Hemispatial Neglect: An evaluation of novel assessment methods and rehabilitation

Charumati Raghavan

Wolfson College
University of Oxford

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ABSTRACT

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Hemispatial neglect, is a major cause of post-stroke disability and poor functional recovery. Hence, identifying sensitive methods to assess and rehabilitate neglect is important.

Chapters 3 and 4 focused on development of novel assessment techniques for representational neglect. The 'Shopping Mall' and 'Clock Cueing' tasks improved upon previous tests and were useful in identifying dissociations in representational neglect based on type of stimuli (topological, non-topological) and time of assessment (pre-stroke, post-stroke) in chronic stroke patients.

Chapters 5 and 6 investigated the efficacy of offline inhibitory repetitive Transcranial Magnetic Stimulation (rTMS) in producing short (<1 month) and long term (>6 months) changes in visual neglect behaviour. Overall, the findings from these chapters were limited due to lack of sufficient power. After controlling for the effect of baseline performance, the Intervention group's Activities of Daily Living scores significantly improved in the short-term post rTMS, as compared to the Control group. The fMRI task attempted to recruit attention-based top down modulation of sensory activity. It revealed relative hypoactivation of the right occipital lobe in the four left neglect patients tested, both pre and post rTMS, when compared to elderly controls.

Chapter 7 explored cognitive predictors of spatial and object neglect in the sub-acute stage after controlling for demographic and stroke related factors, using multivariate blocked logistic regressions. Cognitive performance indicative of spatial attention and selective attention to local features predicted both spatial and object neglect. In addition, coding of spatial relations between features also predicted spatial neglect. Suggestions for combining neglect rehabilitation techniques to target these cognitive processes are discussed.

Overall, this thesis provides novel methods to improve representational neglect assessment and highlights the importance of ancillary cognitive domains in contributing to both representational and visual neglect. The rTMS research provides study design-related insights to incorporate in future studies with larger patient samples.

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CHAPTER 1 – General Introduction

Stroke, a dysfunction caused by disturbance of cerebral blood flow, frequently causes widespread cognitive deficits and is a major cause of disability in patients (Gottesman & Hillis, 2010; Strong, Mathers, & Bonita, 2007). One of the most common cognitive disabilities seen after stroke is hemispatial neglect (Ringman, Saver, Woolson, Clarke, & Adams, 2004; Stone, Halligan, & Greenwood, 1993). Patients with hemispatial neglect fail to attend or respond to stimuli in one or more modalities on the side of space contralateral to brain damage in the absence of sensorimotor deficits (Heilman & Valenstein, 1979; Heilman, Valenstein, & Watson, 1994; Mesulam, 1981).

Neglect can occur for personal space such as failing to acknowledge one's own contralesional body parts; for extra-personal space such that patients may fail to attend to large objects or people on the neglected side; and for imagery space (Representational Neglect) (Beschin & Robertson, 1997b; Bisiach, Perani, Vallar, & Berti, 1986; Bisiach & Luzzatti, 1978; Caggiano, Beschin, & Cocchini, 2014; Li & Malhotra, 2015; Rafal, 1994). Neglect, sometimes along with a lack of insight for the deficit, has been found to be an important predictor of poor functional recovery and inability to complete activities of daily living (Appelros, Karlsson, Seiger, & Nydevik, 2002; Buxbaum et al., 2004; Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001; Denes, Semenza, Stoppa, & Lis, 1982; Jehkonen et al., 2000; Katz, Hartman-Maeir, Ring, & Soroker, 1999; Kinsella & Ford, 1985; Paolucci et al., 1998). Hence, assessment and rehabilitation of neglect have been the focus of active research over the years.

The research in this thesis is intended to improve upon assessment methods available for representational neglect (RN) and extend current knowledge pertaining to rehabilitation of visual neglect. In this Introduction, I will describe and evaluate the existing literature on these topics and provide a rationale for the research undertaken in this thesis.

1.1 Assessment of Representational Neglect (RN)

In comparison to visual neglect, the number of tests available to assess RN are fewer and not standardized (Salvato, Sedda, & Bottini, 2014). Each of the RN tasks can be categorized as assessing topological RN or non-topological RN. Topological images are mental representations for stimuli that can be navigated through and which can correspond to cognitive maps of the environment. Tasks assessing topological RN involve asking participants to imagine public squares, cities, rooms and maps. In contrast, non-topological images are mental representations for objects or visuospatial displays that can be manipulated, but not navigated through and are frequently assessed using task stimuli such as single objects (e.g., clocks) or object arrays (e.g., desktop, the interior of a car, pictures with objects etc.) (Guariglia & Pizzamiglio, 2006; 2007).

1.1.1 Commonly used RN assessment methods

(i) Familiar landmarks task

This test was first used to identify RN was by Bisiach & Luzzatti (1978). They asked two right hemisphere stroke patients with left-sided visual neglect to imagine the landmarks outside Piazza del Duomo in Milan from two opposite perspectives. Both patients reported more landmarks from the right side of their mental imagery than the left, regardless of the perspective taken (Bisiach & Luzzatti, 1978). Since then, researchers have frequently used layouts for familiar squares (adapted to geographical origin of patient), routes and apartments to identify topological RN (Cocchini, Bartolo, & Nichelli, 2006; Committeri, Piccardi, Galati, & Guariglia, 2015; Coslett, 1997; Guariglia et al., 1993; Nico et al., 2008; Ortigue et al., 2003). Scoring is based on relative number of landmarks reported on the left and right sides across vantage points and sometimes, involves the calculation of Laterality Quotients (LQs) (Bartolomeo, D'Erme, & Gainotti, 1994; Guariglia et al., 2013; Piccardi, 2009). LQ is calculated with the formula:

LQ = (left elements - right elements) / (left elements + right elements) x 100

A negative LQ below a specific cut-off, obtained based on norms, is indicative of topological RN to the left side (Guariglia et al., 2013). In some studies, patients were asked to describe two or more familiar squares to increase data points (Bartolomeo, Bachoud-Levi, Azouvi, & Chokron, 2005; Bartolomeo et al., 1994; Committeri et al., 2015; Guariglia et al., 2013; Palermo, Nori, Piccardi, Giusberti, & Guariglia, 2010a). In others, patients were required to learn and imagine a new layout with objects to report verbally or by drawing a map of the newly learnt layout subsequently (Palermo, Ranieri, Nemmi, & Guariglia, 2012; Piccardi, Bianchini, Zompanti, & Guariglia, 2008). These paradigms have also been used to elaborate on the mechanisms of mental imagery (Palermo, Bureca, Matano, & Guariglia, 2008; Palermo et al., 2010b) and representational pseudo neglect (McGeorge, Beschin, Colnaghi, Rusconi, & Della Sala, 2007).

(ii) Geographical Map Description task

Geographical map description is another popular RN assessment method wherein patients are asked to bring to mind an image of the layout of a familiar country's map from memory. From this image, they list cities or towns to the left and right of an imagined central city or vertical axis and sometimes, from two opposite vantage points (Bartolomeo, D'Erme, & Gainotti, 1994; Rode, Rossetti, Perenin, & Boisson, 2004). Topological RN patients with right hemisphere lesions have been reported to have deficits in reporting cities to the left side of the imagined map (Beschin et al., 1997a; Ortigue et al., 2001; Rode, Revol, Rossetti, Boisson, & Bartolomeo, 2007; Rode &

Perenin, 1994; van Dijck, Gevers, Lafosse, & Fias, 2013), despite symmetrical report of towns during free recall independent of imagery (Rode et al., 2010). A variation of this task includes auditory presentation of cities requiring patients to press buttons corresponding to whether a city is to the left or right of a central city (Bartolomeo et al., 2005). This variant allows to measure reaction time (RT) asymmetry in addition to city report. An LQ calculation similar to the familiar squares is also sometimes used for this task based on number of cities reported to the left and right (Bartolomeo et al., 1994; van Dijck et al., 2013).

(iii) o'Clock task

One task frequently used to assess non-topological RN in research settings is the o'Clock task (Committeri et al., 2015; Grossi, Angelini, Pecchinenda, & Pizzamiglio, 1993; Grossi et al., 1989; Guariglia et al., 2013; Palermo et al., 2010b; van Dijck et al., 2013). A clock is a multipart object with parts in both the right and left hemifields allowing neglect testing across hemifields. The o'Clock task facilitates the use of memory and mental imagery for a clock's layout and taps into information acquired prior to pathology onset. Patients are asked to imagine clock hands forming two different times on a clock, usually half hours (e.g. 7:30) or full hours (e.g. 8:00) and to judge which of the angles formed by the clock hands is larger, over multiple trials. Modifications to this task include judgments on whether single or both clock hands are in the left or right hemifield, whether clock hands to a single time subtend an angle greater than 90 degrees (Kukolja, Marshall, & Fink, 2002) or simply reporting whether the clock hands are in the left or right hemifield (Cocchini et al., 2006). Some studies have calculated an LQ for this task using number of correct responses to clock hands on the left and right side of imagined space (e.g. Guariglia et al., 2013; Palermo et al., 2012; van Dijck et al., 2013). In addition to identifying non-topological RN, this task has been used to study mental imagery skills (Palermo, Iaria, & Guariglia, 2008), explore the neural correlates of spatial imagery (Formisano et al., 2002; Trojano et al., 2000) and even explore dissociations between visual and RN using two comparable task versions (Grossi et al., 1989).

(iv) Drawing from memory

One of the classical and quick ways to assess non-topological RN is by asking patients to draw objects, animals or landscapes from memory (Arduino et al., 2012; Beschin et al., 1997a; Chokron et al., 2004). Typically, these stimuli have parts on the left and right side (e.g.: a clock) thus eliciting an assessment of non-topological RN typically based on completeness and symmetry (Cristinzio et al., 2009; Salvato et al., 2014). These tasks have also been used in the diagnosis of visual neglect.

(v) Object array tasks

While the above tasks have been largely used to assess RN for *well-learnt* topological and non-topological information, other tests have been devised to identify RN for *newly learnt* information by using novel object arrays as test stimuli. In these tasks, patients are required to learn a set of objects/object pictures laid out on the left and right side of their midline. Subsequently, the stimuli are taken away from sight and participants are asked to report the objects from imagery. Some versions of the task include object report from opposite vantage points, or imagery facilitated by verbal descriptions (Della Sala et al., 2004; Denis, Beschin, Logie, & Della Sala, 2002; Loetscher & Brugger, 2007; Ortigue et al., 2003). Another type of test using new information involves asking the patient to learn a complex unfamiliar scene with items distributed equally to the right and left side. RN is based on their relative recall of items or from a drawing of the scene to assess spatial relations between objects on the left and right side after a short interval (Beschin et al., 1997a; Cocchini et al., 2006; Della Sala et al., 2004).

The tasks discussed above are typically used in the assessment of RN. Occasionally, other tests such as the Fluff test (Cocchini, Beschin, & Jehkonen, 2001), Comb and Razor test (Zoccolotti & Judica, 1991) and Vest test (Glocker, Bittl, & Kerkhoff, 2006) are used to assess RN for personal space.

1.1.2 Rationale for creating novel RN assessment methods

1.1.2.1 Limitations of existing methods

The RN methods listed above, especially the Familiar Square test and Geographical Map Description tasks are the most commonly used tests for RN (e.g. Bartolomeo et al., 1994; Bisiach & Luzzatti, 1978; Guariglia et al., 2013; Ortigue et al., 2003; Palermo et al., 2010a; Rode et al., 2004). Yet, these tasks have been criticised for several important limitations that may be relevant to the assessment of RN, such as influence of subjectivity in patient's memory and familiarity with the material, lack of access to premorbid long term memory for the material and layout-dependent differences in number of available landmarks and salience of landmarks to the left and right side (for review, see Salvato et al., 2014). Hence, one potential way of overcoming these shortcomings is by creating a novel paradigm that can be utilized more globally with patients in regions that do not have a unanimously popular landmark or in cases where patient's prior knowledge of maps, routes and spatial configurations to assess for RN deficits is unavailable. Additionally, such a novel paradigm could also incorporate a measure of baseline learning of and familiarity with the stimuli, to evaluate their role in RN for the chosen layout.

A second limitation in the currently available RN methods is their reliance on other task-associated ancillary abilities that may influence RN performance such as mental rotation, angle judgement and decision making. For example, the topological RN tasks typically require imagining the layout from opposite vantage points and such perspective shifting in imagery may engage mental rotation. The o'Clock task requires patients to be able to compare angles formed by clock hands to judge which of two angles is larger or greater than 90 degrees (Grossi et al., 1989; Kukolja et al., 2002). However, poor performance on the task can be attributed to deficits in ancillary abilities that may manifest as or contribute to RN on the task. This task and its adaptations are sometimes also used in neuroimaging paradigms to study neural correlates of mental imagery (Formisano et al., 2002; Kukolja et al., 2002; Trojano et al., 2000; Trojano et al., 2004). Time taken to respond in these experiments could in fact indicate difficulties in decision making and angle judgment rather than in imagery. The o'Clock task has several advantages such as its relative simplicity, use of symmetrical objects that are well-learned and amenability to exploration in internal representation. Hence, a novel RN assessment method that can retain these advantages of the o'Clock task while reducing its reliance on ancillary abilities and facilitating measurement of RN-related cognitive abilities such as spatial attention may be useful in contributing to our understanding of non-topological RN. Alternatively, accounting for the use of ancillary mechanisms recruited in the RN task being used can aid in characterising the contribution of such cognitive abilities to RN.

Lastly, there is a need for computerized RN task measures that can provide methodologically standardized, sensitive and quantitative measurement of RN. In the visual neglect literature, computerized methods have been reported to have higher sensitivity to identify sub-clinical deficits and monitor changes in performance over sessions (Bonato, 2012; Bonato & Deouell, 2013; Habekost & Bundesen, 2003;

Habekost & Rostrup, 2006; Rengachary et al., 2013). A review of RN literature has resulted in the identification of only one computerized task that is seldom used in experimental settings (Bisiach et al., 1979; Ogden, 1985). Using this paradigm, Bisiach et al. (1979) asked 19 right hemisphere brain damaged patients with left neglect to make same/ different judgements of pairs of cloud-like shapes moving horizontally on a screen. Patients perceived the shapes through a centrally placed narrow vertical slit requiring the remaining object form to be mentally reconstructed. They showed that performance for objects on the basis of mental reconstructions that differed on the left side were more impaired than right. However, this task has been critiqued for the role of short exposure duration of the stimuli in central vision which may have affected the efficient pick-up of information from the left part of the stimuli (Bisiach & Rusconi, 1990). Additionally, it has received criticism for heavy reliance on visual selective attention and visual discrimination abilities that may interfere with RN identification (Bartolomeo, D'Erme, & Gainotti, 1994; Rapcsak et al., 1989).

Thus, there is a need for improved assessment tasks that while providing the potential for standardization and sensitive identification of RN, also reduce reliance on ancillary task-unrelated cognitive abilities. Additionally, RN methods that can independently or in conjunction with ancillary cognitive tests account for the involvement of key spatial and non- spatial cognitive processes engaged in RN can help to advance theoretical understanding of the syndrome.

1.1.2.2 Advancing theoretical understanding of RN

Amongst the commonly used current RN assessment methods, the Familiar square task has been used to propose a role for impaired mental representations underlying RN (Bisiach & Luzzatti, 1978); the Geographical Map task has proposed a role for spatial attention orienting within the mental representation as the key deficit in RN (Bartolomeo, D'Erme, & Gainotti, 1994; Rode, Revol, Rossetti, Boisson, & Bartolomeo, 2007; Rode, Rossetti, Perenin, & Boisson, 2004) while object array based tasks have helped to explain RN as a deficit of lateralised visuospatial working memory (Beschin, Cocchini, Della Sala, & Logie, 1997a; Della Sala, Logie, Beschin, & Denis, 2004; Logie, Della Sala, Beschin, & Denis, 2005).

To elaborate, initial studies found that both visual and RN patients showed impaired performance on the Familiar square description task and this was thought to be on account of damage to an underlying common mental representation of space (Bisiach & Luzzatti, 1978; Bisiach et al.,1979). However, subsequent dissociations identified in visual and RN demonstrated that the two syndromes could be partially independent and related to two different representations of space in the brain (Bartolomeo et al., 1994; Coslett, 1997; Denis et al., 2002; Guariglia et al., 1993; Ortigue et al., 2001; Salvato et al., 2014).

Hence, some researchers have attempted to explain RN as a disorder of spatial attention using the Geographical map description task (Bartolomeo et al., 2005; Rode et al., 2010). Bartolomeo et al. (2005) asked twelve right hemisphere damaged patients to imagine a map of France and through key presses, indicate if twenty pairs of auditorily presented French cities were to the right or left of Paris. They found that two of the patients showing both visual and RN were able to symmetrically classify cities to the left and right but were slower to classify cities to the left of Paris than to the right. According to them, the dissociation between accuracy and response times in classifying cities indicated that these patients' RN was related to an inability to efficiently *explore* the left side of the imagined map rather than due to an inability to *create* a mental representation.

Thus, similar to accounts of biased attention in visual neglect, they also suggested that attentional biases play a role in RN (Bartolomeo & Chokron, 2002). This account was supported by Rode et al. (2010) who reported a single case study of a right brain damaged patient demonstrating left sided neglect in both visual and imaginal versions of the Geographical Map Description task but showed symmetrical report of towns in a free recall of cities. They explained this observation as neglect on account of deficit in orienting attention to the left side of space across both visual and mental representations.

Alongside attention orienting deficits, difficulty in disengaging attention from the ipsilesional side of a mental representation has also been implicated in RN (Loetscher & Brugger, 2007). In this study, the researchers reported a single case of a right hemisphere brain damaged patient with left neglect. This patient was exposed to four learning trials of ten objects each, with objects presented on the left or right side of a corridor. RN was assessed by blindfolding the patient and guiding him through the corridor at the same pace as during the learning trial. They found that although the number of items recalled was symmetrical on both sides, there was an initial temporal clustering after the first trial where right sided items were reported prior to the left sided items. Loetscher & Brugger (2007) suggested that their patient demonstrated a disengagement deficit from the ipsilesional right side of his mental representation rather than an inability to create a representation for the left side of space.

Finally, some researchers have proposed a role for working memory deficits in RN. For instance, Rode et al. (2010) have suggested that an important factor distinguishing mechanisms of visual neglect from RN is the use of spatial working memory required in actively building, exploring and remembering layouts in RN. They implied that while perceptual neglect involved deficits in stimulus-based attention, RN was likely to manifest on account of an interaction between attention and spatial working memory. A related interpretation that has been proposed using object array tests is that RN is caused by lateralized deficits in visuospatial working memory (Beschin, Cocchini, Della Sala, & Logie, 1997a; Della Sala, Logie, Beschin, & Denis, 2004; Logie, Della Sala, Beschin, & Denis, 2005). These studies used a 2 x 2 array of object pictures from ten different categories and asked patients to name each object and its location in the array. Report could be made from one of two vantage points (so the image had to be transformed) and stimuli could be presented for encoding either visually (by showing the object pictures and locations) or verbally (verbal description involving object name and location relative to spatial position of another object in the array). Della Sala et al. (2004) found that in patients with right hemisphere brain damage and left-sided representational deficits, limited information presented on the left was imagined but none was lost during the mental transformation process. However, some items learnt and imagined on the intact right side were lost when transformed and imagined as being on the left side. Based on these results, it has been proposed that RN is caused by a lateralized deficit to mental images held in visuospatial working memory rather than an inability to orient attention to visual images (Della Sala et al., 2004). However, unlike studies that reported a role for lateralised visuospatial working memory in RN based on task performance in the Object arrays task, others that used supplementary tests to assess visuospatial working memory, did not replicate similar results (Piccardi, Bianchini, Zompanti, & Guariglia, 2008; van Dijck, Gevers, Lafosse, & Fias, 2013). Hence, the relationship between visuospatial working memory and RN is uncertain.

It is interesting to note that each of the proposals on theoretical underpinnings of RN has been put forth based on the use of a single type of RN test involving a specific type of representation. In fact, given the available literature on dissociations in RN based on type of stimuli and space, e.g. near-far, personal-extrapersonal, egocentric-allocentric, topological-non-topological (Arduino, Marinelli, Pasotti, Ferre, & Bottini, 2012; Coslett, 1997; Guariglia, Palermo, Piccardi, Iaria, & Incoccia, 2013; Ortigue et al., 2001, 2003; Ortigue, Mégevand, Perren, Landis, & Blanke, 2006), it is much more likely that RN may rely on multiple spatial and non-spatial cognitive abilities and may be engaged differently depending on the task demands. Hence, rather than a unitary approach to explaining RN as a deficit of mental representation, spatial attention or working memory, it may be beneficial to examine the importance of the various cognitive abilities that may contribute to the syndrome, e.g. visual memory, imagery, mental rotation, in addition to spatial attention and visuospatial working memory. This proposal is in line with suggestions based on a recent review of RN studies published in the 35 years between 1978 and 2013 (Salvato et al., 2014). Based on this review, it has been suggested that the discrete theories put forth to explain RN are inadequate and an integrative model involving inter-communicating cognitive systems may be better suited to explain RN deficits (Salvato et al., 2014). The review makes a special note on the importance of assessing spatial attention in conjunction with spatial working memory in imagery space to identify RN (Salvato et al., 2014). This proposition draws support from other studies that have shown that attention and spatial working memory exert influence over each other (Nobre, Griffin, & Rao, 2007; Olivers, Peters, Houtkamp, & Roelfsema, 2011) and attention can be oriented in internal representations held in working memory (Griffin & Nobre, 2003). Hence, another aim of the RN-related studies included in this thesis was to investigate the importance of some of spatial and non-spatial cognitive mechanisms, including spatial attention and visuospatial working memory, that have been implicated in discrete studies as playing a potentially important role in RN. Given adequate cases, the importance of these cognitive mechanisms can be investigated separately for topological and non-topological tasks since there has been indication that dissociated deficits in imagery skills for places and objects can underlie dissociations in topological and non-topological RN (Palermo, Nori, Piccardi, Giusberti, & Guariglia, 2010a). However, this report was based on two patients and did not incorporate an assessment of other cognitive abilities that may have had separable roles in explaining the observed dissociation.

To address the above issues, Chapter 3 focused on the creation and assessment of suitability of the two new RN tasks (The Shopping Mall, Clock Cueing). The Mall task provided an improvement in methodological standardization of topological RN as well as allowed for testing of participant's memory and familiarity for the landmarks being imagined. The Clock Cueing task was computerized and combined features of the o'Clock task (Grossi, Modafferi, Pelosi, & Trojano, 1989) and the Posner task (Posner, Walker, Friedrich, & Rafal, 1984) to provide sensitive RT measures. It was also intended to reduce the demand on ancillary cognitive abilities made by the o'Clock task while directly assessing spatial attention processes in imagery space. In Chapter 4, the tasks were administered to chronic stroke patients and used as means to identify dissociations based on task stimuli (topological, non-topological) as well as time of acquisition of representation (pre-stroke, post-stroke). Additionally, along with measures of visual memory and spatial attention from the tasks themselves, an ancillary cognitive test battery was used to inform about performance on task-associated cognitive abilities that may be helpful in informing RN theory.

Along with the use of assessment methods to help understand the syndrome of neglect, a large number of studies have focused on processes related to recovery from neglect and efficacy of rehabilitation tools in aiding neglect recovery. This area of work has actively concentrated upon **visual neglect**, rather than RN, likely because the presence of visual neglect is a known unfavourable prognostic factor associated with longer hospital stay (Katz et al., 1999) and significant impairments in sensorimotor skills, cognitive skills, hemiplegia and functional outcomes (Chen, Hreha, Kong, & Barrett, 2015; Denes et al., 1982; Jehkonen, Laihosalo, & Kettunen, 2006; Katz et al., 1999; Paolucci et al., 1996, 2000; Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001). It is also associated with a higher likelihood of institutionalization (Paolucci et al., 2001) and discharge home with caregiver assistance (Katz et al., 1999). Hence, the second part of this thesis aimed to explore questions that may aid recovery from visual neglect.

1.2 Rehabilitation of visual neglect

Over the past sixty years, several methods for neglect rehabilitation have been developed such as visual scanning training, limb activation, space remapping, mental imagery and sustained attention training, feedback training, vestibular stimulation and non-invasive brain stimulation (Luauté, Halligan, Rode, Rossetti, & Boisson, 2006). A review evaluating efficacy of six of these rehabilitation techniques revealed benefits in reducing neglect for four to six weeks using visual scanning training, visual scanning + trunk rotation, visual scanning + neck muscle vibration, mental imagery training, video feedback training and prism adaptation (Luauté et al., 2006). However, most of the reviews reported that the effectiveness of rehabilitation was *transient* and recommended the need for more rigorous clinical trials investigating long lasting effects of rehabilitation and the transfer of benefits to Activities of Daily Living (ADL) (Bowen et al., 2002; Kerkhoff & Schenk, 2012; Luauté et al., 2006; Yang et al., 2013).

Hence, Chapters 5-7 were focused on informing visual neglect literature, i.e. Chapters 5 and 6 were aimed at advancing an understanding of the role of repetitive Transcranial

Magnetic Stimulation (rTMS) in neglect recovery; specifically duration of rTMS effects on neglect performance, and neural mechanisms underlying rTMS induced neglect recovery respectively. Chapter 7 was intended to identify cognitive processes that may be integral to spatial and object neglect and which may potentially be used to guide cognitive retraining efforts for visual neglect in future studies.

1.2.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

The framework for rTMS based rehabilitation in neglect patients is derived from attentional models that suggest right hemisphere dominance in modulating attention in space (Heilman & Valenstein, 1979) and disruption of interhemispheric processes subsequent to stroke (Kinsbourne, 1974; 1977). Thus, based on attentional models, the basic aim of rTMS is to modulate cortical activity in the brain to restore balance between hemispheric networks that serve attentional functions.

1.2.1.1 Theoretical bases

Heilman and Valenstein (1979) proposed that the right hemisphere has a dominant role in directing attention to both sides of space as compared to the left hemisphere that only attends to the right hemispace. Thus, according to this model, lesions to the right hemisphere would result in left neglect whereas lesions to the left hemisphere may only rarely produce right sided neglect due to the ability of the right hemisphere to modulate attention bilaterally (Heilman & Valenstein, 1979). Furthermore, Kinsbourne (1974; 1977) proposed that both brain hemispheres contain reciprocally interactive opponent processors that direct attention along a vector to contralateral space, with the right vector (left hemisphere dependent) prevailing over the left (right hemisphere dependent) vector in both external and internal spatial representations. Thus, the right hemisphere is involved in directing attention to the left hemispace and vice versa. Stroke to one hemisphere causes an imbalance between the opponent processors such that the intact hemisphere is disinhibited and biases attention to ipsilesional space. Hence, in the case of a right hemisphere stroke, the left hemisphere which is disinhibited from the right's influence, is largely in control and results in bias of attention to the right side of space. He also suggested that neglect is subject to an attentional gradient and hence deficits need not follow a sharp unilateral left-right distinction with reference to the midsagittal plane of the trunk. According to him, the attentional gradient also corresponds to the frame of reference, i.e. viewer-centred or object-centred such that attention may be biased for either/or ipsilesional hemispace in a viewer-centred frame or object-centred frame (Kinsbourne, 1993; Vallar & Bolognini, 2014). See Figure 1.1 for a representation of Kinsbourne's Interhemispheric Rivalry theory described above.

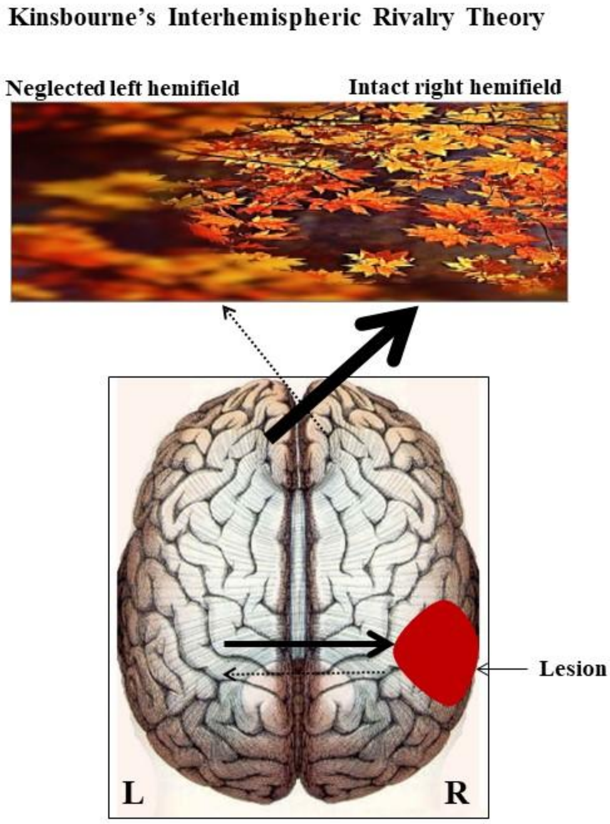

Figure 1.1. Depiction of Interhemispheric Rivalry Theory

L=Left hemisphere; R=Right hemisphere
This figure is a graphical depiction of Kinsbourne's Interhemispheric Rivalry Theory/ Opponent Processor model. A lesion to the right hemisphere causes imbalance between the opponent processors such that the intact (left) hemisphere is disinhibited and biases attention to ipsilesional space (right hemifield). The lesioned right hemisphere is further inhibited by the intact hemisphere and is unable to modulate attention to the contralesional side resulting in left-sided neglect.

Support for this theory has been acquired from animal studies demonstrating that lesioning or cooling of brain regions such as the parietal cortex, contiguous visual areas, the superior colliculus or lateral geniculate nucleus can induce neglect by causing an imbalance in physiological activity between the hemispheres (Payne & Rushmore, 2004; Rushmore, Valero-Cabré, Lomber, Hilgetag, & Payne, 2006). This can be rebalanced and consequently, neglect ameliorated, by creating a second lesion or cooling of specific cortical regions, e.g. posterior middle suprasylvian sulcus in cats (Lomber, Payne, Hilgetag, & Rushmore, 2002) or superior colliculus on the intact side of the cat brain (Lomber et al., 2002; Payne & Rushmore, 2004; Rushmore et al., 2006; Sprague, 1966) or non-invasive brain stimulation to contralesional posterior parietal cortex in cats (Rushmore, DeSimone, & Valero-Cabré, 2013).

