEFICITS AND READING DEFICITS

Part One investigated whether reading deficits in visual spatial neglect are common, and whether they relate to the spatial or non-spatial attentional deficits characterising visual neglect symptoms. The studies presented in Part One showed that generic reading difficulty were more common in neglect patients than other control groups, even relative to non-neglect, other brain damaged patients. Surprisingly, in the meta-analysis study and the analyses of the large data sets, we found no relation between the spatial deficits of visual neglect patients and the type of reading error they made. This suggests that reading error made by visual neglect patients does not relate to their characteristic spatial processing deficits. We further showed that deficits in sustain attention explain reading performances better than spatial deficits. However, when focusing on a single case, UB12, who was selected because he showed strong spatial deficits in his reading - we observed consistent spatial biased deficits in the present of relative mild visual neglect (no impairment in line bisection, figure copy and cancelation tasks). He only showed impairment akin to allocentric neglect.

5.1. Visual Spatial Neglect, Reading and the Attentional Systems

The attentional systems framework (Posner and Peterson, 1991) identifies three core and distinct attentional systems. Vigilance and alert system, which controls our ability to sustain attention for a long time. The orientation system, which controls the ability to shift attention in space, orient to relevant items in the field. Then, a control, executive function mechanism which ensures attention and processing resources are directed toward task relevant items (targets) and away from task irrelevant items (distracters). The most striking impairment in visual neglect patients is their deficit in the orientation system. These deficits produce a strong spatial bias away from the contralesional field and toward the ipsilesional field. However, neglect patients also show non-spatial attention deficits, and the most pronounce one is deficit in sustain attention.

The IAS model (Humphreys and Riddoch, 1993) suggests that reading impairment emerge from deficits in attentional spatial processing of external stimuli and internal representation as well as deficit in sustain attention. The data presented in Part One suggests that deficits in reading primarily driven by deficits in sustain attention. The meta-analyses (CHAPTER 2) showed that visual neglect patients are impaired at reading and that this impairment does not relate to impairment in the spatial bias of their orientation system. The analysis of the post-stroke data sets (CHAPTER 3), confirmed the impairment in reading. It further showed that deficits of sustain attention, measured in the visual and auditory domains, best predicted reading errors of words and sentences across the UK and China writing systems, though the severity of deficits to the spatial orientation system also contributed to reading errors, but not the control attention system. Similarly, UB12 who showed severe reading deficits (CHAPTER 5), mostly suffered from poor sustain attention obtaining a low score on the auditory attention task. His deficits to the orientation system were mild.

Taken together the presented results suggested that deficit in attentional systems, specifically sustain attention, can lead to acquired dyslexia. This highlight a potential for similar mechanism that underlie developmental dyslexia as proposed by the sluggish attentional shifting (SAS) account (Hari et al., 2001). Thus, reading deficits emerge from non-spatial deficit exhibit by visual neglect patients (Corbetta and Shulman, 2011), specifically impairment to the vigilance and alert attentional system, manifested as reduced arousal (Heilman, 1979; Storrie-Baker, 1997).

5.2. Representational versus Perceptual Neglect

The data suggests that reading deficits emerge from a deficit to the core function of attentional systems. It is likely to be more related to inability to process incoming input rather than an inability at the representational stage. Across all chapters, the data showed that reading was affected by the familiarity of the items (words versus non-words, high frequency versus low frequency). Reading non-familiar words is a more difficult task, it heavily relies more on the sensory input, as prior knowledge at a representation level cannot provide top down guidance to the sensory-perceptual processes. Thus, higher vigilance and attentional resources (sustained attention) are likely to be needed to maintain the processing of bottom up, perceptual information. Furthermore, the interference of the fonts mixing manipulation on reading, suggests that bottom up processing of the input stimuli are the core of the deficits.

5.3. Neglect Dyslexia

UB12 showed a clear and robust spatial bias in word reading, omitting letters and words presented in his contralesional field. He is an example of a visual neglect dyslexia case. The presence of an extreme bias in reading in the absence of strong deficits to the attentional orientation symptom is puzzling. UB12 spatial bias was so mild, that in the meta-analysis chapter he would not have been classified as suffering from visual neglect, as he showed no impairment in any of the classical visual neglect tasks (see 1.1.1). Why is it then UB12 had showed such a strong neglect dyslexia which did not a characteristic of most visual neglect patients.

UB12, like NG (Caramazza and Hills, 1990) are atypical patients who show visual spatial disorders. First, both are left-handed and both showed lesion to the left parietal, while most visual neglect patients are right-handed and their lesion is to the right parietal. Left-handed individuals are known to have a different organization of their brain laterality and especially the laterality of the language system. In contrast to right handed individuals who show clear laterality bias toward the right in reading, language laterality bias was weak in left handed (Van der Haegen & Brysbaert, 2018). Therefore, it is possible that in the case of neglect dyslexia, the left lesion affects language areas, which is less likely to be the case following right lesion to the right hemisphere.

Furthermore, in Latin based writing system, reading follows the direction of left-to-right. This direction matches the shifting attentional bias of most neglect patients with right lesions, who showed a biased of scanning form left-to-right, from the contralesional to ipsilesional. In the case of left parietal damage and both neglect dyslexia cases UB12 and NG, the spatial bias was opposite to reading direction (right-to-left), leading to end of words omissions. It is likely that moving opposite to the direction of the attentional horizontal bias, is more taxing, especially in the context of unfamiliar words. Thus, the presence of poor sustained attention resources, this will manifest as spatial biased, as resources are drained before patients reach the end of the word.

5.4. Conclusion

The data converge on the role of non-attentional deficits in spatial neglect in acquired reading deficits. This was demonstrated using three very different methodological approaches: meta-analysis, analysis of large data sets and detailed analysis of a case study.

PART TWO: THE CASE OF WORKING MEMORY

Patients with visual neglect report impairment in working memory (WM) (Husain & Rorden, 2003b). It is hypothesised that WM impairments in neglect emerge from deficits to spatial WM (Masud Husain & Rorden, 2003b; Malhotra et al., 2004; Wojciulik et al., 2001a), which is in line with representational accounts for visual neglect. Yet, despite decades of research into the cognition and neural mechanisms of spatial WM deficit in neglect, very little is known on comorbidity of the non-lateralised working memory deficit in visual neglect. This part aims are to examine the prevalence of WM deficits following acquired visual neglect. I ask whether WM impairments in neglect are associated with the nature of the spatial deficits, specifically in relation to the asymmetry in space and frame of reference.

For the propose of this thesis, I define working memory as the processing involving coding, retaining, maintaining, and retrieving information for a relatively short time, order of seconds to minutes.

I. **Working Memory Models**

Working memory (WM) is an integrated system that consists of 'attentional control' and 'memory stores' (Cowan, 2001). WM allows people to understand their immediate surroundings, to hold information temporarily, to solve problems and to manipulate task-relevant information for guiding actions (Baddeley, 2007). It supports various range of complex cognitive capabilities such as reasoning, problem-solving, decision-making and comprehension (Baddeley, 2003; Just & Carpenter, 1992). The most classic and influential working memory model is Baddeley and Hitch (1974)'s Multi-Component Theory. The model suggested that working memory functions could be fractionated into three primary components: the phonological loop (similar to verbal working memory) - a temporary storage of auditory-verbal information, the visuospatial sketchpad (similar to visual-spatial working memory) - a temporary storage of visual-spatial information, and the central executive component serves to monitor, revise and manipulate the information in active storage, as well as to act on and integrate information retrieved from long-term memory in order to support complex cognitive activities (for recent reviews, see Baddeley, 2003, 2012).

A clear characteristic of working memory, unlike long term memory, is its limited storage capacity, both in time and amount of information. The ability to store information in working memory varied substantially between people, but assumed to be fixed for individuals. Three families of models are proposed as mechanism that limits visual working memory capacity (Donkin et al., 2013) : a discrete number of slots (Zhang & Luck, 2008); continues resource based capacity (Bays & Husain, 2008) and a hybrid between the two (Cowan & Rouder, 2009). The slot-discrete model suggests that there are limited available slots of information to be remembered, around four. Items that are stored in a slot will be remembered, while information of items that are not in slots will be lost, in an all-or-none fashion. The resource-based account postulates limited storage capacity that is based on bits of information to be remembered rather than per items. Hence working memory can store low resolution information on many items, or high resolution on few.

II. **Working Memory and Attention**

It is assumed that items that are in the focus on attention are also stored in working memory. There is a heated theoretical debate on the relationship between working memory and attentional process (see, for example, Awh & Jonides, 2001; Badre, 2012; Fougnie, 2008.; Kiyonaga & Egner, 2013; Myers, Stokes, & Nobre, 2017). Three type of relations were suggested: attention as a gate to working memory assuming two serial distinct systems (Badre, 2008); attention and working memory form two interactive systems by which attention affect internal representation in working memory in the same way it affects external representations (Kiyonaga & Egner, 2008), or attention and working memory are one unified system (Awh & Jonides, 2001).

Functional imaging studies of spatial WM in normal healthy subjects show an involvement of right lateralised network which overlaps the spatial attention network (Courtney et al., 1996; Jonides et al., 1993). For example, Courtney et al. (1996) reported a right-lateralized network of activations, under spatial WM conditions, that includes areas typically lesioned in unilateral neglect syndrome (including the right posterior parietal and lateral prefrontal cortex). The similarity of the neural subtracts in visual neglect and in spatial working memory suggests that neglect disorder is associated with spatial WM deficit.

III. **Visual Neglect and Working Memory**

The representational hypothesis for visual neglect postulates that symptoms emerge from impairment in manipulating the mental representation of the environment, a process carried out by working memory (see Introduction Chapter). That visual neglect limited the capacity of working memory. The remapping hypothesis further suggests that visual neglect reflects impairment in maintaining and updating in the information of the external environment, as patients with neglect may have difficulty in keeping track of spatial locations across saccadic eye movements (Husain et al., 2001; Mannan et al., 2005).

The contribution of spatial working memory to visual neglect is demonstrated by a modified cancellation task. In this task, when feedback regarding which items had been cancelled is removed, neglect patients tended to revisit targets they had already identified (Mannan et al., 2005; Andrew Parton et al., 2006; Wojciulik et al., 2001a) and regarded previously fixated targets as new (Husain et al., 2001b). This shows impairment in remembering target locations across saccades.

There are several studies showing that the consequences of a cancellation response (e.g., whether the response and/or the cancelled item remains in the field) modulates neglect in cancellation tasks. Mark and Heilman. (1988) and Ladavas et al. (1993) had neglect patients explore contralesional space when they were instructed to pick up or erase stimuli compared with when they were simply instructed to point the stimuli. The patients omitted many more lines in contralesional space when they had to cross out the stimuli (and the crossed items remained visible) as opposed when they had to erase the lines in a line cancellation task. This result is consistent with the removal of the attention-capturing stimuli on the ipsilesional side reducing their attention-capturing effect (Olk & Harvey, 2006). Though, some patients still return to stimuli even though they have visibly marked the items (Olk & Harvey, 2002).

Ladavas and his colleagues (1993) compared the performance of patients with and without neglect on a task requiring the patients to point to or to pick up tokens in front of them, under blindfold or no blindfold conditions (akin to with or without visual feedback). When pointing to objects in the blindfolded condition, motor neglect patients omitted more stimuli; while perceptual neglect patients improved. This indicates perceptual neglect may be emerging from attentional capture/poor attentional disengagement from stimuli on the ipsilesional side. When 'visually attractive' stimuli were removed from the ipsilesional side, by blindfolding, the capture/ disengagement deficit was reduced.

Wojciulik et al. (2001) tested a left neglect patient with right inferior frontal and basal ganglia damage using a cancellation task, making either highly visible marks or invisible marks. The results show that neglect was greater for cancellation with invisible marks, consistent with a role for deficient spatial working memory in cancellation deficits, but contrary to account solely in terms of attention capture by salient visible marks made in ipsilesional space.

Husain et al. (2001) and Wojciulik et al. (2001) monitored patient eye movements in a search task and demonstrated many re-fixations where the patients returned to previously fixated stimuli (but were unaware of doing this).

Working memory impairment in visual neglect patients were also reported independent of spatial biases. Malhotra and colleagues (2005) show that neglect patients were impaired in remembering locations of stimuli event when these were organised on a vertical array suggesting the WM impairment is not aligned with the lateralised spatial bias of the deficit (Malhotra et al., 2005). Pisella et al.'s (2004) used change detection task and demonstrate poor ability of visual neglect patients in the detecting change of spatial location compared to detecting change of colour or shape.

In CHAPTER 8, I would present a test of the representational account of visual neglect. Using a similar rational as used for reading, I tested the impact of salient feature on visual neglect symptoms. But here in the context of a cancellation task.

IV. **Developmental Attentional Disorder (ADHD/ADD) and Working Memory**

Similar to developmental dyslexia, working memory is hypothesised to be a core deficit of attentional deficits hyperactivity disorder (ADHD) and attentional deficits disorder (ADD). ADHD is hypothesised to reflect malfunctioning of the executive control and alert attentional systems, though evidence suggests that some show like-neglect symptoms in term of spatial biases (Jones et al., 2008). The functional working memory model for ADHD (Rapport et al., 2009) postulates that working memory deficits should be considered a core deficit of ADHD. In line with this observation, meta-analysis study showed high comorbidity of ADHD and working memory in adults (Alderson et al., 2013).

V. **Chapters Overview**

The aim of this part was to assess comorbidity of visual spatial neglect and working memory deficits and to establish whether these deficits are associated with the visual spatial bias that characterised visual neglect. CHAPTER 6 uses meta-analysis; CHAPTER 7 analysis existing databases from the UK and China, and CHAPTER 8 presents a case study of the impact of reduced memory load on neglect severity.

Working memory in this chapter was defined as an ability to retain information over a delay of minutes. We examined the impact of visual neglect on different types of working memory (verbal, visual and spatial).

CHAPTER 6: THE META-ANALYSIS OF WORKING MEMORY DEFICITS IN VISUAL NEGLECT

6.1. INTRODUCTION

The current study uses meta-analyses methods to assess in details the relations between working memory and visual spatial neglect. We divided WM task in three ways, based on the working memory domain, the stimuli domain, and the display of item in the visual field. Similar analysis approach was used as in CHAPTER 2. The analysis was repeated for each of the three tasks' categorization.

In study 1, we asked whether working memory deficits are more prevalent in visual neglect relative to 1) standardised data, 2) matched healthy control and 3) neurological patients without neglect. We classified patients as suffering from neglect if they failed at least two of the neglect tasks: cancellation task, line bisection, and copying scene tests (i.e., Halligan, Wilson, & Cockburn, 1990; Kerkhoff, Münßinger, Haaf, Eberle-Strauss, & Stögerer, 1992; Kuhn, Heywood, & Kerkhoff, 2010; Weinberg et al., 1977).

In study 2, we asked whether deficits in the orienting system underlie poor working memory performance in neglect patients. This was tested by assessing the number of errors made in each hemifield within each neglect patient.

Finally study 3 further investigated the hypothesis that working memory deficits are related to the nature of the orienting deficits, by examining working memory performance relative to the frame of reference. We first compared working memory performance in neglect patients who showed reliable egocentric neglect (i.e., failed at least two cancellation neglect task) versus those who did not show it. Next, we compare working memory performance in neglect patients who showed a reliable allocentric neglect (i.e., failing in line bisection, figure copy) as opposed to those who did not show this deficit (Doricchi & Galati, 2000; Kleinman et al., 2007; Riddoch & Humphreys, 1983; Walker & Young, 1996) We included all the data from all relevant studies reporting working memory performance of visual spatial neglect patients.

6.2. MATERIAL AND METHODS

In this section, we have applied the same methods as reported in CHAPTER 2. Please refer to 2.2.

6.2.1. Literature Search

See 2.2.1 for details.

Five electronic databases (see 2.2.1) were searched by using the following search keywords and terms: ("spatial neglect" or "unilateral spatial neglect" or "hemispatial neglect" or hemineglect or "visual neglect" or "visual extinction" or "visual inattention") AND ("working mem*" or "short-term mem*" or "short term mem*" or "visual working mem*" or "verbal working mem*" or "working attention*" or "immediate mem*" or "immediate recall*") AND ("acquired brain lesion*" or "acquired brain injur*" or "head injur*" or "brain damag*" or "stroke" or "acquired brain impairment*" or "cerebrovascular accident*" or "traumatic brain injury*" or "patient*").

6.2.2. Eligibility Criteria

See 2.2.2 for inclusion criteria. Figure 6.1 shows a PRISMA flowchart.

6.2.3. Data Extraction and Outcome Measures

See 2.2.3 for data extraction.

The outcome measures extracted were the span scores and error or/and accuracy scores in the working memory tasks. We divided the outcome measures in three ways, based on the types of working memory (e.g. verbal working memory, spatial working memory and visual working memory), types of stimuli in working memory tests (e.g., letters, numbers, and others such as shapes and pictures); and fixation and distribution visual field working memory tests (e.g., centre versus peripheral distributions). For the purpose of meta-analysis, sample sizes and means and standard deviations of performance scores were extracted for each study group (i.e., visual spatial neglect patients, healthy control group and patients with an acquired brain injury without neglect syndrome).

6.2.4. Quality Assessment

See 2.2.4.for details.

6.2.5. Statistical Meta-Analysis

See 2.2.5 for details.

6.3. GENERAL RESULTS

6.3.1. Included Studies and Study Characteristic

Figure 6.1 shows the numbers of identified studies obtained from the literature search process. Of all identified studies, 14 studies met the inclusion as specified in the eligibility criteria under the Methods section. Table 6.1 below illustrates the key characteristics of all the fourteen included studies in the meta-analysis. Briefly, all the included studies evaluated working memory performance in the visual neglect patients with the right hemisphere damaged, with 69 % had sub-acute disease duration and the remaining 31 % was a chronic brain injury.

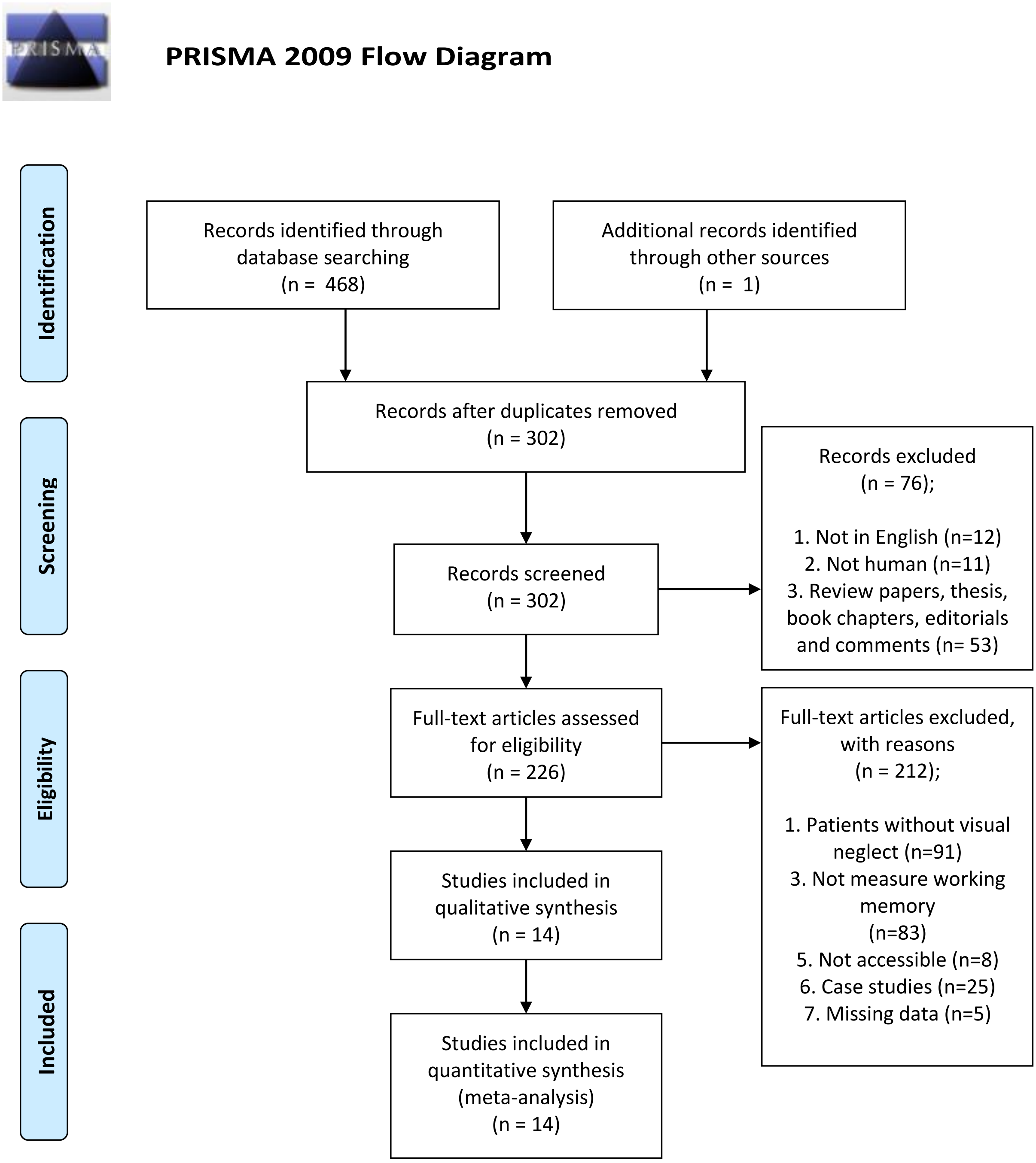

Figure 6-1. Flowchart of the search process. n=numbers; five databases were searched, 1. MEDLINE (n=60 papers), 2. EMBASE (n=98 papers), 3. PsychINFO (n=75 papers), 4. CINAHL Plus (n=21 papers) and 5. The Web of Science (n=214 papers). Additional one record identified was from the lists of reference of the selected papers.

Table 6-1. Key Characteristics of Included Studies.