Further support for Kinsbourne's theory has also been obtained from patient studies. Vuilleumier, Hester, Assal, and Regli (1996) reported a patient whose first stroke involving the right hemisphere's parietal lobe resulted in severe neglect but the neglect was cancelled by a second subsequent stroke involving the left hemisphere's frontal eye field. Thus, these studies paved the way for the rationale that rTMS may have potential to restore balance in functional activity between hemispheres which could be helpful in ameliorating visual neglect.

1.2.1.2 Mechanisms of rTMS

rTMS is a non- invasive brain stimulation technique that is aimed at changing cortical activity in target areas of the brain. It involves short bursts of electrical currents delivered through a coil placed on a focal point on the scalp to create a rapid high intensity magnetic field. This in turn induces perpendicular currents in the brain which are strong enough to depolarize neurons and influence cortical excitability in neural networks. Depending on the stimulation parameters, neuronal activity can either be excited or inhibited. Stimulation at a certain pre-determined percentage of each individual's unique resting or active motor threshold given at 5-20 Hz (high frequency) can enhance activity, whereas stimulation at $\leq$ 1 Hz (low frequency) can inhibit neuronal activity. In the context of Kinsbourne's interhemispheric rivalry theory, low frequency rTMS to the intact hemisphere has the potential to suppress cortical hyperexcitability while high frequency rTMS to the lesioned hemisphere can excite neuronal excitability. More recently, Theta Burst Stimulation (TBS) has been used as a new protocol which induces strong and long lasting effects in the cortex using a lower stimulation intensity and shorter stimulation time than conventional rTMS protocols (Cárdenas-Morales, Nowak, Kammer, Wolf, & Schönfeldt-Lecuona, 2010; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Depending on stimulation pattern, TBS can have inhibitory (continuous theta-burst, cTBS) or excitatory (intermittent theta-burst iTBS) effects on neural activity.

Importantly, the duration of the after-effects of rTMS are shown to outlast the actual period of stimulation and hence, multiple sessions of rTMS applied over days are thought to have therapeutic potential in rehabilitating neglect (Hallett, 2007; Kobayashi & Pascual-Leone, 2003; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Robertson, Théoret, & Pascual-Leone, 2003; Rossi & Rossini, 2004).

1.2.1.3 Evidence that TMS can change functional activity in attention networks

Combined TMS – functional Magnetic Resonance Imaging (fMRI) studies with controls have explored the impact of disruption to core hubs of the attention network such as the parietal and frontal lobe and consequent changes in activity in task associated functional networks (Plow et al., 2014; Ruff et al., 2008; Sack et al., 2007). For example, Ruff et al. (2008) have reported that short bursts of focal TMS over frontal and parietal regions can modulate activity in the visual cortex. Specifically, they found that in four healthy participants, TMS to the left and right frontal eye field reduced activation in the occipital lobe for central visual field representations; but TMS to the right frontal eye field increased activity in the occipital lobe for peripheral field representations. This suggested right hemisphere predominance for frontal influences on visual cortex for processing stimuli in the peripheral visual field. For the parietal lobe TMS to intraparietal sulcus, only right hemisphere stimulation, but not the left, decreased functional activity in the lateral occipital cortex (Ruff et al., 2008). Similarly, in a study with eight healthy participants, Sack et al. (2007) found that TMS induced disruptions of the right parietal cortex but not the left, decreased task performance and cortical activity at the site of stimulation as well as in remote ipsilateral frontal areas (Sack et al., 2007).

The role of offline brain stimulation in affecting interhemispheric activity involving attention networks has also been shown. Plow et al. (2014) in a concurrent rTMS-fMRI study, disrupted activity in the left intraparietal sulcus in ten healthy controls. They found that behavioural performance on a bilaterally presented visual tracking task was reduced contralaterally immediately post parietal TMS as compared to sham. Additionally, functional activity in ipsilateral areas ventrolateral to the intraparietal sulcus (inferior parietal lobe, middle occipital gyrus) showed a decrease in activity whereas dorsomedial areas (superior parietal lobe, superior occipital gyrus, lingual gyrus, middle temporal areas) showed an increase in activity. The activity of most contralateral homologous areas reversed showing an increase in activity in the right intraparietal sulcus and ventrolateral areas and decrease in dorsomedial areas. Increased activity in the right intraparietal sulcus related with increased behavioural accuracy for both left and right visual fields possibly on account of the role of the right hemisphere in modulating responses to both visual fields (Heilman & Valenstein, 1979; Mesulam, 1981). Thus, this study provided evidence for the role of interhemispheric balance in functional activity in the intraparietal sulcus and other regions that are also part of a visuo-attentional network using rTMS (Plow et al., 2014).

In another study with healthy controls, low frequency offline TMS intended to transiently disrupt functional activity in the right parietal lobe, resulted in the abolishment of the typical leftward bias seen in controls in a task involving target detection (Petitet, Noonan, Bridge, Reilly, & Shea, 2015). While covertly monitoring both visual fields for target detection during the baseline fMRI, bilateral networks of activation in the attention networks involving frontal, parietal and visual cortices was noted. Post offline rTMS, a relative shift in the hemispheric balance of parietal lobe activity from the right to the left hemisphere was observed. These results indicated a causal role for the parietal lobe in modulating inter-hemispheric activity when directing attention to both sides of space (Petitet et al., 2015).

1.2.1.4 Evidence that rTMS can aid visual neglect rehabilitation

Given rTMS's potential to modulate inter-hemispheric functional activity in the attentional networks and its ability to produce effects that tend to outlast stimulation duration and affect neglect behaviour, several studies have attempted to evaluate its scope in visual neglect rehabilitation using both inhibitory and excitatory paradigms (For review, see Jacquin-Courtois, 2015; Müri et al., 2013). Table 1.1. provides a comprehensive summary of the studies conducted with visual neglect patients.

Table 1.1. *Summary of rTMS studies designed to rehabilitate visual neglect*

Authors & year	Patients	Time post stroke	Sham	Stimulation parameters	Time of assessment	Main results
(Oliveri et al., 2001)	5 RH N+ 2 LH N+	1-48 w	Yes	Contralesional (P5/ P6), 100 pulses, 15% above MT, single session	During rTMS	Reduced ipsilesional attentional bias in computerized line length judgment of pre-bisected lines after trains of contralateral rTMS
(Brighina et al., 2003)	3 RH N+	3-5 m	No	Contralesional P5, 900 pulses, 1 Hz, 90% MT, 7 sessions (alternate days)	2 w pre/ pre/post/2 w post	Improvement in computerized length judgment or pre-bisected lines, clock drawing and line bisection sustained up to 2 weeks post stimulation
(Shindo et al., 2006)	2 RH N+	175, 186 d	No	Contralesional P5, 900 pulses, 0.9 Hz, 95% MT, 6 sessions (3 per w)	2 w pre/ 1 d pre/ 1 d post/ 2 w/ 4 w/ 6 w post	Improvement in Behavioural Inattention Test for at least 6 weeks
(Koch et al., 2008)	10 RH N+, 5 RH N-	1-6 m	No	Contralesional P3, 600 pulses, 1 Hz, 90% MT, 1 session	Pre/post	Reduced hyperexcitabiliy of LH MEP after rTMS in neglect patients; significant reduction of left-sided omissions in the naming test
(Song et al., 2009)	7 RH N+ treatment, 7 RH N+ controls	15-60 d	No	Contralesional P3, 450 pulses, 0.5 Hz, 90% MT, 14 sessions (2 w, 2 trains per d)	2 w pre/pre/post/2 w post	Significant improvement in line bisection and line cancellation in the treatment group, sustained up to 2 w after rTMS
(Nyffeler et al., 2009)	11 RH N+	0.4-36.1 m	Yes	Contralesional P3, 801 pulses, cTBS, 3 pulses at 30 Hz repeated at 100 ms, 100% MT, 1 session (2 or 4 cTBS trains)	Pre/ 1 h post, 3 h/ 8 h/ 24 h/ 32 h/ 96 h post	Significant improvement in left sided target detection and reduction of RT in Peripheral Perception task of Vienna test system. Stable effects up to 8 h after 2 trains and up to 32 h after 4 trains.

Authors & year	Patients	Time post stroke	Sham	Stimulation parameters	Time of assessment	Main results
(Kim et al.,2010)	19 RH N+	23.73 ± 12.3 m	Yes	Contralesional P3 & ipsilesional P4, 1200 pulses, 1 Hz, 90% MT *or* 1000 pulses, 20 Hz, 90% MT, 10 sessions	Pre/post	Significant improvement in Ota's task after 1 Hz stimulation only
(Lim et al., 2010)	7 RH N+, 7 RH N+ controls	9-313 d	No	Contralesional P3, 900 pulses, 1 Hz, 90% MT, 10 sessions (1 per d over 2 w)	Pre/post	Significant improvement in line bisection for left biased lines
(Koch et al., 2012)	9 RH N+, 9 RH N+ controls	24-102 d	Yes	Contralesional P3, 600 pulses, cTBS at 50 Hz, repeated every 200 ms at 80% MT, 10 sessions (2 trains per d for 2 w)	Pre/ post/ 2 w	Significant improvement in BIT scores sustained up to 2 w post stimulation in treatment condition. Reduction in hyperexcitability of LH MEP after rTMS in treatment condition
(Cazzoli et al., 2012)	16 RH N+ treatment, 8 RH N+ controls	Mean 27 d (SEM 4.5 d)	Yes	Contralesional P3, 801 pulses, cTBS, 3 pulses at 30 Hz repeated every 100 ms, 100 % MT, 4 cTBS trains per d for 2 days	1 w pre/ 1 w/ 2 w/ 3 w post	Significant improvement in ADL related Catherine Bergego scale scores up to 3 w post stimulation. Significant improvement also in Peripheral Perception task of Vienna tests system, random shape cancellation test, two part picture test, reading texts
(Kim, Chun, Kim, & Lee, 2013)	9 RH N+ low freq, 9 RH N+ high freq, 9 RH N+ controls	14.2-16.4 d	Yes	Contralesional P3 & ipsilesional P4, 1200 pulses, 1 Hz, 90% MT *or*1000 pulses, 20 Hz, 90% MT, 10 sessions over 2 w	Pre/post	Significant improvement in line bisection test after high freq rTMS and in Korean-modified Barthel index after both high and low freq rTMS
(Fu et al., 2015)	10 RH N+ treatment, 10 RH N+ controls	17-114 d	Yes	Contralesional P5, 800 pulses at 30 Hz, 80% MT; four trains of 200 pulses of cTBS/ sham applied with an interval of 15 mins for 14 consecutive days.	1 h pre/post/ 4 w post	Significant improvement in star cancellation and line bisection scores between baseline and 4 w follow-up for treatment group when compared to sham

Authors & year	Patients	Time post stroke	Sham	Stimulation parameters	Time of assessment	Main results
(Kim, Jung, & Shin, 2015)	19 RH N+ single session (group 1), 15 RH N+ 10 sessions (group 2)	Group 1: 19.11±12.39 m Group 2: 15.73±12.33 m	No	Contralesional P3, 1200 pulses, 1 Hz, 90% MT, group 1: 1 session, group 2: 10 sessions over 2 w	Pre/post	Ten sessions of rTMS was associated with greater improvement in letter cancellation, line bisection and Ota's task as compared to one session; first study showing object neglect improvement with ten rTMS sessions

RH = Right Hemisphere; LH = Left Hemisphere; N+ = with neglect; N- = without neglect; cTBS = continuous Theta Burst Stimulation; freq = frequency; h = hour; d = days, w = weeks, m = months; ms = milliseconds; MEP = Motor Evoked Potential; ADL = Activities of Daily Living; RT = Reaction Time; SEM = Standard Error from Mean.

A significant amount of heterogeneity is seen amongst the thirteen investigations that have used rTMS to date to evaluate its therapeutic potential for neglect (Table 1.1). All thirteen studies using inhibitory protocols showed improvements in visual neglect (Brighina et al., 2003; Cazzoli et al., 2012; Fu et al., 2015; Kim, Chun, Kim, & Lee, 2013; Kim, Kim, Shin, & Kim, 2010; Kim, Jung, & Shin, 2015; Koch et al., 2008, 2012; Lim, Kang, & Paik, 2010; Nyffeler, Cazzoli, Hess, & Müri, 2009; Oliveri et al., 2001; Shindo et al., 2006; Song et al., 2009). Inhibitory protocols used 0.5/1 Hz rTMS or cTBS to the contralesional parietal lobe (P3/P5). The number of pulses used for conventional rTMS in each study varied, with only two of them using less than 900 pulses (Koch et al., 2008; Song et al., 2009) and most others using 900 (Brighina et al., 2003; Lim et al., 2010; Shindo et al., 2006) or 1200 pulses (Kim et al., 2010; Kim et al., 2013; Kim et al., 2015). For cTBS studies, most protocols used 800/801 pulses (Cazzoli et al., 2012; Fu et al., 2015; Nyffeler et al., 2009) while one used 600 (Koch et al., 2012). The number of days of rTMS stimulation also varied widely across all thirteen investigations listed with both conventional rTMS and cTBS ranging between one and fourteen days. The threshold of stimulation was conventionally determined based on motor threshold. A majority of the conventional rTMS paradigms used 90% of the motor threshold (Brighina et al., 2003; Kim et al., 2010; Kim et al., 2013; Kim et al., 2015; Lim et al., 2010; Shindo et al., 2006; Song et al., 2009), while cTBS studies used either 80% (Fu et al., 2015; Koch et al., 2012) or 100% of the motor threshold to stimulate patients (Cazzoli et al., 2012; Nyffeler et al., 2009).

Inhibitory rTMS related neglect improvement has been noted in varied behavioural outcome measures such as line bisection and cancellation (Brighina et al., 2003; Cazzoli et al., 2012; Fu et al., 2015; Kim et al., 2010; Kim et al., 2013; Kim et al., 2015; Lim et al., 2010; Oliveri et al., 2001; Song et al., 2009), target detection paradigms (Cazzoli et al., 2012; Nyffeler et al., 2009) and the Behavioural Inattention test (BIT) (Koch et al., 2012; Shindo et al., 2006). Interestingly, Koch et al. (2008, 2012) used reduction in excitability of the left hemisphere as measured by motor evoked potential as an outcome measure. Very few investigations have explored improvements in activities of daily living post rTMS (Cazzoli et al., 2012; Kim et al., 2013; Shindo et al., 2006). To date, only one study has explored and found beneficial effects of rTMS for object neglect using the Ota's task (Kim et al., 2015).

Two of the thirteen reports also used excitatory rTMS (Kim et al., 2013; Kim et al., 2010), but only one showed improvement in neglect (Kim et al., 2013). When comparing the two studies to elicit the basis for the difference in results, Kim et al. (2013) used 1000 rTMS pulses of 10 Hz with 27 neglect patients that improved neglect on line bisection and Korean-modified Barthel Index. In comparison, Kim et al.'s (2010) use of 1200 pulses of 20 Hz stimulation with 19 neglect patients did not elicit any significant improvement in line bisection, letter cancellation or Ota's task. As can be noted, the variability in the use of stimulation parameters as well as outcome measures might be important in determining the effects of rTMS in neglect recovery.

In addition to protocol based differences, the sample size in the Intervention Group (range: 2-19), use of sham/ control condition (used in 7 out of 13 investigations) and time since stroke at recruitment (sub-acute stage: 3 studies; chronic stage: 3 studies; mixed recruitment across sub-acute and chronic stages: 7 studies) was also heterogeneous.

Overall, despite the variability in the methodology of the investigations reported, it can be deduced that inhibitory rTMS to the contralesional P3 or P5 at 80- 100% motor threshold, administered over multiple sessions, has the potential to improve left sided visual neglect in right hemisphere stroke patients.

1.2.2 Rationale for investigating long term efficacy of rTMS in rehabilitating visual neglect

The evaluation of whether rTMS can benefit neglect in the long term is especially important given that neglect has been seen to persist in the chronic stage (6 months - 1 year + post stroke) (Chechlacz et al., 2012; Karnath, Rennig, Johannsen, & Rorden, 2011; Lunven et al., 2015; Nijboer et al., 2013; Rengachary et al., 2011), even after spontaneous recovery has plateaued at around three months post stroke (Nijboer, Kollen, & Kwakkel, 2013; Stone, Patel, Greenwood, & Halligan, 1992). When evaluating the studies conducted with patients in the sub-acute stage, Cazzoli et al. (2012) found that 4 cTBS trains to the contralesional parietal lobe delivered on each of two days, improved neglect behaviour in a group of 16 right hemisphere stroke patients, when compared to 8 control group patients. The duration of these benefits was seen to persist when the patients were evaluated three weeks post rTMS. None of the sub-acute stage rTMS studies have evaluated the potency of rTMS in producing lasting changes extending into the chronic stage, when the scope for spontaneous recovery of neglect has diminished.

Research, predominantly based on animal studies, has shown that spontaneous recovery post brain injury is marked by neuroplastic changes and cortical re-organization that occur at both functional and structural levels, and both within and between brain hemispheres (Jung et al., 2016; Kolb & Muhammad, 2014; Nudo, 2013). These may be reflected as development of compensatory mechanisms and experience-dependent changes in the brain that benefit functional recovery, maximally in the immediate aftermath of the injury (Cramer et al., 2011; Murphy & Corbett, 2009; Nudo, 2013;

Teasell, Bayona, Salter, Hellings, & Bitensky, 2006). Thus, one possibility that can be explored is whether non-invasive brain stimulation to the contralesional parietal lobe, in the sub-acute stage, can help to sustain neglect recovery into the chronic stage. If so, this may be an indicator of rTMS's strength and scope as an additive influence on spontaneous recovery.

However, an alternate hypothesis suggested in recent studies is that rTMS induced changes may benefit behaviour in the short- term due to *neuroplasticity*, but effects in the long term may be related to its ability to influence *metaplasticity*, i.e. increase in susceptibility of the neurons to undergo subsequent changes based on past history of neuroplasticity (Abraham, 2008; Cohen et al., 2010; Valero-Cabré, Pascual-Leone, & Rushmore, 2008). Valero-Cabre, Pascual-Leone, and Rushmore (2008) showed that daily sessions of 20 minutes of 1 Hz rTMS to the visuoparietal cortex of two cats led to neglect-like impairments in contralateral target detection that peaked on the 18th and 19th day of stimulation. The magnitude of the effect of daily rTMS was shown to accrue over sessions and affected a larger portion of the contralateral visual field over subsequent sessions. Interestingly, this accrual effect of rTMS was restricted to the immediate offline assessment post the session indicative of short-term neuroplastic effects, and did not affect performance when tested one hour or twenty four hours post stimulation. However, when the researchers stimulated the cats after a one week rTMS-free interval, the observed magnitude of the behavioural effect matched that observed at the peak of facilitation during the cumulative sessions. These results suggest a role for metaplasticity such that the accrual of rTMS sessions may render the targeted region and its connected neural network more susceptible to modify activity levels when re-exposed to subsequent rTMS sessions (Valero-Cabré et al., 2008). If this hypothesis is true, then, it is possible that repetitive rTMS sessions may not be associated with a direct extension of rTMS- induced neglect changes from the sub-acute stage to the chronic stage.

Hence, in Chapter 5, I evaluated the rehabilitation potential of rTMS conducted within the first three months post stroke (sub-acute stage) on long term behavioural performance on visual neglect tasks (spatial and object neglect) at > 6 months post stroke (chronic stage). Specifically, I compared performance of sub-acute stroke patients randomly assigned to intervention and sham groups, on a battery of neuropsychological tests pre rTMS to < 1 month post and > 6 months post rTMS.

1.2.3 Rationale for investigating rTMS based modulation of neural activity in attention networks

The theoretical bases for the use of rTMS in neglect rehabilitation as well as studies with healthy controls demonstrate its potential to influence functional activity in attentional networks (see sections 1.2.1.1, 1.2.1.3). However, no study to date has investigated the neural changes underlying rTMS based neglect recovery in stroke patients.

Studies of patients who have spontaneously recovered from neglect provide a useful framework to understand the nature of changes in inter-hemispheric neuronal activity (section 1.2.3.1). Additionally, a brief review of current literature on neurological bases of neglect rehabilitation (section 1.2.3.2) demonstrates that there is need for further insight into the mechanisms of specific rehabilitation techniques in changing behaviour. Of the available studies, brain bases have been investigated in small- scale patient studies involving conventional rehabilitation (Pizzamiglio et al., 1998; Thimm, Fink, & Sturm, 2008), sustained attention and optokinetic training (Thimm et al., 2009; Thimm, Fink, Küst, Karbe, & Sturm, 2006) and prism adaptation (Luauté et al., 2006; Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013). The relative dearth of available knowledge of neural mechanisms underlying neglect rehabilitation, difficulty in generalizing findings on account of small and heterogeneous samples of patients included in these studies, along with lack of any previous investigation exploring the neural changes accompanying rTMS-induced benefits to neglect behaviour are factors that have motivated the current investigation.

1.2.3.1 Brain bases of spontaneous neglect recovery

Early case studies of neglect patients using imaging have shown that neglect recovery is associated with increased glucose metabolism and regional brain perfusion in both ipsilesional and contralesional hemispheres. Vallar et al. (1988) used Single Photon Emission Computerised Tomography (SPECT) to study if aphasia and neglect were associated with hypoperfusion of cortical areas distant from the subcortical lesions in their patient sample. Upon reassessment one to six months after stroke, spontaneous recovery of behavioural deficits in patients was associated with an improvement in cortical perfusion. Perani, Vallar, Paulesu, Alberoni, and Fazio (1993) used Positron Emission Tomography (PET) imaging and reported that a patient with a right hemisphere subcortical lesion and left neglect demonstrated hypometabolism in both ipsilesional and contralesional hemispheres in the acute stage. Follow-up at chronic stage 8 months later showed that the patient had recovered from neglect and there was a return of left hemisphere metabolic activity to normal and partial recovery of metabolic rate activity in the lesioned right hemisphere. In another study assessing recovery of neglect within the acute stage, reperfusion of dorsal frontoparietal areas were associated with improvements in spatial neglect while reperfusion of ventral occipito-temporal regions was linked to object neglect improvements three to five days post stroke (Khurshid et al., 2012).

fMRI studies of neglect recovery have shown that despite being structurally intact, the interhemispheric balance in some dorsal frontoparietal regions was imbalanced in acute neglect patients. With spontaneous neglect recovery, this abnormal pattern of activity was rebalanced in the chronic stage (Corbetta et al., 2005; He et al., 2007) thus lending support to Kinsbourne's (1974) Interhemispheric Rivalry Theory. Corbetta et al. (2005) conducted a study using functional imaging with 11 stroke patients at the acute (4 weeks post stroke) and chronic stage (~8 months post stroke) while performing the Posner task (Posner, Walker, Friedrich, & Rafal, 1984). At acute stage, patients showed hypoactivation of bilateral occipital, dorsolateral prefrontal cortex as well as right dorsal parietal regions. At chronic stage, spontaneous recovery in neglect correlated with increased activation in many bilateral regions. In the context of Kinsbourne's theory, they reported a 'push-pull' pattern of interhemispheric asymmetry in acute stage functional activity in the dorsal parietal cortex, i.e. intraparietal sulcus and superior parietal lobe which resolved at the chronic stage. Specifically, at the acute stage, the right dorsal parietal cortex was not active but strongly reactivated at the chronic stage, independent of ipsilesional or contralesional target presentation in the task. On the other hand, left dorsal parietal lobe activity was stronger at the acute than at the chronic stage.

Another fMRI study conducting an investigation of neglect recovery was performed by He et al. (2007) with 11 right frontoparietal stroke patients when performing the Posner task (Posner et al., 1984). They reported an interhemispheric imbalance in functional activity of the intraparietal sulcus at the acute stage (~4 weeks post stroke) and found that this abnormal activity had significantly rebalanced at the chronic stage (>6 months post stroke). At both stages, neglect patients' behavioural performance correlated with functional connectivity measures. Additionally, the researchers reported global impairment in functional connectivity in the ventral attention network at the acute stage. Although the task-evoked responses in the ventral network showed trends towards recovery in the chronic stage, these were not statistically significant. In the ventral attention network, task-evoked imbalance was seen in the interhemispheric activity of the supramarginal gyrus. However, unlike the dorsal intraparietal sulcus activity that recovered at the chronic stage, the supramaraginal gyrus activity did not show statistically significant recovery. Another important finding was that the degree of interhemispheric functional connectivity of the supramaraginal gyrus and the intraparietal sulcus both correlated with the disengagement deficit in the left visual field. Taken together, these findings suggested that successful reorienting of attention to neglect space requires interhemispheric co-ordination from the ventral parietal areas involved in target detection and dorsal parietal areas involved in attention shifting (Corbetta & Shulman, 2011; He et al., 2007).

Based on these studies, changes in inter-hemispheric functional activity were seen to accompany spontaneous recovery from neglect.

1.2.3.2 Brain bases of rehabilitation based neglect recovery

In investigating the effects of conventional rehabilitation using PET scans, Pizzamiglio et al. (1998) reported an increase in cerebral blood flow in ipsilesional right hemispheric areas (superior parietal cortex, precuneus) after eight weeks of conventional rehabilitation in three patients with left neglect. However, the lack of a control group and inadequate sample size limit the reliability and generalizability of these results. In another study, Thimm, Fink, and Sturm (2008) conducted fMRI with a small sample of four left neglect patients first at the acute stage (few weeks post stroke) and at the chronic stage post standard rehabilitation for a minimum of three months. As compared to the control group of six chronic neglect patients, all intervention group patients improved on most behavioural neglect tests post rehabilitation. In comparison to their spatial attention task-related functional activity at the acute stage, a significant increase was reported in many areas of the right hemisphere including middle frontal, inferior temporal, fusiform gyri and inferior parietal lobe. Additionally, the left hemisphere showed increase in cingulate and superior temporal gyri activity implying compensatory recruitment of contralesional areas in addition to reactivation of the ipsilesional attentional network. The researchers also reported an interhemispheric asymmetry in functional activity that showed rebalancing post rehabilitation; however the locus of this change in functional activity was the fusiform gyrus which has been shown to play a role in attention orienting in healthy controls (Hopfinger, Buonocore, & Mangun, 2000; Vandenberghe et al., 2000). No significant changes in functional activity were reported in the control group patients, although note that these patients' baseline and repeat scans were both obtained in the chronic stage unlike the intervention group (Thimm et al., 2008). Thus, the control group's scans could be used to control for the effect of inter-session fluctuations in functional activity, but could not be used to delineate the effects of spontaneous recovery and rehabilitation-related changes in intervention group's neural activity from acute to chronic stage.

Thimm, Fink, Küst, Karne & Sturm (2006) evaluated the role of a three week computerized phasic alertness training program (AIXTENT) in seven neglect patients. The patients showed improved alertness and neglect test performance at the short-term follow-up conducted 24 hours after training completion. On fMRI, these improvements were accompanied by a spatial attention task-related increase in ipsilesional activity in the frontal cortex, anterior cingulate cortex, precuneus, cuneus and angular gyrus as well as increased neural activity in the contralesional left frontal, anterior cingulate, middle occipital gyrus, precuneus and cuneus. Follow-up testing at four weeks post training showed that the behavioural improvements on neglect tasks had returned to baseline. Although neural activity had also declined to the level of the short term follow-up, some bilateral increases in neural activity in frontal cortex, right anterior cingulate cortex, angular gyrus and left temporo-parietal cortex remained. The researchers concluded that three weeks of alertness training has the potential to produce short term behavioural improvements and increase activity in both ipsilesional and contralesional areas involved in alertness and visuospatial attention.

Thimm, Fink, Küst, Karbe, Willmes & Sturm (2009) also used Optokinetic Stimulation (OKS) with seven chronic neglect patients and evaluated its behavioural and neural effects using the same treatment study design as the alertness training study (Thimm et al., 2006). Neglect performance improved in the short (24 hours post training) and long term (4 weeks post training) on behavioural tasks as compared to a three week baseline period with no training prior to trial onset. Using an fMRI spatial attention task, they found that these improvements were related to increase in ipsilesional activity in the middle frontal gyrus and precuneus and contralesional activity increase in the cingulate, angular, middle temporal gyri and the occipital cortex. When compared to results from their previous study described above (Thimm et al., 2006), bilateral activation of the precuneus was higher in patients who underwent OKS training; whereas AIXTENT alertness training produced higher bilateral activation in the frontal cortex. They suggested that this difference between the brain activation underlying the two techniques could be because OKS training focused on improving spatial attention whereas AIXTENT involved training of control of attention intensity (Thimm et al., 2009).

In another study that used a different type of rehabilitation, a single session of prism adaptation was used to rehabilitate neglect in seven left neglect patients; fMRI was conducted while they performed three spatial tasks on the same set of stimuli (bisection, visual search and memory). Their performance was compared to a control group without intervention. Behavioural improvements on neglect tasks were accompanied by increase in functional activity in bilateral parietal, frontal and occipital cortices during bisection. Activity increases were observed in the same bilateral areas as well as the right temporo-parietal junction for visual search. No such regions showed a significant increase during memory performance after prism adaptation (Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013). Thus, this study suggested that changes in neglect after prism adaptation were related to bilateral increases in attention networks involved in neglect.

Modulation of bilateral brain activity after a single session of prism adaptation was also shown in five neglect patients using PET imaging (Luauté et al., 2006). Participants' performance post prism adaptation improved on the Behavioural Inattention Test (BIT; Wilson, Cockburn, and Halligan, 1987) test battery and specifically in two cancellation sub-tests. This improvement in neglect performance was associated with increased cerebral blood flow while performing the Landmark task, requiring judgement of pre-bisected line length, during PET, as compared to a control condition where there was no intervention. Improvement in BIT was associated with increased blood flow in the right cerebellum, left thalamus, left temporo-occipital cortex, and decreased blood flow in right posterior parietal cortex and left medial temporal lobe. The researchers proposed that the cerebellum aids realignment of visuomotor co-ordinates after prism adaptation and cerebello-cortical connections aid in the modulation of cortical regions involved in spatial cognition.

In summary, although a wide range of variability exists even within the few studies reported, a broad consensus from neuroimaging data acquired post rehabilitation coincides with studies investigating spontaneous recovery of neglect, i.e. visual neglect at the acute pre-rehabilitation stage is associated with decreased functional activity in the right hemisphere's attentional networks. Post rehabilitation, all studies so far have reported a bilateral increase in functional activity in regions involved in both spatial and non-spatial attention.

It is possible that such activity changes in attention networks are mediated by white matter pathways. For instance, disconnections to corpus callosum and superior longitudinal fasciculus pathways have been found to be important predictors of neglect severity in chronic stroke patients (Lunven et al., 2015). Hence, intra-hemispheric increases in functional activity post rehabilitation may be related to improved structural integrity of white matter tracts including frontoparietal pathways such as the superior longitudinal fasciculus (Chechlacz, Gillebert, et al., 2015; Corbetta et al., 2015; Lunven et al., 2015) while bilateral increases in hemispheric activity may be related to the integrity of the corpus callosum fibres in facilitating interhemispheric communication and compensation (Lunven et al., 2015). Some emerging evidence suggests that improvements in motor and language functions post brain stimulation in stroke patients is associated with improved structural integrity of the corpus callosum, studied using diffusion tensor imaging (Allendorfer, Storrs, & Szaflarski, 2013; Hong et al., 2017). These results indicate a role for brain stimulation in modulating inter-hemispheric interactions that may contribute to the recovery of behavioural impairments post stroke.

Hence, in Chapter 6, I explored whether rTMS related changes in functional activity in the brain can explain neglect recovery in stroke patients. To this end, I studied changes *in functional activity pre and post offline rTMS in a sample of sub-acute and chronic neglect patients using fMRI.*

1.2.4 Rationale for identifying core cognitive abilities engaged in visual neglect

Another approach to neglect rehabilitation is retraining of cognitive components that have been suggested to participate in the syndrome (Ben-Yishay & Diller, 1993; Diller & Gordon, 1981). One example of this is the training of sustained attention deficits to improve spatial attention. Robertson, Tegnér, Tham, Lo, and Nimmo-Smith (1995) assessed the influence of training sustained attention to evaluate its effect on visual neglect amelioration. They trained eight chronic stroke patients with neglect on a self-alerting procedure to increase their phasic (moment-to-moment) alertness and sustained attention and found that with the training, patients improved on both previously untrained sustained attention (tone counting, vertical letter cancellation) and neglect measures (letter cancellation, Baking tray task) for a period ranging from one to fourteen days. No such improvement was seen in the two control tasks involving judging of line orientation and backward digit span. Several other studies have shown the potential of training tonic (generalized) and/or phasic (moment-to-moment) attention in rehabilitating visual neglect (DeGutis & Van Vleet, 2010; Robertson, Mattingley, Rorden, & Driver, 1998; Thimm et al., 2006; Van Vleet & DeGutis, 2013a).

Thus, given that the association between sustained attention and spatial attention processes can be used to rehabilitate neglect, it is possible that identifying other neglect-related cognitive domains may have similar potential. Some research has suggested that combining rehabilitation techniques in order to accommodate the multifaceted symptoms of neglect may have a higher potential for producing neglect related improvements

(Luaute´, Halligan, Rode, Rossetti, & Boisson, 2006; Saevarsson, Halsband, & Kristjansson, 2011). In fact, a recent longitudinal study with three chronic visual neglect patients showed that a single session of combined anodal transcranial direct current stimulation (tdcs) to the contralesional motor cortex and prism adaptation, resulted in a longer duration of neglect improvement (18-46 days) than prism adaptation on its own (O'Shea et al., 2017). This proof-of-principle study suggested that excitatory tdcs aimed at enhancing plasticity in the sensorimotor cortex was able to potentiate the prism adaptation after-effect to produce lasting and stable gains in visual neglect. Such an approach may be especially relevant given that most current research has reported short lasting and transient effects of cognitive rehabilitation on visual neglect (Azouvi, Jacquin-Courtois, & Luauté, 2017a; Bowen et al., 2013; Yang, Zhou, Chung, Li-Tsang, & Fong, 2013). While the heterogeneous nature of the patient sample may render the effectiveness of a unitary approach to cognitive rehabilitation of neglect inadequate to produce sustainable long term effects, another potential reason could be the lack of evidence based research to guide the combination of rehabilitation techniques to optimize neglect related benefits (Saevarsson et al., 2011).

Several spatial and non-spatial cognitive components are known to participate in visual neglect (e.g. Bartolomeo, Schotten, & Chica, 2012; Charras et al., 2012; Corbetta & Shulman, 2011; Husain & Rorden, 2003; Peru & Chelazzi, 2008) which may contribute to its heterogeneous presentation (Ferber & Karnath, 2001; Rorden, Fruhmann Berger, & Karnath, 2006; Toba et al., 2018). Some research has shown that different cognitive tests have variable sensitivity in capturing the various facets of the neglect syndrome and hence a battery of tests is recommended to assess neglect given its multifaceted nature (Azouvi et al., 2006; Ferber & Karnath, 2001). More recently, the multicomponent nature of neglect is being fractionated using sophisticated test paradigms in order to facilitate an understanding of the cognitive components underlying neglect and their relative importance in neglect manifestation (Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2014; Finke, Bublak, Dose, Müller, & Schneider, 2006; Toba et al., 2018).

One other potential method to identify the cognitive components that may be recruited in neglect is to assess the relationship between cognitive tests intended to assess different disorders, but that may draw upon similar cognitive mechanisms. Neglect has been shown to co-occur with other visuospatial disorders such as extinction (Liu et al., 2011; Maguire & Ogden, 2002; Vuilleumier & Rafal, 2000) and constructional apraxia (Hier, Mondlock, & Caplan, 1983; Linden, Samuelsson, Skoog, & Blomstrand, 2005; Maguire & Ogden, 2002). It has also been reported that each of these disorders frequently occurs after lesions to the right parietal cortex (e.g. Chechlacz et al., 2012, 2013, 2014; Chen et al., 2016; Gillebert et al., 2011; Hier et al., 1983; Medina et al., 2009) which may play a role in affecting common cognitive processes served by this region. Thus, scores extracted from tasks (e.g. double simultaneous stimulation, complex figure copy) that may be representative of select cognitive processes engaged in these visuospatial disorders (e.g. spatial attention, selective attention to features in space etc.) may be helpful in providing insight into whether some of these cognitive mechanisms may be shared by these disorders and neglect.

It may also be important to consider the role of these shared cognitive processes separately for spatial and object neglect because (i) several studies assert that the two sub-types of visual neglect are distinct syndromes (Heinke & Humphreys, 2003; Humphreys, 1998; Humphreys & Riddoch, 1994; Rorden et al., 2012) with separate underlying anatomical correlates (Chechlacz et al., 2010; Medina et al., 2009; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010) and, ii) there is a relative dearth of research involving associations between object neglect and its relationship with other cognitive tests/domains.

1.2.4.1 Overview of cognitive components that may be shared between tests

Spatial attention biases are thought to underlie both spatial neglect and extinction (e.g. Heilman & Valenstein, 1979; Hillis et al., 2006; Karnath, 1988; Kinsbourne, 1970) with potentially shared deficits relating to competition for limited attention resources (de Haan, Karnath, & Driver, 2012; Desimone & Duncan, 1995; Duncan, Humphreys, & Ward, 1997; Mattingley, Driver, Beschin, & Robertson, 1997) or difficulty disengaging attention from ipsilesional space (Posner, Walker, Friedrich, & Rafal, 1984).

Spatial neglect is frequently tested using cancellation, line bisection, figure copying/ drawing tasks in which neglect patients often ignore stimuli on the contralesional side of space, bisect (long) lines ipsilesionally and/ or omit or distort contralesional features of figures copied/ drawn (e.g. Adair & Barrett, 2008; Danckert & Ferber, 2006; Li & Malhotra, 2015; Parton, Malhotra, & Husain, 2004). In addition to contralesional deficits indicating attention orienting impairments, patients are also seen to have difficulties in disengaging attention from ipsilesional space. Some examples in support of the spatial attention deficits observed in neglect include: neglect patients tended to start their visual search on cancellation tasks from the ipsilesional side of space (Azouvi et al., 2002; Mark & Heilman, 1997); increase in number of ipsilesional distracters in a cancellation task tended to worsen contralesional target detection (Kaplan et al., 1991) while erasing stimuli instead of cancelling them improved cancellation performance presumably due to diminished influence of ipsilesional 'attention capturing' stimuli (Mark, Kooistra, & Heilman, 1988); drawing performance on contralesional side improved when drawing with eyes closed rather than with eyes open (Chokron, Colliot, & Bartolomeo, 2004); line bisection ipsilesional bias has been linked to perceptual competition between left and right line segments (Anderson, 1996; Marshall & Halligan, 1990; Urbanski & Bartolomeo, 2008). Similar ipsilesional bias has also been observed in extinction patients, but only under conditions of double simultaneous stimulation, i.e. when stimuli are presented to both sides of space, the patient extinguishes the response to contralesional stimulus in favour of the ipsilesional stimulus (Bender & Teuber, 1942; Wortis, Bender, & Teuber, 1948).

Another cognitive component that may be shared based on cancellation and complex figure copy task performance is the ability *to divide attention to selectively process local or global features in space* (Chechlacz et al., 2014; Chechlacz, Mantini, Gillebert, & Humphreys, 2015; Christie et al., 2012; Delis, Robertson, & Efron, 1986; Doricchi & Incoccia, 1998; Halligan & Marshall, 1994; Peru & Chelazzi, 2008). Attention has been shown to be deployed selectively focussed on a single object or features (locally) or distributed over the scene as a whole (globally), together contributing to a holistic representation of space (Tresiman, 2004). Thus focussed attention can facilitate binding of object features and object recognition while distributed attention can facilitate grouping of objects, identifying global shape and gist of the global scene. (Tresiman, 2004). Patients with neglect are frequently biased to attending to local features in space at the expense of ignoring the global features (Bultitude & Woods, 2010; Delis et al., 1986; Doricchi & Incoccia, 1998; Halligan & Marshall, 1994).

One other cognitive process that may be shared based on task performance on cancellation and complex figure copy tests is the *spatial coding of objects in space* which may be indicative of the integrity of the representation of space and could indicate efficacy of spatial remapping in neglect and constructional apraxia (Danckert & Ferber, 2006; Pisella & Mattingley, 2004). Spatial remapping ensures visual integration of successive retinal images over time and space by continuously updating representations of stimulus location in terms of distance and direction over successive saccades (Pisella & Mattingley, 2004). Using double-step saccades, both Duhamel et al. (1992) and Heide, Blankenburg, Zimmermann, and Kömpf (1995) showed that when attention was cued such that an initial saccade was required to be made to contralesional space, neglect patients' second saccade was erroneous and they did not acquire the target in the ipsilesional field. Pissela & Mattingley (2004) proposed that neglect is a combination of ipsilesional attentional bias and spatial remapping deficits. Specifically, they suggested that directing attention to the contralesional field would cause difficulties in remapping the entire visual field whereas directing attention ipsilesionally would only cause problems for spatial remapping of the contralesional field. Spatial remapping mechanisms may also be important for drawing and copying tasks where information needs to be retained and transferred across fixations. Poor spatial remapping of relations between the elements of the drawing would explain the disorganised drawings observed in constructional apraxia and neglect patients (Pisella & Mattingley, 2004).

Lastly, several studies have also shown an association between *sustained attention* and neglect at both sub-acute and chronic stages (Hjaltason, Tegnér, Tham, Levander, & Ericson, 1996; Maguire & Ogden, 2002; Samuelsson et al., 1998) with sustained attention impairments shown to predict impairments on 2 out of 3 neglect tests in chronic stroke patients (Hjaltason et al., 1996). As discussed above, this relationship between sustained and spatial attention has also been exploited in rehabilitation efforts where training sustained attention has shown improvements in spatial neglect measures

(DeGutis & Van Vleet, 2010; Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995; Thimm, Fink, Küst, Karbe, & Sturm, 2006; Van Vleet & DeGutis, 2013a).

1.2.4.2 Heterogeneous patient and lesion profile that may modulate neglect occurrence

It must be noted that visual neglect is a heterogeneous disorder whose presence can be modulated by factors other than cognitive abilities recruited in the syndrome, such as individual differences based on patient's demographic (e.g. age, education) and stroke related characteristics (e.g. lesion location, stroke type) (e.g. Cassidy, Bruce, Lewis, & Gray, 1999; Corbetta et al., 2015; Gottesman et al., 2008; Husain & Kennard, 1996; Karnath, Rennig, Johannsen, & Rorden, 2011; Ringman, Saver, Woolson, Clarke, & Adams, 2004). In two large scale studies with 200+ acute stroke patients, increasing age, was related to increased risk of neglect (Gottesman et al., 2008; Ringman, Saver, Woolson, Clarke, & Adams, 2004). Other factors that may affect presence and severity of neglect could be indicative of premorbid brain (e.g. age, history of strokes, atrophy etc.) as well as cognitive reserve (e.g. IQ, education, occupation etc.) (Umarova, 2017). In terms of lesion location, neglect has been associated with lesions to various locations including the right inferior parietal lobe (Chechlacz et al., 2010; Corbetta et al., 2015; Karnath, Rennig, Johannsen, & Rorden, 2011; Mort et al., 2003; Rengachary et al., 2011; Vallar & Perani, 1986), frontal cortices (Committeri et al., 2007; Husain & Kennard, 1996; Rengachary et al., 2011) and superior and middle temporal cortex and insula (Buxbaum et al., 2004; Chechlacz et al., 2010; Committeri et al., 2007; Karnath, Berger, Küker, & Rorden, 2004; Karnath, Ferber, & Himmelbach, 2001; Karnath et al., 2011). Additionally, the lesion size and degree of premorbid cortical atrophy has been associated with severity of neglect manifestation (Levine, Warach, Benowitz, &

Calvanio, 1986). Thus, various non-cognitive factors may also influence neglect occurrence and presentation.

Similarly, individual differences may modulate co-occurrence of neglect, extinction, constructional apraxia and sustained attention disorders. To elaborate, despite soe studies that report co-occurrence of these deficits in patients that may indicate a role for shared cognitive mechanisms and involvement of common anatomical substrates in the parietal lobe (e.g. Battelli, Alvarez, Carlson, & Pascual-Leone, 2009; Cazzoli, Wurtz, Müri, Hess, & Nyffeler, 2009; Dambeck et al., 2006; Farah, Wong, Monheit, & Morrow, 1989; Johannsen et al., 1997, Lamb, Robertson, & Knight, 1989; Pardo, Fox, & Raichle, 1991; Pisella & Mattingley, 2004; Posner et al., 1984; Robertson et al., 1988; Treisman, 2004), these disorders do not always co-occur and can dissociate (Barbieri & De Renzi, 1989; Farné et al., 2004; Luukkainen-markkula & Tarkka, 2014; Vallar & Perani, 1986; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994; Vossel et al., 2011). Such dissociations could be related to the effect of individual differences between patient profiles in modulating cognitive mechanisms involved in these disorders. For example, age (Oken, Kishiyama, & Kaye, 1994), sex (Pletzer, Scheuringer, & Scherndl, 2017; Roalf, Lowery, & Turetsky, 2006) and mood (Gasper & Clore, 2002; Huntsinger, Clore, & Bar-Anan, 2010) have been known to modulate global/ local processing in healthy controls. Additionally, it is unclear whether the manifestation of local and global processing deficits is contingent upon lesioned hemisphere. While most studies implicate right hemisphere dominance in global processing of overall form and left hemisphere dominance in local processing of features of hierarchical visual objects (Fink et al., 1996; Lamb et al., 1990; Robertson et al., 1988), other research has shown that local processing deficits can occur independent of hemisphere of stroke (Peru & Chelazzi, 2008). In fact, some studies suggest that global processing deficits in neglect patients may be subject to factors such as task demands (Doricchi & Incoccia, 1998) and severity of neglect (Peru & Chelazzi, 2008). Additionally, a majority of the patient studies that show a relation between sustained attention and spatial attention are based on small samples of predominantly right hemisphere injury patients (Manly et al., 2003; Pardo, Fox, & Raichle, 1991; Posner, Inhoff, Friedrich, & Cohen, 1987; Posner & Petersen, 1990; Rueckert & Grafman, 1996; Thakral & Slotnick, 2009; Vallar, 1998; Whitehead, 1991; Wilkins, Shallice, & McCarthy, 1987).

Hence, to delineate cognitive components that can be considered *fundamental* to neglect, their importance in predicting neglect occurrence must be assessed independently of the influence of other important demographic (age, gender, education) and stroke related factors (stroke type, lesion side, lesion size, mood, orientation post injury) that are also known to impact neglect.

Hence, in Chapter 7, I analysed pre-collected large scale patient data from the Birmingham University Cognitive Screen (BUCS) trial conducted between 2006 and 2011 (Principal Investigator: Prof Glyn Humphreys) to explore if after accounting for individual differences in patients' age, sex, education, stroke type, lesion side, lesion size, mood and orientation post stroke, measures depicting shared cognitive components obtained from different neuropsychological tests used in the BCoS test battery can predict spatial and object neglect in a heterogeneous sample of patients.

1.3 Summary of research aims for thesis

Thus, in this thesis, I have focused on two areas pertaining to neglect: assessment of representational neglect and recovery from visual neglect. The **main aims** for each chapter are provided below:

Chapter 2 (Methods): To provide an overview of rTMS and fMRI methods that were used in the thesis along with information on visual neglect and sustained attention tests as well as statistical analyses techniques that were used in multiple chapters of this thesis.

Chapter 3: To create and pilot two new methods for RN assessment (The Shopping Mall task, Clocks Cueing task) designed to overcome limitations of previous task measures and assess the importance of ancillary cognitive mechanisms in RN.

Chapter 4: To identify dissociations in RN based on stimuli to be represented (topological, non-topological) and time of acquisition of stimuli (pre-stroke, post-stroke) in chronic stroke patients using the methods created in Chapter 3. A second aim was to characterise these patients based on their lesion location and task-related cognitive abilities to identify potential commonalities and differences in the manifestation of sub-types of RN.

Chapter 5: To assess the short (< 1 month) and long-term (> 6 months) efficacy of 1 Hz offline rTMS to the inferior parietal lobe in spatial and object neglect recovery in a sample of sub-acute stroke patients.

Chapter 6: To compare brain activity pre and post rTMS in a sample of visual neglect patients using fMRI to explore if changes in functional activity can explain neglect recovery.

Chapter 7: To identify using a large sample of pre-collected patient data, if after accounting for individual differences in demographic and stroke related factors, cognitive performance indicative of spatial attention, selective attention to features in space, spatial coding of features in space and sustained attention can predict spatial and/or object neglect at the sub-acute stage.

Chapter 8: Provides a discussion of key findings across studies, limitations and directions for future research.

CHAPTER 2 - Methods

This chapter includes details of the neuroimaging methods, cognitive tests and statistical methods employed in this thesis.

Section 2.1 discusses two neuroimaging methods, repetitive Transcranial magnetic stimulation (rTMS) and functional Magnetic Resonance Imaging (fMRI), that have been used in Chapters 5 and 6 respectively.

Section 2.2 describes the tests of visual neglect and sustained attention used in Chapters 4-7. Note that other cognitive measures that were chapter-specific are described in the respective chapter's Methods section.

Section 2.3 provides a brief description and list of assumptions that were tested for the statistical methods employed in this thesis.

2.1 Neuroimaging methods

2.1.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

2.1.1.1 Principles underlying rTMS

rTMS is a neuromodulation technique aimed at changing cortical activity in target areas of the brain. The equipment consists of a high current pulse generator, using which short bursts of electrical currents delivered through a coil. The large currents that flow through the coil can have a monophasic or biphasic pulse configuration; while the monophasic current has a strong initial current but a weakened return current, the biphasic pulse configuration produces both an initial and reversed current flow. Thus the monophasic pulse only affects current flow in the stimulated brain in the first phase while the biphasic pulse produces physiologically significant, bidirectional current fluxes in the stimulated brain. These current pulses produce a fast changing, high intensity magnetic field that passes unattenuated through the scalp into the cortex and induces perpendicular currents in the brain in keeping with Faraday's law of electromagnetic induction. The peak magnetic field generated is in the range of 1-2 Tesla and the currents produced are strong enough to depolarize or hyperpolarize neurons, thus influencing cortical excitability in neural networks (Rossini et al., 2015).

Many factors influence the action of current density such as the type and orientation of the coil, pattern of stimulation (conventional/ patterned) and frequency of stimulation (high/ low). For example, round coils are more effective for stimulating larger radius of regions whereas 'figure of eight' coils are intended for focal stimulation and can penetrate up to 1.5-3 cms beneath the scalp (Lefaucheur et al., 2014; Rossi et al., 2009; Rossini et al., 2015; Walsh & Rushworth, 1998).

Conventional stimulation also termed repetitive TMS (rTMS) has been used in the current study (Chapters 5 and 6). Conventional rTMS involves the continuous delivery of trains of stimuli at low (<1Hz) frequency to inhibit cortical activity, or at high (>3Hz) frequency to induce excitatory cortical activity (Rossini et al., 2015). Patterned rTMS refers to the application of repetitive trains of stimulation in short bursts at high frequency interspersed with short intervals of no stimulation. Theta burst stimulation (TBS) is an example of patterned rTMS where short bursts of 50 Hz rTMS repeated in the theta range of 5 Hz are used in a continuous train (cTBS) to inhibit cortical excitability or intermittent train (iTBS) to excite cortical activity (Huang et al., 2005; Rossini et al., 2015).

rTMS based neuromodulation has the ability to outlast the actual period of stimulation ranging from minutes to months (Chervyakov et al., 2015; Lefaucheur et al., 2014; Rossi et al., 2009; Walsh & Rushworth, 1998). This property makes this method amenable to therapeutic intervention of neurocognitive disorders such as in the case of visual neglect and is of relevance to the intervention study in this thesis (Chapters 5, 6). In the context of visual neglect rehabilitation, most studies have used inhibitory rTMS to the contralesional parietal lobe to produce improvements in neglect (See Chapter 1, Table 1.1. for review of studies). The optimal parameters required to extend the duration of stimulation related after effects are not clear, although a relation between cumulative rTMS sessions and metaplastic processes in the brain has been implicated (Abraham, 2008; Cassidy et al., 2014; Cohen et al., 2010; Valero-Cabré, Pascual-Leone, & Rushmore, 2008). For a more detailed discussion on this topic, refer to Chapter 5, section 5.4.

Since the motor cortex allows for an apparent measurement of each individual's unique threshold of cortical activation, motor threshold is frequently used in studies to individualize intensity of rTMS (Lefaucheur et al., 2014; Rossini et al., 2015). This threshold is uniquely identified for each person by first identifying the hotspot in their motor cortex through either anatomical/ functional localization. Stimulation intensity on this location is increased by 5% at each step until motor evoked potentials using electromyography of >50µv peak- to- peak amplitudes or motor twitches, usually in the contralateral first dorsal interosseous are observed in five out of ten stimuli trains (Rossini et al., 2015). Based on a pre-determined percentage of this motor threshold, trains of stimuli are given at high frequency to enhance long term potentiation-like synaptic activity or low frequency to inhibit synaptic activity due to long-term depression-like mechanisms (Cassidy, Gillick, & Carey, 2014; Chen et al., 1997; Chervyakov, Chernyavsky, Sinitsyn, & Piradov, 2015; Hallett, 2007).

In order to determine the location for cortical stimulation, given the relatively consistent relationship between scalp locations and underlying brain areas, the 10-20 Electroencephalography (EEG) system (American Soc. EEG, 1991) is often used. Electrode positions P3/P4 (left/ right intraparietal sulcus; Herwig, Satrapi, & Schönfeldt-Lecuona, 2003; Homan, Herman, & Purdy, 1987; Nyffeler, Cazzoli, Hess, & Müri, 2009; Sack & Linden, 2003) or P5/P6 (left/right angular gyrus; Brighina et al., 2003; Hammond, 2008; Oliveri et al., 2001) are usually chosen in rTMS based rehabilitation studies of visual neglect (see Chapter 1, Table 1.1). Since the EEG based localisation method cannot account for inter- and intra-individual variabilities, some studies perform real time monitoring of coil position using stereotaxic neuro-navigation, to improve accuracy (Rossini et al., 2015).

2.1.1.2 Brief evaluation of rTMS

While other neuroimaging tools such as Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) study correlations between neural functioning and behaviour, TMS is able to explore this relationship in a more direct manner (Bolognini & Ro, 2010). By inclusion of a control condition in interventional studies involving sham stimulation of the target region using a sham coil or real stimulation of a non-target brain area, the efficacy of rTMS in influencing cortical activity in the targeted region can be better evaluated (e.g. Kim et al., 2010, Koch et al., 2012, Cazzoli et al., 2012, Fu et al., 2015).

One of the advantages of rTMS is based on its potential to induce ‘neuronal noise’ (online interference) in targeted brain regions that help to shed light on neural correlates underlying spatial attention (e.g. Bjoertomt, Cowey, & Walsh, 2002; Fierro et al., 2000; Lee et al., 2013; Oliveri et al., 2001). For example, rTMS to the right parietal cortex in healthy controls has shown to elicit neglect like behaviour when performing visuospatial tasks. This effect has been shown using the Landmark task requiring judgements on pre-bisected lines as well as in visual exploration and target detection paradigms (Bjoertomt, Cowey, & Walsh, 2002; Ellison, Schindler, Pattison, & Milner, 2004; Fierro et al., 2000; Hilgetag, Théoret, & Pascual-leone, 2001; Muggleton et al., 2006; Nyffeler et al., 2008; Rushworth, Ellison, & Walsh, 2001; Thut, Nietzel, & Pascual-Leone, 2005). Thus, TMS with healthy controls has been used as a tool to create 'virtual lesions' to study causal relationships between targeted regions and behavioural performance as well as changes in functional brain activity during cognitive tasks (e.g. Battelli, Alvarez, Carlson, & Pascual-Leone, 2009; Hung, Driver, & Walsh, 2005; Nyffeler et al., 2008; Ruff, Driver, & Bestmann, 2009). Use of TMS in conjunction with other neuroimaging methods has helped to inform about inter- and intra- hemispheric connectivity in the brain in relation to behaviour (e.g. Cazzoli & Chechlacz, 2017; Petitet, Noonan, Bridge, Reilly, & Shea, 2015; Plow et al., 2014).

The main shortcomings of this technique are in relation to exclusion of participants with contraindications (e.g. epilepsy, migraine, pacemaker, presence of metal or implants close to the head etc.) and some documented instances of transient side effects (e.g. seizures, headaches, syncope, localized pain) (Rossi et al., 2009). Additionally, although rTMS provides the opportunity to non-invasively study the effects of focal, temporary 'virtual lesions' on brain function (Pascual-Leone, Bartres-Faz, & Keenan, 1999; Ruff, Driver, & Bestmann, 2009), this may preclude study of mechanisms associated with real lesions such as diaschisis and reorganization over time (Walsh & Cowey, 2000).

2.1.2 Functional magnetic resonance imaging (fMRI)

2.1.2.1 Principles underlying fMRI

fMRI is a specialized type of Magnetic resonance imaging (MRI) which allows an indirect measurement of metabolic activity in the brain. Protons in hydrogen molecules possess 'spin' on account of nuclear magnetic resonance. When these protons that are contained abundantly in the human body are placed within a magnetic field such as the MRI scanner bore, they precess around an axis resulting in a net (longitudinal) magnetization that is parallel to the magnetic field. Radiofrequency coils that target energy at the hydrogen atom nuclei's resonant frequency (Larmor frequency) excite the nuclei which converts longitudinal intro transverse magnetization. Removal of this energy at resonant frequency leads to relaxation of the nuclei's spin and return to longitudinal magnetization. Pulse sequences that target recovery of longitudinal magnetization (T_1 relaxation) or decay of transverse magnetization (T_2 relaxation) can be used to obtain images that are specific to properties of brain tissue. Endogenous contrasts are used to delineate tissue properties by varying repetition time (TR, excitation time between longitudinal pulses) and excitation time (TE, time interval between excitation and data acquisition). Gradient magnetic coils are used to cause nuclei at different spatial locations in the brain to spin at different rates. Three dimensional images are acquired by selecting a slice of the brain and applying gradients for spatial and frequency encoding (Huetell, Song & McCarthy, 2009; Logothetis & Wandell, 2004).

Functional images are obtained based on hemodynamic (blood-related) processes in the brain. Any neuronal activity in the brain requires supply of blood to provide energy for maintenance and restoration of action potentials. The Blood Oxygen Level Dependent (BOLD) signal (Ogawa, Lee, Kay, & Tank, 1990) works on the principle of neurovascular coupling and measures changes in inhomogeneity of the magnetic field that are related to changes in the level of oxygen in the blood. An increase in neural activity in the brain (e.g. in response to a cognitively demanding task) results in an initial decrease in the BOLD signal since the active neurons use oxygen from the blood thereby increasing the amount of deoxygenated blood in these regions. Deoxygenated blood has paramagnetic properties which results in a rapid decay of transverse magnetization. However, the deoxygenated blood is displaced by diamagnetic oxygenated blood resulting in continued support for the active neural tissues. This restores uniformity in the local magnetic environment amounting to an overall increase in BOLD signal from the tissue. When the signal finally decays, it returns to baseline after a small undershoot. This function of the BOLD signal against time, in response to changes in neural activity, is known as the hemodynamic response function and forms the basis of image formation in fMRI (de Haan, 2006; Huetell et al., 2009; Logothetis & Wandell, 2004).

Thus, task-evoked changes in functional activity are frequently used in neuroscientific experiments to inform underlying neural processes. In task-based fMRI studies, an experimental condition of interest is contrasted with a control condition using block designs or jittered event related designs. The acquired fMRI data is pre-processed in order to remove artifacts and improve signal to noise ratio (e.g. using slice timing correction, motion correction, spatial smoothing, temporal filtering etc.; for details, see Chapter 6, section 6.3.2), normalized and analysed using the general linear model to obtain statistical maps of brain activation for contrasts of interest.

2.1.2.2 Brief evaluation of fMRI

fMRI is a safe and non-invasive method to study brain activation. It has a relatively high spatial resolution since functional images are mapped to high resolution structural images (Lindquist, 2008). However, its temporal resolution is relatively poor given that hemodynamic BOLD response is slower than neural activity (Glover, 2011; Lindquist, 2008; Huetell et al., 2009). Additionally, those with metallic implants, claustrophobia and other contraindications to fMRI cannot be studied using this method. This is an especially relevant limiting factor in studies involving elderly patients who frequently have implants such as stents, aneurism clips, pacemakers, metallic plates, screws etc. that preclude them from being scanned. For studies with elderly patients such as in this thesis, the task selected for fMRI should be adapted to suit the patient population (Price, Crinion, & Friston, 2006). Additionally, the structural pathology associated with the patient's brain injury may need accommodation during pre-processing such as by constraining non- linear transformations during spatial normalization to prevent distortion of intact tissue or by increasing spatial smoothing (Price et al., 2006).