Study/Year/Location	Matched for	Sample					Comparative Group				
		USN patients									
		Condition	Age	Gender	Education	N	Condition	Age	Gender	Education	N
Antoine et al.(Antoine et al., 2018), Belgium	Age & Gender	Right hemisphere brain lesion, All sub-acute	51.5 (14.8)	6 M 4 F	13.9 (3.2)	10	Standardized normative data				
							Healthy controls	51.5 (13)	20 M 17 F	15.7 (2.2)	37
De Nigris et al. (De Nigris et al., 2013), Italy	Age, Education Level & Disease Duration	Right hemisphere brain lesion (with hemiplegia), All sub-acute	62.83 (13.17)	5 M 1 F	8.17 (4.44)	6	Standardized normative data				
							Healthy controls	58.67 (9.8)	7 M 8 F	11.3 (3.27)	15
							Right brain-damaged without neglect	61 (8)	7 M 1 F	12.14 (3.18)	7
Doricchi et al. (F. Doricchi et al., 2005), Italy	Age	Right hemisphere brain lesion, All chronic	62.2 (NR)	NR	NR	9	Standardized normative data				
							Right brain damaged patients without neglect	NR	NR	NR	5
Dormal et al. (Dormal et al., 2014), Belgium	Age, Gender, Education Level & Disease Duration	Right hemisphere brain lesion, 10 sub-acute & 4 chronic	53 (6.7)	7 M 7 F	NR	14	Standardized normative data				
							Right brain damaged patients without neglect	52 (19.9)	8 M 2 F	NR	10
Ferber & Danckert (Ferber & Danckert, 2006), Canada	Age	Right hemisphere brain lesion, All sub-acute	64 (11.17)	3 M 1 F	NR	4	Standardized normative data				
							Healthy controls	NR	NR	NR	10
							Right brain-damaged without neglect	NR	NR	NR	4
Kristjansson & Vuilleumier (Kristjánsson & Vuilleumier, 2010), Iceland	Age	Focal right-hemispheric lesions, 3 sub-acute & 1 chronic	69.8 (10.4)	3 M 1 F	NR	4	Right brain damaged patients without neglect	72.8 (6.1)	2 M 2 F	NR	4
Low et al. (Low et al., 2016), Australia	Gender	Ischemic stroke (right brain damaged), Sub-acute & chronic	66.67 (9.5)	3 M 0 F	7 (3)	3	Right hemispheric damage without neglect	58.87 (9.01)	8 M 4 F	12.22 (3.05)	12
Malhotra et al. (Malhotra et al., 2005), the United Kingdom	Age & Disease Duration	Right hemispheric stroke, 1 acute, 8 sub-acute & 1 chronic	62.8 (16.7)	NR	NR	10	Right brain-damaged without neglect	69.2 (10.2)	NR	NR	10
							Healthy controls	69.2 (NR)	NR	NR	10
Masson et al.(Masson et al., 2016), Belgium	Age & Education Level	Right hemisphere brain-damaged, 8	57 (13)	9 M 2 F	NR	11	Right brain-damaged without neglect	56 (10)	8 M 3 F	NR	11
							Healthy controls	56 (12)	2 M 9 F	NR	11

Study/Year/Location	Matched for	Sample USN patients					Comparative Group				
		Condition	Age	Gender	Education	N	Condition	Age	Gender	Education	N
		sub-acute & 3 chronic									
Rossit et al. (Rossit et al., 2009), the United Kingdom	Age	Right hemisphere brain-damaged, 5 sub-acute & 2 chronic	67.14 (6.64)	2 M 5 F	NR	7	Standardized normative data				
							Healthy controls	72.1 (4.2)	NR	NR	10
							Right brain-damaged without neglect	69.78 (7.46)	6 M 3 F	NR	9
Vuilleumier et al. (Patrik Vuilleumier et al., 2007), United Kingdom	Age, Gender & Education Level	Right hemispheric stroke, 3 sub-acute & 2 chronic	69.5 (8.85)	3 M 2 F	NR	5	Healthy controls	67.1 (NR)	3 M 2 F	NR	5
Wansard et al. (Wansard et al., 2014) , Belgium	Age	Right hemisphere-damaged, 9 sub-acute & 5 chronic	60 (16.24)	8 M 6 F	7 (5)	14	Standardized normative data				
							Healthy controls	59.21 (15.6)	NR	NR	14
Wansard et al. (Wansard et al., 2015) , France	Age & Education Level	Right hemisphere-damaged, 7 sub-acute & 5 chronic	62.08 (12.29)	7 M 5 F	7 (5)	12	Standardized normative data				
							Healthy controls	62.42 (8.73)	NR	11.25 (3.08)	12
Wansard et al.(Wansard et al., 2016), Belgium	Age & Education Level	Right hemisphere-damaged, 9 sub-acute & 5 chronic	61.1 (10.75)	5 M 9 F	11.86 (4.55)	14	Healthy controls	NR	NR	NR	20

Values provided are mean (standard deviation). M = Male; F = Female; NR = not reported;

6.3.2. Risk of Bias of Included Studies

Figure 6.2 and Figure 6.3 present an assessment of the risk of bias for the included studies using the Cochrane Collaboration risk of bias tool. Overall, as shown in Figure 6.3, we assessed all the studies as being a high risk of bias for random sequence generation. On the other hand, all studies were considered to have an unclear bias to allocation concealment. As it was uncertain whether the patients or the researcher knew of the working memory abilities prior to the formal testing. Also, we concluded that performance bias, detection bias and reporting bias being of least concern across all the included studies.

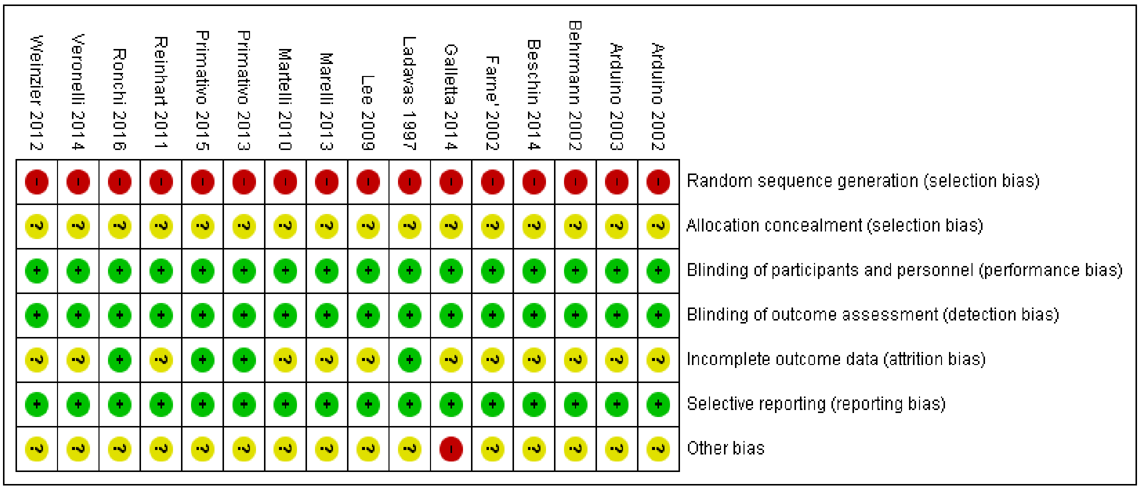

Figure 6-2. Risk of bias summary. Our judgements about each risk of bias item for each included study.

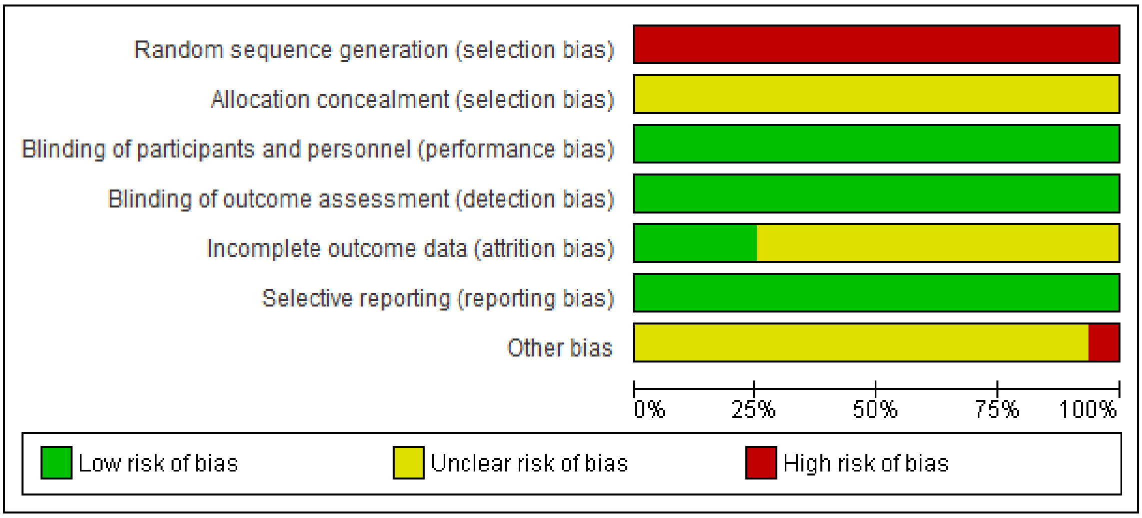

Figure 6-3. Risk of bias graph. Each risk of bias item presented as percentages across all included studies.

6.3.3. How Working Memory Performance was Evaluated

Table 6.2 provides a summary of relevant studies that included for each domain that being tested in this meta-analysis. The most common test used in neglect was a spatial working memory test. Also, other stimuli type that was image pictures and object shapes, was commonly chosen as testing stimuli. Image pictures and object shapes stimuli were put together on others because both were regarded as visual shape. Finally, the numbers of studies that applied whether fixation or distribution of visual fields, are nearly the same.

Table 6-2. Studies Included for Each Working Memory Domains.

Testing measurement domains	Test	Outcome	Studies that use this [Authors (Year)]
1. Types of working memory	a. *Verbal working memory*	1. Span scores	Antoine et al. (2018)
			Doricchi et al. (2005)
			Dormal et al. (2014)
			Masson et al. (2016)
			Wansard et al. (2015)
		2. % of errors	Antoine et al. (2018)
		3. % of accuracy	Ferber & Dankert (2006)
	b. *Spatial working memory*	1. Span scores	De Nigris et al. (2013)
			Doricchi et al. (2005)
			Dormal et al. (2014)
			Malhotra et al. (2005)
			Wansard et al. (2014)
			Wansard et al. (2015)
		2. % of errors	Wansard et al. (2014)
		3. % of accuracy	Ferber & Dankert (2006)
			Wansard et al. (2016)
			Vuilleumier et al. (2007)
		4. # of accuracy	Malhotra et al. (2005)
			Rossit et al. (2009)
	c. *Visual working memory*	1. # of accuracy	Low et al. (2016)
		2. % of accuracy	Wansard et al. (2016)
2. Types of stimuli used in working memory tests	a. *Letters*	1. % of errors	Antoine et al. (2018)
	b. *Numbers*	1. Span scores	Antoine et al. (2018)
			Doricchi et al. (2005)
			Dormal et al. (2014)
			Masson et al. (2016)
			Wansard et al. (2015)
		2. % of accuracy	Ferber & Dankert (2006)
		3. # of accuracy	Low et al. (2016)
	c. *Others**	1. Span scores	De Nigris et al. (2013)
			Doricchi et al. (2005)
			Dormal et al. (2014)
			Malhotra et al. (2005)
			Wansard et al. (2014)
			Wansard et al. (2015)
		2. % of errors	Wansard et al. (2014)
		3. % of accuracy	Ferber & Dankert (2006)
			Vuilleumier et al. (2007)
			Wansard et al. (2016)
		4. # of accuracy	Malhotra et al. (2005)
			Rossit et al. (2009)

Testing measurement domains	Test	Outcome	Studies that use this [Authors (Year)]
3. Fixation and distribution visual fields in working memory tests	a. *Center*	1. Span scores	Antoine et al. (2018)
			Doricchi et al. (2005)
			Dormal et al. (2014)
			Malhotra et al. (2005)
			Masson et al. (2016)
			Wansard et al. (2015)
		2. % of errors	Antoine et al. (2018)
		3. # of accuracy	Low et al. (2016)
			Malhotra et al. (2005)
			Rossit et al. (2009)
	b. *Peripheral*	1. Span scores	De Nigris et al. (2013)
			Doricchi et al. (2005)
			Dormal et al. (2014)
			Wansard et al. (2014)
			Wansard et al. (2015)
		2. % of errors	Wansard et al. (2014)
		3. % of accuracy	Ferber & Dankert (2006)
			Vuilleumier et al. (2007)
			Wansard et al. (2016)

*= includes image pictures and object shapes as stimuli

6.4. CURRENT STUDIES

6.4.1. **STUDY 1: Working memory deficit in visual spatial neglect syndrome – *Analyses 4.1- 1.stand, 1.hc, 1.noneg, 4.1-2.stand, 2.hc, 2.noneg, 4.1-3.stand, 3.hc and 3.noneg.***

6.4.1.1. Methods

In Study 1, we performed nine separate meta-analysis studies for three separate domains (types of working memory, types of stimuli and types of visual fields). First is the type of working memory domain (verbal working memory, spatial working memory and visual working memory) for *Analyses 4.1-1.stand/hc/noneg*. *Analysis 4.1-1.stand* compared data working memory performance of visual spatial neglect with standardized normative data. *Analysis 4.1-1.hc* compared working memory performance data of visual neglect patients with healthy matched controls. *Analysis 4.1-1.noneg* came from working memory deficit performance of acquired brain-injured patients with neglect syndrome versus without neglect syndrome.

Second is the types of stimuli working memory tests (letters, numbers and others such as pictures and object shapes) for *Analyses 4.1-2.stand/hc/noneg*.

Third is the types of fixation and distribution visual field working memory tests (centre and peripheral) for *Analyses 4.1-3.stand/hc/noneg*. Specifically, *Analyses 4.1-1, 4.1-2 and 4.1-3* included all the data from studies examining neglect, diagnosing neglect syndrome either from one of the commonly used neglect tests or a battery of neglect measurement without applying any prior selection criteria (see the eligibility criteria).

Table 6-3. Studies Included in The Meta-Analysis.

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
ANALYSIS** 4.1-**1.stand: **Types of Working Memory**					
1	Antoine et al. (2018)	10	Standardized normative data	*NA*	Verbal working memory
2	Doricchi et al. (2005)	9	Standardized normative data	*NA*	Verbal working memory
3	Dormal et al. (2014)	14	Standardized normative data	*NA*	Verbal working memory
4	Dormal et al. (2014)	14	Standardized normative data	*NA*	Verbal working memory
5	Ferber & Dankert (2006)	4	Standardized normative data	*NA*	Verbal working memory
6	Wansard et al. (2015)	10	Standardized normative data	*NA*	Verbal working memory
	Total	*61*			
7	Doricchi et al. (2005)	9	Standardized normative data	*NA*	Spatial working memory
8	De Nigris et al. (2013)	6	Standardized normative data	*NA*	Spatial working memory
9	De Nigris et al. (2013)	6	Standardized normative data	*NA*	Spatial working memory
10	Wansard et al. (2014)	14	Standardized normative data	*NA*	Spatial working memory
11	Wansard et al. (2014)	14	Standardized normative data	*NA*	Spatial working memory
12	Rossit et al. (2009)	7	Standardized normative data	*NA*	Spatial working memory
13	Rossit et al. (2009)	7	Standardized normative data	*NA*	Spatial working memory
	Total	*63*			
ANALYSIS** 4.1-**1.hc: **Types of Working Memory**					
1	Antoine et al. (2018)	10	Healthy controls	37	Verbal working memory
2	Antoine et al. (2018)	10	Healthy controls	37	Verbal working memory
3	Masson et al. (2016)	11	Healthy controls	11	Verbal working memory
4	Masson et al. (2016)	11	Healthy controls	11	Verbal working memory
	Total	*42*		*96*	
5	Ferber & Dankert (2006)	4	Healthy controls	10	Spatial working memory
6	Malhotra et al. (2005)	10	Healthy controls	10	Spatial working memory
7	Malhotra et al. (2005)	10	Healthy controls	10	Spatial working memory
8	Wansard et al. (2014)	14	Healthy controls	14	Spatial working memory
9	Wansard et al. (2015)	12	Healthy controls	12	Spatial working memory
10	Wansard et al. (2015)	12	Healthy controls	12	Spatial working memory
11	Wansard et al. (2016)	14	Healthy controls	20	Spatial working memory
	Total	*76*		*88*	
12	Low et al. (2016)	3	Healthy controls	29	Visual working memory

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
13	Low et al. (2016)	3	Healthy controls	29	Visual working memory
14	Wansard et al. (2016)	14	Healthy controls	20	Visual working memory
	Total	*20*		*78*	
ANALYSIS** 4.1-**1.noneg**: **Types of Working Memory					
1	Doricchi et al. (2005)	9	Right brain damaged patients without neglect	5	Verbal working memory
2	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Verbal working memory
3	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Verbal working memory
4	Ferber & Dankert (2006)	4	Right brain damaged patients without neglect	4	Verbal working memory
5	Masson et al. (2016)	11	Right brain damaged patients without neglect	11	Verbal working memory
6	Masson et al. (2016)	11	Right brain damaged patients without neglect	11	Verbal working memory
	Total	*63*		*51*	
7	Doricchi et al. (2005)	9	Right brain damaged patients without neglect	5	Spatial working memory
8	De Nigris et al. (2013)	6	Right brain damaged patients without neglect	7	Spatial working memory
9	De Nigris et al. (2013)	6	Right brain damaged patients without neglect	7	Spatial working memory
10	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Spatial working memory
11	Ferber & Dankert (2006)	4	Right brain damaged patients without neglect	10	Spatial working memory
12	Malhotra et al. (2005)	10	Right brain damaged patients without neglect	10	Spatial working memory
13	Malhotra et al. (2005)	10	Right brain damaged patients without neglect	10	Spatial working memory
14	Rossit et al. (2009)	7	Right brain damaged patients without neglect	9	Spatial working memory
15	Rossit et al. (2009)	7	Right brain damaged patients without neglect	9	Spatial working memory
	Total	*73*		*77*	
16	Low et al. (2016)	3	Right brain damaged patients without neglect	12	Visual working memory
17	Low et al. (2016)	3	Right brain damaged patients without neglect	12	Visual working memory
	Total	*6*		*24*	
ANALYSIS** 4.1-**2.stand**: **Types of Stimuli					
1	Antoine et al. (2018)	10	Standardized normative data	*NA*	Numbers stimuli
2	Doricchi et al. (2005)	9	Standardized normative data	*NA*	Numbers stimuli
3	Dormal et al. (2014)	14	Standardized normative data	*NA*	Numbers stimuli
4	Dormal et al. (2014)	14	Standardized normative data	*NA*	Numbers stimuli
5	Ferber & Dankert (2006)	4	Standardized normative data	*NA*	Numbers stimuli
6	Wansard et al. (2015)	10	Standardized normative data	*NA*	Numbers stimuli
	Total	*61*			

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
7	Doricchi et al. (2005)	9	Standardized normative data	*NA*	Others stimuli
8	De Nigris et al. (2013)	6	Standardized normative data	*NA*	Others stimuli
9	De Nigris et al. (2013)	6	Standardized normative data	*NA*	Others stimuli
10	Dormal et al. (2014)	14	Standardized normative data	*NA*	Others stimuli
11	Wansard et al. (2014)	14	Standardized normative data	*NA*	Others stimuli
12	Wansard et al. (2014)	14	Standardized normative data	*NA*	Others stimuli
13	Rossit et al. (2009)	7	Standardized normative data	*NA*	Others stimuli
14	Rossit et al. (2009)	7	Standardized normative data	*NA*	Others stimuli
	Total	*77*			
ANALYSIS** 4.1-**2.hc: **Types of Stimuli**					
1	Antoine et al. (2018)	10	Healthy controls	37	Letters stimuli
2	Antoine et al. (2018)	10	Healthy controls	37	Letters stimuli
	Total	*20*		*74*	
3	Low et al. (2016)	3	Healthy controls	29	Numbers stimuli
4	Low et al. (2016)	3	Healthy controls	29	Numbers stimuli
5	Masson et al. (2016)	11	Healthy controls	11	Numbers stimuli
6	Masson et al. (2016)	11	Healthy controls	11	Numbers stimuli
	Total	*28*		*80*	
7	Ferber & Dankert (2006)	4	Healthy controls	10	Others stimuli
8	Malhotra et al. (2005)	10	Healthy controls	10	Others stimuli
9	Malhotra et al. (2005)	10	Healthy controls	10	Others stimuli
10	Wansard et al. (2014)	14	Healthy controls	14	Others stimuli
11	Wansard et al. (2015)	12	Healthy controls	12	Others stimuli
12	Wansard et al. (2015)	12	Healthy controls	12	Others stimuli
13	Wansard et al. (2016)	14	Healthy controls	20	Others stimuli
14	Wansard et al. (2016)	14	Healthy controls	20	Others stimuli
	Total	*90*		*108*	
ANALYSIS** 4.1- **3.noneg: **Types of Stimuli**					
1	Doricchi et al. (2005)	9	Right brain damaged patients without neglect	5	Numbers stimuli
2	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Numbers stimuli
3	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Numbers stimuli
4	Ferber & Dankert (2006)	4	Right brain damaged patients without neglect	4	Numbers stimuli
5	Low et al. (2016)	3	Right brain damaged patients without neglect	12	Numbers stimuli

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
6	Low et al. (2016)	3	Right brain damaged patients without neglect	12	Numbers stimuli
7	Masson et al. (2016)	11	Right brain damaged patients without neglect	11	Numbers stimuli
8	Masson et al. (2016)	11	Right brain damaged patients without neglect	11	Numbers stimuli
	Total	*69*		*75*	
9	Doricchi et al. (2005)	9	Right brain damaged patients without neglect	5	Others stimuli
10	De Nigris et al. (2013)	6	Right brain damaged patients without neglect	7	Others stimuli
11	De Nigris et al. (2013)	6	Right brain damaged patients without neglect	7	Others stimuli
12	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Others stimuli
13	Ferber & Dankert (2006)	4	Right brain damaged patients without neglect	10	Others stimuli
14	Malhotra et al. (2005)	10	Right brain damaged patients without neglect	10	Others stimuli
15	Malhotra et al. (2005)	10	Right brain damaged patients without neglect	10	Others stimuli
16	Rossit et al. (2009)	7	Right brain damaged patients without neglect	9	Others stimuli
17	Rossit et al. (2009)	7	Right brain damaged patients without neglect	9	Others stimuli
	Total	*73*		*77*	
ANALYSIS** 4.1-3.**stand**: Fixation vs. Distribution Visual Fields**					
1	Antoine et al. (2018)	10	Standardized normative data	*NA*	Center
2	Doricchi et al. (2005)	9	Standardized normative data	*NA*	Center
3	Dormal et al. (2014)	14	Standardized normative data	*NA*	Center
4	Dormal et al. (2014)	14	Standardized normative data	*NA*	Center
5	Wansard et al. (2015)	10	Standardized normative data	*NA*	Center
6	Rossit et al. (2009)	7	Standardized normative data	*NA*	Center
7	Rossit et al. (2009)	7	Standardized normative data	*NA*	Center
	Total	*71*			
8	Doricchi et al. (2005)	9	Standardized normative data	*NA*	Peripheral
9	De Nigris et al. (2013)	6	Standardized normative data	*NA*	Peripheral
10	De Nigris et al. (2013)	6	Standardized normative data	*NA*	Peripheral
11	Dormal et al. (2014)	14	Standardized normative data	*NA*	Peripheral
12	Ferber & Dankert (2006)	4	Standardized normative data	*NA*	Peripheral
13	Wansard et al. (2014)	14	Standardized normative data	*NA*	Peripheral
14	Wansard et al. (2014)	14	Standardized normative data	*NA*	Peripheral
	Total	*67*			
ANALYSIS** 4.1-3.**hc**: Fixation vs. Distribution Visual Fields**					
1	Antoine et al. (2018)	10	Healthy controls	37	Center

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
2	Antoine et al. (2018)	10	Healthy controls	37	Center
3	Low et al. (2016)	3	Healthy controls	29	Center
4	Low et al. (2016)	3	Healthy controls	29	Center
5	Malhotra et al. (2005)	10	Healthy controls	10	Center
6	Malhotra et al. (2005)	10	Healthy controls	10	Center
7	Masson et al. (2016)	11	Healthy controls	11	Center
8	Masson et al. (2016)	11	Healthy controls	11	Center
	Total	*68*		*174*	
9	Ferber & Dankert (2006)	4	Healthy controls	10	Peripheral
10	Wansard et al. (2014)	14	Healthy controls	14	Peripheral
11	Wansard et al. (2015)	12	Healthy controls	12	Peripheral
12	Wansard et al. (2015)	12	Healthy controls	12	Peripheral
13	Wansard et al. (2016)	14	Healthy controls	20	Peripheral
14	Wansard et al. (2016)	14	Healthy controls	20	Peripheral
	Total	*70*		*88*	
ANALYSIS** 4.1-3.**noneg: **Fixation vs. Distribution Visual Fields**					
1	Doricchi et al. (2005)	9	Right brain damaged patients without neglect	5	Center
2	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Center
3	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Center
4	Low et al. (2016)	3	Right brain damaged patients without neglect	12	Center
5	Low et al. (2016)	3	Right brain damaged patients without neglect	12	Center
6	Malhotra et al. (2005)	10	Right brain damaged patients without neglect	10	Center
7	Malhotra et al. (2005)	10	Right brain damaged patients without neglect	10	Center
8	Masson et al. (2016)	11	Right brain damaged patients without neglect	11	Center
9	Masson et al. (2016)	11	Right brain damaged patients without neglect	11	Center
10	Rossit et al. (2009)	7	Right brain damaged patients without neglect	9	Center
11	Rossit et al. (2009)	7	Right brain damaged patients without neglect	9	Center
	Total	99		*109*	
12	Doricchi et al. (2005)	9	Right brain damaged patients without neglect	5	Peripheral
13	De Nigris et al. (2013)	6	Right brain damaged patients without neglect	7	Peripheral
14	De Nigris et al. (2013)	6	Right brain damaged patients without neglect	7	Peripheral
15	Dormal et al. (2014)	14	Right brain damaged patients without neglect	10	Peripheral
16	Ferber & Dankert (2006)	4	Right brain damaged patients without neglect	10	Peripheral

No.	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
17	Ferber & Dankert (2006)	4	Right brain damaged patients without neglect	4	Peripheral
	Total	*43*		*43*	

6.4.1.2. Results

6.4.1.2.1 Types of Working Memory

For *Analysis 4.1-1.stand*, we identified 7 relevant studies (124 patients with visual spatial neglect; a total of 13 experiments on verbal working memory and spatial working memory; see Table 3). Their performance scores were compared to the standardized normative data. Significant differences were found in verbal working memory tests (Z=5.31, *p*=<.00001) and spatial working memory tests (Z=4.96, *p*=<.00001). No studies tested on visual working memory (see Figure 6.4). Additionally, the results reported high significant overall effects estimates on deficit working memory performance associated with visual spatial neglect symptoms (Z=7.47, *p*=<.00001). The data used in *Analysis 4.1-1.stand* (I^2) was homogenous.