Both rTMS and fMRI have made valuable contributions to advancing cognitive neuroscience even as they undergo further methodological inquiry and refinement. Chapter 5 uses offline inhibitory rTMS to explore its short and long term effects on visual neglect in sub-acute stroke patients while Chapter 6 uses task-based fMRI to investigate neural changes in the brain as a function of this offline rTMS in a subset of the patients.

2.2 Cognitive screening and behavioural measures

2.2.1 Visual neglect measures

2.2.1.1 Cancellation test

The cancellation tests for spatial and object neglect were extracted from the Birmingham Cognitive Screen (BCoS) (Humphreys et al., 2012) for Chapter 7 and from the Oxford Cognitive Screen (OCS) (Demeyere et al., 2015) for Chapters 5 and 6. Both cancellation tests were similar with the key differences being in the shapes used in the layout ('apples' in BCoS, 'hearts' in OCS) and the time allowed for cancellation (5 minutes in BCoS, 3 minutes in OCS).

The layout described here is for the BCoS apples cancellation test (Figure 2.1); this layout is identical for the OCS Hearts Cancellation test barring the different shapes. In this test, participants were presented with an A4 sheet in landscape orientation at midline. The sheet had 50 target apples to be cancelled spread over 5 invisible columns (one column in the middle and two each to the left and right of the middle column). The sheet was also divided in two equal halves by an invisible horizontal line such that each column was further divided into two. Each column contained ten full apples (5 each in the top and bottom half of the sheet) and ten distracter apples that were incomplete to the left and right sides respectively ('bitten' apples/'broken hearts' in OCS; distributed as 5 left and 5 right bitten apples in the top and bottom halves respectively, of each column). Thus, 50 full apples and 100 distracter apples (50 left bitten, 50 right bitten) were pseudorandomly distributed across the sheet. The participant's task was to cancel as many full apples as possible within the given time limit as per the test used. Prior to the task, they were given up to two practice trials to ensure their understanding of the task instructions. The task was discontinued if participants did not respond during the practice trials.

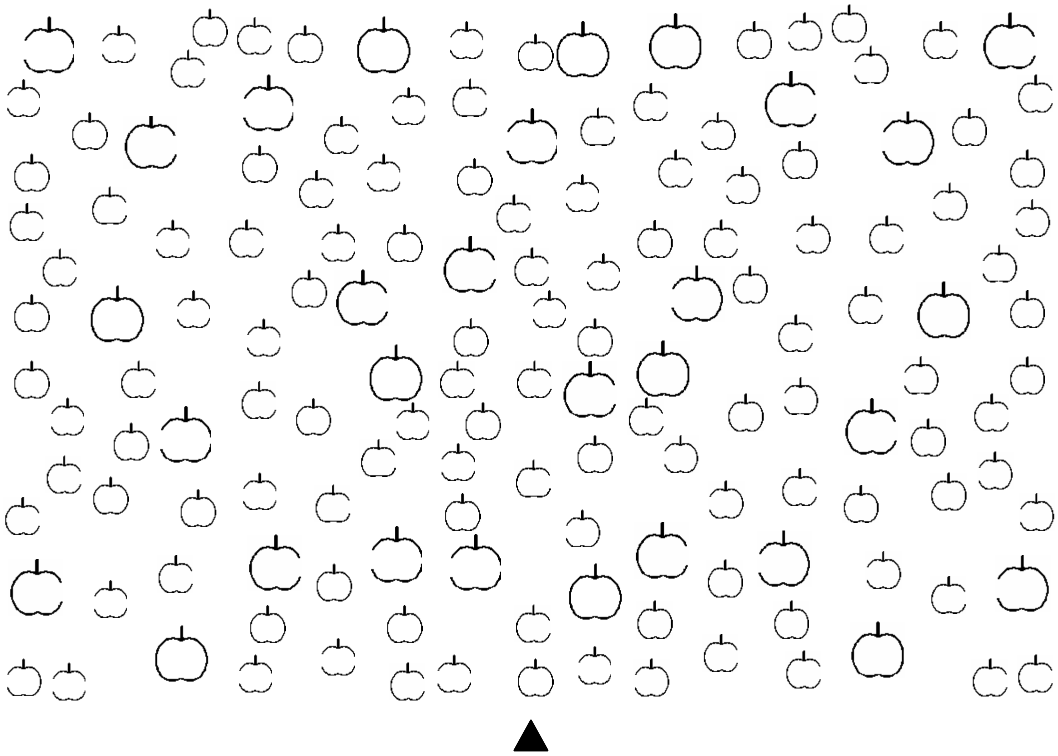

Figure 2.1. BCoS Apple Cancellation Task

This test of neglect assessment was presented to participants at midline (indicated by the black triangle at the bottom of the sheet). They were asked to cancel as many full apples as they could within a maximum time limit of 5 minutes. Spatial neglect was calculated by assessing whether they missed targets predominantly on one side of the page and object neglect was measured by assessing the number of false positive responses made by cancelling left or right sided bitten apples.

Spatial asymmetry was calculated by subtracting number of target apples cancelled on the two left columns from the two right columns of the sheet. Positive scores indicated that participants cancelled more targets on the right side of the midline than left. Object asymmetry was calculated by subtracting number of right-sided bitten apples from left sided bitten apples. Again, a positive score indicated more left-sided bitten apple distracters cancelled than right. Thus, for both spatial and object neglect, a *positive* score exceeding cut-offs was indicative of *left-sided* spatial and/or object neglect respectively.

Spatial asymmetry = Number of targets cancelled in right columns – left columns

Object asymmetry = Incorrectly cancelled left distracter – right distracter shapes

For spatial neglect, the BCoS cut-offs were age-based on < 5th percentile or > 95th percentile: <-2 or >2 (≤64 years) and <-2 or >3 (65-74 and ≥75 years). For object neglect, the cut-offs were: < -1 or > 1 across all age-ranges. For OCS cancellation, cut-offs were based on 140 controls, but were not broken down according to age (Spatial neglect: scores <-2 or >3; Object neglect: scores < 0 or > 0).

In Chapter 4, Centre of Cancellation (CoC, Binder, Marshall, Lazar, Benjamin, & Mohr, 1992; Rorden & Karnath, 2010) was also extracted based on cancellation performance on the OCS Hearts Cancellation. Note that CoC, a measure of direction and severity of neglect, captures an attentional gradient rather than a binary classification of neglect as left or right. It is the average horizontal position of all the cancelled targets calculated using a computer program and standardized such that scores approaching -1 indicate right-sided neglect whereas scores approaching +1 indicate left-sided neglect (Rorden & Karnath, 2010). The computer program is available from

http://www.mccauslandcenter.sc.edu/crnl/tools/cancel.

2.2.1.2 Line Bisection test

This test was adapted from the Behavioural Inattention Test (Wilson et al., 1987).

Participants were presented with lines of varying lengths on a horizontal A4 sheet. Each line was presented one at a time and the participant was instructed to bisect the line into two equal halves. A total of eighteen lines were used, six each of long (16.5 cm), medium (8 cm) and short (1.8 cm) lengths. Of these, placement of three long, three medium and three short lines was biased to the left side of the midline by two cm and the remaining lines' placement was biased to the right side of the midline by two cm. Each sheet was presented to the participant at midline. Distances from the left of each line to marked and actual midpoints were used to calculate deviation as follows:

$$\textit{Deviation} = \frac{\textit{marked left side distance - true half length}}{\textit{true half length}}$$

A score of -1 indicated maximum leftward deviation and a score of +1 indicated maximum rightward deviation.

2.2.1.3 Neglect-specific Activities of Daily Living (ADL)

In this test created by Eschenbeck et al. (2010), participants were administered eight standardized ADL tasks to be performed in front of the examiner. The tasks assessed personal neglect (apply face cream, comb hair), peri-personal neglect (copy an address, dial a telephone number, fill out a form, assemble a tray, count money from a set of coins) and extra-personal neglect (read time from an analogue clock).

Seven of the eight tasks had two scoring criteria to grade neglect severity. For use in this thesis, the scoring guidelines from the original study have been reversed for ease of interpretation, i.e. a higher score indicates better performance in the task. Thus, neglect-specific scoring criteria were used, wherein successful task completion was scored as 1, failure on one of the two criteria required for task completion (e.g.: locating a clock in contralesional space) was classified as mild neglect with a score of 0.5 and failing both criteria (e.g. locating a clock in contralesional space *and* identifying the position of the contralesional clock hand) implied severe neglect on the task with a score of 0. Total scores on the task were calculated, with a maximum score of 8 implying perfect performance.

2.2.2 Sustained attention testing

Sustained attention was measured using the BCoS Auditory Attention task (Humphreys et al., 2012). Participants were presented a pre-recorded set of words lasting for a period of 3 minutes. The word list consisted of six words randomly intermixed and presented nine times each. They were informed that three of the words were target words (‘no’, ‘hello’, ‘please’) that should be responded to by tapping the table whilst ignoring three other distracter words (‘yes, ‘goodbye’, ‘thanks’). The words were presented in three blocks of 18 words each. Each word was preceded an equal number of times by a silent gap of 2, 3 or 4 seconds. Participants were provided with three opportunities to practice the target words and also asked to recall the target and distracter words at the end of the task. The task was discontinued if participants could not recall at least one of the target words after all three practice trials or if made more than 8 errors in blocks one or two.

Scores from the Sustained Attention Index which was calculated by subtracting the number of correct responses in block 3 from block 1. Thus, the most severe impairment in sustained attention would be indicated by a score of 18 if all targets were accurately detected in block 1 while none were accurately responded to in block 3. The cut-off scores were: > 1 (for both ≤ 64 years and 65-74 years) and > 2 for (≥ 75 years).

2.3 Statistical analyses

Guidance for statistical analyses and assumption testing was obtained from Field (2009).

2.3.1 Correlations

Pearson’s product moment correlation (*r*) was used to identify if a linear relationship existed between two variables. This correlation was conducted when the variables in question were two paired continuous variables (ratio/ interval level) which had a linear relationship between them. Linearity of relationship was ascertained by visual inspection using a scatter plot. The scatter plot was also used to identify outliers and a decision to include/ exclude outliers was made in each case after data inspection. The assumption of normality for the data was determined using the Shapiro-Wilk test (Shapiro & Wilk, 1965). In Chapter 7, the **Point biserial correlation (r_{pb})** which is a special case of the Pearson's correlation involving pairs of one continuous variable and one nominal dichotomous variable (e.g. neglect: present/ absent) was used.

If the assumptions of normality was not met and/ or the data was ordinal, **Spearman's correlation (r_s)** was used. This test involved assigning a rank to the values in the dataset and calculating a Pearson's correlation on the ranked data. Spearman's correlation (r_s) was used when the two paired continuous/ ordinal variables being tested were not normally distributed.

For Pearson's and Spearman's correlations, the outcome '*r*' value obtained was used to measure the strength and direction of the relationship between the two variables, where the sign (+/-) depicts direction of the relationship and value depicted the effect size. Thus, *r* could range between -1 and +1, with -1 indicating a perfect negative linear relationship, 0 indicating lack of association between the variables and +1 indicating a perfect positive linear relationship. Note that for the point biserial correlation, the sign of the value indicated the manner of coding of the variables, and not the direction of the relationship.

Relationship between the variables was considered statistically significant if alpha value $p<0.05$, indicating less than 5% probability that the relationship between the two variables occurred by chance.

2.3.2 T-tests

2.3.2.1 Independent samples t-test & Paired t-test

T-tests were conducted when two samples of data had been obtained and there was a need to assess if based on the means of the two groups, whether both samples belonged to the same population. In an **independent samples t-test** where there is independence of observation between the two groups, a statistically significant difference between the means of the groups would indicate that the two groups came from different populations allowing for the null hypothesis to be rejected. In the case that the two groups reflect pairs of observations from the same sample, a **paired t-test** was conducted to assess whether the mean difference between the paired associations was significantly different from zero.

Both independent and paired t-tests are parametric tests and hence, the assumption that the sampling distribution is normal was checked using the Shapiro-Wilk test (Shapiro & Wilk, 1965) in SPSS. While in the case of the independent t-test, assumption that the dependent variable was normally distributed for each group was checked, for the paired t-test, the sampling distribution of the *difference* between scores in each group was checked for normality. A second assumption for both tests was that data was measured at least at the interval level.

For the independent t-test, other assumptions involved checking that the homogeneity of variances (variance in the population) was comparable between groups (Levene's test of equality of variances in SPSS) and that there was independence of observations between the two groups.

The effect size for the independent t-test was obtained by calculating Cohen's *d* (Cohen, 1992), which was obtained by dividing the absolute mean difference between the two groups by the pooled standard deviation,

$$\text{Cohen's } d = \frac{|\text{mean 1} - \text{mean 2}|}{SD_{pooled}}$$

where $SD_{pooled} = \sqrt{((SD_1^2 + SD_2^2) / 2)}$

According to Cohen (1992), an effect size of 0.2 can be considered small, an effect size value of 0.5 can be considered medium and an effect >0.8 can be considered large.

2.3.2.2 Mann Whitney U test

When the data was not normally distributed, a rank-based non-parametric alternative test to measure significance of between group means was used, i.e. **Mann Whitney U** (Mann & Whitney, 1947). This test assesses the significance of the differences in ranks between scores in the two groups. The assumptions checked for this test were that data was ordinal/ continuous, and the two groups were categorical involving independent sets of observations, i.e. different samples. Additionally, the distribution of scores in both groups followed the same shape based on visual inspection of the spread of scores using histograms. The results reported from this analysis include the standardized z-score in addition to the U-value, which enabled calculation of the effect size 'r '

$$r = \frac{z}{\sqrt{n}}$$

where z=standardized value of U

n=sample size

The strength of the effect size can be interpreted using Cohen's guidelines (Cohen, 1992).

2.3.2.3 One sample t-test

This test is a special case of the t-test where the mean obtained from a single sample is compared to a population mean or criterion measure. In the current thesis, one sample t-test was used in Chapter 3 to evaluate whether test performance on average in the control group (sample mean) was significantly higher than performance at chance level, i.e. 50% accuracy (criterion).

The main assumptions checked for the **one sample t-test** were that the data were measured on a continuous level and were normally distributed. Also, the data was obtained from separate individuals, i.e. there was independence of observations.

Effect size for this test was estimated using Cohen's *d* as follows:

$$d = \frac{\textit{mean difference between criterion and sample mean}}{\textit{standard deviation}}$$

2.3.2.4 Crawford and Howell's t-test

In the current thesis, the **Crawford and Howell's t-test** was employed in Chapter 4 where individual patients' performance on the novel methods were compared to healthy controls to identify those with representational neglect. This test is known to be appropriate for use in neuropsychological studies comparing single cases to small samples of normative control groups ($n<20$). Given that with small or moderately sized samples, it is not appropriate to convert the patient's raw score to a z score, i.e. the sample's mean and standard deviation cannot be considered as population parameters. In fact, the Crawford and Howell method (Crawford & Howell, 1998) treats them as sample measures. Further, it uses a t-distribution to estimate the abnormality of the patient's score relative to the controls rather than a standard normal distribution so as to have better control over Type I errors (Crawford & Garthwaite, 2005). The formula for Crawford and Howell's test is:

$$t = \frac{x - \overline{X}}{s\sqrt{n + 1/n}}$$

where x=patient's score; $\overline{X}$=controls' sample mean; s= controls' standard deviation; n= size of controls' sample.

2.3.3 Analysis of Variance (ANOVA)

ANOVA was used to compare mean differences in scores when there were more than two groups. In this thesis, repeated measures ANOVA, i.e., when the same group of subjects were measured repeatedly across more than two conditions or sessions, and mixed ANOVA involving a combination of between and within group factors have been used in Chapters 3 and 5. In principle, the ANOVA allows for the parcellation of the observed variance in the dependent variable (DV) into components based on different sources (within group variance, between group variance). The *'F'* value obtained from this analysis reflects the ratio of variation in the DV explained by the model (with the independent variables) and the variation explained by unsystemic factors (error).

$$F = \frac{\text{Model mean squares}}{\text{Residual mean squares}}$$

The type of ANOVA (repeated or mixed) was determined by the study design and analysis goals. Across both types of ANOVA, the assumptions that were checked were that the DV was continuous and normally distributed for each level of the independent variable (IV) (tested using Shapiro Wilk test in SPSS). For mixed ANOVA, it was ensured that there was homogeneity of variances between groups (tested using Levene's test of equality of error variances in SPSS) and homogeneity of covariances (tested using Box's test of equality of covariance matrices in SPSS). For each of mixed or repeated measures ANOVAs, if the variance of differences between groups or between levels was not equal, i.e. if the assumption of sphericity was violated (tested using Mauchly's test of sphericity in SPSS), then, Greenhouse -Geisser corrected values were used.

Since ANOVA is an omnibus test which informs about whether an experimental manipulation had a significant effect, these effects were broken down using post hoc tests to inform about the contribution of specific groups/ conditions in explaining the variation in the DV.

2.3.4 Analysis of Covariance (ANCOVA)

The **ANCOVA** is an extension of the ANOVA that allows incorporation of covariate in the analysis. The use of covariate in the analysis helps to eliminate the effect of confounding variables that may bias the DV. For example, in Chapter 5, I used a mixed ANCOVA to control for the variability in neglect patients' baseline performance on behavioural measures when comparing the intervention and control group's scores at different time points post brain stimulation (immediately post, < 1 month, > 6 months). Thus, the use of a covariate to reduce within group error variance was intended to increase the sensitivity of the analysis.

The ANCOVA requires categorical IV, continuous DV and covariate. In addition to ensuring independence of observations between groups, additional assumptions for the ANCOVA included checking that the covariate and IV were not significantly related (by comparing effect of group on the covariate), the DV and the covariate were linearly related for each level of the IV (by visual inspection of scatter plot), there was homogeneity of regression slopes (by ensuring lack of significance for the interaction between IV and covariate), standardized residuals for the intervention and overall model were normally distributed (by using Shapiro-Wilk's test) and there was homoscedasticity and homogeneity of variances (visual inspection of scatterplot of standardized and unstandardized residuals, and lack of significance on Levene's test of homogeneity of variance). Wherever Mauchly's test of sphericity was significant, Greenhouse-Geisser corrected values were used.

To measure effect size of ANOVA and ANCOVA results, partial eta squared (η_p^2) was calculated, which measures the proportion of variance that the IV explains that is not explained by other variables in the analysis (Field, 2009).

$$\eta_p^2 = \frac{SS_{ef}}{SS_{ef}+SS_{er}}$$

where SS_{ef}= sum of squares for the effect

SS_{er}= sum of squared errors

2.3.5 Binomial logistic regression

Logistic regression was used to model a relationship between multiple independent variables and a single dichotomous categorical dependent variable. Logistic regression was used in Chapter 7 to identify cognitive predictors of spatial and object neglect after controlling for other individual differences between patients. This regression analysis uses the maximum likelihood method to form the best fitting equation that can predict the probability or odds that an observation falls into one of two categories of the dependent variable, DV (e.g. spatial neglect: present/ absent) based on one or more continuous/ categorical independent variables (predictors).

2.3.5.1 Assumptions testing

The first assumption that was checked was to ensure a linear relationship between the predictor variables and the logarithmic transformation of the DV. To elaborate, since a linear relationship between the predictor variables and a dichotomous categorical DV cannot be established as in linear regression, data is transformed in logistic regression to express a non-linear relationship in a linear way. Hence, the data are first converted into *odds* (probability that the DV would be classified as an event or non-event for different values of the predictor variables) and then into *odds ratio* with a logarithmic transformation (logit/log odds) to normalize the distribution and create a continuous transformed measure of the DV. Thus, one of the assumptions of the regression was to ensure a linear relationship between the predictor variables and the logarithmic transformation (logit/ log odds) of the DV (Field, 2009). In SPSS, this assumption was tested by ensuring that the interaction terms of each continuous variable and their log odds included in the model were non-significant (Box-Tidwell, 1962).

Another assumption of logistic regression that was checked for was that there was independence of observations between each category of the DV and between the included variables, i.e. they were not from repeated measurements over time.

Finally, multicollinearity between variables was tested using Pearson/ Point biserial correlation coefficients, variance inflation factor: VIF, i.e. an indicator of whether a predictor has a strong linear relationship with another predictor and tolerance values:1 divided by the VIF. Criteria to reject multicollinearity was correlation coefficient $r < 0.8$, VIF <10 and tolerance > 0.1 (Field, 2009). If variables were found to be multicollinear, they were included in separate models.

2.3.5.2 Outcome measures from the regression

Logistic regression used the maximum likelihood method to find the best fitting coefficients (*b*) for each predictor variable, and intercept (*a*), such that it allows the closest possible estimation of the DV. The overall goodness of fit of the model was estimated using the log likelihood ratio test which is a test of the significance of the model of interest with predictors in comparison to the constant only null model. A significant model is one in which the values of the predictors significantly adds to the prediction of the DV in comparison to the null model (where coefficient of predictors are zero) and is assessed using **chi square (χ2).**

For each variable in the model, **significance of each predictor** in contributing to the model was provided by the Wald test which estimated whether the 'b' coefficient for that predictor was significantly different from zero and thus allowed the predictor to make a significant contribution to the prediction of the DV. Importantly, the regression also provided **odds ratios** of each of the predictor variables along with their confidence intervals. This allowed for the estimation of the odds of an outcome occurring, i.e. neglect being categorized as present or absent, based on one unit change in the significant predictor variable's values.

Lastly, the sensitivity and specificity of the model to identify cases was obtained as an outcome measure along with an estimate of the relative variance in the DV that could be explained by the model using Nagelkerke's R^2 (Nagelkerke, 1991).

CHAPTER 3 - Assessing topological and non-topological Representational Neglect using novel tasks

3.1 Introduction

To date, there is no consensus on a gold standard for assessing Representational Neglect (RN). Consequently, different types of tests have been devised to evaluate RN in clinical and experimental settings. Most tasks in RN literature can be categorized as topological or non-topological in nature. Some of the common tasks used to study topological RN have been descriptions of familiar squares and maps (Bartolomeo, D'Erme, & Gainotti, 1994; Bisiach & Luzzatti, 1978; Ortigue et al., 2003; Rode, Rossetti, Perenin, & Boisson, 2004), while the o'Clock task and object arrays (Della Sala, Logie, Beschin, & Denis, 2004; Grossi et al., 1989; Guariglia et al., 2013; Logie, Della Sala, Beschin, & Denis, 2005) have been frequently used to study non-topological RN. While some of the tasks test for representations of familiar stimuli learnt prior to brain injury (e.g., familiar landmarks, clocks), others test for RN based on newly learnt information acquired post brain injury (e.g., object arrays, pictures of scenes with objects).

Many of the existing RN tasks have been criticized for their limitations. For example, familiarity with landmarks and geographical map description are two of the most popular tests measuring topological RN (e.g, Bartolomeo, Bachoud-Levi, Azouvi, & Chokron, 2005; Bisiach, Luzzatti, & Perani, 1979; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993; Rode et al., 2010). However, both tasks lack methodological standardization because the geographical location of the patient determines the choice of squares/ maps. Furthermore, there is a lack of control on whether they are balanced in the availability of sufficient landmarks for report from imagery. The patient's familiarity with and salience of landmarks/ towns is subjective and not necessarily, symmetrical. Lastly, both tasks rely on long term memory representations and it is impossible to establish an objective baseline measure for information acquired prior to brain damage. While more recent tasks testing RN based on new information consider naming and categorization of objects to the left and right as a measure of familiarity with the scene/array prior to RN assessment (Della Sala et al., 2004; van Dijck, Gevers, Lafosse, & Fias, 2013), these tests do not provide a quantitative assessment to confirm that participants have successfully learnt the association between object and location or can recollect the stimuli they are asked to report. Hence, new tests to overcome these limitations are warranted.

Another role of RN tasks has been to advance the understanding of cognitive processes underlying RN. The identification of RN in perceptual neglect patients using the description of a familiar square task contributed to the account that both disorders were caused by damage to the underlying common mental representation of space (Bisiach & Luzzatti, 1978; Bisiach, Luzzatti, & Perani, 1979). Other theories imply deficits in attention exploration as underlying RN. For instance, in an object array task, a patient with right hemisphere stroke and left sided visual neglect showed difficulty in disengaging attention from the ipsilesional side of imagery space (Loetscher & Brugger, 2007). On the other hand, deficits in orienting attention to contralesional side of imagery space has also been shown based on the administration of the Geographical map description task (Bartolomeo, Bachoud-Levi, Azouvi, & Chokron, 2005; Rode, Cotton, Revol, Jacquin-Courtois, Rossetti, & Bartolomeo, 2010). Of note, Rode et al. (2010) have suggested that an important factor that distinguishes mechanisms of perceptual from RN is the use of spatial working memory required in actively building, exploring and remembering layouts in RN. These authors imply that while perceptual neglect involves deficits in stimulus-based attention, RN is likely to manifest on account of an interaction between attention and spatial working memory. A related interpretation that has been proposed using object array tests is that RN is caused by lateralized deficits of mental images held in visuospatial working memory (Beschin et al., 1997a; Della Sala et al., 2004). Thus, some of the more recent RN models imply the importance of assessing spatial attention in conjunction with spatial working memory in imagery space to identify RN (for review, see Salvato, Sedda, & Bottini, 2014). This proposition draws upon other studies that have shown that attention and spatial working memory exert influence over each other (Nobre, Griffin, & Rao, 2007; Olivers, Peters, Houtkamp, & Roelfsema, 2011) and have also been shown to underlie internal representations (Griffin & Nobre, 2003).

In this chapter, I discuss the creation of two novel tasks of RN (The Shopping Mall task and the Clock Cueing task) aimed at overcoming some of the discussed limitations in current RN assessment tools and to test the proposition that spatial attention and working memory may mutually contribute to RN. While the Shopping Mall task is a measure of topological RN enlisting representations for newly learnt information post brain injury, the Clock Cueing task is a measure of NRN that draws upon knowledge of a clock's layout usually acquired prior to brain injury.

The 'Shopping Mall' task is described in Experiment 1 of the chapter. It required the participant to learn 10 carefully selected shops each from the left and right side of the presented 2D image and tested for the recall of these shops from imagery. This was followed by recognition tests to assess shop identity as well as its binding to a given spatial location. This task addressed three concerns pertaining to previously used tests of topological RN: i) It involved learning an equal number of shop identities and locations on both sides in order to ensure a sufficient number and adequate distribution of landmarks, ii) The shops in the Mall were chosen based on familiarity ratings of age matched controls in the UK and each participant's subjective familiarity rating for each shop was also noted down and iii) Recognition memory performance was recorded for both shop identities and its binding to locations to acquire a baseline measure of learning/ recollection of landmarks and their positions. Participants were required to draw a mental image of the Mall and report shops as imagined from two opposite perspectives. Thus, the task required them to draw upon their memory of the Mall, maintain it in their working memory while performing tasks such as perspective shifting and scanning the image in order to report shops from each side of the mental image. Hence, it is hypothesized that participants will recruit processes involving visuospatial working memory, mental rotation and spatial attention while reporting from the Mall's mental image.

The 'Clock Cueing' task which forms Experiment 2 of the chapter, combined the principles of generating and maintaining an *internal* spatial representation of a clock similar to the o'Clock task, (Grossi et al., 1989) and the Clock Drawing test (Arduino et al., 2012; Chokron, Colliot, & Bartolomeo, 2004) as well as exploring attention shifting mechanisms within this representation. Participants were cued by a central digital time about where to expect items at specific locations on the clock face. Locations were cued in a valid or invalid fashion just as for classical cueing tasks such as the Posner task (Posner et al., 1984). To test the core principle behind this task's construction, i.e. whether validity based effects can be obtained as a function of the spatial cue; the task was first administered as an experiment with healthy young controls. Upon successful testing of the principle, the task was further adapted to suit an elderly population since the eventual aim of the task was to be administered to stroke patients to screen for RN. Some of the key adaptations included reduced number of trials, shorter stimulus target asynchrony, increased inter trial interval and closer monitoring of participants to ensure that they were attending to the task. This adaptation was tested for validity effects with a sample of healthy elderly participants.

Thus, the main aim of this chapter was to assess the suitability of the novel methods for subsequent RN testing with patients. The key hypotheses tested to assess suitability of the tasks were:

i) Recall from imagery and recognition performance of the shops in the Mall for each side would be higher than chance, but not at ceiling (Shopping Mall).
ii) Recall from imagery performance would be highly correlated with recognition memory and familiarity ratings of the shops in the Mall (Shopping Mall).
iii) Responses to invalidly cued trials would be significantly worse than to neutral and validly cued trials (Clock Cueing).

3.2 Experiment 1: The 'Shopping Mall'

3.2.1 Participants

Twenty elderly controls participated in this experiment (*Mean Age* = 67.75, *SD* = 9.23; *females* = 16; *right handed* = 19). All participants were recruited from the Cognitive Neuropsychology Centre at the Department of Experimental Psychology, University of Oxford. The study protocol was approved by the local ethics committee (Central University Research Ethics Committee, University of Oxford) and was in agreement with the ethical principles in the Declaration of Helsinki. All participants provided written consent to participate in the study, were able to understand conversational English and were tested over multiple sessions in a quiet testing room at the Centre.

3.2.2 Stimuli & Procedure

In this task, participants were exposed to a 2D five-storey, vertically orientated Shopping Mall-layout sized 24.3 cm x 28 cm created using Prezi (https://prezi.com/) (Figure 3.1).

Two parallel versions of the Mall were created in order to have adequate data points for evaluation. Each version had pictures of five shops each on the left and right sides and one each in the centre top and bottom, from an egocentric perspective (the participant looking towards the shops). Thus, across both versions, participants were required to learn ten shops each on the left and right sides for subsequent RN assessment. Each version was administered to the participant in different sessions with a minimum interval of one week and the order of which version was administered first was counterbalanced across participants.

The shops were selected based on familiarity ratings from 14 local UK residents who rated 67 UK based chains of shops on a scale of 1 (least familiar) to 10 (most familiar). The respondents were mostly female (n = 11, *Mean age*= 61.7 years, *SD* = 10.3 years). Twenty-four shops were selected in total for the two parallel Mall versions with eight shops each that received high, medium and low familiarity ratings respectively. The distribution was such that each version had two shops of high familiarity, two shops of low familiarity and one of medium familiarity on each side. The shops in the centre of the Mall were always those with medium familiarity ratings.

Viewing distance from the centre of the screen was fixed at 72.5 cm. Each shop picture on the left and right side was 5.45° x 3.35° placed at 9.5° eccentricity from the midpoint of the Mall's picture.

Figure 3.1. Shopping Mall Version A

The Shopping Mall task assessed topological RN for new information. In this figure, one version of the Mall comprising of 5 shops on the left and 5 shops on the right is shown. A second parallel version of the Mall was also administered with the participant after a minimum of one week. Order of the versions was counterbalanced across participants. Thus, 10 shops each were shown on the left and right side across two versions of the Mall and four shops were shown in the center of the layout using the software, Prezi. Each participant learned the shop identity and location and this was followed by the imagery phase, where participants were asked to imagine the Mall in their mind from two vantage points (top and bottom of the Mall) and report shop identities and locations from both perspectives. Perspective taking from the top and bottom locations was counterbalanced across participants.

Step 1: Learning the Mall

The participants were shown the layout of the Shopping Mall. The experimenter instructed participants to take a good look at the Mall since questions would follow into how the shops looked and where they were located in the Mall. The experimenter also emphasized that the test to follow will involve their creating a detailed mental image of the Mall and they should not actively try to rely on any other strategies (e.g.: mnemonics) to perform the task. Participants were given unlimited time to encode shop details and locations at this stage. Prezi also allowed for zooming in to each shop picture one at a time by clicking on it, so that each shop takes centre stage. Each participant zoomed into each shop picture once, to get a closer look at the details.

In order to allow for self-assessment, the participant was then shown the same Mall layout empty of the shops, and each shop picture was presented sequentially in the centre of the Mall, one picture at a time. They were asked to look at the shop carefully to identify whether they had seen this shop previously and then point to its correct location in the Mall. Responses were noted down. Participants were then shown the correct locations of the shops to provide an opportunity for self-correction. Testing self on newly acquired information has been shown to enhance long term retention (Roediger & Karpicke, 2006) as well as enable transfer of learning across test formats, e.g. between recognition and recall modalities (Carpenter, 2012).

Step 2: Perspective taking in imagery based recall

Each participant had to imagine the Mall from two opposite perspectives (from the top of the Mall and from the bottom of the Mall) and to report both the identity of the shop and its location. The order of perspective taking (top first, bottom first) was counterbalanced across participants. To facilitate perspective taking in imagery, participants were shown the picture of a (cartoon) man standing at the bottom level of the empty Mall (looking inwards towards the shops) and in the opposite perspective, at the top level (looking outwards from the shops). Once the participant had understood the perspective to be taken, the picture of the empty Mall was taken away from sight. They had to close their eyes and create an image of the original Shopping Mall in their mind from the assigned perspective and report shop identities and locations from imagery.

<u>Step 3: Recognition memory</u>

Two tests of recognition memory were conducted to test for recognition of shop identity and for binding of shop and its location within the Mall respectively. For shop identity, the twelve correct shops were intermixed with twenty four new pictures. Of these new pictures, twelve were of the same shop identities but a different picture than was originally shown to the participant and twelve were pictures of new shops not seen or heard of during the task. For shop location, each shop was shown once in the correct location and once in an incorrect location on the opposite side. For each task, the participant pressed designated arrow keys to indicate whether the shop identity and location were as shown in the original Mall or not.

<u>Step 4: Familiarity ratings</u>

In the last phase of the Shopping Mall task, participants rated how familiar they were with each of the shops on a scale of 1 (very familiar) to 5 (not at all familiar).

No time limit was imposed at any stage of this task.

3.2.3 Scoring

Scoring guidelines for this task are divided into three sections: imagery based recall (fundamental to RN assessment), recognition task and familiarity rating based scoring (to inform about RN performance).

3.2.3.1 Imagery based recall scores

Step 1: Scoring guidelines based on shop's features

Two scores were calculated based on the participants' performance on the Shopping Mall task.

Shop Identity **(SId)**: 1 point was given for every shop correctly reported, irrespective of the shop location in the Mall.

Shop Identity + Location **(SIdLoc)**: 1 point was given for each shop correctly identified *and* reported in the correct location within the Mall (measure of shop's binding with its location).

For each of SId and SIdLoc, the left and right sided shop reports across perspectives were combined for each participant. Since two Mall arrays were shown (each with five shops on the left and five on the right), the maximum number of left sided shops that could be reported was 20 (10 shops represented on the left from the top perspective + 10 shops represented on the left from the bottom perspective = maximum shop report of 20).

Step 2: Accounting for perspective taking in scoring

Both SId and SIdLoc scores were used to assess the impact of perspective taking using a viewer-independent perspective and a viewer-dependent perspective. *Viewer-independent* perspective focused on the patient's shop report based on imagery like in other topological RN tests (e.g. Bartolomeo et al., 2005; Bisiach et al., 1979; Guariglia et al., 1993); i.e., for left-sided shops: shops imagined on the left side from the bottom perspective and shops imagined on the left side from the top perspective were combined, irrespective of their original side of presentation during the learning phase. For *viewer-dependent* scores, the shop reports for the same side of visual space shown at learning (encoding), rather than imagery were combined; i.e. shops imagined on the left side from the bottom perspective were combined with shops imagined on the right side from the top perspective.

Step 3: Calculating Laterality Quotients

To explore *differences* between left and right side's shop recall performance for each of the four sets of scores obtained, i.e. viewer-independent SId, viewer-independent SIdLoc, viewer-dependent SId, viewer- dependent SIdLoc, Laterality Quotients (LQs), as used in other RN tests, were calculated (e.g. Guariglia et al., 2013; Palermo, Piccardi, Nori, Giusberti, & Guariglia, 2010b; Piccardi, 2009; van Dijck et al., 2013).

LQ = (Left shops - Right shops)/ (Left shops + Right shops) * 100

A negative LQ implied impaired performance on shop report for left sided shops (right shops> left shops) and a positive LQ implied impaired shop report for right sided shops (left shops>right shops).

3.2.3.2 Recognition memory based scores

D prime (d'), and response bias, were calculated to account for random and/or biased responding in the shop identity and shop location (measure of shop's binding with location in the Mall) recognition tests. Based on signal detection theory, d prime (d') is a bias-free measure of the sensitivity/ discriminability of the participant's ability to distinguish between seen and unseen pictures in the recognition task. This is assessed in the context of their response bias (c) / tendency to respond to a picture as previously 'seen' or 'unseen' and is based on each participant's subjective criterion for familiarity with the picture (Macmillan & Creelman, 1991; Stanislaw & Todorov, 1999). Both these measures assess the authenticity of the recognition test performance.

During recognition testing, when participants were shown previously seen pictures (signal trials) their response indicating ‘seen’ implied hits and ‘not seen’ implied misses; for pictures that were new and intermixed with the seen pictures as distracters (noise trials), ‘seen’ response indicated false alarms and ‘unseen’ implied correct rejections. d’ uses normalized values of the hit rate (probability of responding ‘seen’ in signal trials) and false alarm rate (probability of responding ‘seen’ in noise trials) to determine the participant’s ability to discriminate between seen and unseen pictures.

$d' = z(H) - z(FA)$

$c = -0.5*(z(H) + z(FA))$

A d’ value of zero implies inability to distinguish between signal and noise whereas higher d’ values indicate higher discriminability (Stanislaw & Todorov, 1999).

A c-score of zero was preferred and indicated no bias, negative c values indicated a bias towards judging the pictures as seen previously, while positive values indicated a bias towards judging the pictures as previously unseen (Stanislaw & Todorov, 1999).

3.2.3.3 Familiarity ratings based scores

Average familiarity ratings were calculated for left sided and right sided shops based on participants’ self-ratings.

3.2.4 Data Analyses

In addition to the main analysis for assessing suitability of the task for RN, supplementary analyses were also planned to explore biases in shop recall from imagery and to explore the relationship of imagery based recall with recognition and familiarity measures obtained for the shops.

3.2.4.1 Assessing suitability of the Mall task

Controls' shop report for each side of the Mall was evaluated using one sample t-tests to identify if the number of shops was optimal for retention and imagery based retrieval, i.e if the controls' performance on recall and recognition was each significantly different from the chosen test value (i.e. chance level performance) *and* neither at ceiling (too easy) nor floor (too difficult) for each side, then the Mall's layout will be considered to be suitable to test for RN.

For the imagery based recall, eight one-sample t-tests were done in all, two each (for left, right sided shops respectively) for viewer-independent SId, viewer-independent SIdLoc, viewer-dependent SId and viewer-dependent SIdLoc. Since the maximum score on each of these indices for each side was 20, the test value against which the t-tests were conducted was 10 (50% of 20). For recognition memory, four one sample t-tests were done, two each (left, right side) for shop identity recognition and shop location recognition. Note that raw scores were used instead of d' for recognition in this analysis. This was because perfect discrimination of signal from noise as measured by d', can extend to infinity, i.e. there is no expected maximum score. On the contrary, raw scores for recognition provided an opportunity to use a test value of 5 (50% of 10 shops to be recognized) against which each side's recognition memory performance was assessed for significance.

Also note that this analysis could not be done with familiarity data because the ratings were not on an interval or ratio scale (Please see Chapter 2, section 2.3.2.3 for details of one sample t-test).

3.2.4.2 Assessing biases in performance

For recall performance, three way repeated measures ANOVA was conducted to assess any biases in shop report based on side of the Mall (left, right), type of scoring (SId, SIdLoc) and perspective taking (viewer-independent, viewer-dependent).

For recognition and familiarity, paired t-tests were conducted to identify if participants were biased in their responses to shops on the left or right side of the Mall.

3.2.4.3 Assessing relationship between imagery, recognition and familiarity

Correlations were conducted to compare overall scores as well as to compare lateralized biases between imagery based recall and recognition performance, as well as between imagery based recall and familiarity ratings. Note that for imagery based shop recall, comparisons involved only viewer- dependent perspective scores (SId, SIdLoc). Viewer-independent perspective scores were not chosen since they implied use of an additional mechanism prior to shop report, i.e. manipulation of perspective, which was different from that tested in the recognition memory task. For recognition memory, d' measures were used to represent overall recognition performance for each of shop identity and shop location recognition, while for familiarity, average ratings of all shops included in the Mall was used. Laterality based performance for recall, recognition and familiarity was also compared using LQs. Pearson's correlations were used unless data was non-parametric in which case Spearman's correlation was used for those comparisons (Please see Chapter 2, section 2.3.1 for Pearson's and Spearman's correlations' assumptions).

All comparisons were assessed for significance after controlling for multiple comparisons using Bonferroni correction (p=0.05/12=0.004).

3.2.5 Results

3.2.5.1 Suitability of the Mall task

Results from the one sample t-tests for imagery based recall performance and recognition tests are given in Table 3.1.

Table 3.1: *One sample t-test results for recall and recognition scores*

Scores	*t* (*df*=19)	95% *CI*	Mean (SD)	Effect size (d)
		Imagery based recall		
VD-SId-Left	14*	6.7-9.1	17.9 (2.5)	3.1
VD-SId-Right	10.3*	5.2-7.9	16.6 (2.9)	2.3
VId-SId-Left	13.3*	6.2-8.4	17.3 (2.5)	3
VId-SId-Right	12.9*	6-8.4	17.2 (2.5)	2.9
VD-SIdLoc-Left	4.7*	2.5-6.5	14.5 (4.3)	1
VD-SIdLoc-Right	2.7	0.6-5.2	12.9 (4.9)	0.6
VId-SIdLoc -Left	3.8*	1.6-5.7	13.7 (4.3)	0.8
VId-SIdLoc- Right	3.7*	1.6-5.9	13.8 (4.6)	0.8
		Recognition		
Shop identity Left	13.3*	3.1-4.2	8.7 (1.2)	3
Shop identity Right	15*	3.4-4.4	8.9 (1.2)	3.3
Shop location Left	11.7*	2.7-3.9	8.3 (1.3)	2.6
Shop location Right	9.1*	2.3-3.8	8.1 (1.5)	2

**p<0.004 (post Bonferroni correction);*
Chance level test value for t-test: recall=10 (max=20); for recognition=5 (max=10)
df: degrees of freedom; CI: Confidence Interval; SD: Standard Deviation
Effect size Cohen's d= mean difference/SD
VD: Viewer-dependent; VId: Viewer-independent; SId: Shop identity recall; SIdLoc: Shop identity + location recall.

For recall performance, the one sample t-tests showed that the average number of shops recalled from imagery, when taking into account type of scoring and perspective, was significantly different than performance at chance level, $p<0.004$, for all except viewer-dependent right sided SIdLoc scores. Even for this exception, the controls performed above chance level and the results tended towards significance ($p=0.02$), but did not meet the criteria post Bonferroni correction.

For recognition performance, one sample t-tests revealed that controls' recognition of shop identities and shop locations within the Mall was significantly higher than at chance level for each side of the Mall ($p < 0.004$, Table 3.1).

To summarize, imagery based recall and recognition of shops from both sides of the Mall were higher than at chance level and not at ceiling based on controls' performance. These results were true across both types of scores (SId, SIdLoc) and perspective taking (viewer-independent, viewer-dependent). Thus, recall of shops from each side of the Mall based on memory and imagery based performance was found suitable for assessing biases in shop report in RN patients, as per the criteria set out.

3.2.5.2 Biases in representational space

Table 3.2 provides average performance of controls on SId and SIdLoc scores for left and right sided shops as well as LQs for viewer- independent and viewer-dependent perspectives. For data on individual controls' performance, please refer to Appendix, A, Tables 3a and 3b.

Table 3.2 *Perspective based average shop report and LQs for SId and SIdLoc*

Scores	Left		Right		Viewer independent scores			Viewer dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
					SId					
Mean	8.25	9.05	8.85	8.35	17.3	17.2	0.33	17.9	16.6	3.94
SD	1.55	1.15	1.46	1.35	2.45	2.5	3.44	2.53	2.85	7.5
					SIdLoc					
Mean	6.25	7.4	7.1	6.65	13.65	13.75	-0.14	14.5	12.9	7.04
SD	2.63	2.06	2.47	2.35	4.34	4.58	8.9	4.27	4.89	12.93

*SD = Standard Deviation; LQ = ((left shops-right shops)/(left shops+ right shops)) *100*

These shop report scores were used in a 3 x 2 repeated measures ANOVA to assess the relationship between side of shop report (left, right), type of scoring (SId, SIdLoc) and perspective taking (viewer-independent, viewer-dependent). Results showed that overall shop report (combined across scores and perspectives) was modulated by side of Mall being considered $F(1,19) = 5.83$, $p = .03$, $\eta_p^2 = 0.24$ with marginally higher report of left sided shops, *Mean* = 15.84, *SD* = 3.9; than right sided shops, *Mean* = 15.11, *SD* = 4.2. Side of shop report significantly interacted with perspective taking, $F(1,19) = 6.1$, $p = .02$, $\eta_p^2 = 0.24$. A breakup of this result using composite average of shops across SId and SIdLoc scores showed a significant bias toward reporting left sided shops (*mean*= 16.2 (*SD*=3.17)), over right sided shops (*mean*= 14.8 (*SD*=3.7)) for viewer dependent perspective, $t(19)=2.84$, $p=0.01$, *Cohen*'s $d=0.41$. However, almost equivalent shop report for left (*mean*= 15.48 (*SD*=3.23) and right sided shops (*mean*= 15.48 (*SD*=3.41) was obtained based on viewer-independent perspective, which was not significantly different, $p>0.05$. Finally, the type of scoring modulated side-based recall, $F(1,19)$ =

35.75, p < .01, η_p^2 = 0.65; with higher report of shops for shop identity (SId) scores, *Mean* = 17.25, *SD* = 2.58; than for shop identity + location (SIdLoc), *Mean* = 13.7, *SD* = 4.48.

For recognition memory based performance (Table 3.3 for average performance, Appendix A, Table 3c for individual participants' data), controls were comparable in accuracy of shop identity recognition, t(19)= -0.9, p=0.38, *Cohen*'s d=0.17 and shop location recognition, t(19)=0.71, p=0.49, *Cohen's d*=0.18, on average, for shops on the left and right side of the Mall. d' values calculated for both shop identity and location recognition showed that controls' were able to discriminate satisfactorily between original and new distracter information. Additionally, bias for responding to pictures as 'seen' or 'unseen' based on 'c' index was close to zero indicating no apparent bias for both shop identity (c=-0.05, *SD*=0.3) and location (c=0.1, *SD*=0.2).

Table 3.3. *Average recognition memory performance for shop identity and shop location*

Scores	Shop identity					Shop Location				
	Left	Right	LQ	d'	**c**	Left	Right	LQ	d'	**c**
Mean	8.65	8.9	-1.47	2.4	-0.05	8.3	8.05	1.79	2.3	0.14
SD	1.23	1.17	7.6	0.79	0.33	1.26	1.5	9.46	0.86	0.19

*SD: Standard deviation, Laterality Quotient = (left shops - right shops)/ (left shops + right shops))*100;*
d'= z(Hits) - z(False alarms), response bias c=- 0.5(z(Hits) + z(False alarms))*

With regard to familiarity ratings for the shops, average familiarity ratings for shops was 2 (*SD*=0.7) (Table 3.4; For individual participant ratings, please see Appendix A, Table 3d), indicating that controls were well-acquainted with the shops included in the Mall on average (1=most familiar, 5=least familiar). Average LQ was 5.05 (*SD*=10.5) indicating that controls' ratings for left sided shops was higher than for right sided shops, although this was not found to be significant in the paired t-test, $t(19)=1.79$, $p=0.09$, *Cohen's* $d=0.26$.

Table 3.4. *Average familiarity ratings for left and right-sided shops in the Mall and familiarity LQ*

Rating	Left sided shops	Right sided shops	Combined ratings	LQ
Mean	2.2	2	2	5.05
SD	0.76	0.77	0.72	10.51

*SD=Standard deviation; Laterality quotient = (left shops - right shops)/ (left shops + right shops))*100.*

Overall, participants' recall from imagery showed a significant bias toward reporting shops from the left side of the Mall than the right. This result was only true for viewer-dependent perspective, i.e. regardless of perspective shifting during recall, number of shops originally learnt and represented on the left side were reported better than those learnt and imagined as being on the right side of the Mall. No significant side-based biases were noted for recognition of shop identities or locations within the Mall, or with regard to familiarity ratings for shops on the left or right side.

3.2.5.3 Relationship between recall, recognition and familiarity performances

Table 3.5 provides results from the correlations conducted between recall, recognition and familiarity scores obtained on the Shopping Mall.

With regard to LQs, no significant correlations were seen when comparing any of the recognition based LQs or familiarity ratings LQ with recall LQs. This implied that any leftward bias in side based shop report in imagery based recall was not associated with biased recognition or familiarity with the shops.

However, when using raw scores, a significant and strong positive correlation was seen between cumulative (left+ right) shop location recognition d' and both, cumulative SId recall (r_s = 0.64) and cumulative SIdLoc recall (r_s = 0.73) implying that recognition of shop identity-location binding in the Mall was associated with better shop recall performance from imagery.

Table 3.5: *Correlation results for viewer-dependent recall, recognition and familiarity*

Scores	SId		SIdLoc	
	Total scores	LQ	Total scores	LQ
Shop identity recognition	ns$^{\$}$	ns$^{\$}$	ns	ns$^{\$}$
Shop location recognition	**0.64***	ns$^{\$}$	**0.73***	ns
Familiarity ratings	ns	ns	ns	ns

**p<0.004 (post Bonferroni correction); $ Spearman's correlation;*
*Laterality quotient (LQ) = (left shops - right shops)/ (left shops + right shops))*100.*

Thus, the results were found to support the first hypothesis pertaining to suitability of the task for RN testing, i.e. recall and recognition performance for each side of the Mall was significantly higher than chance, but not a ceiling level. With regard to the second hypothesis pertaining to relationship of imagery based recall with memory for and familiarity with the shops in the layout, only shop location recognition was found to correlate with recall performance from imagery.

3.2.6 Discussion

The main aim of Experiment 1 was to create a task to overcome some of the limitations identified with previous topological RN tasks. The Shopping Mall task achieved this aim by providing an equal number of landmarks to be represented from both sides of the layout that were both recognized and recalled from imagery above chance level. Given that elderly controls' performance on the task was not at floor or ceiling, it can be concluded that the number of shops, their identity as well as recall of identity in conjunction with their location information in the Mall were suitable to being learnt and represented in imagery by neurologically healthy elderly controls, for manipulation and recall. Additionally, this task also allowed for a more thorough investigation of RN deficits by taking into account scoring based on both shop features (identity, shop-location binding) as well as perspectives (viewer-dependent and viewer- independent perspectives). Thus, the various indices obtained for the Mall task with controls can be used as preliminary norms to study RN in patients post stroke. In conjunction with consideration for and assessment of the role of memory and familiarity for the layout, the Mall task is suggested to be an improvement over previous RN tests (see section 3.4, General Discussion).

When testing biases in imagery space, a significant difference in shop report for left and right sided shops (for both SId and SIdLoc), with higher number of shops reported from the left hand side of imagery, was revealed. This finding is in keeping with other studies that make a case for representational pseudoneglect (Bisiach, Capitani, Luzzatti, & Perani, 1981; Darling, Logie, & Della Sala, 2012; Della Sala, Darling, & Logie, 2010; Loftus, Nicholls, Mattingley, Chapman, & Bradshaw, 2009; McGeorge, Beschin, Colnaghi, Rusconi, & Della Sala, 2007). A left lateralized bias in reporting landmarks from a mental image has been shown for a familiar square with a greater bias seen for older than younger adults in a sample of 100 participants (McGeorge et al., 2007). Della Sala et al. (2010) have further probed the existence of lateralized biases in short term memory recall over three experiments involving object feature binding in healthy controls (Della Sala, Darling, & Logie, 2010). They reported that for object arrays shown for duration of 2 seconds each and comprising of 2D geometrical shapes requiring arbitrary binding of object features such as shape, colour and location, participants made significantly lesser errors in remembering the locations of objects presented to the left of the midpoint than right, during immediate recall. Additionally, participants made more colour-shape binding errors for objects presented on the right side than left. These findings were true regardless of one or two objects shown to each side and regardless of order of object report. Thus, the results from this study showed that in healthy controls, temporary arbitrary bindings between object features are lateralized with better recall for objects presented to the left than right side (Della Sala et al., 2010).

Importantly, LQ based correlations showed that this bias for recalling more shops from the left than right side of imagery, was not related to biases in recognition memory (identity/ shop-location binding) or familiarity for the shops included in the left as compared to right side of the Mall. The lack of correlation between lateralized biases in recognition and recall performance provides further support to studies that report differences between these measures assessing memory (Cabeza et al., 1997; Fisher, 1979; Staresina, 2006). It may also be indicative of retrieval differences modulated by use of imagery for representation of the layout, although these findings cannot be explored in greater resolution based on the available data and provide interesting avenues for future research.

Lastly, two significant findings were observed involving assessment of shop location in the Mall. Firstly, significantly higher numbers of shops were reported when considering only shop identity (SId) rather than when considering both identity and location (SIdLoc). Secondly, shop location recognition, but not shop identity recognition, was significantly correlated with both SId and SIdLoc recall scores. Both these results can be attributed to the nature of SIdLoc and location recognition assessment. Although both SIdLoc and shop location recognition measured additional spatial information within the Mall for the shops, this information was always implicitly tested in the context of the shop's identity, i.e. SIdLoc scores credit shop report only when participants identify the shop in conjunction with its location within the Mall. Similarly, in shop location recognition, shop pictures were shown in correct and incorrect locations in the Mall requiring participants to recognize the correct shop picture-location combination, indicating correct shop identity-location binding.

3.3 Experiment 2: Clock Cueing task

This experiment was conducted separately with young and elderly controls. However, since most elements pertaining to task design and analyses across both (original version administered with young controls and adapted version with elderly controls) were identical, both experiments are discussed together, for the sake of brevity.

3.3.1 Participants

Twenty-two young participants, *Mean age* = 22.68, *SD* = 2.85, 15 *females* and twenty elderly participants with no prior history of neurological injury, *Mean Age* = 66.06, *SD* = 8.53, 16 *females* performed the Clock Cueing task. All participants were right handed and had normal or corrected-to-normal vision. The study protocol was approved by the local ethics committee (Central University Research Ethics Committee, University of

Oxford) and was in agreement with the ethical principles in the Declaration of Helsinki. All were students at Oxford University and signed a written consent form approved by the University of Oxford research ethics committee prior to the experiment.

3.3.2 Stimuli & Procedure

Prior to task onset, all participants were asked to rate their familiarity with analogue clock layouts on a Likert scale from 1 (most familiar) to 5 (least familiar). If the participant gave a rating of 3 or above, they were not included in the study due to inadequate familiarity with the clock's layout.

Stimuli were displayed on a desktop computer in a quiet testing environment using Presentation software (Neurobehavioral Systems Inc., San Francisco, CA, USA). Viewing distance from the centre of the screen was fixed at 72.5 cm by use of a head-chin rest. A circular analogue clock layout was presented in a grey background with a central white fixation subtending 0.2° x 0.2° (Figure 3.2). The face of the clock was black with 12 white placeholders depicting the locations indicating time on a clock. These placeholders subtended 6° visual angle and were placed each at 30° from the central fixation point on the circular clock layout, i.e., with times 15 and 45 minutes past the hour ranging from 0° to 180° and forming the horizontal midline of the stimulus. Each side of the square placeholder measured 2.25 cm.

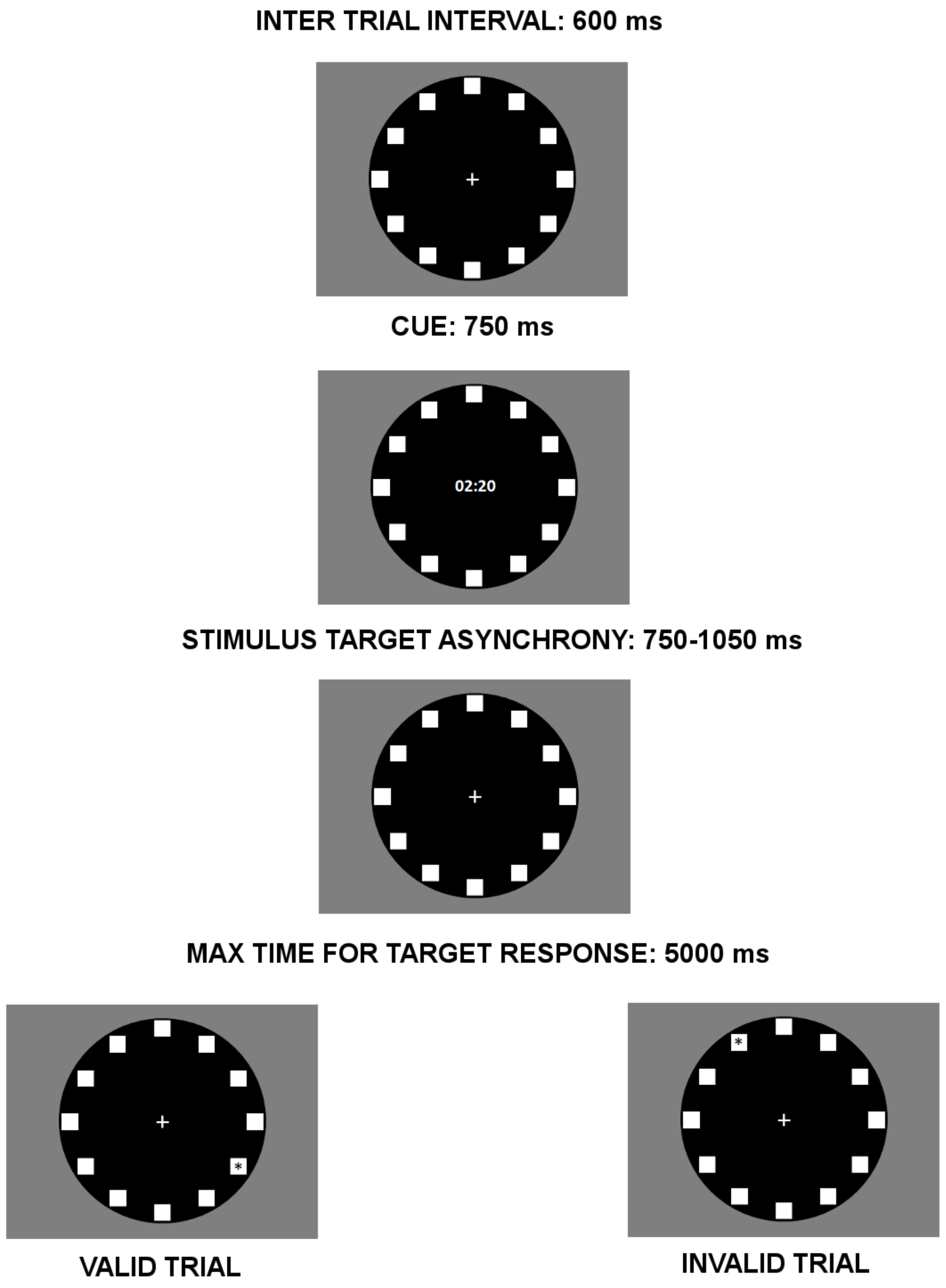

Figure 3.2. Clock Cueing task layouts, timings and procedure (young controls)

The Clock Cueing task was a cue priming task assessing non-topological RN for old and familiar object layouts. The participant was cued to the left or right side of a mental representation of a clock using a digital time as cue (750 ms). After a stimulus target synchrony of 750-1050 ms, a target asterisk was shown in the cued location (valid trials =560) or un-cued location on the same or opposite hemifield as the cue (invalid trials= 280). 17 catch trials and 17 neutral trials were interspersed in the experiment. Participants were instructed to press the designated button on the Cedrus response box as quickly as possible on target detection and were allowed up to 5000 ms to do so. The adaptation of the Clock Cueing task for elderly participants followed the same procedure as listed here. Trial features were adjusted such that stimulus-target asynchrony was shorter at 200-500 ms and inter trial interval was longer at 1500 ms. The number of valid trials was 90, invalid trials in which target always occurred in the opposite hemifield from the cue were 30, catch trials were 10 and neutral trials were eliminated. Lastly, the spacebar on the computer was used for response detection.