For *Analysis 4.1-1.hc*, we identified eight studies (138 visual spatial neglect patients and 262 healthy matched controls; a total of 14 experiments on verbal working memory, spatial working memory and visual working memory; see Table 6.3). Significant differences can be seen on verbal working memory tests (Z=2.79, *p*=.005) and spatial working memory tests (Z=5.46, *p*=<.00001), but not on visual working memory (see Figure 6.5). Additionally, the results reported high significant overall effects estimates on deficit working memory performance associated with visual spatial neglect symptoms (Z=5.29, *p*=<.00001), though we note that I^2 values were 73.6%, indicating moderate heterogeneity between studies.

Then we compared the working memory performance between visual neglect patients with brain damaged patients without neglect symptoms (*Analysis 4.1-1.noneg*). Eight studies identified (142 visual neglect patients and 152 brain damaged patients without neglect; a total of 17 experiments on verbal working memory, spatial working memory and visual working memory; see Table 6.3). The working memory performance scores were found significant differences in spatial working memory tests (Z=3.98, *p*=<.00001) and visual working memory (Z=2.21, *p*=.003), but not on verbal working memory tests (see Figure 6.6). At the same time, the results showed high significant overall effects estimates on working memory deficit when compared between these two groups (Z=4.09, *p*=<.00001), though we note that I^2 values were higher than 75%, indicating large heterogeneity between studies.

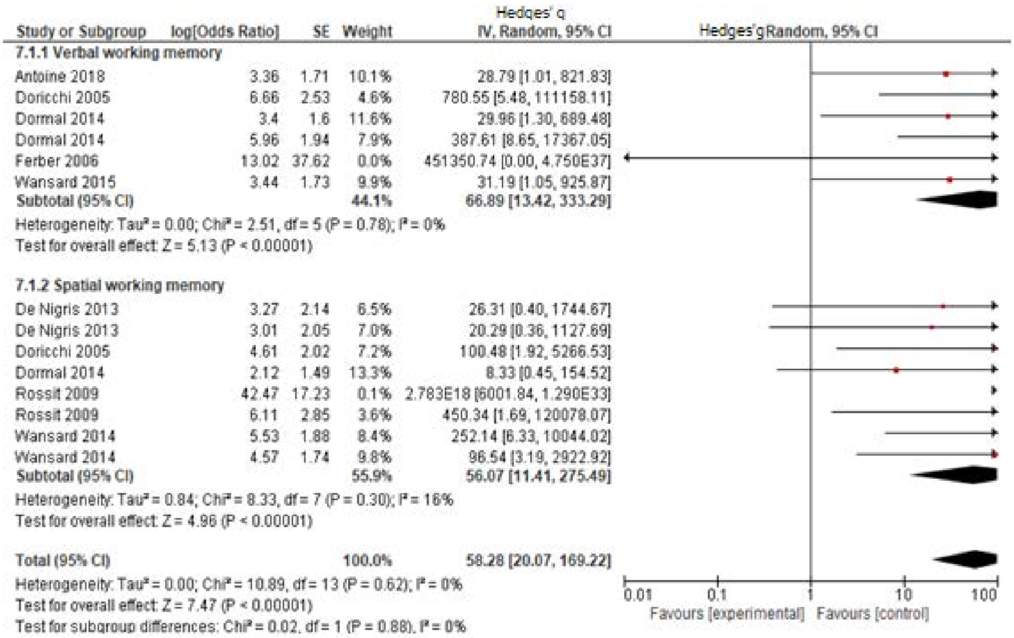

Figure 6-4. Forest plot of outcome Analysis 4.1-1.stand: the number of error responses. Visual spatial neglect patients compared with standardized norms.

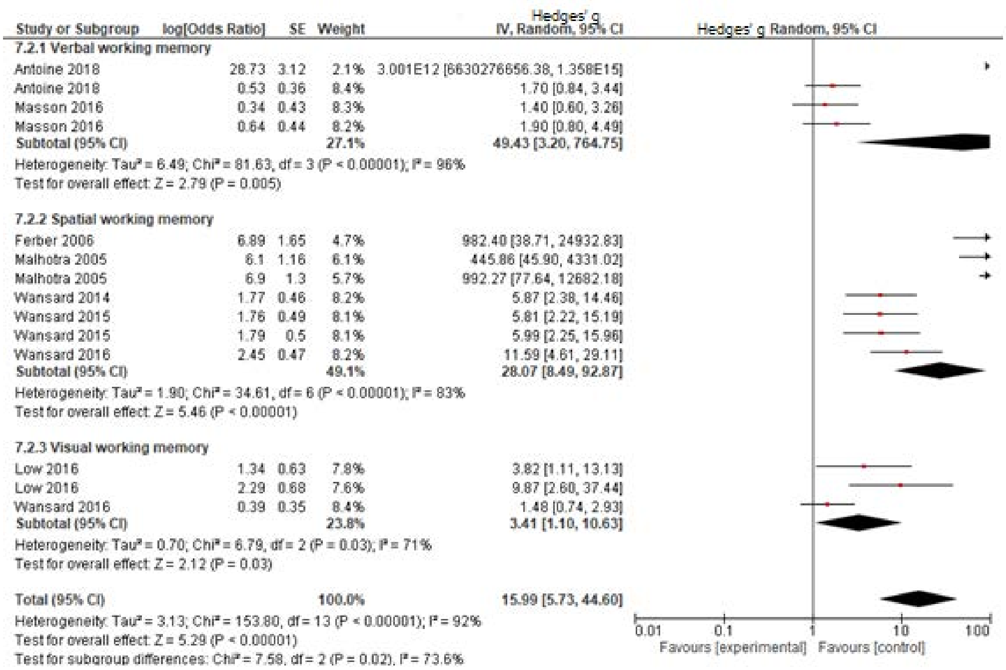

Figure 6-5. Forest plot of outcome Analysis 4.1-1.hc: the number of error responses: Visual spatial neglect patients compared with matched healthy controls.

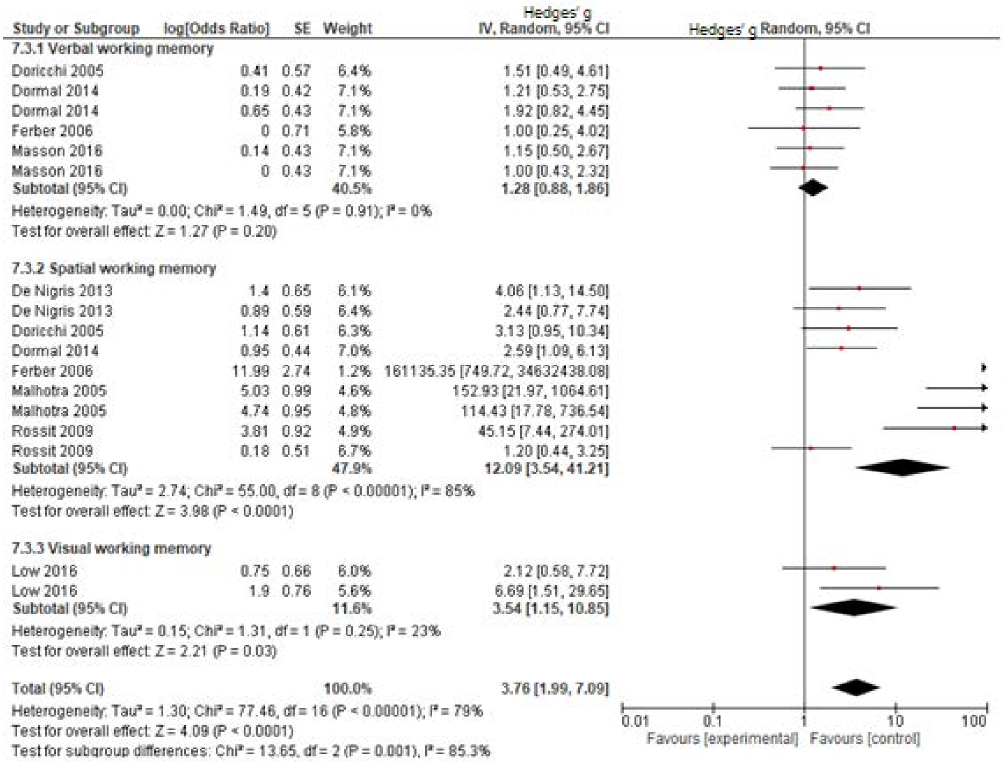

Figure 6-6. Forest plot of outcome Analysis 4.1-1.noneg: the number of error responses. Visual spatial neglect patients compared with brain damaged controls without spatial neglect.

6.4.1.2.2 Types of Stimuli of Working Memory Tests

For *Analysis 4.1-2.stand*, we identified 8 relevant studies (138 patients with visual spatial neglect; a total of 14 experiments on numbers stimuli and others stimuli; see Table 3). Their performance scores were compared to the standardized normative data. Significant differences were found in numbers stimuli (Z=5.13, *p*=<.00001) and others stimuli (Z=4.96, *p*=<.00001). No studies tested on letters stimuli (see Figure 6.7). Additionally, the results reported high significant overall effects estimates on deficit performance on different types of stimuli associated with visual spatial neglect symptoms (Z=7.47, *p*=<.00001). The data used in *Analysis D* (I^2) was homogenous.

For *Analysis 4.1-2.hc*, we identified eight studies (138 visual spatial neglect patients and 262 healthy matched controls; a total of 14 experiments on letters stimuli, numbers stimuli and others stimuli; see Table 6.3). Significant differences can be seen on letters stimuli tests (Z=2.78, P=.005), numbers stimuli (Z=2.58, p=.01) and others stimuli (Z=4.88, p=<.00001) (see Figure 6.8). Additionally, the results reported high significant overall effects estimates on deficit performance on different types of stimuli, associated with visual spatial neglect symptoms (Z=5.67, p=<.00001), though we note that I^2 values were 77.9%, indicating large heterogeneity between studies.

For *Analysis 4.1-2.noneg,* we compared performance scores between visual neglect patients with brain damaged patients without neglect symptoms. Eight studies identified (142 visual neglect patients and 152 brain-damaged patients without neglect; a total of 17 experiments on numbers stimuli and others stimuli; see Table 6.3). Significant differences can be seen only other stimuli (Z=3.08, p=.002), but not on numbers stimuli (see Figure 6.9). No studies tested on letters stimuli. At the same time, the results showed high significant overall effects estimates on different types of stimuli when compared between these two groups (Z=7.56, p=.006), though we note that I^2 values were higher than 75%, indicating large heterogeneity between studies.

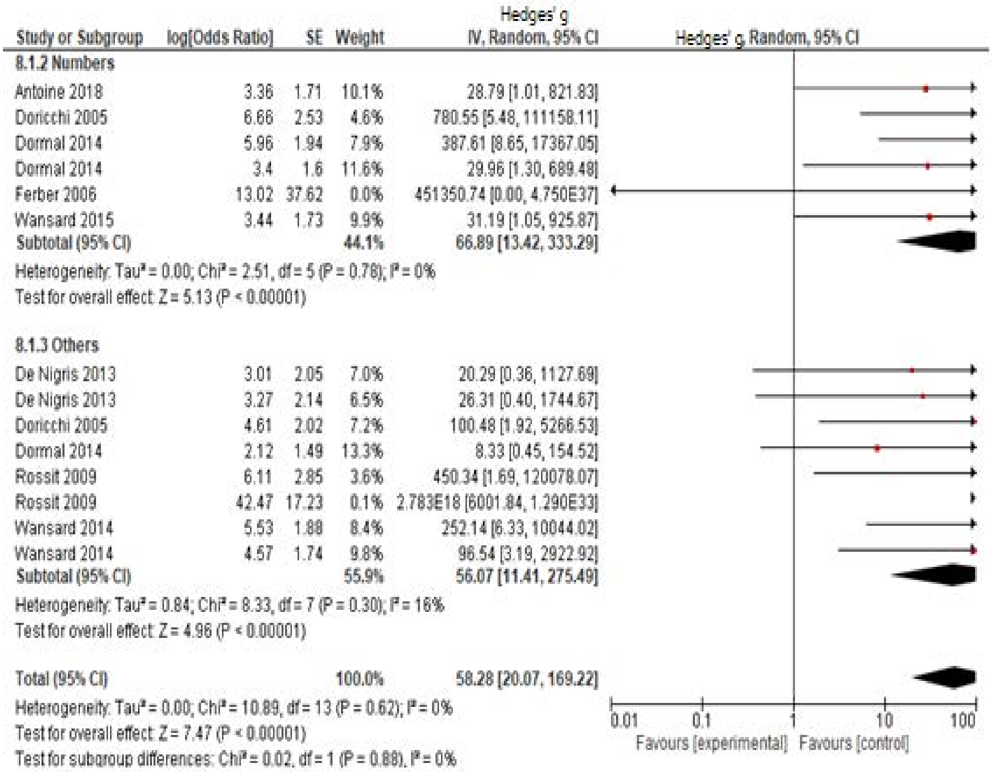

Figure 6-7. Forest plot of outcome Analysis 4.1-2.stand: the number of error responses. Visual spatial neglect patients compared with standardized norms.

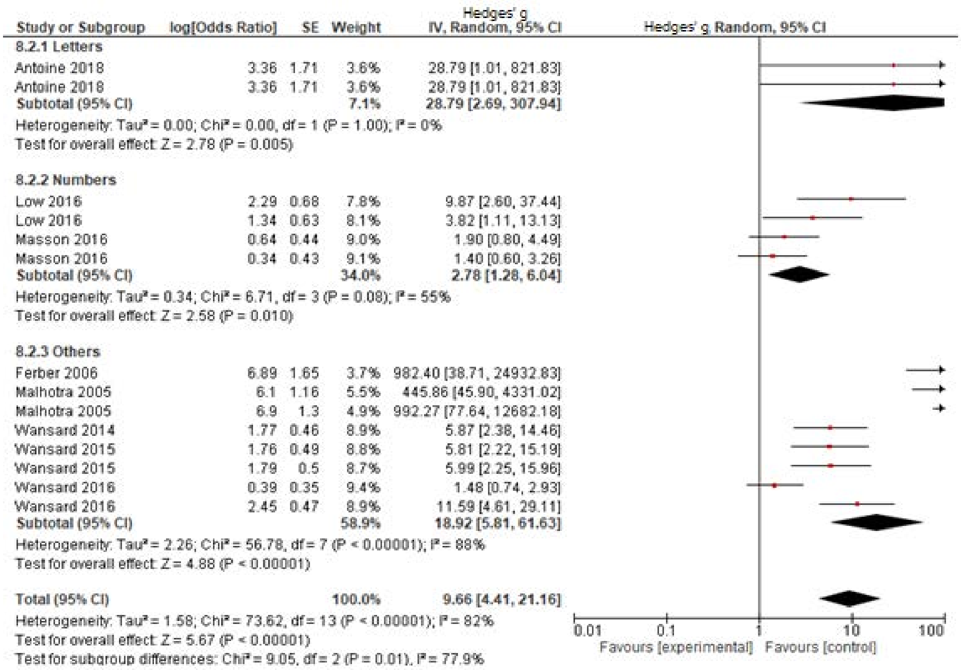

Figure 6-8. Forest plot of outcome Analysis 4.1-2.hc: the number of error responses: Visual spatial neglect patients compared with matched healthy controls.

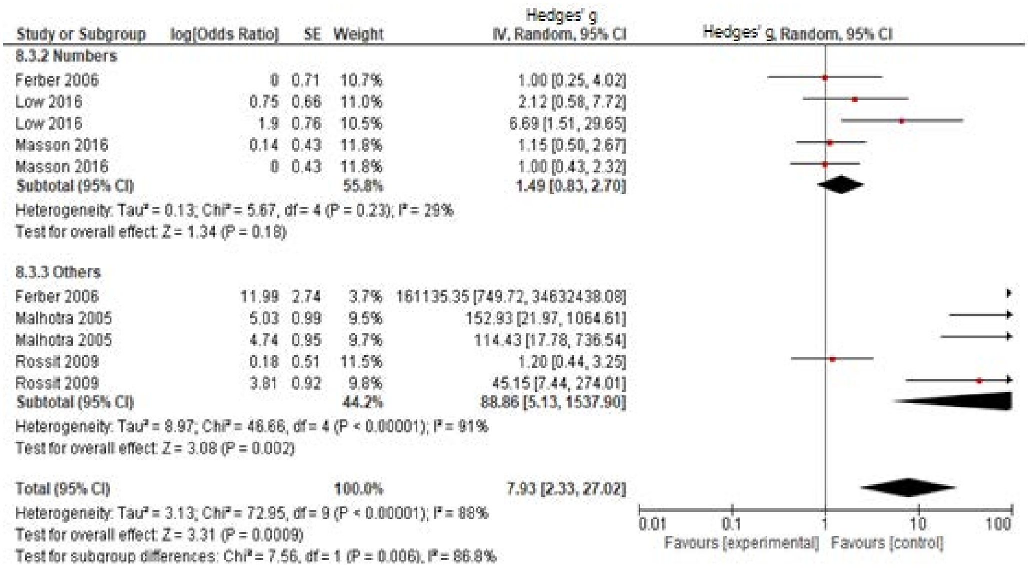

Figure 6-9. Forest plot of outcome Analysis 4.1-2.noneg: the number of error responses. Visual spatial neglect patients compared with brain damaged controls without spatial neglect.

6.4.1.2.3 Visual Field Display

For *Analysis 4.1-3.stand*, we identified 8 relevant studies (138 patients with visual spatial neglect; a total of 14 experiments on centre (fixation) and peripheral (distribution) visual fields; see Table 6.3). Their performance scores were compared to the standardized normative data. Significant differences were found on peripheral (distribution) visual field only (Z=4.97, p=<.00001), but not on centre (fixation) visual field (see Figure 6.10). Additionally, the results reported high significant overall effects estimates on deficit performance on different types of visual field associated with visual spatial neglect symptoms (Z=5.79, p=<.00001). The data used in *Analysis G* (I^2) was homogenous.

For *Analysis 4.1-3.hc*, we identified eight studies (138 visual spatial neglect patients and 262 healthy matched controls; a total of 14 experiments on centre (fixation) and peripheral (distribution) visual fields; see Table 6.3). Significant differences can be seen on centre (fixation) visual field (Z=4.08, p=<.00001), and peripheral (distribution) visual field (Z=4.04, p=<.00001)(see Figure 6.11). Additionally, the results reported high significant overall effects estimates on deficit performance on different visual fields associated with visual spatial neglect symptoms (Z=5.29, p=<.00001), though we note that I^2 values were 70.5%, indicating moderate heterogeneity between studies.

For *Analysis 4.1-3.noneg,* we compared performance scores based on visual fields between visual neglect patients with brain damaged patients without neglect symptoms. Eight studies identified (142 visual neglect patients and 152 brain-damaged patients without neglect; a total of 17 experiments on centre (fixation) and peripheral (distribution) visual fields; see Table 6.3). Significant differences were found on centre (fixation) visual field (Z=3.26, p=.001), and peripheral (distribution) visual field (Z=2.34, p=.02) (see Figure 6.12). At the same time, the results showed high significant overall effects estimates on different types of stimuli when compared between these two groups (Z=4.09, p=<.00001). The data used in *Analysis I* (I^2) was homogenous.

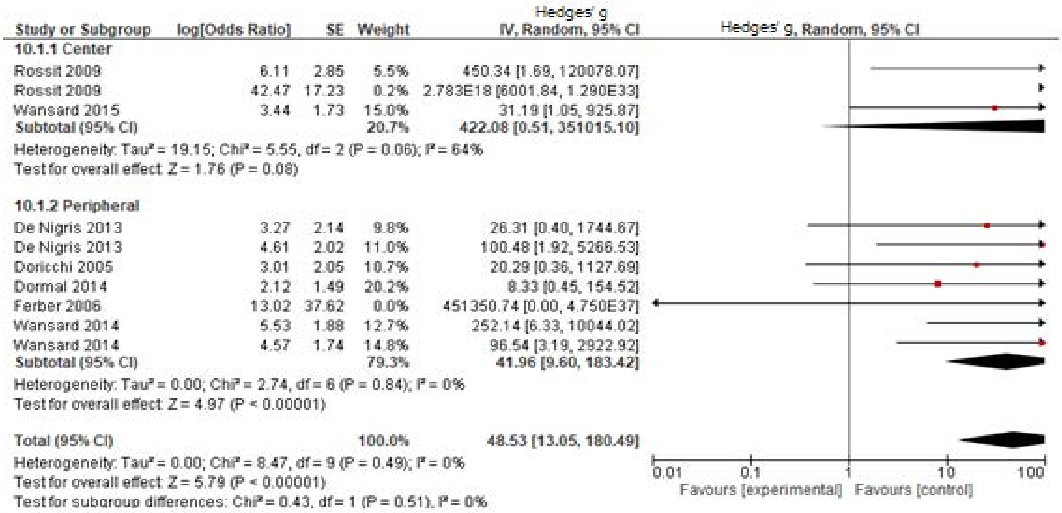

Figure 6-10. Forest plot of outcome Analysis 4.1-3.stand: the number of error responses. Visual spatial neglect patients compared with standardized norms.