The participant was asked to fix their eyes on the central white fixation point throughout the task. The fixation was replaced by a spatial cue that was aimed at orienting the participant's attention to a specific placeholder in the layout. Spatial cues were presented in the form of *digital time*, which was presented centrally (e.g.: 05:20), subtended 0.4° in white using font Calibri, size 34. Participants were asked to pay attention to only the minute part of the time and to bring the corresponding clock hand to their mind's eye and to use this as a cue to the subsequent presentation of a visual target. Since the minute hand did not directly correspond to the number of a clock, the cue was intended to promote the use of imagery to match the hand to the corresponding location on an analogue clock face. Following a brief and varied interval, a target black asterisk would appear either in the cued placeholder (valid trials) or un-cued placeholder (invalid trials). For invalid trials, the distance between cue and target was manipulated to range between 1 placeholder away and 6 placeholders away from the cue corresponding to eccentricities of 3°, 6°, 8°, 10°, 11.57° and 12° from the cued placeholder. In neutral trials, the target had an equal probability of occurring in any placeholder. Neutral trial cues for this task were an array of numbers that resembled the structure of a digital time, i.e. 70:85. These cues did not direct attention to any particular placeholder and were hence considered neutral. In catch trials, the cue would not be followed by a target to respond to. Participants were instructed to fixate at the centre and not move their eyes/ head towards the cued box. They were asked to press a designated centrally presented button on a Cedrus button box with their right index finger, as quickly as possible on noting the target. Reaction times (RTs) and proportion of targets detected were the primary outcome measures of this task.

Young controls (original task): The experimental phase for each task version included 874 trials (64% valid, 32% invalid, 2% catch and 2% neutral trials). Each participant completed 14 practice trials inclusive of valid, invalid, neutral and catch trials.

Elderly controls (adapted task): An additional criteria for elderly controls, participants was that they were only included in the study if they were able to draw the layout of an analogue clock with numbers, depict the time '7:20' and point correctly to the minute and hour hands of the clock. The main adaptations to the task were a reduced number of trials, i.e. 90 valid trials (45 left, 45 right), 30 invalid trials (15 left, 15 right), 10 catch trials, and neutral trials were eliminated. Invalid trials in this version implied that the target always occurred on the hemifield opposite to the cued location. The stimulus target asynchrony was reduced to last between 200 and 500 ms while the inter-trial interval was increased to last 1500 ms. The participants were monitored closely and only allowed to go to the next trial when the experimenter judged them to be alert and motivated. If this was not the case, the experiment was paused until the participant was able to concentrate again. Lastly, for ease of administration if using the task for bedside testing in hospitals and in order to allow for easier responding for stroke patients, the spacebar button was chosen for target response instead of the Cedrus button box. Each participant completed 7 practice trials to ensure that they had understood the task.

3.3.3 Data Analyses

For both versions of the task (original and adapted), the main aim of the analysis was to test the principle of validity effects (invalid RTs > valid RTs) using the clock's representation in imagery. A supplementary aim was to assess side-based biases in attending to an internal representation of the clock.

Even though the tasks shared the same principle, they differed along several parameters (see 3.3.2). Hence, the performances of the young and elderly controls cannot be directly compared.

For both versions of the task, all RTs longer or shorter than 2 SDs from the mean were trimmed before data analysis.

3.3.3.1 Young controls

A repeated measures ANOVA was planned to explore the effect of trial type (valid, neutral, invalid) on each outcome measure (RTs, target detection). The expectation was that RTs to valid trials will be significantly faster than to invalid trials. However, since the target detection task was only intended to ensure that participants were attending to the task and relatively simple requiring a button press upon seeing the target without any additional decision making, no significant differences between trial types was expected for this measure.

To explore side- based differences in the clock's layout, repeated measures ANOVA with side of cue (left, right) and side of target (left, right) was used. Note that in the Posner task (Posner et al., 1984) (upon whose principle the Clock Cueing task was modelled), *both cues and targets occurred in visual spa*ce and target outcome measures were reflective of attention orienting and shifting in visual space. On the other hand, the Clock Cueing task used cues to *orient attention in imagery space whereas targets occurred in visual space.* Since this task was concerned with spatial attention processes in *imagery* space which was facilitated by the cue, analyses of side- based outcome measures were also explored with relevance to the *cued side*, rather than side of target occurrence.

3.3.3.2 Elderly controls

Since neutral trials were excluded, paired t-tests were used to compare performance between valid and invalid trials. For side based comparisons, two repeated measures ANOVA were conducted to assess the effects of cue side (left, right) and target side (left, right) on RTs and proportion of targets detected respectively. All analyses were adjusted for multiple comparisons using Bonferroni's correction.

Note: In addition to the validity and side based explorations in the Clock Cueing task, the data from the elderly controls was also used to suggest scoring guidelines for RN. Hence, the following three indices were calculated with the aim of providing normative data for the identification of RN in Chapter 4:

1) Overall validity effect (OVE): All invalid trials -all valid trials
2) Right validity effect (RVE): Right invalid trials-right valid trials
3) Left validity effect (LVE): Left invalid trials -left valid trials

Left invalid indicated trials where the cue targeted attention to the left side, but targets occurred in the right side of space.

3.3.4 Results

3.3.4.1 Young controls

All participants reported that their familiarity with the clock's layout was 5 (most familiar). The exclusion criteria for poor task performance on all the tasks was set as false positive responses to 30% or more of the catch trials. Based on this criterion, data for five participants was excluded from the analysis of the young controls performance on the Clock Cueing task. Thus, the included sample for the task was 17.

All participants identified all targets across all trials. Hence, target detection was not analysed.

A significant effect of trial type was seen on RTs, $F(2,32)=10.91$, $p<0.005$, $\eta_p^2 = 0.41$ (Figure 3.3). Specifically, as expected, RTs to valid trials were significantly faster than to invalid trials, *Mean difference*=25.23 ms, *SE*= 6.6 ms, *95% CI*=7.5-43. Neutral trials had significantly faster RTs than invalid trials, *Mean difference*= 15.12 ms, *SE*= 5 ms, *95% CI*=1.5-28.7. However, valid trials were not significantly faster to respond to than neutral trials, $p>0.05$.

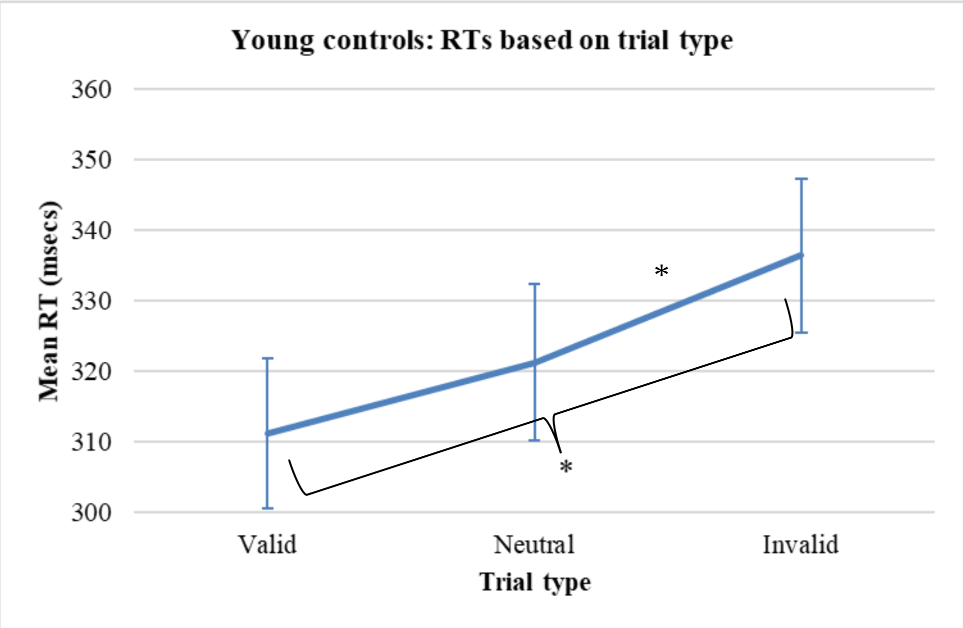

Figure 3.3: Young controls: RTs based on trial type

**p<0.05 in pairwise comparison; Error bars depict standard error.*
RTs were seen to be fastest for valid trials followed by neutral and invalid trials. Significant difference was seen between valid trials and invalid as well as neutral and invalid trial RTs.

Repeated measures 2 x 2 ANOVA to assess side-based effects revealed a significant interaction between cue and target side, $F(1,16)=26.32$, $p<0.005$, $\eta_p^2=0.62$, with paired t-tests showing that for each of left, $t(16)=5$, $p<0.005$, *Cohen's d*=0.55, and right sided cues, $t(16)=4.6$, $p<0.005$, *Cohen's d*=0.71, invalid trial RTs were significantly slower than valid trial RTs (Figure 3.4).

Additionally, the repeated measures ANOVA also revealed an overall significant effect of cue side on RTs, $F(1,16)=6.1$, $p=0.03$, $\eta_p^2=0.28$, with slower RTs when cues were directed to the left side of the clock's representation, Left sided cues: *Mean*=329.7 ms, *SE*=10.6, Right sided cues: *Mean*=325.3 ms, *SE*=9.8. A breakdown of this effect by trial type showed that these cue-based RT differences were significant only for validly cued trials, i.e. for left vs right valid trials ($t(16)=2.8$, $p=0.01$, *Cohen's d*=0.18) but not for invalid trial RTs ($t(16)=0.5$, $p=0.66$, *Cohen's d*=0.02). This suggests that even within validly cued trials, the fastest speed of processing was observed for the right hemisphere targets when cues also directed attention to the right side of space (Figure 3.4).

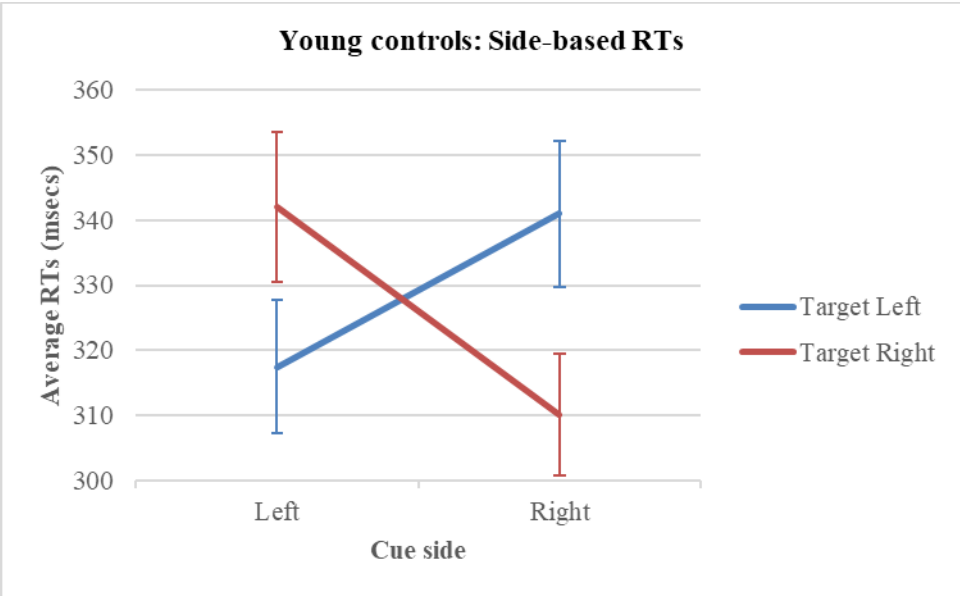

Figure 3.4: Young controls: RTs to left and right, valid and invalid trials

RTs to valid trials for each side were faster than invalid. Right valid trials were significantly faster than left valid trials implying faster processing of targets in the right hemifield than left when targets were validly cued. No such significant difference was seen when comparing right and left invalid trial RTs.

3.3.4.2 Elderly controls

All participants were able to draw the layout of a clock, mark the time requested and identify the hour and minute hands correctly. Data for two participants were excluded from the elderly controls analysis on the Clock Cueing task due to false positive responses to more than 30% of the catch trials. Thus, the included sample for this analysis was 18.

Although not at ceiling like in the case of the young controls, target detection in the elderly controls was close to perfect performance implying that the task was not difficult for elderly participants, i.e. 99.93% of the targets were detected overall. Table 3.6 lists the average RTs, proportion of targets detected and validity indices for left and right sides in the Clock Cueing task.

Table 3.6: *Indices calculated from the Clock Cueing task*

Outcome Measures	Left valid	Left invalid	Right valid	Right invalid	Overall validity effect	Left validity effect	Right validity effect
Mean RT	539.6	684.5	532.5	648.07	130.2	144.9	115.5
SD (RT)	161.3	264.2	168.8	259.4	157.8	169	159.9
Mean TD	1	1	1	1	0.001	0.001	0.001
SD (TD)	0.006	0	0.0006	0	0.004	0.005	0.005

TD: Proportion of targets detected; SD: Standard Deviation
Note: 1) All RTs shown in msecs; 2) Left invalid trials = when attention had to shift from left side of representational space to right side of visual space to detect target.

Paired t-tests showed that RTs to invalid trials were significantly slower than to valid trials, *Mean* = 536.07, *SD* = 163.01; and invalid trials' RTs, *Mean* = 666.31, *SD* = 258.49 for Clock Cueing, t (17) = -3.34, p = 0.004, *Cohen's d* = 0.5 (Figure 3.5). However, no such significant effects were seen between valid and invalid trials for target detection, t(17) = -1.46, p = 0.16, *Cohen's d* = 0.42, Valid trials *Mean* (*SE*)=0.99 (0.0009), Invalid trials *Mean* (*SE*)= 1(0).

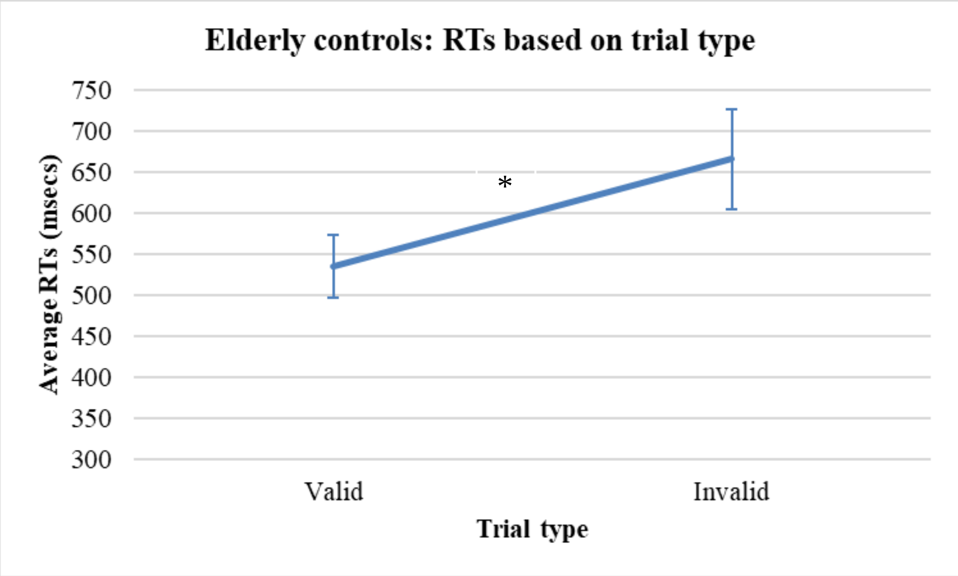

Figure 3.5: Elderly controls: RTs based on trial type

**p<0.05; Error bars depict standard error.*
RTs to valid and invalid trials were significantly different in elderly controls, post task adaptations.

With regard to side-based analyses, repeated measures 2 x 2 ANOVA showed that an interaction between side of cue and side of target on RTs was significant, $F(1,17)=12.3$, $p=0.003$, $\eta_p^2=0.42$ (Figure 3.6). Paired t-tests showed that this difference was significant between valid and invalid trials on both the left, $t(17)=3.6$, $p=0.002$, *Cohen's d*=0.66 and right sides, $t(17)=3.07$, $p=0.007$, *Cohen's d*=0.53. Unlike young controls, no significant effect of cue side was seen in this experiment ($p>0.05$), although elderly controls also showed a trend towards faster RTs to right than left side (*Mean RT* (*SE*), Right sided cue: 590.3 (48); Left sided cue: 612.1 (47.6)). No significant side-based results were seen for proportion of targets detected ($p > 0.05$).

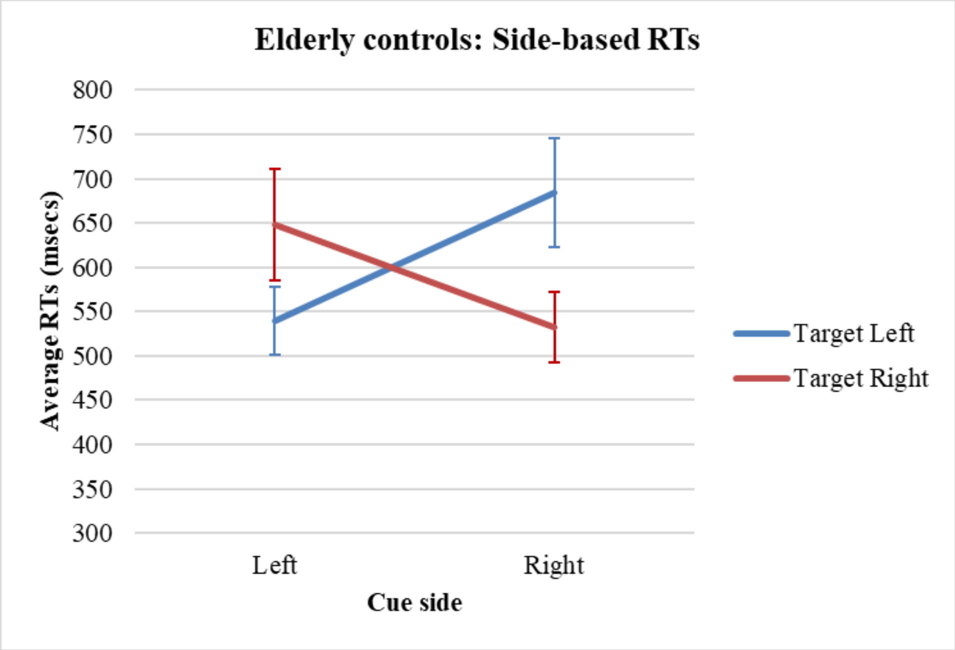

Figure 3.6: Elderly controls: Side-based RTs

Significant difference in RTs was seen when comparing valid and invalid trials in the left and right side of space. However, no significant differences were seen for side when comparing the same type of trial, e.g. valid trial RTs were not significantly different between right and left sides.

Data for each control's average RT and proportions of targets detected to each trial type, along with the overall, left and right validity effects is given in Appendix A, Tables 3e and 3f respectively.

To summarize findings from the Clock Cueing task, both young and elderly controls' data supported the hypothesis that the task was able to elicit validity effects in the expected direction (valid>invalid) in imagery space. Participants identified targets significantly faster when cues were valid rather than when they were invalid. These effects were significant for both left and right hemifields in the clock's layout. As predicted, target detection performance was at (young controls), or close to ceiling (elderly) and was not significantly different across trial types. Finally, in young but not elderly controls, RTs to validly cued trials were significantly faster for the right than to left side of imagery space.

3.3.5 Discussion

The suitability of this task for RN measurement was assessed using trial- type based analysis. The results showed that both young and elderly controls responded significantly faster to validly cued trials than invalid trials, indicating suitability of the tasks for RN assessment. The significant validity effects implied that when the cue that was targeting attention to a location in *imagery* space <u>overlapped</u> with the location of target occurrence in *visual* space, participants were significantly faster than when they were required to <u>disengage</u> attention from incorrectly cued location and <u>reorient</u> to target location. It should be noted that the shift of attention between imagery and visual space occurred for both valid and invalid trials, i.e. any difference in RT performance between trial-types can be interpreted to be on account of attention orienting and shifting processes subject to the type of cue (valid, invalid), rather than to the type of space (visual, imagery).

While no neutral trials were used in the task adaptation with elderly controls, data from young controls showed that RTs to valid trials were not significantly faster than to neutral trials, i.e. the benefit of being shown a valid cue was not significantly more than having no cue to predict target occurrence. Both neutral and valid trials are known to evoke a general level of preparedness to engage a target and the key difference between them is that the valid cue provides additional spatial information regarding the target (Jonides & Mack, 1984). In principle, the neutral and valid cues have been recommended to be as identical as possible (Chica, Martín-Arévalo, Botta, & Lupiáňez, 2014; Jonides & Mack, 1984), and although the current study emphasized similarity in the physical features of the cue, there was a substantial discrepancy in the frequency of valid and neutral trials which could be critical to exploring RT based effects (Chica et al., 2014; Feher da Silva & Baldo, 2015). On the other hand, despite the relatively infrequent neutral trials (n=17), a marginal, but significant difference in RTs was seen between neutral and invalid trials in this task. Although both neutral and invalid trials required disengaging from fixation to orient attention to a location in imagery space, neutral trials required orienting attention to a *target* in an unexpected location whereas invalid trials required orienting attention to a *wrongly cued location* (Posner, Walker, Friedrich, & Rafal, 1984). Critically, the subsequent violation of expected cue-target congruency in invalid trials and additional cognitive operations required for disengaging attention from the wrongly cued location to reorient to the correct target location were unique to invalid trials (Giessing, Thiel, Stephan, Rösler, & Fink, 2004; Nobre, Coull, Frith, & Mesulam, 1999; Posner et al., 1984; Thiel, Zilles, & Fink, 2004) and may account for their significantly longer RTs as compared to neutral trials.

Hemifield analyses in the young controls data revealed that along with being significantly faster in responding to valid than invalid trials, controls were faster to respond when cued to the right side of the clock's representation in imagery. This is in contrast to controls' studies that report leftward bias in tasks assessing attention mechanisms in *visual* space (e.g. Gigliotta, Malkinson, Miglino, & Bartolomeo, 2017; Jewell & McCourt, 2000; McCourt & Jewell, 1999; Zago et al., 2017), including the Posner cue priming paradigm (Thiebaut de Schotten et al., 2011). Similar leftward bias in controls' performance has also been reported for tasks in *imagery* space (Darling et al., 2012; Della Sala et al., 2010; Loftus et al., 2009; McGeorge et al., 2007), including in the Shopping Mall task included in the current chapter (section 3.2.5.2). Given this context, the results from the Clock Cueing task showing faster processing in the right side of space may be considered surprising. However, such results have been noted previously in the context of the analogue clock's layout. In two previous studies requiring controls to imagine clock hands based on times provided, participants were significantly faster in responding to clock hands imagined in the right side of imagery space, than left (Formisano et al., 2002; Kukolja, Marshall, & Fink, 2002). Formisano et al. (2002) suggested that since the left hemisphere is involved in generating mental images, this may explain the speedier processing of clock hands in the contralateral right side of imagery. According to them, for responses to the left side of the clock, the mentally generated image of the clock would need to be transferred to the right hemisphere through transcallosal pathways thus explaining the additional time taken to process clock hands imagined in the left side. An alternative explanation proposed by Kukolja et al. (2002) was that conversion of digital time to clock hands in their study may have engaged participants to mentally rotate the clock hands in a clockwise direction from 12 facilitating quicker responses to the right sided clock hands than left. Thus the faster processing of right sided cues in the Clock Cueing task provides further support to the observation that the clock's layout is special in its preferential processing of the right side.

Finally, on the adapted task administered with elderly controls, target detection performance was close to ceiling (99.93%) suggesting that elderly participants were able to sustain attention for the duration of the task. Elderly controls' data for RN identification based on calculation of overall validity effect as well as right and left validity effects is provided (Table 3.6).

3.4 General Discussion

The main aim of this chapter was to create and explore the suitability of two novel RN tasks designed to overcome shortcomings of existing RN tests. The key results from each task have been discussed in sections 3.2.6 and 3.3.5 respectively. This section focuses on the utility of these tasks in contributing to RN identification and theoretical bases of RN.

3.4.1 Shopping Mall task

(i) Evaluation of RN theories of attention and spatial working memory

Results from the Shopping Mall task can be used to assess the relative role of spatial attention and working memory in the identification of RN. Difficulties in orienting attention to one side of space would imply that representations from that side of space cannot be manipulated successfully such as during mental rotation/ perspective shifting (Della Sala et al., 2004). Thus, for stroke patients who may have attention related difficulties in mental rotation or perspective shifting, this can be easily accounted for in the Shopping Mall task by using viewer-dependent perspective LQs. In the case that mental transformation is unaffected, RN on this task can also be used to evaluate a lateralized deficit in visuospatial working memory store (Della Sala et al., 2004). In such a case, even though fewer shops might be retrieved from the impoverished neglected side, these will not be lost from report during perspective shifting. On the other hand, after mental rotation, fewer shops might be reported from the intact side when they are to be imagined as part of the neglected side. In Della Sala et al.'s study (2004), RN was thus shown to be related to lateralized impairments in the system involved in temporary storage of information in working memory, rather than as a deficit in directing attention. Each of these accounts can be investigated separately based on the Shopping Mall's viewer-dependent and viewer-independent perspective scores respectively.

(ii) Consideration of perspective based scoring

Traditionally, most studies report lateralized loss of landmark, city or object report when comparing item report across perspectives from imagery (Bisiach & Luzzatti, 1978; Della Sala et al., 2004; Guariglia et al., 2013). However, previous studies have not explored topological RN biases that are independent of mental transformations and assumption of vantage points (i.e. viewer-dependent perspective scoring). This scoring method is especially relevant when assessing patients with difficulties in mental rotation where perspective taking may be compromised. Topological RN when considering item report from viewer-dependent perspective is especially credible when supplemented with quantitative memory performance and familiarity scores. For example, along with controlling for mental rotation deficits by using viewer-dependent topological RN scores, other potential reasons for poor performance such as biases in memory or familiarity with the shops need to be evaluated before the deficits can be attributed to difficulties in representing/ exploring the layout in imagery.

3.4.2 Clock Cueing task

(i) Evaluation of spatial attention deficits in non-topological RN

In Experiment 2, Clock Cueing was investigated for its suitability as a non-topological RN task enlisting spatial attention and working memory processes. While the task did not assess the role of spatial working memory directly, it was implicitly assumed that working memory was integral to holding the clock's representation active and to supporting the manipulation of the digital time cue into a meaningful spatial location within the clock's representation. The cue priming paradigm provided a sensitive method to test difficulties in attention orienting and shifting in space (Posner et al., 1984; Rengachary, D'Avossa, Sapir, Shulman, & Corbetta, 2013). Posner et al. (1984) used this paradigm to propose that attention shifting in space requires disengaging attention from its current focus, moving attention to target location and engaging the target. Of these, parietal lobe patients with visual neglect may be especially impaired in disengaging attention from stimuli in ipsilateral space in invalid trials. The Clock Cueing task results replicated Posner-like validity effects, but in imagery space, with controls such that participants responded significantly faster to validly cued trials than invalid trials. Hence, this task can be considered suitable to explore difficulties in spatial attention processes in imagery with RN patients.

(ii) Identifying non-lateralized deficits versus lateralized attention deficits

If a patient's scores for overall validity effect is significantly different from controls' and worse than the worst control's performance, an investigation of right and left validity index is proposed to identify if the neglect is for the right or left side of imagery space. Since the focus of the task is to assess performance in the left and right side of mental representations (contrary to as traditionally assessed in visual space by the Posner task), the side of representational space that the *cue directs attention to* will be considered relevant to RN identification rather than the side of target detection. However, if the deficits are non-lateralized, then the patient would show impairments in both right and left validity effects as compared to controls' suggesting an overall difficulty in shifting attention between imagery space (based on cued location) and visual space (based on target occurrence).

3.4.3 Brief evaluation of novel RN tasks

Overall, the Mall and Clock Cueing tasks provided for the potential to discover new facets of RN including identification of dissociations both within topological RN (viewer-independent/ dependent scoring, SId/ SIdLoc) and between topological and non-topological (Mall/ Clock Cueing) RN. The Shopping Mall task improved upon criticisms of previous topological RN tasks by allowing for a visually balanced paradigm with carefully selected landmarks and locations as well as by providing due consideration for the role of subjective memory and familiarity with the landmarks used. Additionally, neglect literature has discussed spatial attention processes such as orienting and shifting of attention only with regard to visual space. The Clock Cueing task has for the first time allowed for an exploration of these spatial attention processes in imagery space as well.

Both the Mall task and the Clock Cueing task have some limitations that need consideration. The Shopping Mall task cannot be administered with stroke patients who have severe cognitive deficits, especially pertaining to attention and memory. This task also requires a prolonged administration over two separate sessions. The Clock Cueing task does reduce the dependence on angle judgment and decision making abilities as seen in the o'Clock task and its adaptations. However, it cannot be administered with patients, who are unfamiliar with the clock's layout, have constructional apraxia or visuo-motor difficulties. Another important consideration is the need to evaluate the role of visual field deficits or visual neglect, if present, in contributing to RN. Hence, the Clock Cueing task must be used in conjunction with other relevant tests in the patient population.

In Chapter 4, I will use both the novel tasks with chronic stroke patients in conjunction with a battery of task relevant cognitive tests to explore dissociations in RN. Elderly controls' performance on the two tasks from the current chapter will be used as normative data to identify patients with RN in Chapter 4.

CHAPTER 4 - Dissociating Representational Neglect based on type of representation and time of acquisition of memory for representation

4.1 Introduction

Representational neglect (RN) is a disorder frequently seen in stroke patients where they fail to or inaccurately report stimuli from one side (mostly from the left side) of internally generated images (Bartolomeo, D'Erme, & Gainotti, 1994; Beschin, Cocchini, Della Sala, & Logie, 1997a; Bisiach & Luzzatti, 1978; Bisiach, Capitani, Luzzatti, & Perani, 1981; Della Sala, Logie, Beschin, & Denis, 2004; Grossi, Modafferi, Pelosi, & Trojano, 1989; Guariglia, Palermo, Piccardi, Iaria, & Incoccia, 2013; Rode, Revol, Rossetti, Boisson, & Bartolomeo, 2007). As discussed in Chapter 1, dissociations in RN have been demonstrated in the literature for topological RN (with navigational content) and non-topological RN (without navigational content) (Guariglia & Pizzamiglio, 2006; 2007; Guariglia et al., 2013). These dissociation findings have been important in furthering discussions pertaining to the possible mechanisms underlying RN.

One hypothesis postulates the existence of two separate mental representation systems for topological and non-topological stimuli and a possibility for selective damage to either system in RN (Guariglia, Piccardi, Iaria, Nico & Pizzamiglio, 2005). The dissociations in topological and non-topological RN have also been linked to associated dissociation in imagery deficits (Palermo, Nori, Piccardi, Giusberti, & Guariglia, 2010a; Palermo, Piccardi, Nori, Giusberti, & Guariglia, 2009). However, other proposals involving attention exploration mechanisms and visuospatial working memory have been shown to contribute to *both* topological and non-topological RN. Using the Familiar squares and map description tasks, it was suggested that RN was caused by ineffective exploration of the left side of visual mental images (Bartolomeo, Bachoud-Levi, Azouvi, & Chokron, 2005; Bartolomeo et al., 1994; Rode, Cotton, Revol, Jacquin-Courtois, Rossetti, & Bartolomeo, 2010; Rode et al., 2004).