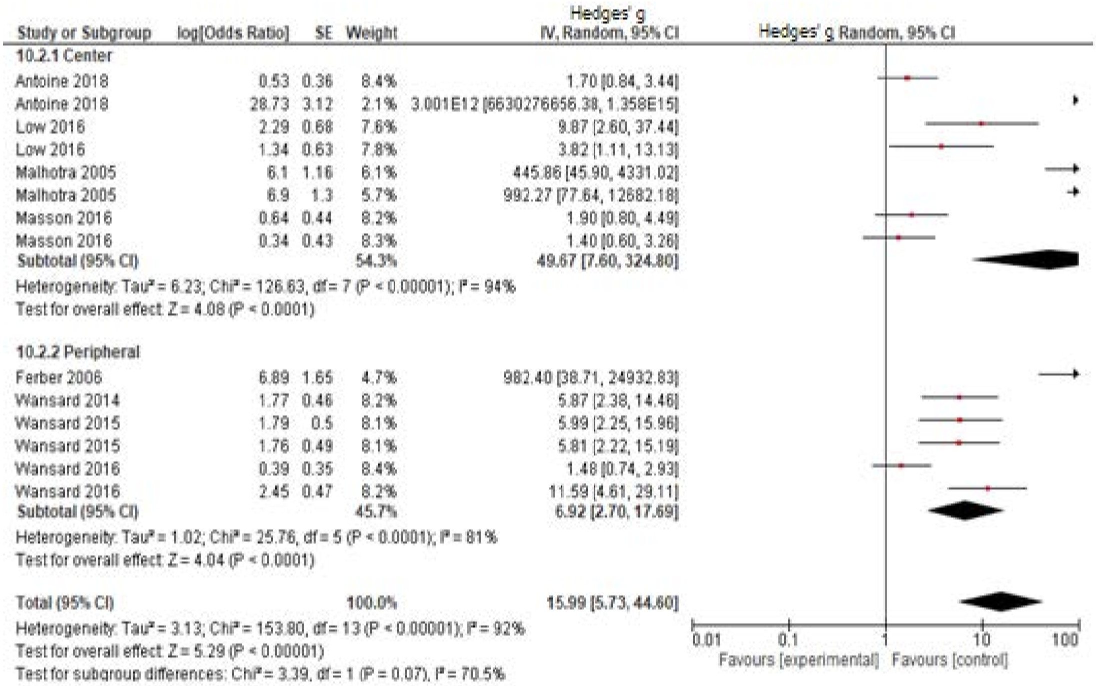

Figure 6-11. Forest plot of outcome Analysis 4.1-3.hc: the number of error responses: Visual spatial neglect patients compared with matched healthy controls.

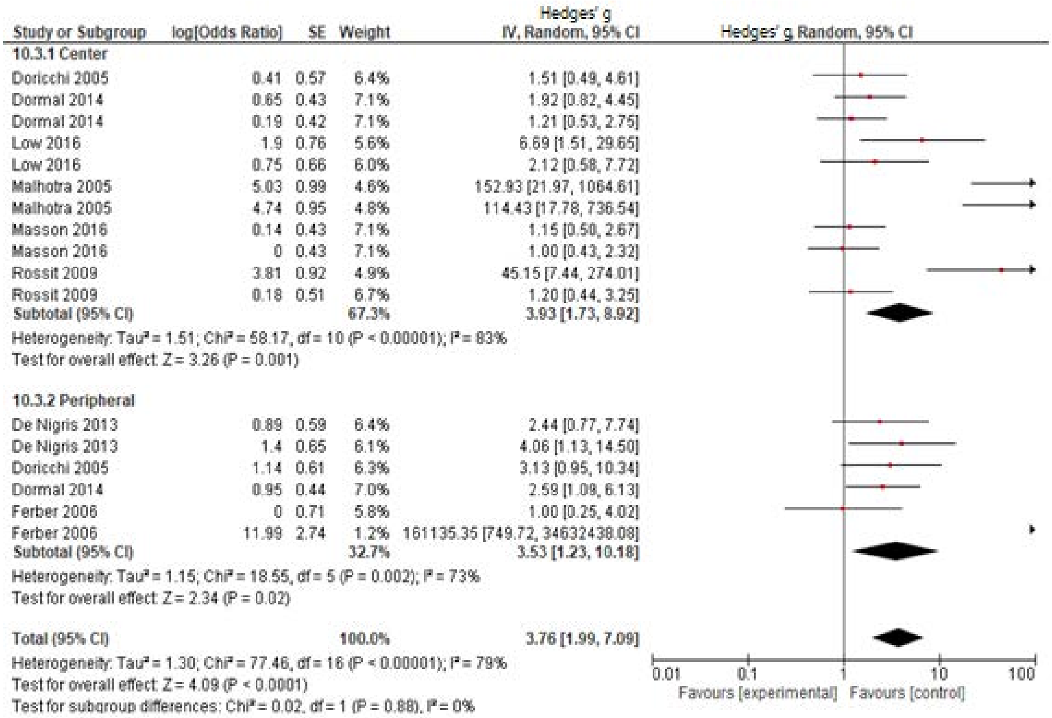

Figure 6-12. Forest plot of outcome Analysis 4.1-3.noneg: the number of error responses. Visual spatial neglect patients compared with brain damaged controls without spatial neglect.

6.4.1.3. Discussion

The objective of the study was to examine working memory abilities in visual spatial neglect patients. Performances of neglect patients were compared with normative data (stand), matched healthy controls (hc) and non-spatial neglect patients (noneg). To answer the above questions, we classified working memory tasks in three ways, (i) the types of working-memory tests (type of information needed to be remembered), (ii) the types of test stimuli used in the working memory tests and (iii) the display area. Across all tests and analyses, patients with acquired visual neglect showed reliably less efficient working memory. This comorbid deficit was most pronounced in spatial memory tests, when using non graphemes visual items and when items were presented in the peripheral visual field. Next, in Study 2, we tested whether working memory deficits emerged due to the spatial nature of the syndrome.

6.4.2. **STUDY 2: Effects of spatial location in working memory deficit – *Analyses 4.2-1-3***

6.4.2.1. Methods

Study 2, aimed to test whether the spatial pattern of working memory errors matches the spatial deficit common in neglect. To this aim, we assumed that if working memory errors are related to the spatial deficit, they should be more prevalent in the contralesional side; while showing a like-normal pattern in the ipsilesional side. To this aim we performed three meta-analyses based on types of working memory (*Analysis 4.2-1*), types of tests stimuli (*Analysis 4.2-2*) and types of different visual fields in working memory tests (*Analysis 4.2-3*). All analyses included only patients with neglect syndrome. In these analyses, we compared errors made on contra versus ipsilesional side.

Table 6-4. Studies Included in The Meta-Analysis *(Analyses 4.2)*

No	Study ID	No. of Neglect Patients	Type of Controls	No. of Controls	Working Memory Test
ANALYSIS 4.2-1: Effects of spatial location in working memory					
1	Wansard et al. (2015)	12	*NA*	*NA*	Spatial working memory
2	Wansard et al. (2015)	12	*NA*	*NA*	Spatial working memory
3	Wansard et al. (2015)	12	*NA*	*NA*	Spatial working memory
4	Wansard et al. (2015)	12	*NA*	*NA*	Spatial working memory
5	Wansard et al. (2015)	12	*NA*	*NA*	Spatial working memory
6	Vuilleumier et al. (2007)	5	*NA*	*NA*	Spatial working memory
7	Vuilleumier et al. (2007)	5	*NA*	*NA*	Spatial working memory
8	Vuilleumier et al. (2007)	5	*NA*	*NA*	Spatial working memory
	Total	*75*			
ANALYSIS 54.2-2: Effects of spatial location in working memory					
1	Wansard et al. (2015)	12	*NA*	*NA*	Others
2	Wansard et al. (2015)	12	*NA*	*NA*	Others
3	Wansard et al. (2015)	12	*NA*	*NA*	Others
4	Wansard et al. (2015)	12	*NA*	*NA*	Others
5	Wansard et al. (2015)	12	*NA*	*NA*	Others
6	Vuilleumier et al. (2007)	5	*NA*	*NA*	Others
7	Vuilleumier et al. (2007)	5	*NA*	*NA*	Others
8	Vuilleumier et al. (2007)	5	*NA*	*NA*	Others
	Total	*75*			
ANALYSIS 4.2-3: Effects of spatial location in working memory					
1	Wansard et al. (2015)	12	*NA*	*NA*	Peripheral
2	Wansard et al. (2015)	12	*NA*	*NA*	Peripheral
3	Wansard et al. (2015)	12	*NA*	*NA*	Peripheral
4	Wansard et al. (2015)	12	*NA*	*NA*	Peripheral
5	Wansard et al. (2015)	12	*NA*	*NA*	Peripheral
6	Vuilleumier et al. (2007)	5	*NA*	*NA*	Peripheral
7	Vuilleumier et al. (2007)	5	*NA*	*NA*	Peripheral
8	Vuilleumier et al. (2007)	5	*NA*	*NA*	Peripheral
	Total	*75*			

6.4.2.2. Results

We evaluated working memory performance based on two spatial locations. (Contralesional and Ipsilesional sides) within visual spatial neglect patients. In *Analysis 4.2-1* (types of working memory), we identified two studies (75 visual neglect patients; a total of 8 experiments on spatial working memory test; see Table 6.4) to assess the effects of contralesional spatial location on working memory tests. None significant differences were detected (see Figure 6.13).

Next, in *Analysis 4.2-2* (types of tests stimuli), we further evaluated the working memory performance based on types of tests stimuli within these visual neglect patients. We identified two studies (75 visual neglect patients; a total of 8 experiments on other type of stimuli; see Table 6.4). Also, none significant differences were detected (see Figure 6.14).

Finally, in *Analysis 4.2-3* (types of different visual fields in working memory tests) we evaluated the working memory performance based on fixation and distribution visual fields within these visual neglect patients. We identified two studies (75 visual neglect patients; a total of 8 experiments on peripheral visual fields; see Table 6.4). None significant differences were detected (see Figure 6.15).

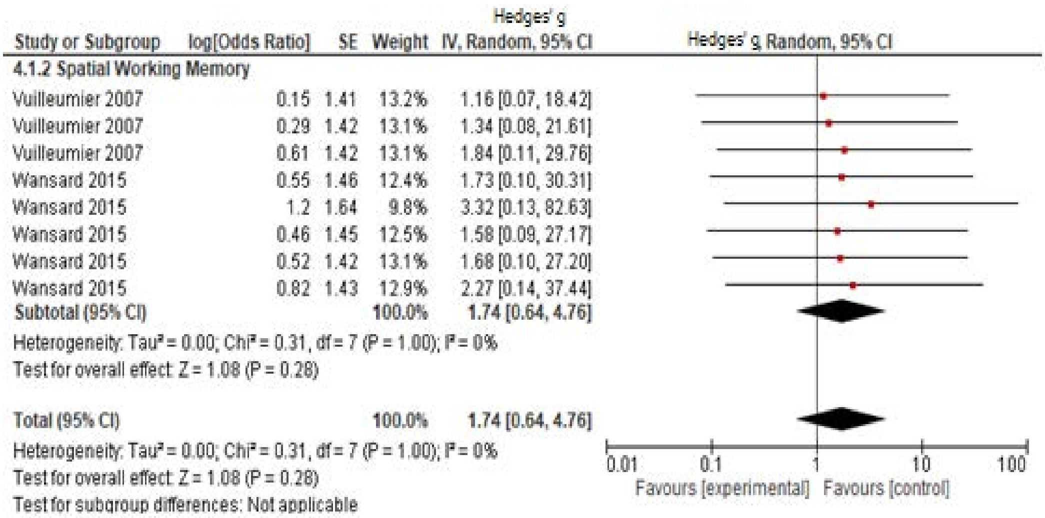

Figure 6-13. Forest plot of outcome Analysis 4.2-1: the number of error responses on types of working memory tests: Effects of spatial location on working memory deficit in visual spatial neglect syndrome.

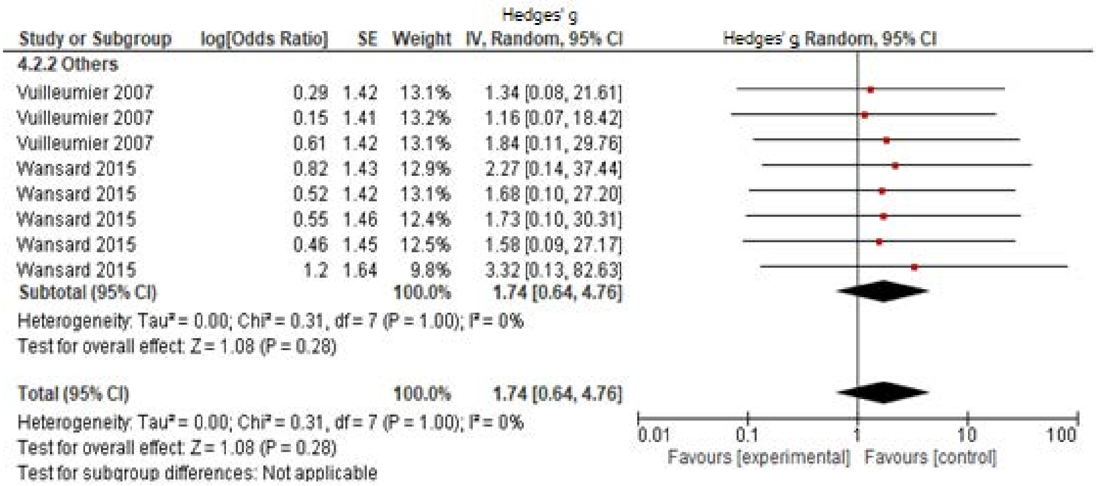

Figure 6-14. Forest plot of outcome Analysis 4.2-2: the number of error responses on types of stimuli of working memory tests: Effects of spatial location on working memory deficit in visual spatial neglect syndrome.

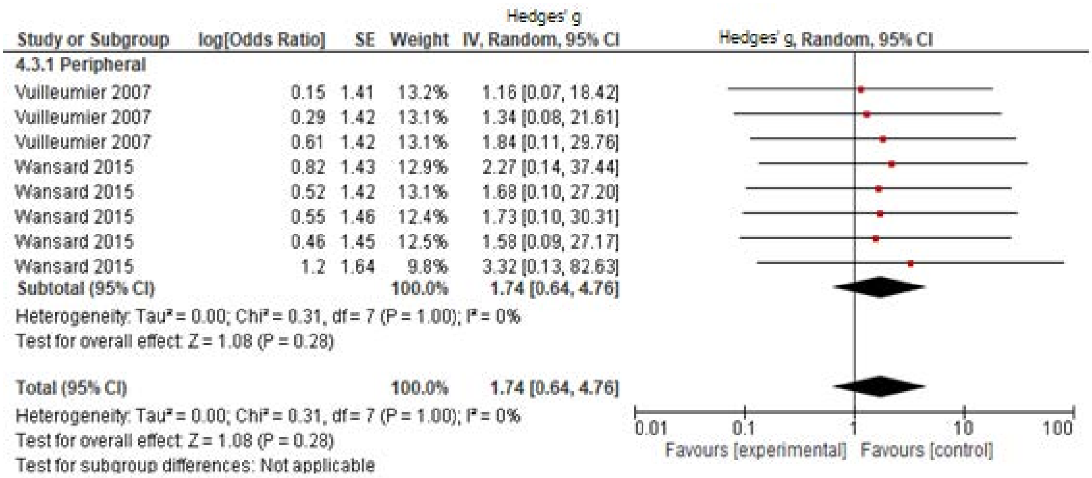

Figure 6-15. Forest plot of outcome Analysis 4.2-3: the number of error responses on types of visual fields in working memory tests: Effects of spatial location on working memory deficit in visual spatial neglect syndrome.

6.4.2.3. Discussion

Study 2 set out with the aim of assessing the effects of spatial nature in working memory difficulty within visual neglect patients. It is somewhat surprising that the meta-analysis failed to show evidence of spatial location effects in working memory difficulty in all testing domains within patients with visual neglect. Next, in Study 3, we tested whether working memory deficits emerged due to the neglect symptoms (egocentric versus allocentric). Is different spatial allocation can account for the working memory deficits?

6.4.3. **STUDY 3: Effects of neglect symptoms in reading deficit – *Analyses 4.3.ego-1/2/3 (Egocentric)* and *Analyses 4.3.allo-1/2/3 (Allocentric)***

6.4.3.1. Methods

In Study 3, we examined the link of between the working memory performance associated with impairments in allocating spatial attention either across space (using an egocentric frame of reference, *Analyses 4.3.ego*) or within objects (using an allocentric frame of reference, *Analyses 4.3 allo*). *Analyses 4.3.ego* included the data from the studies that employed the neglect tests that reflected symptoms on egocentric deficits such as *Letter Cancellation* (Diller & Weinberg, 1977), *Bells Cancellation Test*, *The Star Cancellation Task* (P. Halligan et al., 1990) and *Detection task* (Bonato et al., 2013), *TAP task* (Zimmermann & Fimm, 1995) (see Table 6.5). In *Analyses 4.3.allo*, we included the data from the relevant studies that used neglect tests which measured allocentric deficits such as *A Clock Drawing from Memory* (Kerkhoff et al., 1992), *Figure Copying* (star, flower, cube) (Kerkhoff et al., 1992), *A Copy of Geometrical Shapes* (Arrigoni & De Renzi, 1964), *Complex Figure Drawing*

(Gainotti et al., 1972) and *Line Bisection Task* (Azouvi et al., 2002), *Landscape drawing* (Azouvi et al., 2002) (see Table 6.6).

6.4.3.2. Results

6.4.3.2.1 <u>Egocentric neglect patients versus non-egocentric neglect patients</u>

In *Analysis 4.3.ego-1* (types of working memory tests), we identified six studies (138 neglect patients with egocentric symptoms and 180 neglect patients without egocentric symptoms; total of 26 experiments on verbal working memory, spatial working memory and visual working memory; see Table 6.5) to assess the effects of egocentric deficit on working memory performance. No significant differences were observed in all working memory tests. (see Figure 6.16)

Next, in *Analysis 4.3.ego-2* (types of working memory stimuli test), we identified six studies (138 neglect patients with egocentric symptoms and 180 neglect patients without egocentric symptoms; total of 26 experiments on letters stimuli, numbers stimuli and others stimuli; see Table 6.5) to assess the effects of egocentric deficit on various stimuli tests. No significant differences were observed in all types of stimuli (see Figure 6.17).

Finally, in *Analysis 4.3.ego-3* (fixation and distribution of visual fields), we identified six studies (138 neglect patients with egocentric symptoms and 180 neglect patients without egocentric symptoms; total of 26 experiments on centre (fixation) and peripheral (distribution) visual fields; see Table 6.5) to assess the effects of egocentric deficit on different presentation of visual fields. No significant differences were observed in all types of visual fields (see Figure 6.18).

Table 6-5. Studies Included in The Meta-Analyses-*Analysis 4.3.ego*.

No	Study ID	No. of Egocentric Patients	No. of patients without egocentric symptoms	Neglect test detecting egocentric symptoms	Working memory test
ANALYSIS 4.3.ego-1					
1	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Verbal working memory
2	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Verbal working memory
3	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Verbal working memory
4	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Verbal working memory
5	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Verbal working memory
6	Masson et al. (2016)	5	6	Cancellation task, TAP task	Verbal working memory
7	Masson et al. (2016)	5	6	Cancellation task, TAP task	Verbal working memory
8	Wansard et al. (2015)	4	6	Bells cancellation, Letter cancellation	Verbal working memory
	Total	*42*	*48*		
10	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Spatial working memory
11	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Spatial working memory
12	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Spatial working memory
13	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Spatial working memory
14	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
15	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
16	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
17	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
18	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
19	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
20	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
21	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
22	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
23	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
24	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
25	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Spatial working memory
26	Wansard et al. (2016)	5	9	Bells cancellation, Letter cancellation	Spatial working memory
	Total	*91*	*123*		
27	Wansard et al. (2016)	5	9	Bells cancellation, Letter cancellation	Visual working memory
	Total	*5*	*9*		
ANALYSIS 4.3.ego-2					

No	Study ID	No. of Egocentric Patients	No. of patients without egocentric symptoms	Neglect test detecting egocentric symptoms	Working memory test
1	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Letters stimuli
2	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Letters stimuli
	Total	*4*	*16*		
3	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Numbers stimuli
4	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Numbers stimuli
5	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Numbers stimuli
6	Masson et al. (2016)	5	6	Cancellation task, TAP task	Numbers stimuli
7	Masson et al. (2016)	5	6	Cancellation task, TAP task	Numbers stimuli
8	Wansard et al. (2015)	4	6	Bells cancellation, Letter cancellation	Numbers stimuli
	Total	*38*	*32*		
9	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Others stimuli
10	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Others stimuli
11	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Others stimuli
12	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Others stimuli
13	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
14	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
15	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
16	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
17	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
18	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
19	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
20	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
21	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
22	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
23	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
24	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Others stimuli
25	Wansard et al. (2016)	5	9	Bells cancellation, Letter cancellation	Others stimuli
26	Wansard et al. (2016)	5	9	Bells cancellation, Letter cancellation	Others stimuli
	Total	96	132		
ANALYSIS 4.3.ego-3					
1	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Center
2	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Center
3	Antoine et al. (2018)	2	8	Star cancellation, Detection task	Center

No	Study ID	No. of Egocentric Patients	No. of patients without egocentric symptoms	Neglect test detecting egocentric symptoms	Working memory test
4	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Center
5	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Center
6	Masson et al. (2016)	5	6	Cancellation task, TAP task	Center
7	Masson et al. (2016)	5	6	Cancellation task, TAP task	Center
8	Wansard et al. (2015)	4	6	Bells cancellation, Letter cancellation	Center
	Total	*42*	*48*		
9	Dormal et al. (2014)	11	3	Letter cancellation, Star Cancellation	Peripheral
10	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Peripheral
11	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Peripheral
12	Wansard et al. (2014)	5	9	Bells cancellation, Letter cancellation	Peripheral
13	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
14	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
15	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
16	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
17	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
18	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
19	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
20	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
21	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
22	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
23	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
24	Wansard et al. (2015)	5	7	Bells cancellation, Letter cancellation	Peripheral
25	Wansard et al. (2016)	5	9	Bells cancellation, Letter cancellation	Peripheral
26	Wansard et al. (2016)	5	9	Bells cancellation, Letter cancellation	Peripheral
	Total	*96*	*132*		

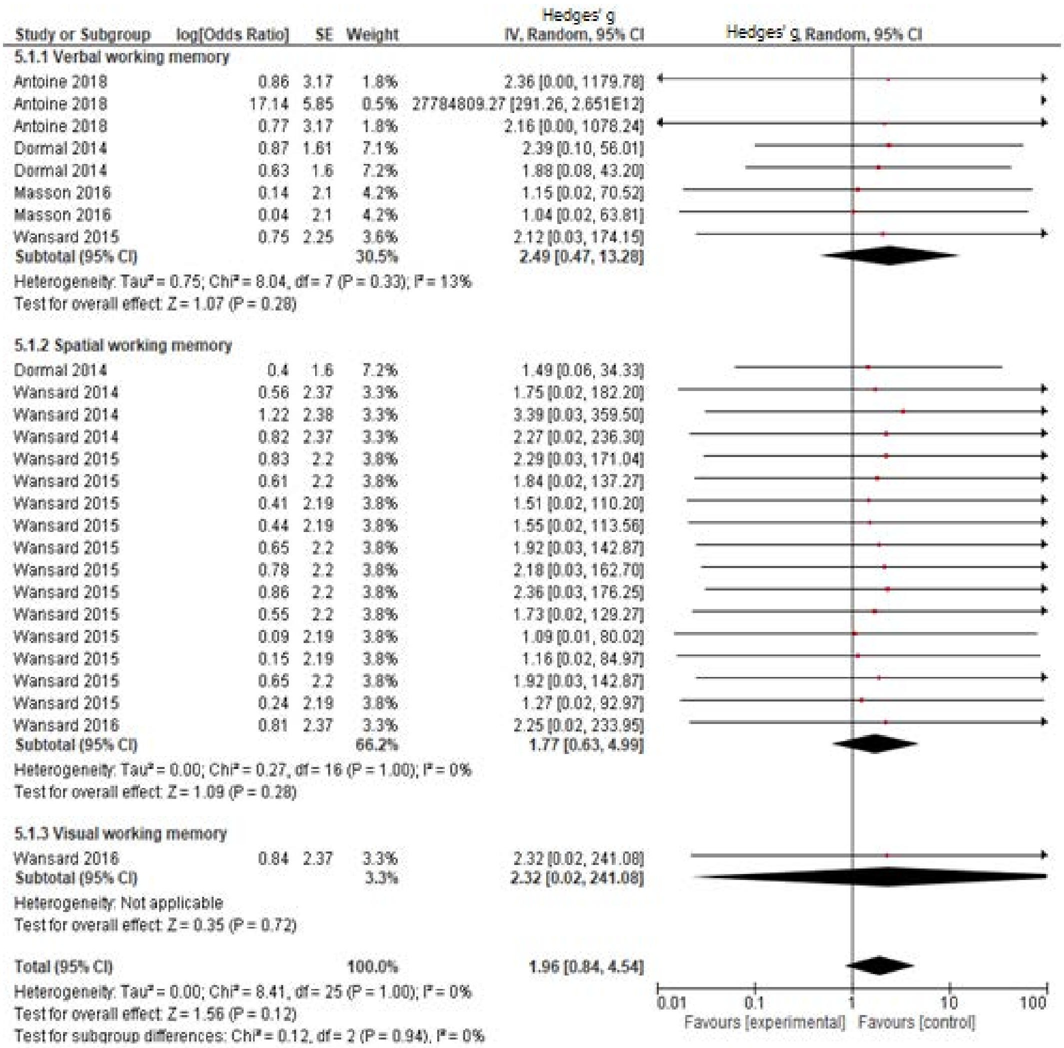

Figure 6-16. Forest plot of outcome Analysis 4.3.ego-1: the number of error responses on types of working memory tests: Neglect patients with egocentric symptoms were compared with neglect patients without egocentric deficits.

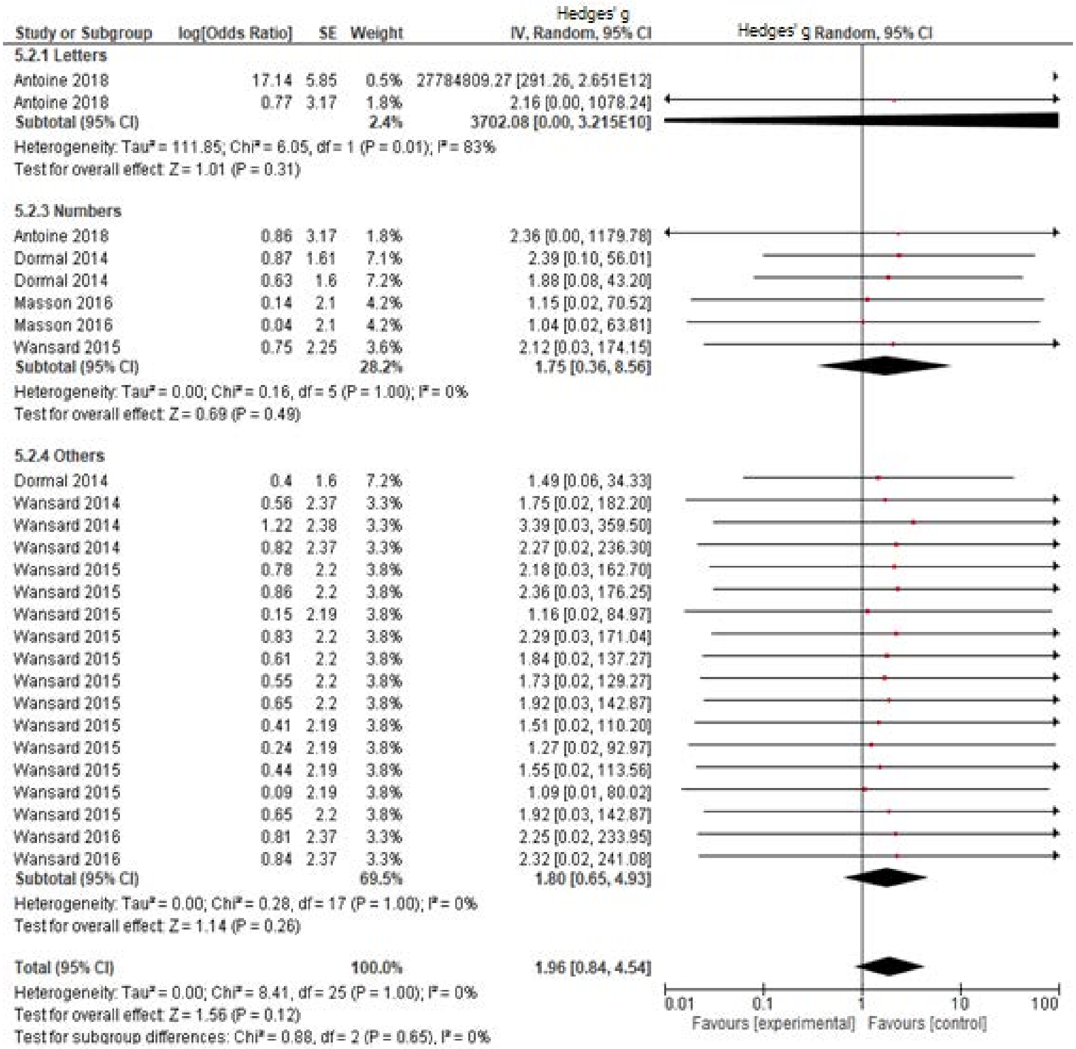

Figure 6-17. Forest plot of outcome Analysis 4.3.ego-2: the number of error responses on types of stimuli tests: Neglect patients with egocentric symptoms were compared with neglect patients without egocentric deficits.

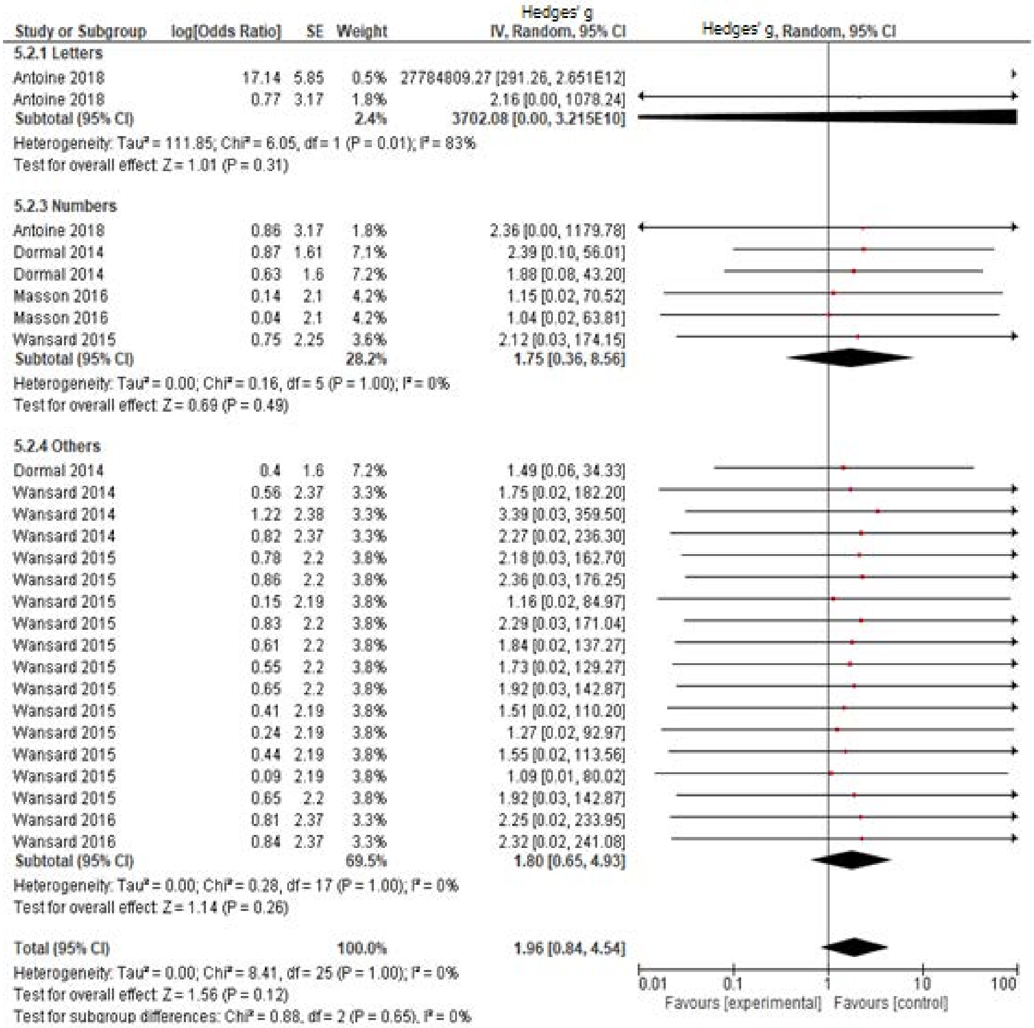

Figure 6-18. Forest plot of outcome Analysis 4.3.ego-3: the number of error responses on fixation or distribution visual fields: Neglect patients with egocentric symptoms were compared with neglect patients without egocentric deficits.

6.4.3.2.2 Allocentric neglect patients versus non-allocentric neglect patients

In *Analysis 4.3.allo-1*, we identified five relevant studies (105 neglect patients with allocentric symptoms and 191 neglect patients without allocentric symptoms; a total of 24 experiments on verbal working memory, spatial working memory and visual working memory; see Table 6.6) to assess the effects of allocentric neglect on working memory performance.

Similar to the egocentric neglect, we found none significant differences on working memory tests between these two groups (see Figure 6.19).

Next, in *Analysis 4.3.allo-2* (types of working memory stimuli test), we identified five studies (105 neglect patients with allocentric symptoms and 191 neglect patients without allocentric symptoms; total of 24 experiments on letters stimuli, numbers stimuli and others stimuli; see Table 6.5) to assess the effects of egocentric deficit on various stimuli tests No significant differences were observed in all types of stimuli (see Figure 6.20).

Finally, in *Analysis 4.3.allo-3* (fixation and distribution of visual fields), we identified five studies (105 neglect patients with allocentric symptoms and 191 neglect patients without allocentric symptoms; total of 24 experiments on centre (fixation) and peripheral (distribution) visual fields; see Table 6.5) to assess the effects of egocentric deficit on different presentation of visual fields. No significant differences were observed in all types of visual fields (see Figure 6.21).

Table 6-6. Studies Included in The Meta-Analysis-*Analyses 4.3.allo.*

No.	Study ID	No. of Allocentric Patients	No. of patients without allocentric symptoms	Neglect test detecting allocentric symptoms	Working memory test
ANALYSIS 4.3.allo-1					
1	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Verbal working memory
2	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Verbal working memory
3	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Verbal working memory
4	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Verbal working memory
5	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Verbal working memory
	Total	*24*	*34*		
6	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Spatial working memory
7	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Spatial working memory
8	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Spatial working memory
9	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Spatial working memory
10	Wansard et al. (2015)	4	6	Landscape drawing, Clock drawing	Spatial working memory
11	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
12	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
13	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
14	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
15	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
16	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
17	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
18	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
19	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
20	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
21	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
22	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Spatial working memory
23	Wansard et al. (2016)	4	10	Clock drawing, line Bisection	Spatial working memory
	Total	*77*	*147*		
24	Wansard et al. (2016)	4	10	Clock drawing, line Bisection	Visual working memory
	Total	*4*	*10*		
ANALYSIS 4.3.allo-2					
1	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Letters stimuli

No.	Study ID	No. of Allocentric Patients	No. of patients without allocentric symptoms	Neglect test detecting allocentric symptoms	Working memory test
2	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Letters stimuli
	Total	*4*	*16*		
3	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Numbers stimuli
4	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Numbers stimuli
5	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Numbers stimuli
6	Wansard et al. (2015)	4	6	Landscape drawing, Clock drawing	Numbers stimuli
	Total	*24*	*24*		
7	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Others stimuli
8	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Others stimuli
9	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Others stimuli
10	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Others stimuli
11	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
12	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
13	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
14	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
15	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
16	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
17	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
18	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
19	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
20	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
21	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
22	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Others stimuli
23	Wansard et al. (2016)	4	10	Clock drawing, line Bisection	Others stimuli
24	Wansard et al. (2016)	4	10	Clock drawing, line Bisection	Others stimuli
	Total	*77*	*151*		
ANALYSIS 4.3.allo-3					
1	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Center
2	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Center
3	Antoine et al. (2018)	2	8	Figure and shape copying, Line bisection	Center
4	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Center
5	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Center
6	Wansard et al. (2015)	4	6	Landscape drawing, Clock drawing	Center

No.	Study ID	No. of Allocentric Patients	No. of patients without allocentric symptoms	Neglect test detecting allocentric symptoms	Working memory test
	Total	*28*	*40*		
7	Dormal et al. (2014)	9	5	Figure and shape copying, Line bisection	Peripheral
8	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Peripheral
9	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Peripheral
10	Wansard et al. (2014)	4	10	Line bisection, Landscape drawing	Peripheral
11	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
12	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
13	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
14	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
15	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
16	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
17	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
18	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
19	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
20	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
21	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
22	Wansard et al. (2015)	4	8	Landscape drawing, Clock drawing	Peripheral
23	Wansard et al. (2016)	4	10	Clock drawing, line Bisection	Peripheral
24	Wansard et al. (2016)	4	10	Clock drawing, line Bisection	Peripheral
	Total	*77*	*151*		

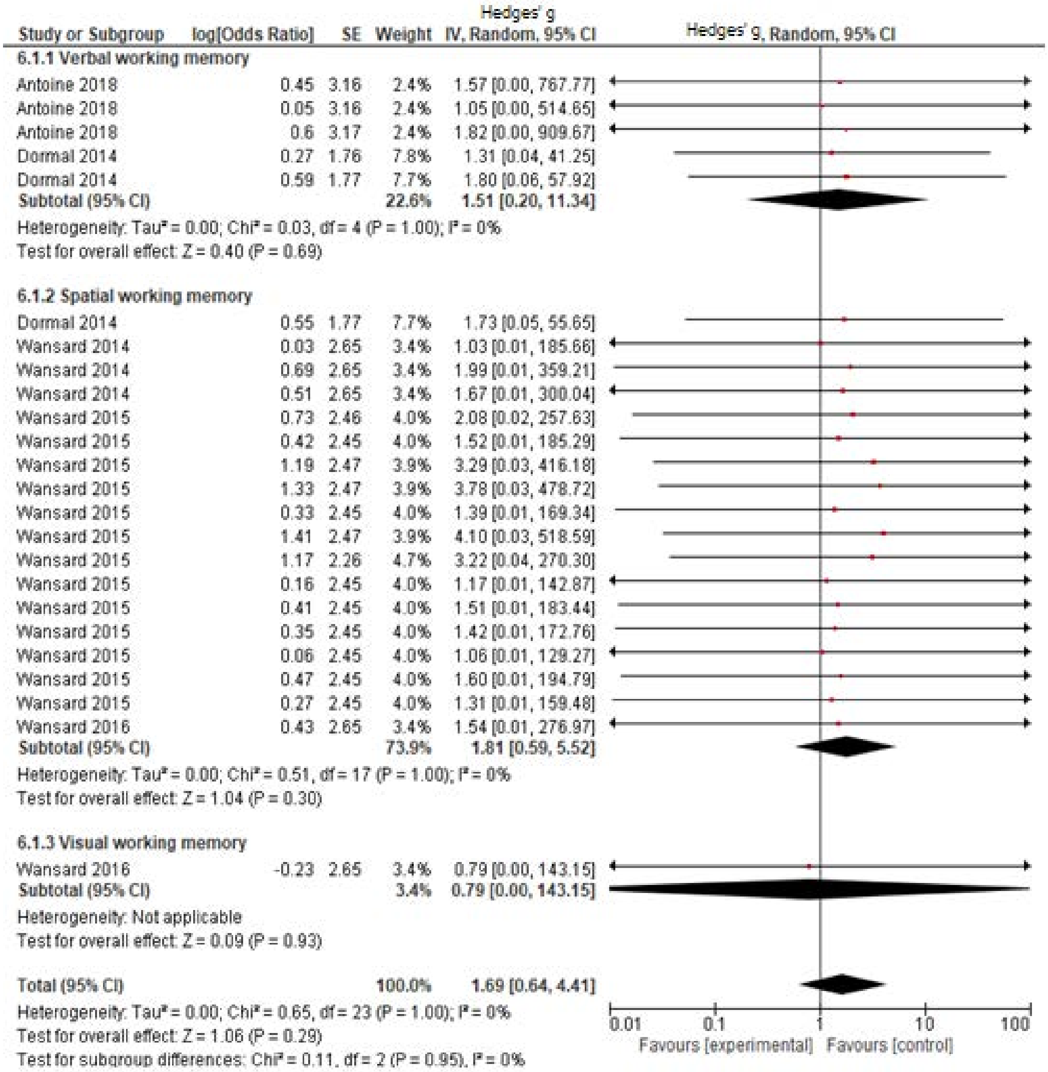

Figure 6-19. Forest plot of outcome Analysis 4.3.allo-1: the number of error responses on types of working memory tests: Neglect patients with allocentric symptoms were compared with neglect patients without allocentric deficits.

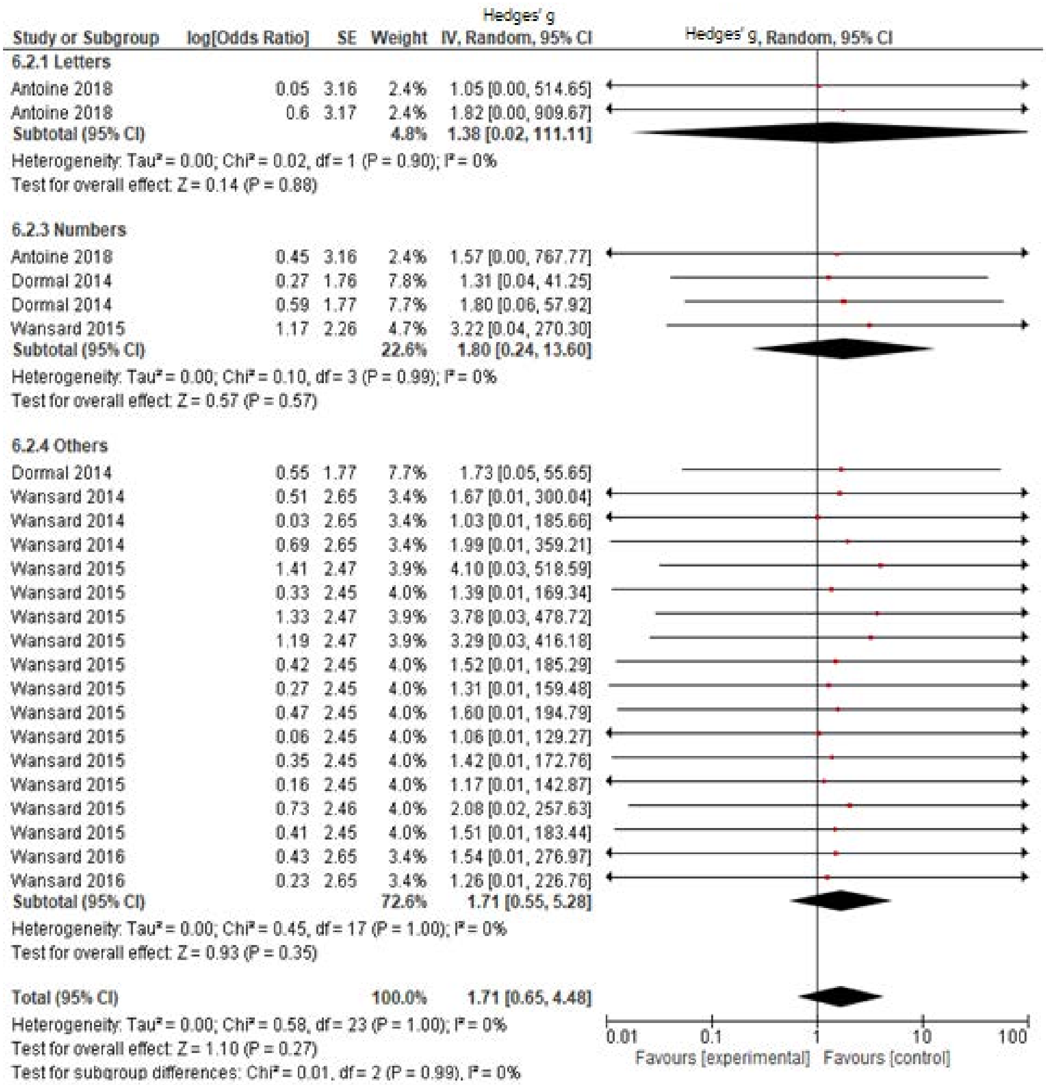

Figure 6-20. Forest plot of outcome Analysis 4.3.allo-2: the number of error responses on types of stimuli tests: Neglect patients with allocentric symptoms were compared with neglect patients without allocentric deficits.

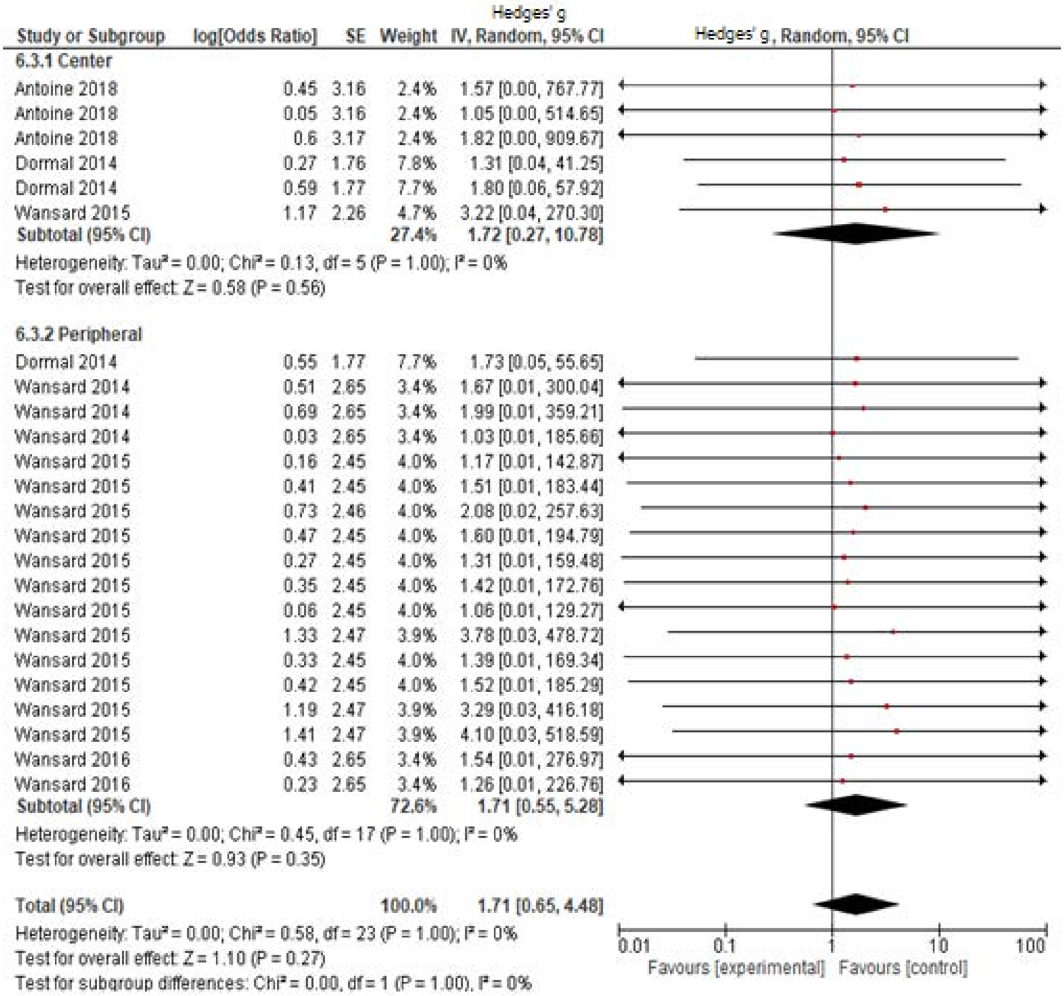

Figure 6-21. Forest plot of outcome Analysis 4.3.allo-3: the number of error responses on fixation or distribution visual fields: Neglect patients with allocentric symptoms were compared with neglect patients without allocentric deficits.