Impairments in visuospatial working memory have also been implicated using both topological and non-topological material acquired before and after brain damage (Beschin et al., 1997a; Della Sala et al., 2004; Denis, Beschin, Logie, & Della Sala, 2002). Specifically, Della Sala et al. (2004) proposed a lateralised deficit to the mental representation held in visuospatial working memory as underlying RN. However, it must also be noted that there have been cases of RN reported without working memory deficits (Palermo, et al., 2010b; Piccardi, Bianchini, Zompanti, & Guariglia, 2008; van Dijck, Gevers, Lafosse, & Fias, 2013).

Many of these RN studies have used the Familiar squares task (e.g. Bartolomeo, D'Erme, & Gainotti, 1994; Della Sala, Logie, Beschin, & Denis, 2004; Denis, Beschin, Logie, & Della Sala, 2002; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993; Guariglia, Palermo, Piccardi, Iaria, & Incoccia, 2013; Ortigue et al., 2003; Piccardi, Bianchini, Zompanti, & Guariglia, 2008) to test topological RN and o'Clock task (e.g. Grossi, Modafferi, Pelosi, & Trojano, 1989; Guariglia et al., 2013; Palermo, Piccardi, Nori, Giusberti, & Guariglia, 2009; van Dijck, Gevers, Lafosse, & Fias, 2013) to test for non-topological RN. Several limitations have been identified in the existing RN task measures (see Chapter 3, 3.1 for detailed review). To summarize, these tasks involve ancillary cognitive mechanisms (e.g., mental rotation, angle judgement, decision making) that are not traditionally accounted for in RN testing; Familiar squares is dependent on availability and patient's familiarity with a famous layout, subject to geographical boundaries based on the patient's location of residence, unequal number of landmarks remembered on each side, biased representation on account of salience and familiarity with individual landmarks within a layout and lack of an objective baseline memory measure for the layout from prior to the stroke.

Consequently, the first aim of this study was to investigate the utility of the two novel methods (The Shopping Mall, Clock Cueing task) created in Chapter 3 for identifying topological and non-topological RN respectively, in a sample of chronic stroke patients. These tasks were designed to improve upon some of the limitations identified with existing tasks in RN literature, as well as to inform about the role of spatial attention and visuospatial working memory abilities in RN.

The Shopping Mall task was created to identify topological RN for newly learnt information. It was designed to improve upon other topological RN tasks by providing symmetrical number of landmarks on both sides of a spatial representation and the landmarks were matched for familiarity. In addition, this task provided a quantitative measure of memory performance for the task stimuli and layout. The Clock Cueing task was created to identify non-topological RN for information acquired prior to brain damage. Specifically, this task studied attention exploration processes using a Posner-like cue priming paradigm (Posner, Walker, Friedrich, & Rafal, 1984) within the context of a clock's layout which has a well-known intrinsic spatial code. The task specifically explored attention exploration processes in an internal representation recalled from long term memory and maintained online in working memory. Additionally, it was also designed to minimize dependence on angle judgment and decision making abilities that the o'Clock task was contingent upon.

The second aim of this study was to investigate whether the dissociations in topological and non-topological RN are affected by time of acquisition of memory to be represented – that is, whether the layout to be represented draws on long-term memory from before the lesion or requires the representation of new information. A dissociation based on time of acquisition of memory has to date been assessed only once, in a single case study of a left hemisphere stroke patient. van Dijck et al. (2013) used a 2 x 2 design and reported that there was right- sided RN across all tasks irrespective of the content and the patient's familiarity with the stimuli. However, the dissociations in topological and non-topological RN has not been systematically explored in a larger patient sample to identify if they are modulated by the time of acquisition of material. To this end, two supplementary RN tasks from the existing literature were administered to comprise a 2 x 2 design. The Geographical map description task (Bartolomeo et al., 1994; Rode et al., 2010) was adapted to the UK population and used as a task to identify topological RN in representations acquired pre-stroke; and the Object arrays task (Della Sala et al., 2004; Denis et al., 2002) was used to assess non-topological RN for layouts learnt post- stroke.

Lastly, as discussed earlier, RN tasks typically depend on a number of ancillary cognitive processes such as imagery formation, visual and spatial working memory (WM), the ability to transform a representation in WM using mental rotation and the ability to make judgements/ inspect the WM representation. To account for these, a formal assessment of visual memory, visuospatial memory, visual imagery and mental rotation was also conducted to enable an understanding of the RN task results.

Thus, the main aim of the current study was to assess the utility of the novel RN in improving upon limitations identified in existing tests and identifying patients with topological and non-topological RN. In patients identified with RN on the novel tasks, an additional aim was to study if their RN manifestation varied based on time at which layout was learnt (pre, post stroke). The last aim of the study was to explore the contribution of ancillary cognitive mechanisms to these representational deficits. Thus, three main hypotheses were proposed:

i) Dissociations in RN manifestation will be observed in patients based on type of layout being represented (topological, non-topological) and time at which layout was learnt (pre-stroke, post-stroke).

ii) Patients with RN would show an impairment contralesional to their cortical lesion on the RN tasks.

iii) All patients with RN would show deficits in one or more ancillary cognitive mechanisms assessed such as visual imagery, visual memory, visuospatial working memory and mental rotation.

4.2 Methods

4.2.1 Participants

Patients: Fifteen chronic stroke patients (*Mean Age* = 62.88, *SD* = 15.84; *Mean Education* = 12.56 years, *SD* = 2.87 years; *males* = 11, *right handed* = 15) were recruited from the Cognitive Neuropsychology Centre (CNC) at the Department of Experimental Psychology, University of Oxford. At the time of testing, the patient group was on average 414 days post stroke (*SD* = 189 days). Patients were not pre-selected on the basis of their lesion location (9 right hemisphere lesions, 5 left hemisphere lesions, 1 bilateral hemisphere lesion). Nor were they pre-selected using any RN assessment before the study for the following reasons: (i) there is no gold standard or standardized test available for RN testing; (ii) commonly used RN measures, i.e. the Familiar squares and o'Clock tests had shortcomings that compromised their ability and sensitivity to screen for RN in relation to this study's aims. For example, there were no unanimously agreed upon famous squares in the UK that could be used for Familiar squares test. Additionally, most available tasks relied on representations from long term memory for which a baseline assessment from prior to brain injury could not be acquired. All patients were medically stable. Patient details including age, gender, handedness and side of lesion are provided in the Supplementary material (Appendix B, Table 4a).

For each patient, neuroimaging used to identify the lesion were structural scans obtained from either a 1.5 Tesla Siemens MRI scanner at Oxford Centre for Clinical Magnetic Resonance Research (OCMR, 7 patients) or a 3 Tesla Phillips MRI scanner at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB, 8 patients) at the time closest to the behavioural testing. For all except two patients who were claustrophobic and could not be re-scanned (LB, MG), research scans and behavioural testing was performed at the chronic stage of stroke. For LB and MG, scans available were from the acute stage post stroke; but behavioural testing was done in the chronic stage. Lesions were manually drawn and smoothed at 5 FWHM using MRICron and co-registered to MNI space using FMRIB Software Library (FSL) v5.0.8. For lesion descriptions, FSL (FMRIB Software Library)'s Harvard-Oxford cortical structural atlas and Diedrichsen et al's probabilistic cerebellar atlas were used (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009).

Healthy controls: For the novel RN measures, twenty healthy controls (*Mean Age* = 66.9, *SD* = 8.6; *Mean Education* = 13.6 years, *SD* = 4.2 years; *Males* = 4; *Right Handed* = 19) were recruited from the CNC (described in Chapter 3). There was no significant difference in the distribution of age (Mann Whitney U = 111.5, z = -0.34, *ns*, r = -0.10) or education (Mann Whitney U = 91, z = -1.16, *ns*, r = -0.30) between the patient and healthy control groups. For the supplementary RN tasks, the Object arrays task was conducted with 10 age-matched controls and the Geographical map description task was conducted with 9 age-matched controls. For the ancillary cognitive tasks, control data was obtained for tests where published normative data were not available. The number of controls who performed each task varied between 15 and 19. There was no significant difference in the average age of the control groups and each of the RN patients ($p >$ 0.05).

The study protocol was approved by the local ethics committee (Central University Research Ethics Committee, University of Oxford) and was in agreement with the ethical principles in the Declaration of Helsinki. All participants provided written consent to participate in the study, were able to understand conversational English and were tested over multiple sessions in a quiet testing room at the Centre.

4.2.2 Procedure

Each patient was administered the Shopping Mall (topological) and Clock Cueing (non-topological) task to identify individuals with topological and non-topological RN respectively. Those patients identified with RN on the novel tests were also assessed on supplementary RN measures to identify if their RN was modulated by time of acquisition of stimuli, thus creating a 2 x 2 design (type of layout, time of acquisition of layout). While both the Shopping Mall and Geographical map description tasks assessed topological RN, the Mall tested post-stroke learning while the Map task assessed pre-stroke information. Similarly, both Clock Cueing and Object Arrays tasks assessed non-topological RN, but for post-stroke and pre-stroke information respectively. Each patient's performance on each task was compared to age-matched controls to identify RN. Finally, for each of the patients identified with RN, an ancillary cognitive test battery was administered to help in characterising their deficits.

4.2.3 Outcome measures

4.2.3.1 Novel RN tests

The Shopping Mall (Mall task): Topological RN for memory acquired post-stroke

Please refer to Chapter 3, Section 3.2.2 for details of the task and Figure 3.1 for depiction of the Shopping Mall.

Clock Cueing: Non-topological RN for memory acquired pre-stroke

Please refer to Chapter 3, sections 3.3.2 for relevant details of the Clock Cueing task and Figure 3.2 for the task's layout and procedure.

4.2.3.2 Supplementary RN tasks

Geographical map description (Map task): Topological RN for memory acquired pre-stroke

This task was taken from existing literature (Bartolomeo et al., 1994; Rode et al., 2010) and adapted to suit the United Kingdom (UK) population. Participants were instructed to imagine that they were standing at Oxford on a virtual map of the UK facing Inverness in the north. They were required to report from imagery, the cities/towns falling on the left or right of an imaginary line drawn between Oxford and Inverness. They also had to rotate their mental image of the map, i.e. imagine themselves standing at Inverness and looking south towards Oxford and then to report cities/towns from this new perspective (Figure 4.1).

Figure 4.1. Map of UK with cities for Geographical Map Description task

Participants were asked to imagine the map of UK in their mind and report cities from their mental image of the map from two perspectives, i.e. while imagining standing at Oxford facing Inverness and vice versa. In the above figure, the red dotted line decided the criteria for slotting cities into left and right. When imagining standing at Oxford and facing Inverness, 36 cities were categorized as being to the left of the line and 28 to the right of the line. 5 cities including Oxford and Inverness were on the imaginary line.
Figure obtained from public domain:
https://en.wikipedia.org/wiki/List_of_cities_in_the_United_Kingdom

After the imagery phase of the task, participants received a list of the 69 cities in England, Scotland, Wales and Northern Ireland. They indicated for each city whether they were familiar with the city or not and if it was located on the left or right of the imagined demarcation line or on the line itself. Additionally, in a subsequent visit separated by at least one month, RN patients who were deficit on this task were asked for free recall of UK cities.

The Object arrays task: Non-topological RN for memory acquired post-stroke

This task was also adapted from existing RN literature (Della Sala et al., 2004; Denis et al., 2002; Logie, Della Sala, Beschin, & Denis, 2005). Participants were shown 2 x 2 arrays of ten categories of objects which they would first name and then report from imagery when the object pictures were taken away each time. The categories were birds, mammals, body parts, Christmas, desk tools, fruits, vegetables, kitchen items, sports and transportation vehicles. For each category, two A3 sheets were joined together forming a 58 cm x 41.5 cm area showing one each of the category's 15 cm x 10 cm object picture in the left and right, upper and lower quadrant. Each layout was visually presented to the participant one at a time and the participant was asked to name and report the location of each object. After 90 second exposure duration, the layout was taken away from sight and participants were asked to report the objects and their locations from memory. The experimenter requested participants to create a visual image of each layout that they were exposed to.

Recall was required from the standard or reversed perspective. In the standard perspective, participants recalled the objects and their locations from the position they had seen them. In the reversed perspective, they were asked to imagine sitting at the other side of the table and recall objects and their placement from this new perspective.

Since the same object pictures were to be used for both the standard and reversed perspectives, the task was administered to the participant over two sessions with one perspective each being tested in each session. The order of perspective taking between sessions was counterbalanced across participants. Please see Figure 4.2 for an example of the Object arrays task.

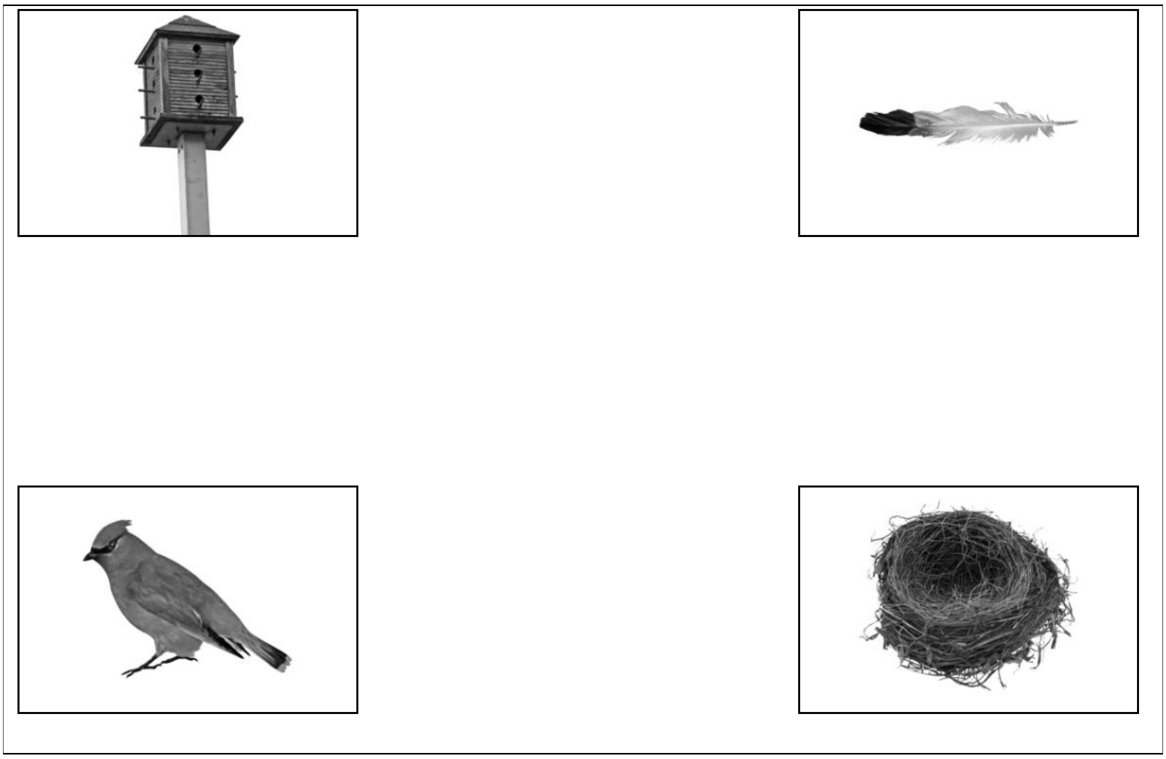

Figure 4.2. Sample layout from Della Sala's Object arrays task adaptation

The above layout depicts four pictures from the category 'birds' presented to the left (top and bottom) and right (top and bottom) of the participant's midline. Participants were presented the layout for 90 seconds as they named each object and its location on the sheet. The layout was then taken away from their vision. They were asked to create a visual image of the layout from either the standard or reversed perspective and name the object and its location from the assigned perspective. The order of perspective taking was counterbalanced and conducted in two separate sessions.

Please note that the original Object arrays study also had a 'verbal' condition where participants were asked to imagine the layout of objects based on verbal descriptions by the examiner. This condition was used in the study to omit any impact of visual neglect as well as to assess whether patients with RN were able to construct and mentally transform images based on verbal descriptions (Della Sala et al., 2004). In the current study, the identified RN patients did not have visual neglect. Since the aim of using this task was only to identify non-topological RN for novel material, the 'verbal' condition was omitted to keep the test battery relevant to the study's dominant aims.

4.2.3.3 Ancillary cognitive test battery

In order to characterise the patient's deficits, a short RN task-associated test battery was conducted with those identified as having deficits on the Mall and Clock Cueing tasks. Please refer to Table 4.1 for details of the test battery including the name of the test, cognitive domain being tested, a brief description of the task and references.

Table 4.1. Ancillary cognitive test battery for RN patients

Domain	Task	Brief Description	Reference
Visual Neglect	Hearts cancellation	Cancel full hearts amidst distractors distributed on both sides of an A4 sheet presented at midline. Time limit three minutes. Spatial asymmetry scores indicate visual neglect.	*Demeyere, N., Riddoch, M. J., Slavkova, E. D., Bickerton, W.L., & Humphreys, G. W. (2015). The Oxford Cognitive Screen (OCS): Validation of a Stroke-Specific Short Cognitive Screening Tool. Psychological Assessment, 27(3), 883–894.*
Visual Imagery	Colour Task	Imagine an object and name its characteristic colour from imagery (*trials*=20)	*Farah, M.J., Hammond, K.M., Levine, D.M., & Calvanio, R.. (1988). Visual and spatial imagery: dissociable systems of representation. Cognitive Psychology, 20, 439-462.*
	Bigger/ Smaller Task	Imagine two objects and state which is bigger in size (*trials*=16).	
	Tails Task	Imagine an animal and state whether its tail is long or short in proportion to its body (*trials*=20).	
Mental rotation	Letter Rotation Task	Four letters in their original or mirror reversed form were presented in various degrees of rotation. Participants had to identify if the letter was in the original or mirror reversed form (*trials*=20).	*Farah, M.J., Hammond, K.M., Levine, D.M., & Calvanio, R. (1988). Visual and spatial imagery: dissociable systems of representation. Cognitive Psychology, 20, 439-462.*
Visuospatial memory	Location Learning Test *(Immediate & Delayed Recall)*	Required learning of 10 object pictures shown in specific locations on a 5 x 5 grid. Test assessed immediate and delayed recall for object picture and location binding.	*Bucks, R.S., & Willison, J.R. (1997). Development and Validation of the Location Learning Test (LLT): A Test of Visuo-Spatial Learning Designed for Use with Older Adults and in Dementia. The Clinical Neuropsychologist, 11, 273-286.*
	Spatial span task *(Forward & Backward)*	Participants had to learn the order in which examiner tapped on a series of blocks and in separate trials, immediately repeat in the same order or in the reversed order for the backward version. Blocks ranged from two in number to seven, in ascending order of difficulty.	*Wechsler, D. Wechsler Memory Scale-Revised. 1987; San Antonio, TX: The Psychological Corporation.*
Visual memory	Shapes test from Doors & People test battery *(Immediate and Delayed Recall)*	Tested immediate and delayed visual recall of four line drawings.	*Baddeley, A.D., Emslie, H., Nimmo-Smith, I. (1994). Doors and people: a test of visual and verbal recall and recognition. Bury St. Edmunds, England: Thames Valley Test Co.*

4.2.4 Scoring and Data Analyses

4.2.4.1 Novel RN tasks

Statistical analyses comparing patient and control group performances on the novel tasks are not directly relevant to the aims of the study and are included in Appendix 4.

The Shopping Mall task

Please see Chapter 3, section 3.2.3 for scoring details. In brief, shop identity (SId) and shop identity+ location (SIdLoc) scores were calculated for each patient separately and combined across top and bottom perspectives for each side of the Mall. These scores were computed separately for viewer-independent and viewer-dependent perspectives. Additionally, Laterality Quotients (LQ) were calculated as:

LQ = (Left shops- Right shops)/ (Left shops+ Right shops) * 100

Thus, four LQs were calculated for each patient and control: viewer-independent SId LQ, viewer-dependent SId LQ, viewer-independent SIdLoc LQ and viewer-dependent SIdLoc LQ. *A negative LQ implied impaired performance on shop report for left- sided shops and vice versa.*

To identify if a patient in the group had topological RN, each patient's performance was compared to controls' performance using the Crawford and Howell's t-test (Crawford & Garthwaite, 2005; Crawford & Howell, 1998). Please refer to Chapter 2, section 2.3.2.4 for details of the test. Using this test, each patient's LQ was compared to age- matched healthy controls to identify those with significant impairments. In order to avoid false positive errors, in addition to being significantly different from controls' performance, the patient was only classified as having topological RN on the task if his/ her score was worse than the worst control their performance was being compared to (Guariglia et al., 2013).

Recognition memory: Each RN patient's d prime (d') and response bias (c) scores were also compared to controls' to assess if their recognition memory performance and tendency to respond to shop pictures and locations as previously seen or unseen was significantly different from controls. Additionally, to assess whether there were any side-based differences in recognition memory, an LQ was calculated for each of shop identity recognition and shop location recognition scores. Each topological RN patient's LQ was compared to the controls' LQs to identify whether laterality based differences in left and right-sided shop recognition might contribute to their imagery performance.

Familiarity ratings: Each RN patient's overall familiarity ratings for shops included in the Mall was compared to controls' average ratings. To identify if there were any significant laterality effects between familiarity for shops in the left and right side, a Familiarity LQ was calculated and compared with controls' LQs.

Clock Cueing task

1) Overall validity effect (OVE): All invalid trials -all valid trials
2) Right validity effect (RVE): Right invalid trials -right valid trials
3) Left validity effect (LVE): Left invalid trials -left valid trials

Left invalid trials indicated trials where the cue directed attention to the left side of imagined clock and right invalid trials indicated trials where the cue directed attention to the right side of the imagined clock.

Each patient's speed of performance (measured by reaction time, RTs) and proportion of targets detected was compared to controls' for each of the indices using the Crawford and Howell's t-test (Crawford & Howell, 1998). As the first step, if a patient's OVE performance for either RTs or target detection was significantly different from controls' AND worse than the worst control's performance, their scores on LVE and RVE indices were further assessed for non-topological RN to identify side of neglect. If a patient was significantly slower than controls when considering both left and right validity effects, this would be explained as a non-lateralized deficit in attention shifting from imagery space to visual space or on account of an overall slowness in processing speed as compared to controls, rather than RN. However, if they were impaired only on LVE, then they were thought to show left-sided non-topological RN or if they were impaired only on RVE, then they were considered as showing right-sided non-topological RN.

4.2.4.2 Supplementary RN tasks

The supplementary RN tasks (Geographical map description, Object arrays task) were only conducted with those patients who were identified as having RN on the novel tasks. Hence, for these, between group analyses were not possible. Instead, within group analyses was performed for the control group to compare their representations of task stimuli for the left and right side of the layout.

<u>Geographical map description task (Map task)</u>

The number of cities reported from the left and right side using both perspectives in imagery space was combined as in the Shopping Mall task, i.e. viewer-independent and viewer-dependent perspectives. Controls' performance for left and right- sided cities for both perspectives was compared using paired t-tests. A viewer-independent LQ and a viewer-dependent LQ was calculated for each of the RN patients and was compared to controls' LQs using the Crawford and Howell's t-test. Topological RN was considered if either of the patient's perspective based LQs was significantly different from the controls AND worse than the worst control's LQ.

Familiarity and accuracy: To further inform about imagery based performance, familiarity for city location and accuracy of each city's report as being to the left or right of the imagined demarcation line was also scored. This was performed to assess the participant's overall familiarity and semantic knowledge for the layout of towns in the UK. Controls' accuracy for categorizing cities as being to the left and right of the demarcation line was compared using a paired t-test. Additionally, a familiarity based LQ was calculated to identify if there were any significant differences in the patient's familiarity with cities to the left or right when compared to controls.

The Object arrays task

Object report for the left and right side was combined across standard and reversed imagery report. Controls' performance for left and right- sided object recall for each perspective was compared using paired t-tests. Object report scores for the left and right sides were used to calculate viewer-independent and viewer-dependent LQs. Each RN patient's LQ for viewer-independent and viewer-dependent perspectives was compared to controls using the Crawford and Howell's t-test. A patient was only considered to have non-topological RN on this task if their LQ was significantly different from controls AND was worse than the worst control's performance as depicted by their LQ.

4.2.4.3 Ancillary cognitive test battery

Test manuals were used to convert raw scores to standard scores and refer to age-appropriate tables to interpret task performance. Where tests were experimental tasks, the published test articles were referred to for scoring and interpretation guidelines.

Normative data for these tests was obtained with a sample of healthy controls who were age-matched to the identified RN patients.

4.3 Results

Identification of individual RN patients is covered in Results section 4.3.1 below, while patient's demographic, lesion and cognitive profile is covered in section 4.3.2.

4.3.1 Identification of RN patients

4.3.1.1 Novel RN tasks

The Shopping Mall task

Two patients (DR and EH) showed topological RN based on their Shop identity (SId) and Shop identity+location (SIdLoc) LQs (Table 4.2). Patient DR had impaired shop report for left-sided shops from imagery, i.e. impaired viewer-independent LQ, $t(19) = -5.1$, $p = 0.00003$ while EH showed impairments for reporting right sided shops as seen in both viewer- independent, $t(19) = 4.39$, $p = 0.0002$ and -dependent LQs, $t(19) = 2.91$, $p = 0.004$, when compared to controls. Data for all other non-RN patients tested on these indices is given in (Appendix B, Table 4b).

Table 4.2. *Topological RN patients' perspective based shop report and LQs for Shop Identity (SId)*

Shop Identity scores (SId)										
Patient ID	Left		Right		Viewer- independent scores			Viewer- dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
DR	3	4	5	5	**7**	**10**	**-17.65***	9	8	5.88
EH	5	6	6	2	**11**	**8**	**15.79***	**12**	**7**	**26.32***
Mean (SD) Ctrls *n*=20	8.25 (1.55)	9.05 (1.15)	8.85 (1.46)	8.35 (1.35)	17.3 (2.45)	17.2 (2.5)	0.33 (3.44)	17.9 (2.53)	16.6 (2.85)	3.94 (7.5)

**p ≤ 0.005 and patient's LQ is worse than the worst control performance being compared to.*
*Ctrls = Controls; SD = Standard Deviation;LQ = ((left shops-right shops)/ (left shops+ right shops)) *100*
Maximum score for each of left and right, top and bottom shop report was 10. Thus, total shops reported from the left and right each for viewer-independent and viewer-dependent scoring was out of 20.

When considering SIdLoc scores (Table 4.3), DR continued to show impaired left-sided shop report from imagery based on viewer- independent LQ, $t(19) = -2.18$, $p = 0.02$ and EH continued to show right-sided deficits when considering viewer- dependent LQ, $t(19) = 5.76$, $p = 0.00001$ as compared to controls. Data on these measures for all other patients is given in Supplementary material (Appendix B, Table 4c).

Table 4.3. *Topological RN patients' perspective based shop report and LQs for Shop identity+ Location (SIdLoc)*

Shop Identity + Location scores (SIdLoc)										
Patient ID	Left		Right		Viewer- independent scores			Viewer- dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
DR	2	4	5	4	**6**	**9**	**-20***	9	6	20
EH	0	5	6	1	5	7	-16.67	**11**	**1**	**83.33***
Mean (SD) Ctrls *n*=20	6.25 (2.63)	7.4 (2.06)	7.1 (2.47)	6.65 (2.35)	13.65 (4.34)	13.75 (4.58)	-0.14 (8.9)	14.5 (4.27)	12.9 (4.89)	7.04 (12.93)

**p* ≤ 0.05 and patient's LQ is worse than the worst control performance being compared to*
*Ctrls = Controls; SD = Standard Deviation;LQ = ((left shops-right shops)/ (left shops+ right shops)) *100*
Maximum score for each of left and right, top and bottom shop report was 10. Thus, total shops reported from the left and right each for viewer-independent and viewer-dependent scoring was out of 20.

Recognition memory:

For shop's identity based on picture recognition, DR did not show any significant laterality biases (LQ=0) as compared to controls (Controls' *Mean* (*SD*): LQ=-1.47 (7.6); in fact he recognized all 10 shops that he had learnt to the left and right side of the Mall. For shop's location (spatial) recognition, his LQ of 25 was significantly worse than controls, $t(19) = 2.39$, $p = 0.01$; controls' spatial recognition LQ *Mean* = 1.79, *SD* = 9.46. Specifically, his recognition of locations of shops for the right side of the Mall was worse than the left (left-sided shops correct = 10/10, right-sided shops correct = 6/10).

EH's shop identity recognition LQ was significantly different from controls' LQ, $t(19) = 2.76$, $p = 0.006$; EH's LQ=20; Controls' *mean* LQ=-1.47, *SD*=7.6. Not surprisingly, his recognition of shop identities for right- sided shops (6/10) was worse than left- sided shops (9/10). No such significant biases were noted for shops' location recognition scores, EH's LQ = 14.29, $t(19) = 1.29$, $p > 0.05$, controls' spatial recognition LQ *Mean* = 1.79, *SD* = 9.46.

For d' and response bias (c) measures for shop identity and shop location recognition, both DR (shop identity: d'=3.16, c=-0.17; shop location: d'=2.35, c=0.21) and EH (shop identity: d'=1.43, c= 0.16; shop location: d'=1.24, c=0.19) were comparable to controls ($p>0.05$), indicating that their ability to identify previously seen pictures from amidst distracters and tendency to respond to pictures as seen or unseen were both comparable to controls (Controls *Mean* (*SD*): shop identity recognition: d'=2.4 (0.79), c=-0.05 (0.33); shop location recognition: d'=2.3 (0.86), c=0.14 (0.19)).

Familiarity ratings:

Familiarity ratings of shops, on average, for DR (1.41) and EH (1.98) were not significantly different from controls' familiarity (*Mean* (*SD*)= 2.09 (0.76), $p>0.05$). There were no significant biases in DR or EH's familiarity for shops on the left and right side when compared to controls, *p's* > 0.05; DR's LQ=16.98; EH's LQ = -1.9; Controls' *mean* LQ=5.05, *SD*=10.51.