6.4.3.3. Discussion

These meta-analyses sought to determine whether neglect symptoms (egocentric and allocentric reference of frame) are associated with working memory difficulty in spatial neglect patients. Again, surprisingly the meta-analysis results failed to show evidence of egocentric neglect symptom effects in working memory difficulty in all testing domains within patients with visual neglect. Similarly, no evidence of allocentric neglect symptom effects in working memory difficulty in all testing domains within patients with visual neglect. It is worth noting, that most of this data emerge from a handful of labs, which potentially repeatedly assessed the same patients. Therefore, there is a paucity of data to firmly answer the question.

6.4.4. **Publication Bias**

We generated a funnel plot depicting the standard error of Hedges' g to visually inspect for asymmetry of the potential for publication bias for each meta-analysis. Some biases are present (see Figure 6.22, Figure 6.23, Figure 6.24).

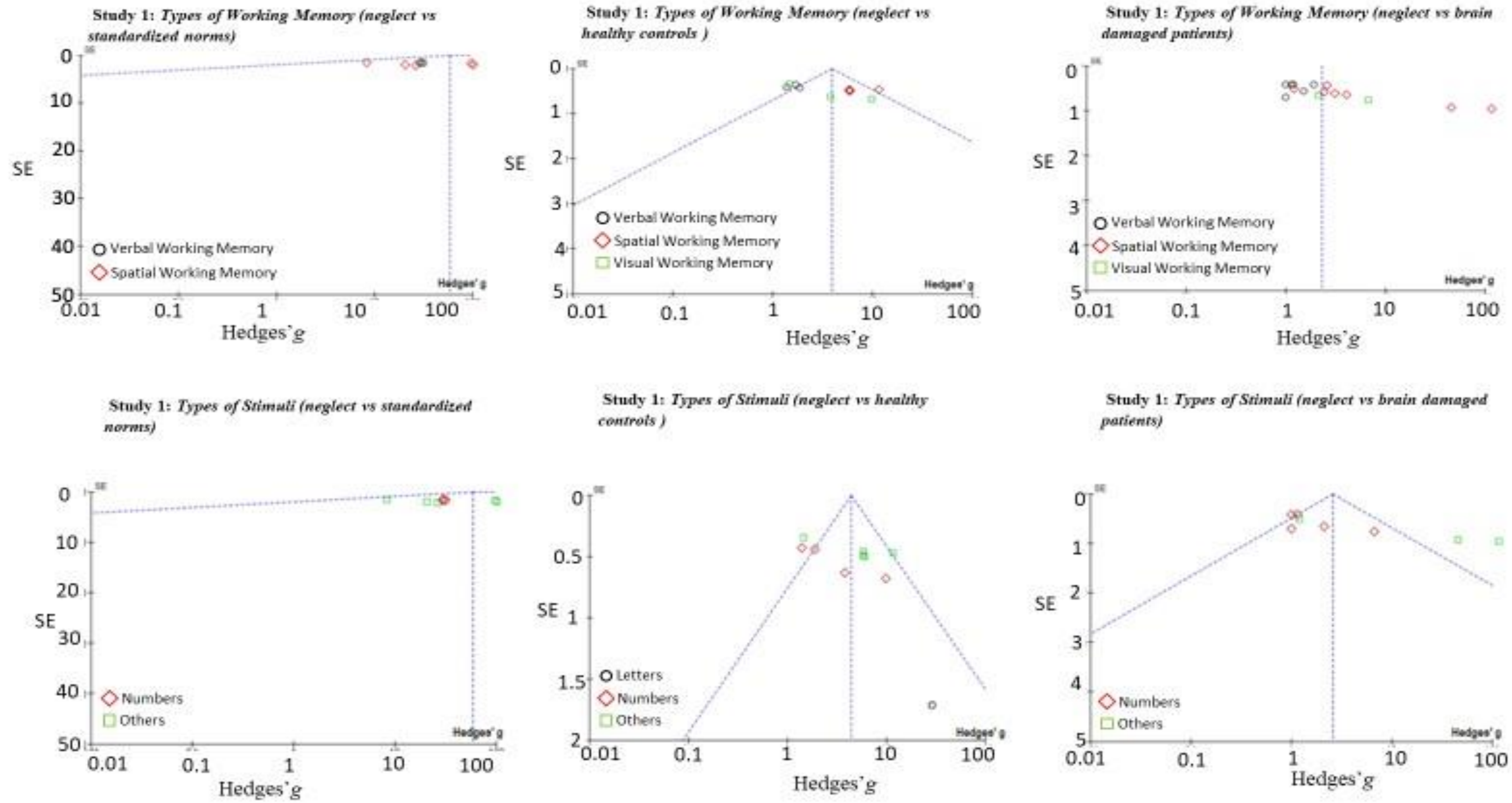

Figure 6-22. Funnel plot of the standard error of hedges' g (Study 1)

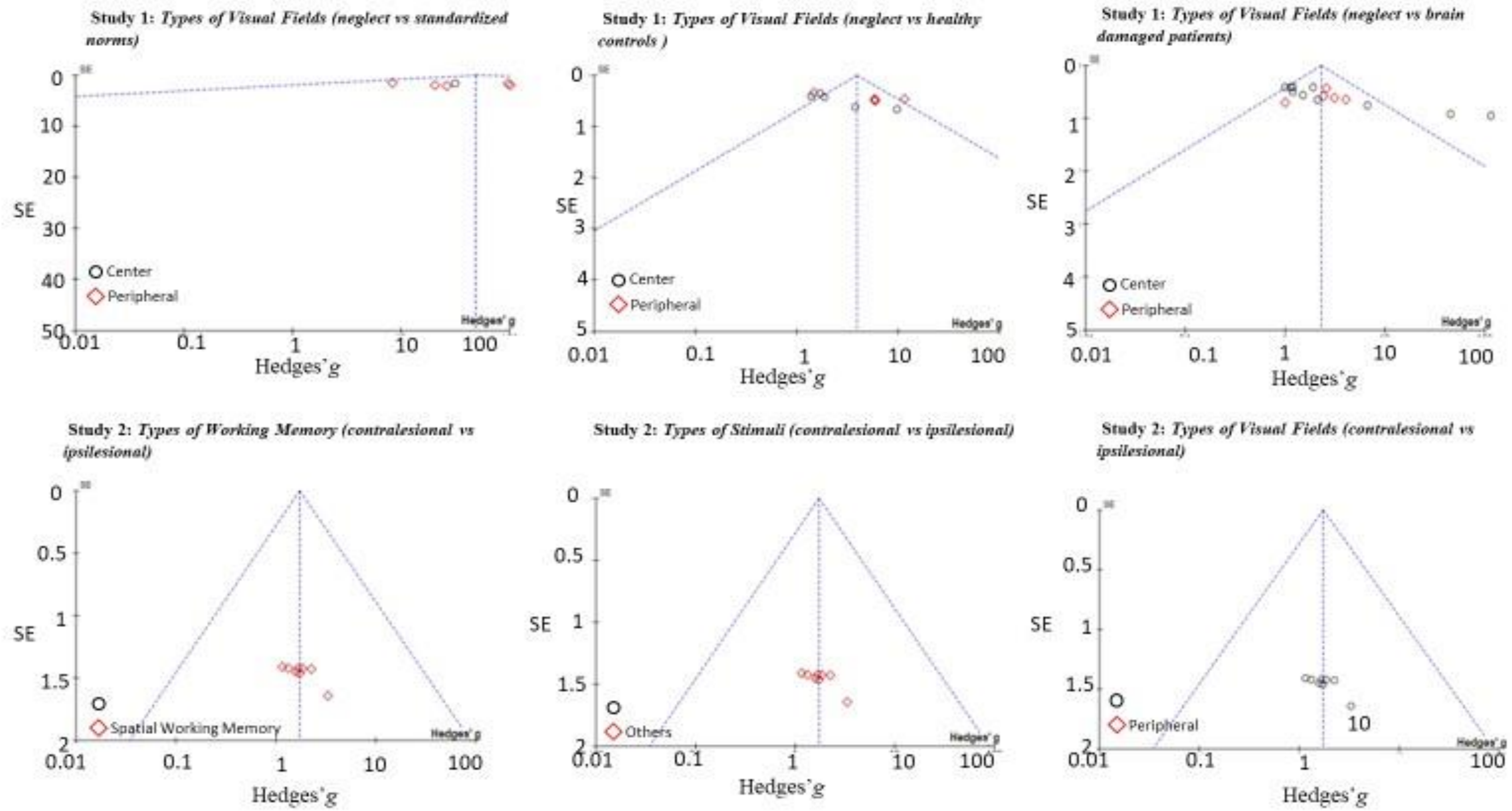

Figure 6-23. Funnel plot of the standard error of hedges' g (Study 1 and Study 2).

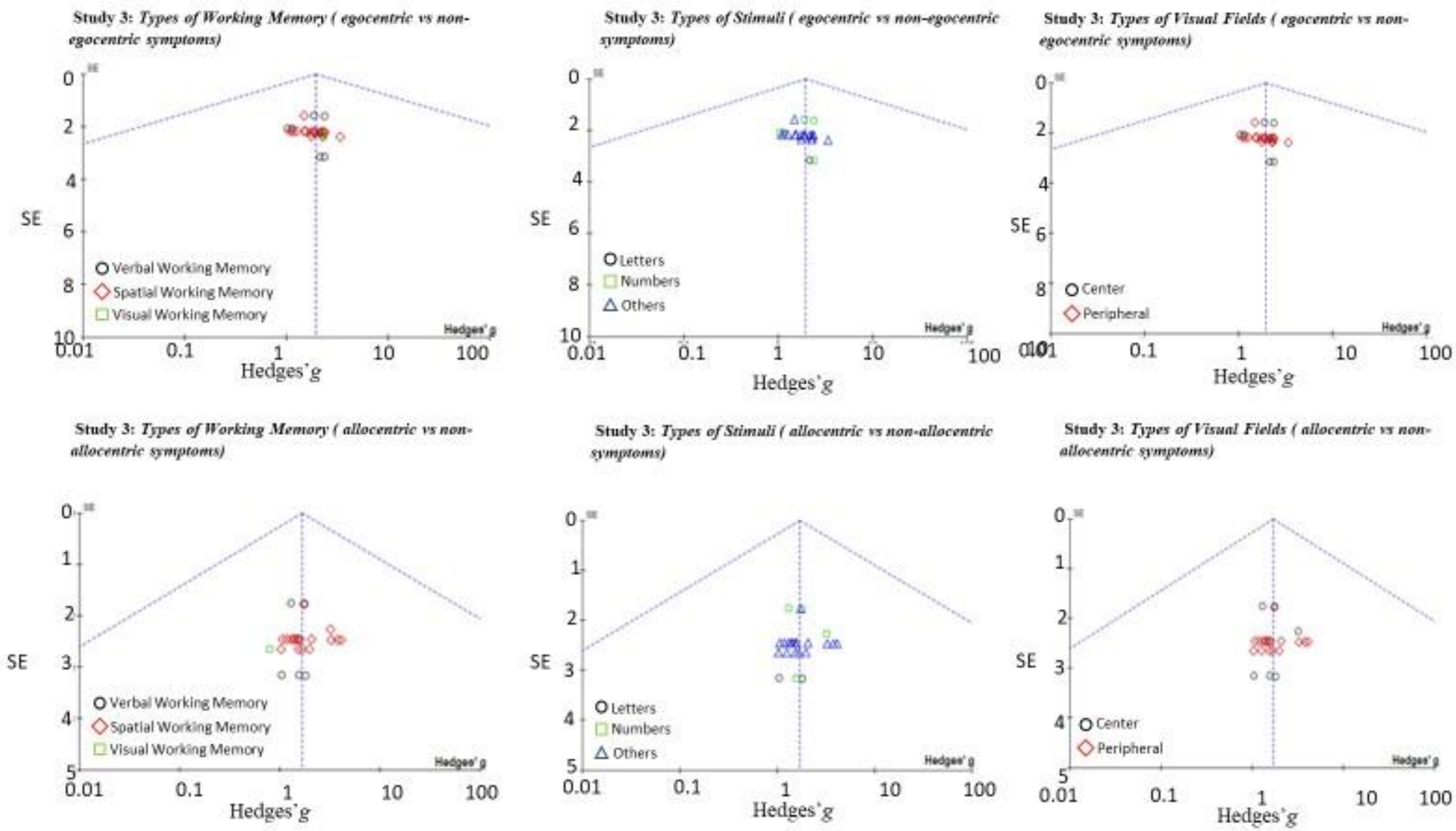

Figure 6-24. Funnel plot of the standard error of hedges' g (Study 3).

6.5. GENERAL DISCUSSION

The current set of meta-analyses studies aimed to establish the prevalence of working memory deficits in patients with acquired spatial neglect. We found that patients with neglect symptoms are more likely to show deficits in all types of working memory domains than expected in the population and when compared to age-matched healthy controls. Neglect patients are also more likely to show working memory deficits when compared with non-neglect patients, specifically when visual and spatial memory is assessed. Surprisingly, like in reading deficits (Part One), the characteristic of spatial biases of neglect patients was not reflected in the pattern of working memory deficits. In other words, neglect patients did not show a biased memory towards items in their non-neglected hemisphere, or as a function of their frame of reference.

This data re-enforces the notion that the interplay working memory deficits and attention-deficit here may reflect malfunctioning of the non-spatial attentional deficits experienced by visual neglect patients.

6.5.1. **Limitations**

As reported in CHAPTER 2, there are several limitations in this meta-analysis study here. Only English language studies were included and non-English language studies may influence the overall findings here. Again CHAPTER 7, will include a study with Chinese participants. Moreover, it should be noted that we did not include unpublished studies. Therefore, the meta-analyses should be interpreted with caution, as positive results are more likely to be published and have a higher chance to be cited than negative results (Cooper &

Hedges, 2009; Greco, Zangrillo, Biondi-Zoccai, & Landoni, 2013). Also, studies lacked large enough sample sizes that required to match for multiple comparisons across visual neglect patients that had different symptoms. In addition, some studies excluded due to key statistical information. For example, we did not report the mean and standard deviation in a few of the studies with interesting findings and therefore were excluded from the analyses. Reporting of this missing data would have allowed us to conduct a more substantial analysis with the addition of more neglect patients for a wider sample.

Finally, similar to the studies reported in CHAPTER 2, all studies included the meta-analysis were evaluated to be in severe risk of sampling and measurement bias, as neither researcher nor patients were blind to their conditions when recruited and when the data was collected and analysed. Again, analysing a large unbiased sample in CHAPTER 7, will allow me to test whether the results can be generalized.

6.5.2. **Future research**

Future research should aim to include neglect patients globally in order to attain a more generalised result. It is also pertinent to examine neglect patients working memory in all kinds of domains in order to identify their working memory disorder and help implement effective treatment strategies to unilateral neglect patients.

6.5.3. **Conclusion**

To summarize in this chapter, this systematic evaluation of the existing working memory performance literature in unilateral neglect provides evidence which characterises generic working memory deficits as a consequence of multiple deficits of attentional systems.

CHAPTER 7: VISUAL ATTENTION AND WORKING MEMORY DEFICITS: BCoS AND C-BCoS

7.1. INTRODUCTION

Similar to CHAPTER 3, CHAPTER 6 report the analyses of a large unbiased sample of patients using the existing UK-BCoS (United Kingdom) and C-BCoS (China) databases to answer whether working memory deficits relate to the spatial bias are common in patients who suffer from neglect syndrome.

The same subjects were analysed as in CHAPTER 3. Patients were classified as suffering from visual neglect if they failed at least two of the neglect tasks: Key Cancellation Test, Apple Cancellation Test, Visual Extinction Test and Figure Copy Test. We asked whether working memory impairment in neglect patients across the United Kingdom and China are related to spatial or non-spatial attentional components. Similar to CHAPTER 3, this was tested by comparing the number of working memory errors in neglect patients relative to neurological patients without neglect. We further examine the effect of spatial bias frame of reference using the four groups and used regression to test whether a spatial or non-spatial component of attention predicts working memory abilities. We considered four types of working memory test; Story Recall-Immediate, Story Recognition-Immediate, memory of target words in the auditory attention task and Task Recall. Note, that only the last task is visual and is based on pictorial cues, the other task relies on verbal auditory stimuli; though in the case of immediate recognition words were also presented in written format.

7.2. METHODS

7.2.1. **Participants**

We included the same participants as in CHAPTER 3. See 3.2.1

7.2.2. **Assessment of Working Memory Abilities**

i. *Story Recall and Recognition*

This assessment consists of a story that includes 15 segments that must be recalled. The tasks basically measure episodic memory for newly learned verbal information. Both recall and recognition measures are scored.

For the recognition test, a question is presented for every segment in the story that patient neglects and recalls inaccurately. In each case, there are four response selections which consist of the correct response and three other plausible responses to the question. The selections are presented as written words and spoken by the examiner. The scores here can be used to derive indices of encoding, retrieval and forgetting and consolidation.

Generally, an encoding deficit is revealed when there are poor recall and recognition in the immediate test. A retrieval deficit is revealed when performance is poor on the free recall but improves in recognition when a cue is given to help with the retrieval process. Problems in forgetting or consolidation are shown by a relatively large drop in performance from immediate recall/recognition to delayed recall/recognition.

ii. *Auditory Attention Task – Memory of Target Words*

This task consists of pre-recorded words. There are six words presented nine each time each. Half of the words are target words need to respond to; half are distractor words that need to be ignored. For each target word (no, hello, please), it has a closely related distractor (yes, goodbye, thanks). All words here are high in familiarity, and were chosen to be suitable for individuals with aphasia. The words are presented randomly, and each word being preceded an equal number of times by a 2 s, 3 s or 4 s silence gap. The task is performed in three blocks, providing a measure of how patients can sustain their attention across the blocks. It also measures whether patients can selectively attend to the target words and prevent themselves from responding to the related distractor words at the end of the task. It also provides a measure of whether patients can store items in memory over the short term when they are engaged in another activity (a measure of working memory).

Poor selective attention is revealed when patients respond to distractors as well as targets. Poor sustained attention is revealed when performance drops across test blocks. Poor working memory is indicated when the patient cannot recall the target words at the end of the task. This last measure was used.

iii. Task Recall

This task measures an ecological or unintentional memory. There are 10 items and for each item. Patients are asked which of the four stimuli/actions they have been given earlier. The distractors are chosen to be closely related to the correct response (sharing, for example, the same action but on a different material). The task measures a functional measure of memory for ongoing events e.g. which of these did I ask you to use?

7.2.3. **Data Analysis**

See details in CHAPTER 3; 3.2.4.

7.3. RESULTS

Visual spatial neglect is associated with increased deficits in working memory. The effects are more reliable in the UK cohort, but the effect sizes in the Chinese cohort are similar. Table 7-1 shows reliable decrease performance on story recognition by people with visual neglect, intriguingly this task has no spatial or visual component to it. Remembering the three targets words from the auditory sustain attention task, appear to also be more difficult for patients with visual neglect. Finally, the task recall test is based on pictorial recognition of items presented during the cognitive assessment and this is also more impaired following visual neglect.

Table 7-1. Visual neglect and working memory.

A. UK

Working Memory Tests	**Group**	***N***	***M***	***SD***	***t***	***df***	***p***	***Hedges'g effect size***
Story Recall-Immediate Recall	Neglect patients	221	5.83	3.49	1.89	356	.060	-0.15
	No neglect patients	584	6.34	3.07				
Story-Immediate Recognition	Neglect patients	240	11.06	3.83	2.77	372	.006	-0.21
	No neglect patients	614	11.83	3.16				
Auditory Attention Task	Neglect patients	210	37.83	16.1	-5.11	763	.000	-0.4
	No neglect patients	555	43.73	13.48				
Task Recall	Neglect patients	223	7.43	2.61	-4.98	783	.000	-0.38
	No neglect patients	562	8.34	2.17				

B. China

Working Memory Tests	**Group**	***N***	***M***	***SD***	***t***	***df***	***p***	***Hedges'g effect size***
Story Recall-Immediate Recall	Neglect patients	42	5.14	3.33	-1.31	52.12	n.s.	-0.22
	No neglect patients	259	5.86	2.97				
Story-Immediate Recognition	Neglect patients	44	10.76	3.46	-1.10	56.89	n.s.	-0.18
	No neglect patients	264	11.38	3.31				
Auditory Attention Task	Neglect patients	43	39.26	15.15	1.40	56.47	n.s.	-0.25
	No neglect patients	251	42.73	14.74				
Task Recall	Neglect patients	38	8.6	1.83	1.72	46.63	n.s	-1.46
	No neglect patients	250	8	2.02				

df=degree of freedom; FA=false alarm; M=mean; *N*=total; n.s=not significant; p=P-value; t= t-test; *SD*=standard deviation.

Next, we assessed whether the spatial bias frame of reference affects the error and difficulty in working memory. As in CHAPTER 3, we divided each cohort into four groups depending on the presence or absence of allocentric or egocentric symptoms (Figure 7.1).

In the UK-BCoS database working memory performances were affected by the grouping of visual neglect condition and type: *Immediate Story recall* , $F(3,801)=3.695$, $p=.008$; Bonferroni corrected post-hoc analysis showed that the egocentric only group were more impaired than the group who showed no spatial attention symptoms, surprisingly the egocentric only group were also more impaired than the group who showed egocentric and allocentric visual neglect, but they did not differ from those who showed allocentric neglect only. *Immediate story recognition* $F(3,850) = 2.75$, $p=.042$; none of the group reliably differed from each other. *Task recall*, $F(3,705) = 11.035$, $p=.000$. Here all patients who showed any type of visual spatial neglect were more impaired than those who had none. I did not compute statistics for the Chinese cohort as the number of patients who showed allocentric symptoms was too small, with two groups having only 2 members in each.

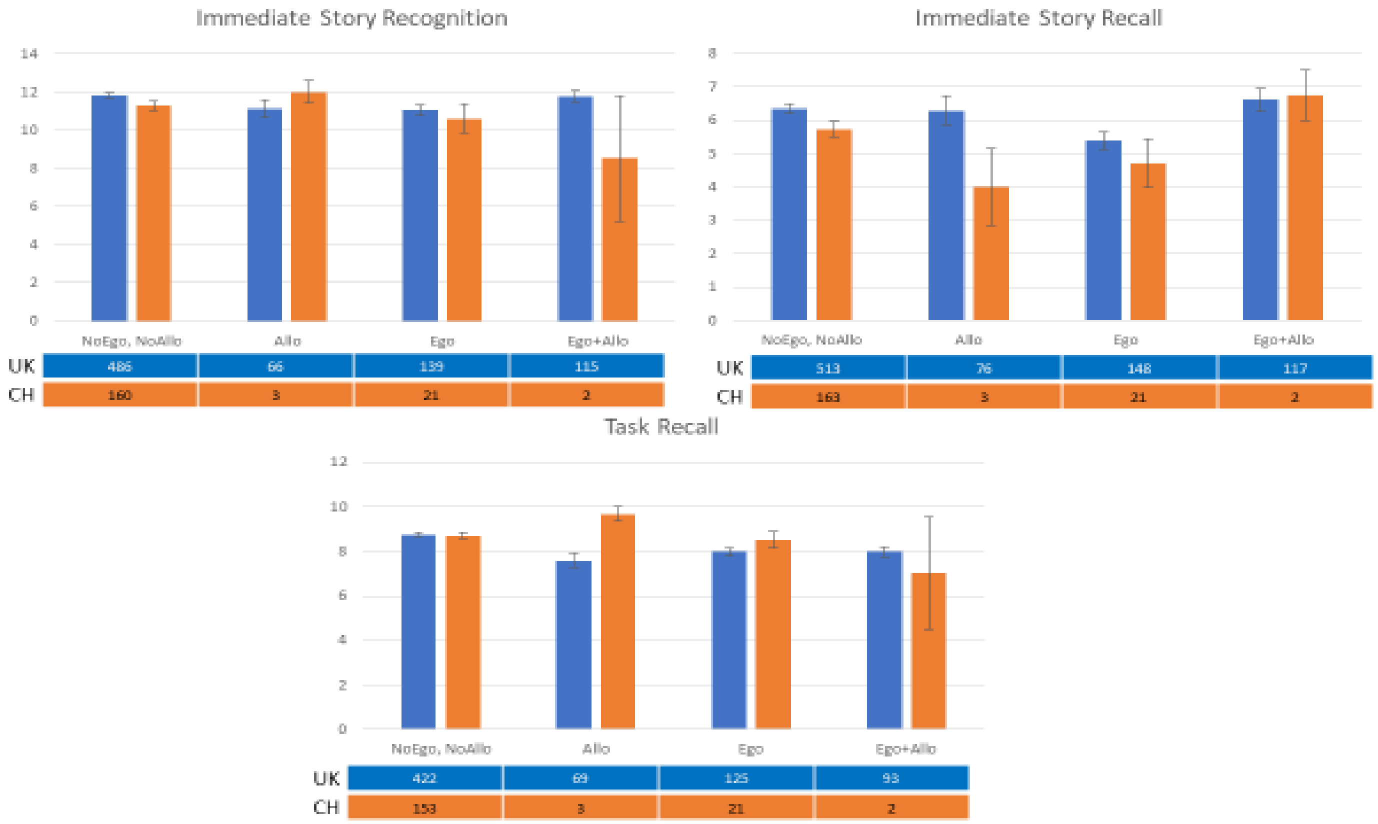

Figure 7-1. Allocentric, egocentric and working memory, error bars represent the standard error of the mean. The number of patients in each group is presented below the charts

7.4. GENERAL DISCUSSION

This study replicated the results of the meta-analysis reported in CHAPTER 6. Namely, patients who suffer from spatial neglect are more likely to experience difficulty in working memory, which is most pronounced for visual working memory. Like with reading, the attentional frame of reference that was impaired did not affect performances. Surprisingly, visual neglect was associated with deficits in recall and recognition memory, even though these memory tests are based on auditory speech and have no visual component.

CHAPTERS 6 and 7 provide compelling evidence that the impact of spatial neglect on memory is not restricted to spatial bias.

The data farther highlights the close association between attentional processes and working memory. It is possible that similar to developmental ADHD, working memory need to be considered as a core deficit of visual neglect.

More detail discussion will be provided in PART TWO discussion.

CHAPTER 8: REDUCED MEMORY LOAD AND CANCELLATION TASK: EMPIRICAL CHAPTER

8.1. INTRODUCTION

CHAPTERS 6 and 7 showed a clear association between working memory impairment and attentional deficits. The aim of this empirical work was to test whether reducing the working memory load ameliorate visual neglect symptoms in cancellation task.

As the meta-analyses suggest, neglect patients are likely to show working memory deficits. the representational account for visual neglect is the core feature of the syndrome. In line with this hypothesis, reducing the amount of information that needed to be held in memory by offloading it as marker on the page should ameliorate the visual neglect symptoms. In other words, if visuo-spatial memory has a limited capacity, then removing the marks should exacerbate neglect symptoms, since patients would need to remember where they had cancelled in order not to return there. This is indeed demonstrated by many studies (e.g. Mark and Heilman. (1988) and Ladavas et al. (1993), see Introduction Part Two).

The question I asked in this chapter, is what will the impact of highly salient mark. The representation account predicts that any mark – offloading memory – is better than no mark. The alternative hypothesis is based on the IAS (Humphreys and Riddoch, 1993), arguing that the visual neglect emerges at visual-perceptual level, highlight malfunction of attentional systems assumed to be distinct from working memory. According to this view, high salient marks on the paper will capture patients orienting attentional system, exasperating the spatial bias characteristic of visual neglect symptom.

These predictions were investigated here using the Apple Cancellation test, which is designed to measure both egocentric and allocentric neglect (Bickerton *et. al.*, 2011; Chechlacz, at. al., 2010). In one condition the patients were asked to cross out all the targets using a red marker which produced a highly visible mark. In a second, they performed the same cancellation task again with the same marker but with the cap on so that no visible mark appeared. We expected that patients without neglect and the healthy group would perform better in the visible cancellation compared to the invisible cancellation condition, since memory demands were greater in the invisible condition. The question was whether patients with visual neglect would perform in the same way?

8.2. METHODS

8.2.1. Participants

A total of thirty chronic (>1 year following insult) brain-damaged patients were tested for the current study (27 males and 3 females), with ages ranging from 37 to 78 years (mean = 66.23 years; *SD* = 10.65 years). All patients had acquired brain lesions, were at a chronic stage (> 9-month post-injury). Lesion information was obtained from the Birmingham University Imaging Centre. All patients were recruited from the panel of neuropsychological volunteers established in the Behavioural Brain Sciences Centre at the School of Psychology, University of Birmingham, United Kingdom (BCoS database). Demographic and full clinical data of these patients are shown in Table 8.1. Another 10 (5 males, 5 females) healthy control participants with no history of neurological disorder were also tested. The mean (*SD)* age of controls was 68.8 (6.76) years (range 58-77). Of the 10 control participants, two were left-handed and eight were right-handed. All participants provided written consent in agreement with ethics protocols at the School of Psychology University of Birmingham and Birmingham University Imaging Centre. All participants had a normal or corrected-to-normal vision.

Like previous chapters, patients were categorized as showing visual spatial neglect, if they presented with defective scores in at least two neglect tests. See 1.1.1. Out of 30 brain-injured patients in this chapter, 14 patients have visual spatial neglect disorders. 11 patients have egocentric neglect symptom, nine have allocentric neglect symptom and six patients have both symptoms.

Table 8-1. Demographic and neurological data of the 30 brain-damaged patients.

BCoS ID	Sex	Age (years)	Handedness	Aetiology	Lesions	†Egocentric Neglect	†Allocentric Neglect
UB53, 54	M	77	R	S	L	0	-1
UB09	M	55	R	S	B	0	0
UB19	F	78	R	S	R	2	0
UB30	M	68	R	S	L	0	-6*
UB03	M	55	R	HSE	B	2	-1
UB23	M	60	L	A	R	15*	2*
UB75	M	67	R	S	R	20*	23*
UB26	M	74	R	S	B	0	1
UB60	M	72	R	HSE	B	-1	0
UB66	M	60	R	S	R	0	0
UB36	M	65	R	S	R	0	0
UB11	M	37	R	S	L	0	0
UB34	M	78	R	S	L	-4*	3*
UB13	M	56	R	CM	B	0	-4*
UB14	M	76	R	S	L	-1	-1
UB25	M	77	R	S	L	-3*	1
UB15	M	38	R	CM	B	-6*	0
UB20	M	73	R	S	R	15*	1
UB50	M	69	R	S	L	-2	0
UB10	F	61	R	S	R	-3*	-1
UB49	M	74	R	S	B	0	0
UB07	F	74	R	S	R	0	-1
UB55	M	62	R	S	L	0	0
UB48	M	75	R	S	R	19*	-12*
UB57	M	70	R	S	L	-2	0
UB73	M	73	R	S	B	-8*	-5*
UB67	M	63	R	S	L	3*	5*
UB37	M	78	R	S	B	-1	0
UB51	M	68	L	S	B	-2	3*
UB17	M	74	R	CM	B	-3*	0

A= aneurism; CM= carbon monoxide poisoning; F=Female; HSE= herpes simplex encephalitis; L=Left hand; M=Male; R=Right hand; S=Stroke; †=data of presence or absence of egocentric or allocentric neglect was taken from the BCoS database on Apple Cancellation Test; *=presence of neglect

8.2.2. **Procedure**

Working memory abilities were assessed through performance on the newly developed cancellation test, Apple Cancellation test (Bikerton et al., 2010) Figure 7.1. (See 3.2.2.1 for details).

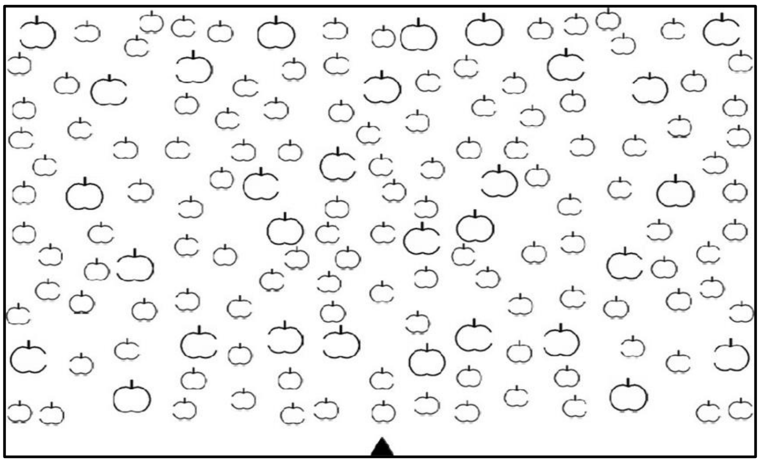

Figure 8-1. Apple Cancellation sheet.

Each participant completed 10 trials in total (5 apple cancellation sheets for the visible task, 5 apple cancellation sheets for the invisible task). Participants were instructed to cross out all the full apples (targets) while disregarding all the incomplete apples (distracters). We used a thick marker red for visible cancellation and the same marker also used for invisible cancellation but with the cap on (Wojciulik et al., 2001b, p. 20, 2004). For the invisible cancellation task, we marked the responses made by the participants on a different sheet. One practice trial was presented before the test in order to ensure the participants understood the task instructions. Before the trial, each participant was reminded to cross out all the relevant targets *once* only. The identical sheets were used across the two tasks. Order of tasks is AABBAABBAB, (for visible cancellation versus invisible cancellation). A maximum of five minutes was allowed for the completion of the test. This test was repeated for five times for each participant. The participants were given between two to three minutes break between each test.

8.3. <u>RESULTS</u>

We asked first whether malfunctioning of the executive control and alert attentional systems account for working memory deficits in acquired neglect (see Part Two: IV). We calculated the accuracy scores.

8.3.1. **Accuracy Scores (Based on Targets (Full Apples) Scores)**

8.3.1.1. Neglect patients vs. No neglect patients vs. Healthy controls

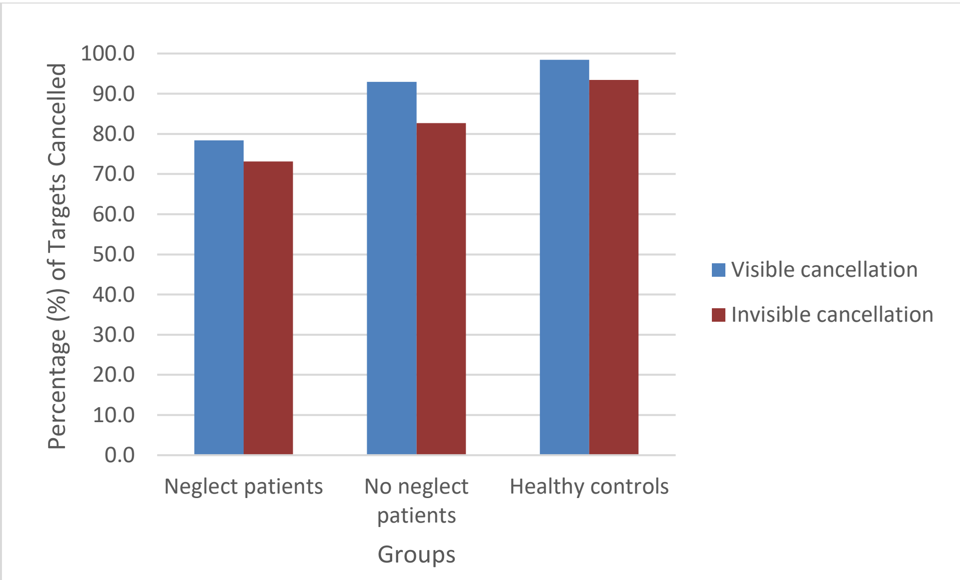

Figure 8-2. Full apples (targets) cancelled based on groups (Neglect vs No neglect vs Healthy controls) and types of visibility.

The data were analysed in a repeated ANOVA with the within-subjects factor being: type of tasks (visible vs. invisible) and group (neglect vs. no neglect vs. healthy controls). A significant difference was found between the group, F (2,18) =13.281, p=.000. Reliable main effects of the visibility of the tasks were found, (F(1,9)=18.301, p=.002. Contrast tests revealed that neglect patients (F(1,9)=15.327, p=.004) and patients without neglect symptoms (F(1,9)=5.664, p=.041) were significantly poorer at cancelling targets (full apples) than healthy individuals. The visibility of the cancellation marks influenced performance, with more targets cancelled when the visible marks were left (F(1,9)=18.301, p=.002). There was no significant interaction between group and type of test used, F(2,18)=.461,p>.05. (Figure 8.2).

8.3.1.2. Egocentric neglect patients vs. No neglect patients vs. Healthy Controls

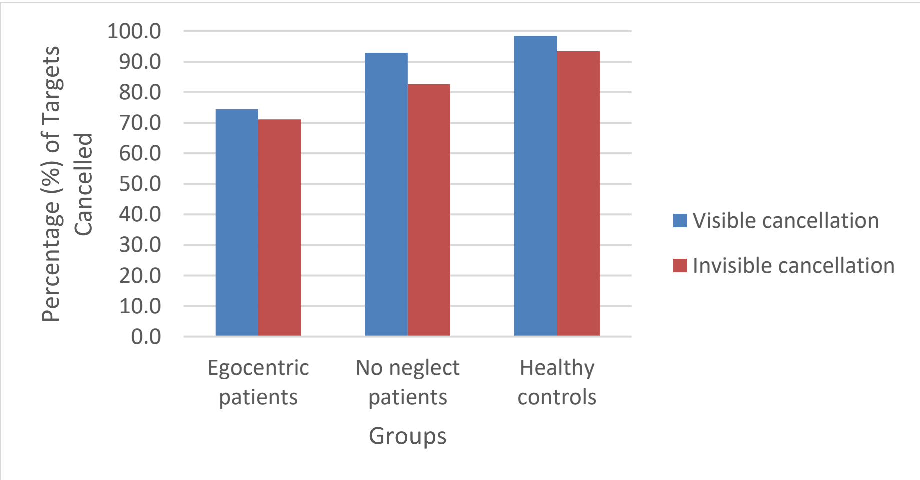

Figure 8-3. Full apples (targets) cancelled based on groups (Egocentric vs No neglect vs Healthy Controls) and types of visibility.

Similar to the above results, both groups of patients and the healthy group were more impaired in the invisible cancellation than in the visible cancellation condition (see Figure 8.3).

There was a main effect of group, $F(2,18)=13,281$, $p=.002$. There was a main effect of visibility of the marker used when assessing neglect, $F(1,9)=18.301$, $p=.002$, with scores on the visible cancellation test higher than on the invisible cancellation test. Contrast tests revealed that patients with egocentric symptom $F(1,9)=15.327$, $p=.004$ and patients without the symptom $F(1,9)=5.664$, $p=.041$, were significantly worse at cancelling targets (full apples) than healthy controls. There was no significant interaction between group and type of test used, $F(2,18)=0.461, p=.562$. However contrast tests revealed significant interaction term when comparing visible cancellation and invisible cancellation, $F(1,9)=18.301, p=.002$. Inspection of Figure 8.3 suggests that the interaction was due to the patients (in general) showing a greater effect of visibility than the controls.

8.3.1.3. Allocentric neglect patients vs. No neglect patients vs. Healthy Controls

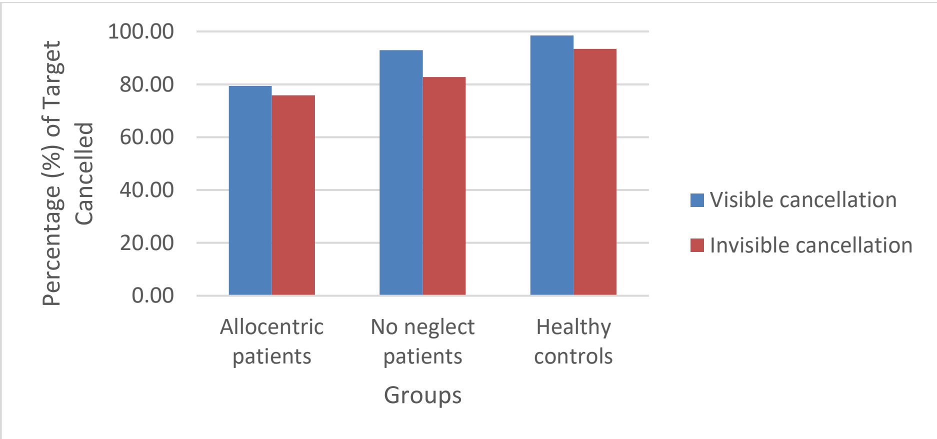

Figure 8-4. Full apples (targets) cancelled based on groups (Allocentric vs No neglect vs Healthy Controls) and types of visibility.

As the above results, the cancellation performance of both groups of patients and the healthy group were more impaired in the invisible cancellation than in the visible cancellation condition (see Figure 8.4). There was a main effect of group, $F(2,16)=7.693$, $p=.005$. There was a main effect of visibility of the tasks, $F(1,8)=8.532$, $p=.019$. All groups have high scores on the visible cancellation test than on the invisible cancellation test. Also, there was no significant interaction between group and type of test used, $F(2,16)=1.272$,$p=.307$.

Contrast revealed that patients with the allocentric symptom ($F(1,8)=12.500$, $p=.008$) and patients without the symptom ($F(1,8)=7.314$, $p=.027$), were significantly impaired at cancelling targets (full apples) than healthy controls. There was no significant interaction between group and type of test used, $F(2,18)=0.461$,$p=.562$. However contrast also revealed significant interaction term when comparing visible cancellation and invisible cancellation, $F(1,8)=8.532$,$p=.019$.

8.3.1.4. Egocentric neglect patients vs. Allocentric neglect patients vs. Neglect patients

There was a main effect of group, $F(2,16)=5.294$, $p=.019$. There was no effect on the visibility of the maker $F(1,8)=3.884$ $p=.084$ and no effect on the interaction between group and visibility of the marker $F(2,16)=1.440$, $p=.268$. Contrast revealed that patients with the egocentric symptom ($F(1,8)=11.370$, $p=.010$) were significantly impaired at cancelling targets (full apples) compared to non-neglect patients, but not for patients with allocentric ($F(1,8)=3.226$, $p=.110$).

8.3.2. **Effects of visibility on egocentric neglect (based on asymmetry full apples** scores)

To answer the second question of whether the spatial features of visual neglect (egocentric and allocentric) were associated with working memory impairment, we assessed the effects of marker visibility. We assessed the page-based asymmetry scores of the apple tests that were based on the difference between the number of targets (full apples) selected on the right side and the number targets selected on the left side (excluding the middle column) of the page.

8.3.2.1. Egocentric neglect patients

When the asymmetry (i.e., specific neglect) scores were assessed, no significantly different effect of marker visibility emerged. For example, based on the asymmetry full apples scores, egocentric neglect patients tended to show stronger asymmetry bias in the visible cancellation test (*M*=23.73, *SE*=9.02) than invisible cancellation test (*M*=13.45, *SE*=6.23), $t(10)=2.008$, $p=.072$. No reselection occurred in the visible test but some patients made asymmetry reselection errors in the invisible condition, significant differences in reselection were manifested by this group between the visible (*M*=.00, *SE*=.00) and invisible cancellation conditions (*M*=.323, *SE*=.089), $t(10)=-3.674$, $p=.004$.

The full-page asymmetry scores were submitted to a mixed ANOVA, with test (visible test versus invisible test) as a within-subjects factor and subject groups (egocentric neglect patients vs. no neglect patients vs. healthy controls) as a between-subjects factor. This revealed a main effect of group on asymmetry score, $F(2,18)=6.667$, $p=.007$, and no main effect of marker visibility $F(2,18)=.363$, $p=.562$. More importantly, there was significant interaction between group and marker visibility, $F(2,18)=5.236$, $p=.021$. Contrast tests revealed that visibility of marker increased asymmetric bias in egocentric patients than non-neglect patients $F(1,9)=6.011$, $p=.037$.

8.3.3. **Effects of visibility on allocentric neglect (Asymmetry incomplete apples scores)**

The incomplete apple asymmetry scores were the difference between the total number of distractor items cancelled with a left opening and the total number of distractor items cancelled with a right opening (see Bickerton et al., 2011).

8.3.3.1. Allocentric neglect patients

In this group, no significant differences were apparent between the asymmetry score for incomplete apples in the visible cancellation task ($M=26.11$, $SE=18.91$) versus the invisible cancellation condition (M=27.44, SE=18.02), $t(8)=.502$, $p=.629$. No reselection occurred in visual cancellation but some patients made reselection errors in the invisible cancellation condition. Differences in reselection under visible $M=.00$, $SE=.00$) and invisible cancellation conditions ($M=.07$, $SE=.043$), $t(8)=1.709$, $p=.126$ did not reach significance.

The incomplete apple scores were analysed using a repeated-measures ANOVA, with test (visible test versus invisible test) as a within-subjects factor and subject groups (allocentric neglect patients vs. no neglect patients vs. healthy controls) as a between-subjects' factor. This revealed no significant main effect on the group, $F(2,16)=.859$, $p=.442$, type of visibility $F(1,8)=.046$, $p=.835$, and interaction between the group and marker visibility, $F(2,16)=.270$, $p=.766$.

8.4. <u>DISCUSSION</u>

Patients with visual neglect typically show a reduced of exploration of contralesional visual space, both when this is defined relative to the body (e.g., the visual field) and when it is defined allocentrically, based on the left-right relations of parts relative to a whole object. This deficit was clearly manifested in our tasks. Patients with visual neglect omitted more stimuli on the contralesional field than patients without neglect and healthy subjects (egocentric neglect) and patient also made more false-positive responses to distractors with a gap on the contralesional side of the objects (allocentric neglect). There were some dissociations between the patients showing each type of neglect, consistent with the prior literature (e.g., Bickerton et al., 2011; Chechlacz et al., 2010).

In terms of the overall numbers of targets cancelled, all participants fared better when the cancelled targets were marked and visible relative to when they were not. This provides evidence that the lack of a marked record imposes a greater memory and worsens performance by increasing omissions. Interestingly, though, these increases due to a lack of a marked record were not asymmetric and occurred across the field.

More importantly, the visibility of the marker had a negative impact on spatial bias, exasperating the asymmetric biased in the cancelation task.

These data indicate a contrast between the effects of visual memory on search performance and the effects of ipsilesional attentional capture. The benefit to visual memory (with performance worse in the invisible cancellation task) was observed independent of the target location in the visual field.

Our results contradicted previous studies by Husain et al. (2001) and Wojciulik et al. (2001). These authors claimed that there is a significant role of spatial working memory deficit in generating the spatial asymmetry in neglect patients. The present results though indicate that, while working memory problems may be contributory, they elicit non-spatial errors and are unlikely to create spatial asymmetries in performance.

In this chapter, the data suggests that ipsilesional capture of attention and /or poor disengagement of attention from the ipsilesional stimuli may exacerbate both egocentric and allocentric spatial biases in patients, while imposing a greater working memory worsens performance but in a non-lateralised manner. Ipsilesional capture and/or impaired attentional disengagement appear more critical for the key lateralised symptoms of neglect than poor working memory. This supports the visual-spatial attention model for visual neglect, highlighting that the deficits emerge at the perceptual and not the representational level.

8.4.1. **Limitations**

In the invisible marker condition, in contrast to the visible, the experiment recorded the responses of the patients, and hence there was a potential of bias. Given the experimenter was not blind to the conditions.

The tested patients were highly familiar with the tasks and were regular participants in research, making the participant informed, which potentially can introduce biased to their performances.

The study would have benefitted if it included a direct replication of previous studies using more settle marker.

CHAPTER 9: DISCUSSION OF PART TWO: VISUAL-SPATIAL DEFICITS AND WORKING MEMORY DEFICITS

9.1. Visual Spatial Deficits, Working Memory and The Attentional Systems

The data presented in Part Two, suggested that deficits in working memory experienced by patients with visual neglect emerge from the non-spatial component of the syndrome. As no data showed specific that working memory was asymmetrical biased in space. In fact, memory impairment emerged irrespective of the nature of the stimuli and their laterality. Memory impairment where also observed for stimuli at fixation and for stimuli who were presented not to the visual domain.

I suggest that it is the malfunctioning of the alert attentional system that contributes to these impairments, rather than the orienting attentional system.

9.2. Representational versus Perceptual Neglect

The data suggests that working memory deficits observed in visual neglect patients emerge at the perceptual stage, rather than he representational stage. This conclusion is primarily based on the observation that reducing working memory using salient marker (CHAPTER 8) had the opposite effect on performances in the cancellation task. Thus, attentional spatial biases cannot be caused due to malfunctioning of working memory, but are due to inability to shift and orient attention in space. An ability that is further hindered by presence of salience information.

9.3. Conclusions

The data converge on the role of non-attentional deficits in spatial neglect in hindering working memory capacity. This was demonstrated using three very different methodological approaches: meta-analysis, analysis of large data sets and experimental data.

CHAPTER 10: GENERAL DISCUSSION AND CONCLUSION

10.1. DISCUSSION

The work presented in this thesis has aimed to elucidate comorbidities of cognitive deficits in patients with lateralised visual deficits, specifically in the case of reading and working memory deficits. I specifically asked whether comorbidities are related to spatial or non-spatial components of the syndrome. Visual neglect is a relatively common clinical disorder, found in substantial numbers of stroke survivors especially after right hemisphere damage, and both disorders impact everyday living (Bickerton et al., 2011). Attempts to understand the disorder may thus have important practical implications to patients' rehabilitation pathways.

In this thesis, the first part of the thesis (Part One) was related to the case of reading and the second part of the thesis (Part Two) was related to the case of working memory. Each part contained three separate chapters. I assessed comorbid using three methodological approaches: First, I investigated prevalence and nature of each comorbidity by using a meta-analysis of the literature; (in Part One: CHAPTER 2 and Part Two: CHAPTER 6). Then, I assessed each comorbidity based on two large unbiased samples of stroke patients using the existing databases BCoS (United Kingdom) and C-BCoS, (China) (in Part One: CHAPTER 3 and Part Two: CHAPTER 7). Finally, I conducted two experimental case studies that aimed to specify the impact of saliency on spatial bias symptoms (letters' fonts on related theoretical question neglect dyslexia; memory cues and selective attention). First, I assessed neglect dyslexia in a patient showing an apparent high-level problem at the level of abstract word-level representation in current models of word recognition (in Part One: CHAPTER 4). Then I investigated the interplay between memory and attentional capture by ipsilesional stimuli by assessing cancellation performance in neglect patients when they marked stimuli with a visible or invisible marker (in Part Two: CHAPTER 8). The results of the investigation as a whole suggest that the generic reading and working memory impairments of visual attention neglect may arise from multiple deficit attentional system and with these data helping to constrain current models. This suggests that patients who suffer from visual spatial neglect are more likely to experience problems in reading and in working memory. Surprisingly the spatial attention biases of visual neglect did not affect errors in reading or working memory. The experimental chapters showed that non-spatial saliency cues exasperate the spatial bias symptoms. Taken together the current thesis provide evidence supporting a non-spatial attention deficit as a core symptom of visual neglect.

10.2. REVIEW OF CHAPTERS

The aim of Part One was to systematically assess comorbidity of visual neglect and reading deficits and to test whether these are related to the spatial bias associated with the syndrome.

In CHAPTER 2, I applied a meta-analysis of previous literature method. The aim of the chapter was to test whether reading deficits are a common feature of visual spatial neglect (Study 1). Study 2 and 3 specifically assessed whether reading deficits relate to the spatial bias common to neglect syndrome. In study 1, I asked whether generic attention deficits (sluggish attention) account for reading deficits in acquired neglect. To this end, I compared the number of reading errors in neglect patients relative to standardised data, matched healthy control and neurological patients without neglect. I classified patients as suffering from neglect if they failed at least two of the neglect tasks such as cancellation task, line bisection, and copying scene tests. In study 2, I asked whether deficits in the orienting system underlie reading errors in neglect patients, as hypothesised by the neglect dyslexia model. This was tested by assessing the number of errors made in each hemifield within each neglect patient. Finally, study 3, I further investigated the hypothesis that reading disorder is related to the nature of the orienting deficits, by examining reading errors relative to the frame of reference. I first compared reading errors in neglect patients who showed reliable egocentric neglect (i.e., failed at least two cancellation neglect task) vs. those who did not showed it. Next, I compared reading errors in neglect patients who showed a reliable allocentric neglect (i.e., failing in line bisection, figure copy) as opposed to those who did not show this deficit (Doricchi & Galati, 2000; Kleinman et al., 2007; Riddoch & Humphreys, 1983; Walker & Young, 1996). I included all the data from all relevant studies reporting reading performance of visual spatial neglect patients. I considered four types of reading tests. The most common tests are reading single words and reading meaningless pronounceable letter strings, also known as non-words. Less common are tasks that requires reading sentences, texts or passages of proses, even though the latter is regarded as more sensitive diagnostic tools (Siéroff, 2017) and most commonly used in the clinical assessment of visual spatial neglect (Pizzamiglio, Judica, Razzano, & Zoccolotti, 1989; Towle & Lincoln, 1991).

As I identify that previous studies were at risk of sampling and measurement biased, CHAPTER 3 examined the relation between visual neglect and reading in two large databases of sub-acute stroke patients. One cohort from the UK and a second form China. These databases were created to validate a cognitive screen test for stroke, and as such are not biased in the way stroke patients were recruited. The data provides evidence that patients who suffer from visual neglect showed more deficits when reading sentences and when reading single words (non-words in English or exceptional words in simplified Chinese). Visual neglect patients also took longer to read. The difference was more reliable in the UK database this is potential as the UK sample was much larger. However similar effects sizes were observed in China and the UK.

In CHAPTER 4, I presented data from a detailed single case study of patient UB12, who presented with neglect dyslexia. UB12 showed an interesting pattern of reading problems. Like patient NG (Caramazza & Hillis, 1990a), who has been highly influential on models of reading, UB12 showed an apparently high-level reading deficit. He neglected the ends of words and this also holds when words were written vertically and when they were inverted (when the end letters fell on the left rather than the right of the visual field). This pattern of the deficit has been interpreted as indicating a lesion in a word-level representation in which letters are coded in their spatial position relative to a reference frame based on the word's standard orientation (Caramazza & Hillis, 1990a). Also consistent with this proposal, UB12 made similar word-end errors in spelling and in copying letters from memory. This fits with the idea that the word-level representation is used both for input in reading and output in spelling, and that it should thus code letters in a relatively abstract way. In addition, UB12 was perfectly able to read individual letters in words and to copy the letters when they remained visible, suggesting that low-level representations of the stimuli (e.g., a feature-level map) were spared.

Other evidence, however, was more difficult for this account to sustain. Notably, neglect was more apparent when UB12 attempted to read mixed relative to single case words and when he attempted to read handwriting. Damage to a relatively abstract word-centred representation should not be sensitive to the visual properties of the stimuli. Also, there was no evidence for a high-level deficit for the right sides of objects. UB12 did show neglect of the right sides of chimeric figures, but this switched to a deficit to the left sides of the figures when the stimuli were inverted – so in this case, the right position of the features in the field was affected. The data can be conceptualised in at least two ways. One is that there was a word-centred deficit, but that this was also sensitive to the attentional demands of the task. When the attentional demands were increased (for mixed as opposed to single case stimuli) then greater neglect was apparent within the word-centred representation. There may also be distinct representations supporting the identification of words and objects. An alternative, perhaps more parsimonious account, is that there is a single deficit in encoding retinotopic/allocentric representations of stimuli which affects both words and objects. However, with words, UB12 carried out mental rotation processes to map the letters into the (impaired) allocentric representation in order to read and/or spell the stimulus. In this case, problems emerged at the ends of the words irrespective of whether they were upright or inverted. Mixed case words may again require more attention than single words as they are mapped into the allocentric representation, and so neglect is more apparent with mixed case stimuli.

One other interesting aspect of UB12 is that he is able to perform spatial cancellation tasks perfectly (indicating the good encoding of an egocentric representation of space) and he also shows minimal deficits on classical Posner-cueing tasks (Posner et al., 1984). Corbetta and Shulman (2002) have presented an overall framework of visual attention in which they distinguish between voluntary attentional processes represented within a dorsal network in the brain and automatic attentional processes recruited through activation of a ventral attentional system. The classic marker of the dorsal network is voluntary scanning of the field in cancellation tasks. The classic marker of the ventral network is whether a disengagement deficit is apparent in the Posner cueing task. UB12 has neither of these problems, yet he also presented with a clear attentional deficit in reading whole words (and indeed note that he had no problem in scanning and identifying the individual letters). The results do not fit easily into the Corbetta and Shulman framework. Instead, the data suggest that there may be third attentional processes involved in the distribution of attention across stimuli as they are identified. This ability to distribute attention to single ‘perceptual objects’ was impaired in UB12.

In CHAPTER 6, I use meta-analyses methods to assess in details the relations between working memory and visual spatial neglect. I found that patients with neglect symptoms are more likely to show deficits in all types of working memory domains than expected in the population and when compared to age-matched healthy controls. Neglect patients are also more likely to show working memory deficits when compared with non-neglect patients, specifically when visual and spatial memory is assessed. Surprisingly, the characteristic spatial biases of neglect patients reflecting impairment in their attention orientation system were not reflected in the pattern of the working memory deficits. In other words, neglect patients did not show a biased memory towards items in their non-neglected hemisphere, or as a function of their frame of reference.

In CHAPTER 7, I analysed a large unbiased sample of patients using the existing BCoS (United Kingdom) and C-BCoS (China) databases to answer whether working memory deficits relate to the spatial bias common to neglect syndrome.

Finally, in CHAPTER 8, I assessed cancellation performance in patients showing visual neglect according to whether stimuli were cancelled using a visible or invisible marker. There is prior work indicating that neglect is associated with poor visual working memory for previously inspected locations (Husain et al., 2001). Hence it might be expected that conditions that stress visual memory (e.g., having to cancel using an invisible marker) would increase neglect. There is other work showing that neglect can be associated with an abnormal bias of attention to the ipsilesional side, perhaps also coupled with poor disengagement of attention from ipsilesional stimuli (Posner et al., 1984). According to the ipsilesional-capture account, cancellation might be more difficult when visible marks are left on ipsilesional stimuli – and the marks would be more likely to be left on the ipsi- rather than the contralesional side because the initial orienting bias will lead patients to start cancellation on the ipsilesional side. The contrasting predictions of the working memory and ipsilesional capture accounts were put to the test. The results clearly supported the ipsilesional capture account, since cancellation performance was less spatially biased when invisible markers were used than when visible marks were made – even though the overall performance was more difficult (and for controls as well as patients) when invisible markers were employed. This last result indicates that the invisible markers stressed visual working memory and hence that the memory manipulation was effective. However, the spatial bias was less affected by this than by the attentionally-capturing properties of the ipsilesional marks.

10.3. COMORBIDITIES OF VISUAL NEGLECT SYMPTOMS AND THE ATTENTIONAL SYSTEMS

The current thesis used the framework proposed by Posner and Peterson (1990) to describe the function of attention. According to this model, attention is divided to three distinct systems: alertness, orientating and control. The orientating system is responsible on distributing and shifting attention across space.

Two family of theories of visual neglect hypothesis assume observed deficits emerge form malfunctioning of attention. The visual spatial family of models postulate that visual neglect symptoms are primarily experienced due to malfunctioning of the orientation system (e.g. Kinsbourne, 1987; Ladavas, 1990). Deficits of the orienting system, or to the mechanism that controls attention across space is the most common explanation of the syndromes. The spatial and non-spatial attention family of models (e.g. Corbetta & Shulman, 2011; Priftis, Bonato, Zorzi, & Umiltà, 2013; Robertson, 2001) suggest that visual neglect syndrome emerge due to combined deficits to the orientation and the alertness systems, both involve the right inferior parietal cortex. A third family of models of visual neglect suggest that the deficits emerge at a representational level, presumably in working memory where information is temporarily stored and can be reported (e.g. Bisiach & Luzzatti, 1978; Bisiach, Capitani, Luzzatti, & Perani, 1981).

In the current thesis, the assumption made by visual spatial account was to identify visual neglect patients. In other word, identifying patients based on evidence of malfunctioning of the orientating system. Specifically, only patients who showed reliable asymmetry performances as a function of space (favouring ipsilesional over contralesional) were classified as visual neglect patients.

I first demonstrated that despite using a spatial asymmetry-based classification of visual neglect symptoms, these patients were more impaired in reading and working memory compared with non-visual neglect patients. This demonstrated high level of impairment comorbidities across these cognitive abilities. While clear theoretical and neurocognitive link exists between attention and working memory, no such clear link exists between attention and reading. In addition, working memory impairment of visual neglect patients was evident in remembering non-spatial visual information (CHAPTER 6), and also in remembering (encoding and retrieving) speech and verbal information from a story (CHAPTER 7).

Surprisingly, despite the selection bias of patients with impaired orienting system, the error patterns of the two comorbidities examined: working memory and reading showed no spatial asymmetry. Type and severity of spatial asymmetry did consistently relate to the severity of the comorbid deficits. Finally, formal regression analyses showed that deficits in sustain attention were better predictors of reading deficits. This highlight an important role of malfunctioning of the non-spatial components in visual neglect in leading to comorbidities.

We also note that the case of neglect case, maybe a very rare case, which requires a-typical combination of specific neurological development (left-handed), specific lesion (left parietal) and pronounced allocentric neglect. Thus, using these rare cases as evident for the neurocognitive architecture of reading and attentional systems is very problematic.

Is it possible that the malfunctioning of sustain attentional system also drives the spatial biases observed in the orienting attentional system? The current thesis provided few evidences to show that stimuli who are more taxing in term of processing also lead to increase asymmetry and deficits. In reading, this was observed in the familiarity effect, where non-words, low frequency and mixed case words lead to increase errors and magnify spatial asymmetry symptoms. There have been similar reports in the literatures where increase cognitive/perceptual load lead to magnifying the spatial asymmetry symptoms. It is also a common clinical feature that spatial biases are exasperated when patients are tired. Taken together, this data suggests that malfunctioning of the alertness system maybe partly responsible to the dramatic spatial biases typically reported in visual neglect.

The two empirical chapters further highlight the role of attention at the level of visual perception in visual neglect syndrome, over a role of malfunction at a representational level. In both experiments, I demonstrated that manipulation of features saliency in the visual display (mixed cases in reading; red bright marker in working memory) exasperated the visual neglect symptoms, rather than ameliorating them as would be predicted by the representational account.

10.4. CLINICAL IMPLICATIONS

Visual neglect syndrome and specifically the spatial bias symptoms have attracted many researches and was the target of many rehabilitation programmes and protocol. The data presented in the current thesis suggests that focusing on the alertness attentional system in developing rehabilitation programmes maybe a more beneficial way in supporting patient's recovery of visual neglect as well as of comorbid deficits.

10.5. LIMITATIONS

One important caveat for all reported studies, is that none have control for symptoms severity across visual neglect patient and non-neglect patients. Thus, an alternative interpretation of the data presented, is that the non-visual neglect patients who served as control, may also on average show a much milder cognitive impact post-stroke. Hence, overall symptom severity and lesion size should be considered as potential confounding factors.

The work presented in the thesis supports the idea that there are non-spatial components that may contribute to visual spatial neglect syndrome. It would be interesting for future work to do this.to carry out a more detailed analysis of the brain lesions linked to the different patterns of performance reported in the thesis. For example, are impairments linked to a generic reading deficit in neglect that may be associated with a particular lesion location? Is this lesion location different to that linked to effects of increased visual memory load (contrasting cancellation with visible and invisible markers, as in CHAPTER 8 here)? These issues can be assessed by larger group-based analyses and using forms of lesion-symptom mapping, to provide converging neuroanatomical evidence to the behavioural evidence for dissociations reported here.

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APPENDICES

APPENDIX A: META-ANALYSIS REFERENCES: CHAPTER 2

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APPENDIX B: CHAPTER 4

4.3.1.1

List of words in 4.3.3.1. (Stark & McClelland, 2000)

BOND	CORM
BORE	DASK
BORN	DETO
CARE	DILD
DEAR	DOLD
DEEP	FUDE
DIET	HART
DRAW	HIPE
EASE	HULY
EASY	JALK
EDGE	JARE
EVIL	JOLK
FATE	JOPY
FURY	JORT
GAIN	KIPE
GAZE	KISE
GULF	KIZE
HARM	MOKE
HATE	MOPY
LACK	NOPY
LEAP	NUND
LIFT	PAKE
MAMA	PALK
OILY	PRAN
PEAK	PUZZ
POEM	RIRE
REEF	RUMB
RELY	SASK
RIPE	SERE
SELL	SERO
SOFT	TALM
SOON	TICH
STAY	TIKE
TINY	TOLK
TOUR	TOPY
TRIM	VACK
TYTH	VASH
VIEW	VESS
VOTE	WINT
BARE	ZINT

List of words in 4.3.1.2. MRC Psychololinguitic Database

High frequency + High Imageability	High frequency + Low Imageability	High Imageability + Low frequency	Low frequency + Low Imageability
AREA	AWAY	ARCH	AGUE
BEST	CAME	AUNT	DAIS
CASE	DOES	BABE	ELSE
CITY	EVER	BABY	EVER
COME	KNEW	BAND	FAZE
DONE	KNOW	BARK	GIST
DOOR	LESS	BARN	KEPT
FACE	THUS	BASS	KEEP
FACT	TOLD	BEAR	LEES
FELT	VERY	BOAT	MIEN
FIND	YOUR	BONE	NOLL
FORM	HERE	BOIL	OKAY
FOUR	JUST	CAFÉ	PALL
GIVE	ONLY	CAGE	SEAR
HAND	MUST	CHEW	SEEM
HEAD	WERE	COAL	SLOE
HELP	WHAT	COAT	SOON
HIGH	WHEN	IRON	SURE
HOME	THAN	ISLE	VARY
KIND	THAT	HORN	YORE

Lists of words in 4.4.1.1.1. MRC Psychololinguitic Database

Words	Non-words
ACID	ACED
AGED	AGID
AKIN	AKIE
ALAS	ALIS
ALEC	ALAC
AMID	AMED
ARCH	AREH
ATOM	ATUM
AUNT	AUNE
AUTO	AUTI
AXIS	ATIS
BAKE	BAZE
BARE	BARU
BARK	BARI
BARN	BAKN
BASS	BASF
BATH	BAUH
BEAM	BEIM
BEEF	BEUF
BEER	BEIR
BELL	BEKL
BELT	BELU
BEND	BENI
BENT	BENU

BIRD	BIRI
BITE	BITU
BLEW	BLET
BLOC	BLOI
BLOW	BLOZ
BOIL	BOTL
BOLD	BOLM
BOLT	BOWT
BOMB	BOUB
BOND	BONM
BONE	BONT
BOOT	BOUT
BORE	BERE
BOSS	BOSD
BOWL	BOHL
BUCK	BUKT
BULK	BULT
BULL	BUUL
BUNK	BUNE
BURN	BURT
BUSH	BUTH
BUTT	BUTI
BUZZ	BUZH
CADY	CAXY
CAFE	CAFN
CAKE	CAKI
CALF	CALR
CALM	CALK
CANE	CAXE
CAPE	CAQE
CARD	CARG
CARL	CARW
CASH	CISH
CAST	CAUT
CHIN	CHIE
CHIP	CHIY
CLUE	CLUJ
COAL	COAD
COAT	COAK
CODE	COIE
COIN	COIZ
COLT	COYT
CONE	COIE
COOK	COOG
COPE	COPD
COPS	COGS
COPY	COTY
CORE	CORQ
CORN	COTN
CORP	CORB
CREW	CRUW
CROP	CROX
CULT	CUIT
CURB	CURW
CURE	CURI
DAMP	DEMP

Lists of words 4.4.5.1

RIGHT
GREAT
EARLY
STATE
PLACE
GROUP
WATER
SMALL
WHILE
THING
HOUSE
WHITE
THINK
WHOLE
WORLD
YOUNG
LARGE
NIGHT
LIGHT
THREE

Lists of words in 4.4.6.

Completed Words		Derived Words	
4-Letter Words	5-Letter Words	4-Letter Words	5-Letter Words
KING	RULER	LAWS	PAINS
TAPE	PLEAT	FURS	LIVES
BUNK	PLUMB	SINS	GRADS
CARD	LIVER	DENS	RULES
DENT	PAINT	FINS	MODES
PANE	GRADE	PEAS	HANKS
SINK	PEARL	RAMS	PLUMS
FUND	HANKY	CARS	PLEAS
DAMP	MODEL	FUNS	PAGES
PEAK	PAGER	DAMS	PEARS
LAWN		KINS	
FUSE		BUNS	
WARD		TUBS	
TUBE		PANS	
FINE		WARS	
CUBE		GAPS	
RAMP		TAPS	
TONE		FURS	
FURY		CUBS	
GAPE		TONS	

APPENDIX C: META-ANALYSIS REFERENCES: CHAPTER 6

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