To summarize the Mall results, two patients (DR and EH) showed at least one form of topological RN for post-stroke information. While DR demonstrated left-sided viewer-independent RN, EH showed right- sided viewer-dependent RN on this task. This indicated that DR's left sided representational bias was only evident when perspective shifting was attempted, whereas EH's right-sided deficits were not contingent upon mental rotation of the layout. There were no significant biases in either of their reported familiarity with shops for the left and right side. However, when comparing recognition based LQ performance between these patients and controls, DR's shop location recognition and EH's shop identity recognition for right- sided shops was worse than for *left- sided shops. EH's right- sided shop recognition deficits were in line with his viewer-dependent right- sided RN.*

<u>Clock Cueing task</u>

Two controls and one left hemisphere patient (KP) were excluded from the analysis due to >50% false positive responses to catch trials. One other left hemisphere patient was excluded (NB) as he was unable to draw an analogical clock from memory during screening. Thus, the final sample for this task was 18 elderly controls and 13 patients.

When comparing individual patients to controls, RT data showed that three patients (EL, MG, EH) had impaired OVE; EL: $t(17) = 4.03$, $p= 0.0004$; EH: $t(17) = 3.54$, $p = 0.001$ and MG: $t(17) = 3.95$, $p = 0.0005$. Each of these patients performed worse than the worst control's OVE of 485.14 msecs (C7, refer to Appendix, A, Table 3e). EL was significantly impaired in both RVE and LVE implying non-lateralized deficits in switching from imagery space to visual space, rather than RN, RVE: $t(17) = 4.82$, $p < 0.0005$; LVE: $t(17) = 2.97$, $p = 0.004$. However, both MG and EH only showed evidence of right-sided non-topological RN; MG: $t(17) = 6.23$, $p = 0.0005$; EH: $t(17) = 6.42$, $p < 0.0005$.

Table 4.4 shows each non-topological RN patient's RTs whereas Appendix B, Table 4d shows all patients' RTs for each trial type and on OVE, RVE and LVE indices.

Table 4.4 *Non-topological RN patients RTs for all trials and indices in the Clock Cueing task*

Patient ID	Left cue-left target	Left cue-right target	Right cue-right target	Right cue-left target	All invalid trials	All valid trials	Overall validity effect (OVE)	Right validity effect (RVE)	Left validity effect (LVE)
EL	949.93	1611.00	903.16	1810.10	1710.55	926.55	**784.00***	**906.94***	**661.07***
MG	1445.42	1848.23	1323.20	2461.85	2155.04	1384.31	**770.73***	**1138.65***	402.81
EH	1867.11	2106.49	1229.73	2399.21	2252.85	1548.42	**704.43***	**1169.48***	239.38
Mean (SD) Ctrls *n*=18	539.61 (161.26)	684.55 (264.21)	532.54 (168.79)	648.07 (259.36)	666.31 (258.49)	536.07 (163.01)	130.24 (157.84)	115.53 (159.87)	144.94 (168.98)

**p ≤ 0.001;Ctrls = Controls; SD = Standard Deviation; All RTs are in milliseconds.*

Table 4.5 provides each non-topological RN patient's proportion of targets detected for each trial type and for each of the validity indices. None of the patients with impairments in RTs (EL, MG, EH) showed impairments in target detection. However, another patient, AR's target detection based OVE was significantly worse as compared to controls, $t(17)= 7.06$, $p < 0.0005$, and was worse than the worst two controls' whose OVE were 0.01 (C7, C17, refer to Appendix 3, Table 3f). However, AR's performance on both RVE and LVE was significantly worse than controls implying non-lateralized deficits in switching from imagery space to visual space, rather than RN (RVE: $t(17)= 7.59$, $p<0.0005$; LVE: $t(17) = 3.7$, $p = 0.0008$). The target detection data for all patients' tested is given in Supplementary material (Appendix B, Table 4e).

Table 4.5. *Non-topological RN patients' proportion of targets detected for all trials and indices in the Clock Cueing task*

Patient ID	Left cue- left target	Left cue- right target	Right cue- right target	Right cue- left target	All invalid trials	All valid trials	Overall validity effect (OVE)	Right validity effect (RVE)	Left validity effect (LVE)
EL	0.98	1	1	1	1	0.99	0.01	0	0.02
AR	0.98	1	0.96	1	1	0.97	**0.03***	**0.04***	**0.02***
MG	1	1	1	1	1	1	0	0	0
EH	1	1	1	1	1	1	0	0	0
Mean (SD) Ctrls *n*=18	1 (0.006)	1 (0)	1 (0.006)	1 (0)	1 (0)	1 (0.004)	0.001 (0.004)	0.001 (0.005)	0.001 (0.005)

**p* $\leq$ *0.001; Ctrls = Controls; SD = Standard Deviation*

Overall, when reviewing RTs and target detection performances, EH and MG showed lateralized deficits indicative of right- sided non-topological RN for pre-stroke information.

Thus, three RN patients were identified on the novel measures and each was administered the supplementary RN tasks (discussed below).

4.3.1.2 Supplementary RN tasks

Geographical map description task (Table 4.6)

Controls' report of cities from imagery did not significantly differ for the left and right side of the demarcation line for either the viewer-independent, $t(8)$ =-1.33, p = 0.22, *Cohen's d* = 0.12 or viewer-dependent perspectives, $t(8)$ = -0.33, p = 0.75, *Cohen's d* = 0.04, i.e. their recall of cities from both sides was comparable.

Of the three RN patients, only EH's viewer-dependent LQ was significantly different from controls, $t(8)$ = 10.04, $p < 0.0005$. Specifically, his representation for the *right side* of the map was significantly worse than controls based on viewer-dependent LQ (similar to Shopping Mall task results), i.e. when perspective taking was ignored, he could not report any cities on the right side of his visual image, but he could report 12 cities from the left side of the map.

Familiarity and accuracy: Following the imagery phase, the participants rated their familiarity with each city and categorized it as being to the left or right of the demarcation line from long term memory/ general knowledge. Of the 69 cities in the UK, controls reported that they were familiar with 55 cities on average. Paired t-test showed that controls' accuracy for cities on the left of the demarcation line was significantly better than for the right side, $t(8) = 5.2$, $p = 0.001$, *Cohen's d* = 1.35; Left- sided cities *Mean* = 27.56, *SD* = 7.3; Right- sided cities *Mean* = 18.22. *SD* = 6.55.

EH's self-rated familiarity with all the cities in the UK (n=61) was higher but not significantly so, as compared to the controls' (*Mean* (*SD*)= 55.3 (9.5)) and found not to be significantly different ($t(8)=-0.57$, $p=0.29$). Of the cities rated as familiar, the controls' got a much higher proportion of accurate answers when categorizing each city's placement to the left or right of the demarcation line (*Mean* (*SD*)=0.82 (0.16)) than EH (0.56), although again, this difference was not statistically significant, $t(8)=-1.5$, $p=0.08$. When comparing LQs, EH's knowledge/ categorization of city locations to the left and right of the demarcation line was not biased significantly differently than controls' (EH LQ=17.65, Controls *Mean* LQ (*SD*)= 21.07 (13.2), $t(8)=-0.25$, $p=0.4$. Notably, on free recall of cities conducted with EH one month later, his performance was symmetrical and he reported 5 cities each from the left and right of Oxford.

To summarize, on this task EH showed lateralized deficits indicative of right-sided topological RN for pre-stroke information. Interestingly, his familiarity with UK cities *and accuracy of city placement to the left or right side of the demarcation line from memory, was not significantly different from controls. His free recall of cities from long term memory did not show any lateralized biases.*

Details of the RN patients' performance on the Geographical map description task is provided in Table 4.6.

<u>*The Object arrays task (Table 4.7)*</u>

Paired t-tests showed no significant difference in controls' viewer-independent performance for left and right- sided items, $t(9) = -1.31$, $p = 0.22$, *Cohen's d* = 0.27. However, a significant difference was seen for object report when scoring the same objects from the viewer-dependent perspective, $t(9) = 2.25$, $p = 0.05$, *Cohen's d* = 0.41; Left- sided items , *Mean* = 19.2, *SD* = 1.32; Right- sided items, *Mean* = 18.6, *SD* = 1.58, i.e. controls reported more objects from the left side of the image than the right when perspective taking was ignored. Each RN patient's LQ was compared to the controls' LQ scores and neither their viewer-independent nor viewer- dependent based LQs were significantly different from controls'(p's>0.05).

Thus, none of the RN patients were impaired on the Object arrays task.

Table 4.6. *Performance of RN patients on Geographical map description task using viewer-independent and viewer-dependent perspective based scoring*

Patient ID	Familiarity				Imagery Oxford-Inverness		Imagery Inverness-Oxford		Viewer-independent perspective			Viewer-dependent perspective		
	L	*R*	*Total correct*	*LQ*	*L*	*R*	*L***	*R***	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
EH	20	14	34/61	17.65	6	0	0	6	6	6	0	**12**	**0**	**100***
MG	9	8	17/52	5.88	3	2	2	2	5	4	11.11111	5	4	11.11111
DR	25	20	45/65	11.11	5	5	4	3	9	8	5.882353	8	9	-5.88235
Mean (SD) Controls (*n*=9)	28 (7.3)	18.7 (6.55)	46.7/49.22	21.07 (13.2)	11.78 (5.07)	12.67 (6.04)	10.56 (6.27)	11.00 (6.22)	22.33 (10.93)	23.67 (11.66)	-1.59 (9.19)	22.78 (10.91)	23.22 (11.85)	0.76 (9.38)

**p = 0.0005*
***For imagery (Inverness-Oxford), L: Left = perceived left; R: Right = perceived right; SD = Standard Deviation;*
LQ= ((left- sided cities-right- sided cities)/ (left -sided cities+ right- sided cities)) x 100

Table 4.7. *Performance of RN patients on the Object arrays task using viewer-independent and viewer-dependent perspective based scoring*

Patient ID	Imagery Standard view		Imagery Reversed view		Viewer-independent perspective			Viewer-dependent perspective		
	Left (max=10)	*Right (max=10)*	*Left* (max=10)*	*Right* (max=10)*	*Total left (max=20)*	*Total right (max=20)*	*LQ*	*Total left (max=20)*	*Total right (max=20)*	*LQ*
EH	9	9	8	9	17	18	-2.86	18	17	2.86
MG	10	10	6	7	16	17	-3.03	17	16	3.03
DR	10	10	2	2	12	12	0	12	12	0
Mean (SD) Controls (*n*=10)	10 (0)	9.9 (0.32)	8.7 (1.64)	9.2 (1.32)	18.78 (1.72)	19.11 (1.36)	-0.95 (2.75)	19.22 (1.39)	18.67 (1.66)	1.52 (2.44)

**Left = perceived left; Right = perceived right; SD = Standard Deviation*
LQ = ((left- sided objects – right- sided objects)/ (left- sided objects + right- sided objects)) x 100

As per the results so far, patient data from the RN tasks support the first hypothesis, i.e. dissociations between topological and non-topological RN as well as based on time of acquisition of representation were observed. DR showed impairments only for topological material learnt post-stroke (Shopping Mall); while MG showed deficits only for non-topological material learnt pre-stroke (Clock Cueing). Additionally, EH showed more extensive deficits involving topological RN for both pre- and post-stroke information and non-topological RN for pre-stroke information. Please refer to Table 4.8 for tabular summary of these results.

Table 4.8. *Overview of patients identified with deficits on the RN tasks*

Time of memory acquisition	Type of representation	
	Topological	*Non-topological*
Pre-stroke	Geographical map description ***EH***	Clock Cueing ***EH, MG***
Post-stroke	The Shopping Mall ***EH, DR***	The Object arrays task

4.3.2 Characterisation of RN patients

Three patients with RN were identified on the RN tasks (DR, EH, MG).

4.3.2.1 Patient and lesion profiles

Figure 4.3 depicts the lesion profiles of each RN patient. Surprisingly, each patient identified with RN on the novel tasks, despite the dissociations based on type of stimuli and time of acquisition of memory, had a right- sided cerebellar lesion.

DR (born in 1935), a 79 year old right-handed male, had 14 years of formal education and retired as a bar inspector. At the time of testing, he was still working part-time as a tailor. He had a stroke in July 2013, causing right cerebellar lesions to lobules V, VI and the right crus I (Figure 4.3a).

EH (born in 1947), a 67 year old right-handed male, left school at the age of 16. He retired as a MOD squadron labourer. EH had two separate strokes in the same year (2013), with one stroke resulting in infarcts in the right inferior frontal gyrus and insula and the second stroke resulting in right cerebellar lesions involving lobules VIIa-b, VIIIa-b and right crus II (Figure 4.3b).

MG (born in 1944), a 70 year old right-handed female, with 15 years of formal education, retired as a student organizer. She had a stroke in May 2013 and her lesions included right cerebellar lobules I-VI, VIIIa, VIIIb, IX and right crus I and II (Figure 4.3c).

Each patient was tested in the chronic stage (approximately 1 year post stroke, between July and November 2014). For patients DR and EH, the scans were obtained at the chronic stage when the behavioural assessments were conducted. However, for MG, the only scan available was a lower resolution clinical MRI scan from the acute stage of her stroke, i.e. one day post stroke. She could not be scanned again in the chronic stage on account of contraindications. In the figure, DR and EH's lesions are shown on their respective structural T1 scans from the chronic stage while MG's lesion is shown on her acute stage FLAIR scan.

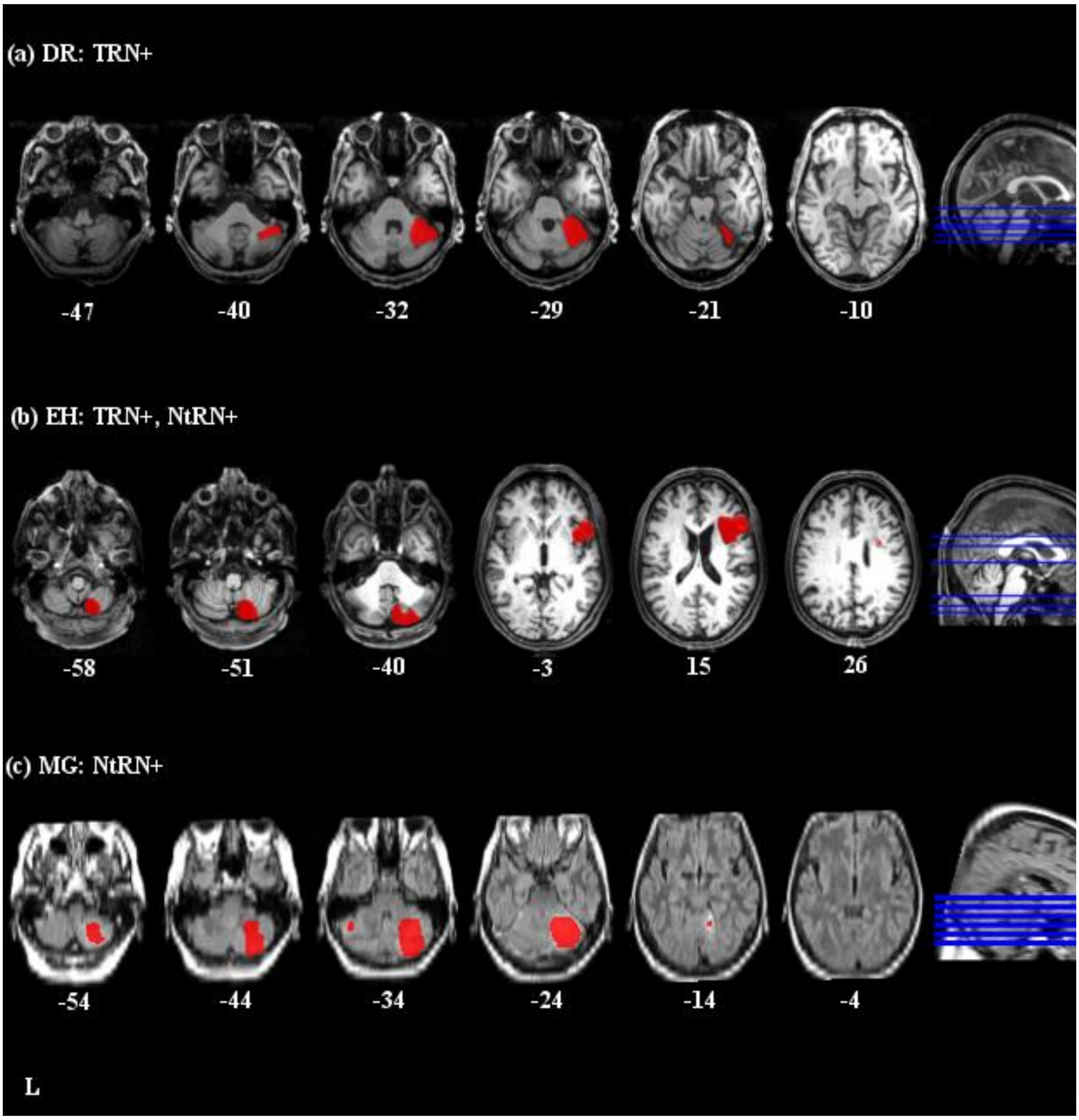

Figure 4.3. Lesion profile of DR, EH and MG

L = left side of brain. Axial z co-ordinate corresponding to each slice depicted is shown below the slice. Lesions of the three RN patients (a) DR (b) EH (c) MG. DR and EH's lesions were drawn on T1 structural scans obtained in the chronic stage whereas MG's lesion was drawn on a structural scan obtained in the acute stage of stroke. All three patients showed lesions in the right cerebellar region with EH showing an additional lesion in the right frontal and insula region. Within the right cerebellum, DR's lesion included lobules V, VI and the right crus I, EH's lesion included lobules VIIa-b, VIIIa-b and right crus II and MG's lesion included lobules I-VI, VIIIa, VIIIb, IX and right crus I and II

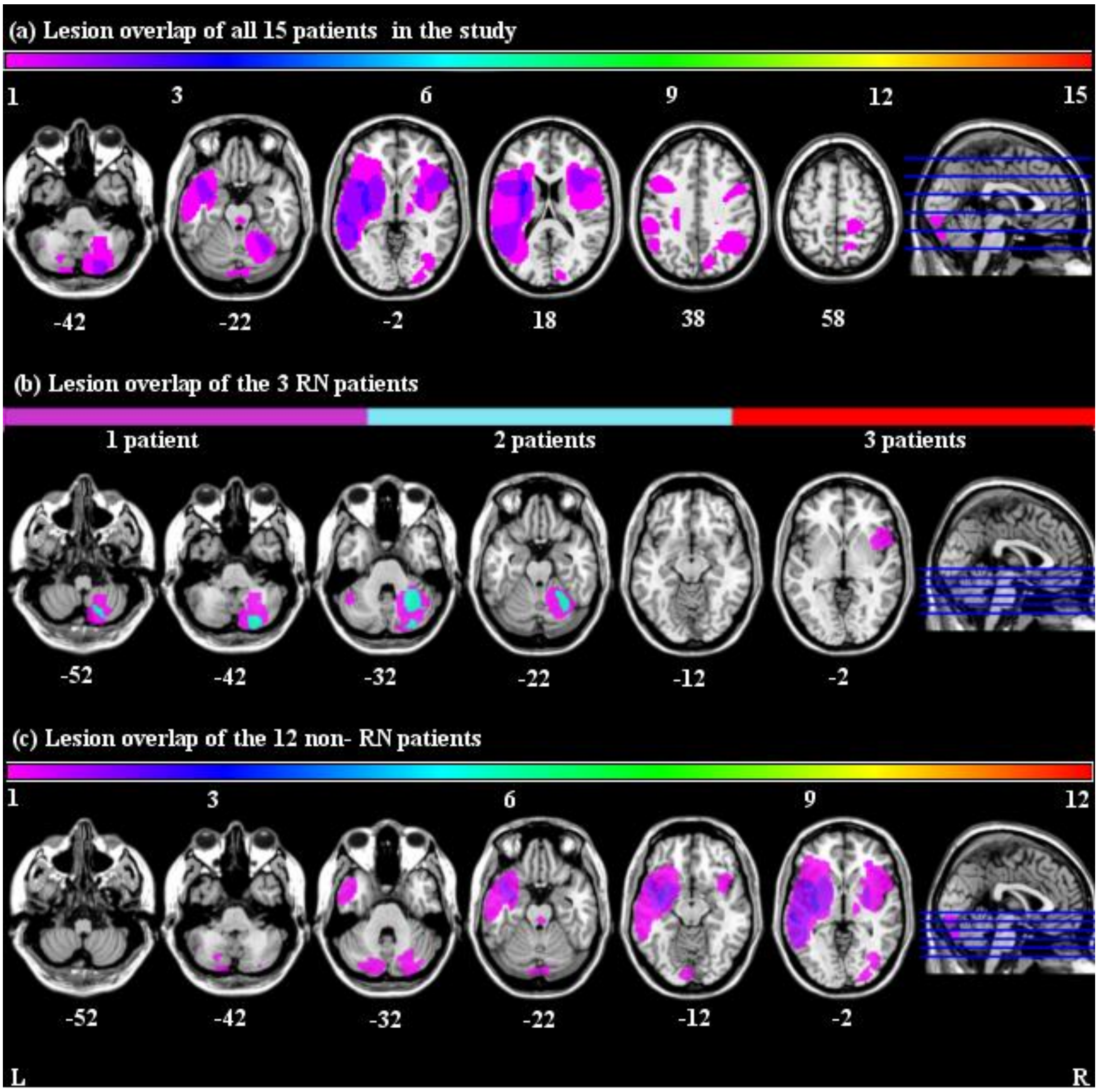

Figure 4.4. Lesion overlaps of all patients and sub-group of RN patients

L = left side of brain. Axial z co-ordinate corresponding to each slice depicted is shown below the slice.

Figure (a) shows lesion overlaps of all patients included in the study with maximum overlaps seen in bilateral insula, left temporal lobe, putamen and right cerebellar crus. Non-overlapping lesions of individual patients extended across all four lobes and cerebellum in the left hemisphere. In the right hemisphere, individual patients' lesions were seen to occupy temporal and occipital lobes, insula and cerebellum.

Figure (b) shows an overlap of lesions from all three RN patients. The figure depicts that there was no overlap between all three patients, however lesions of DR & MG and EH & MG overlapped. Overall, MG's lesion in the right cerebellum was large and overlapped with DR's lesion in lobule VI and with EH's lesion in crus II. EH also had lesions in the right frontal cortex and insula.

Figure (c) shows an overlap of lesions of the remaining 12 non-RN patients (6 right hemisphere lesions, 5 left hemisphere lesions, 1 bilateral hemisphere lesions). Note that the bilateral hemisphere patient had lesions on both sides of the cerebellum.

Figure 4.4 (a) shows overlaps between lesions of all 15 patients included in the study. The slices are shown in the axial view on a normalized MRI template from MRIcron (ch2.nii.gz) with the corresponding z co-ordinate given below each slice. The maximum overlaps were seen in bilateral insula, left temporal lobe, putamen and right cerebellar crus. Of non-overlapping regions, individual patients were seen to have lesions involving both hemispheres' temporal lobes, insula, occipital lobes and cerebellum as well as the left frontal and parietal lobes.

Figure 4.4 (b) shows overlaps between lesions of the RN patients. Although there was no overlap in lesions between all three RN patients, DR's lesion overlapped with MG's lesion in the anterior part of the right cerebellum (lobule VI) whereas EH's lesion overlapped with MG at the posterior part of the right cerebellum (crus II). EH's lesions in the right frontal anterior territory including inferior frontal gyrus, frontal operculum cortex and the right insula are also visible in this figure.

Figure 4.4 (c) shows lesion overlap of the remaining 12 non-RN patients. Of these, most patients had visible lesions in the cerebral cortex (6 patients had right hemisphere lesions, 5 had left hemisphere lesions) while one patient had bilateral lesions which included the cerebellar hemispheres.

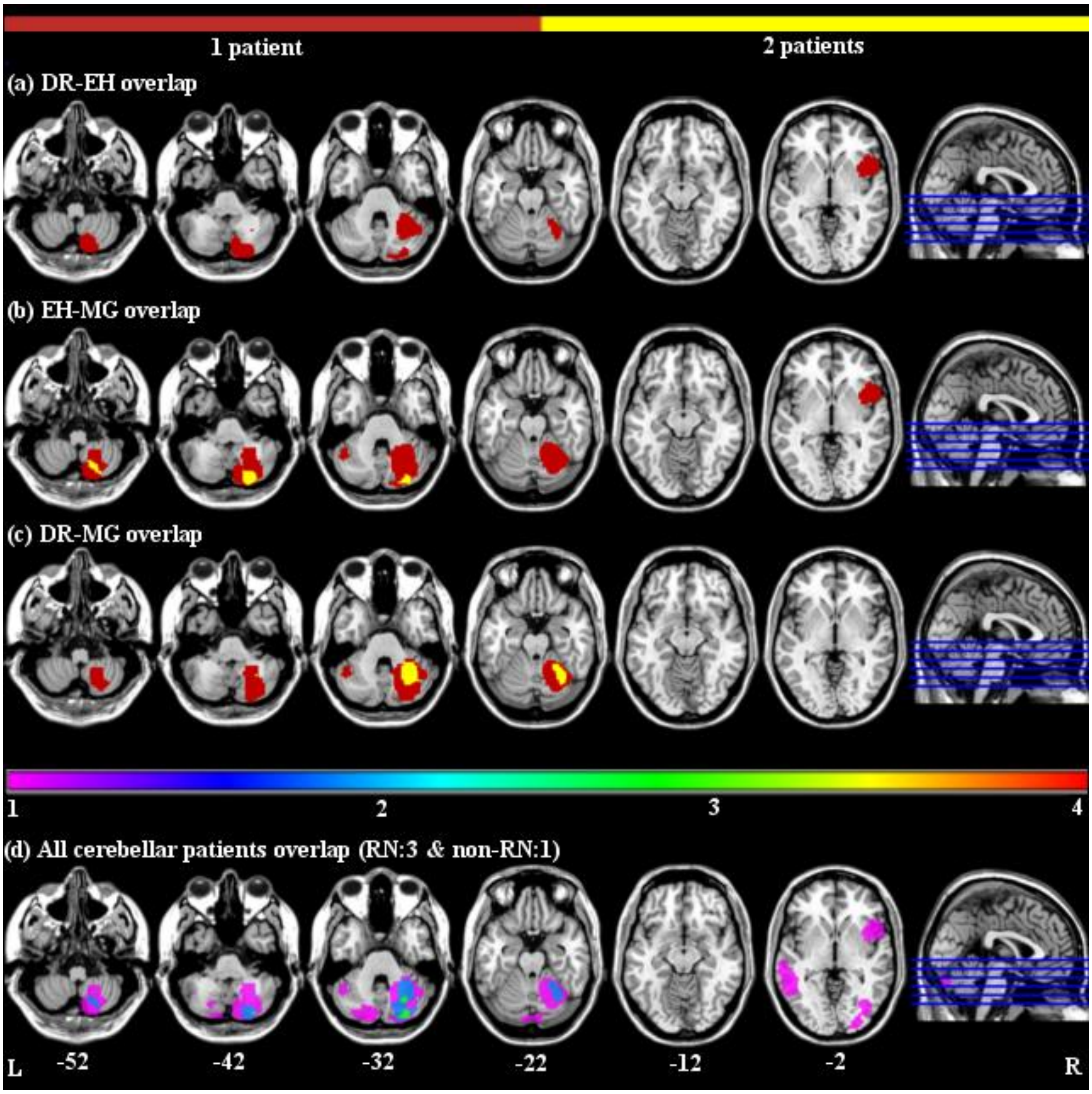

Figure 4.5. Lesion overlaps between DR-EH, EH-MG, DR-MG and all right cerebellar lesion patients' irrespective of RN

L=left side of brain;
Figure (a) shows that between DR and EH, there was no common region of overlap in the cerebellum.
Figure (b) depicts overlap between MG and EH in crus II.
Figure (c) shows overlap between MG and DR in lobule VI.
Figure (d) shows overlap between all tested patients with right cerebellar damage irrespective of RN diagnosis. It can be noted that one non-RN patient (NB) with bilateral damage also showed a right cerebellar lesion which overlapped with EH and MG's lesions in crus II. NB's lesion overlap with MG's lesion was seen to extend to crus I.
The same slices using the axial view on a normalized MRI template (ch2nii) from MRIcron have been used to depict the overlaps in the figure. Axial z co-ordinate corresponding to the slice depicted is provided at the bottom of the figure.

Figure 4.5 shows lesion overlaps in the right cerebellum for DR-EH, MG-EH and MG-DR. DR and EH's lesions were in different regions of the cerebellum. DR's lesion was more anterior and EH's lesion was more posterior. As seen in 4.5a, their lesions did not overlap. MG's lesion was large and extended to both anterior and posterior areas of the cerebellum. Her lesion overlapped with DR in lobule VI (4.5c) and with EH in crus II (4.5b). One patient (NB) who did not have RN, also had bilateral cerebellar lesions. Figure 4.5d shows regions of overlap between the three RN patients (DR, EH, MG) and the 1 non-RN patient (NB) with lesions in the right cerebellum. As can be seen, there were no common regions of overlap between all four patients. However, EH, MG and NB's lesions were seen to co-occupy space in right crus II. While EH and NB's lesions overlapped only in crus II, NB and MG's lesion overlap also extended to crus I. In the figure, these are shown on the same slices using the axial view on a normalized MRI template from MRIcron (ch2.nii.gz).

Based on these results, please note that the second hypothesis, that RN patients would show deficits contralesional to their cortical lesion, needs modification since the RN patients identified had unexpected cerebellar lesions. The extant literature on perceptual neglect has shown mixed findings such that cerebellar lesions can be accompanied by either ipsilesional or contralesional visual neglect (Hildebrandt, Spang, & Ebke, 2002; Kim et al., 2008; Silveri, Misciagna, & Terrezza, 2001). Hence, the second hypothesis for cerebellar patients is revised to expect patients with a mixed profile of representational deficits, i.e. either ipsilesional or contralesional. This hypothesis is supported based on the study's findings, i.e. all three RN patients had right cerebellar lesions; however, while EH and MG showed ipsilesional representational deficits, DR's left-sided RN on the Mall task was contralesional to his cerebellar lesion.

4.3.2.2 Cognitive profiles

For brief description of tests, refer to Table 4.1 and for specific details of each patient's task performance on the ancillary cognitive test battery, please refer to Appendix B, Table 4f.

Table 4.9 gives an overview of each RN patient's performance on the ancillary cognitive test battery. Impairments are shown by a red 'X'. The number of 'X' indicates the number of measures (tests/ aspects of the tests: immediate recall, delayed recall) that the patient was impaired in. Overall, none of the patients showed visual neglect (Oxford Cognitive Screen Hearts Cancellation), but all patients were impaired in visual memory (Shapes test). Only EH and MG were impaired in visuospatial memory (Location learning, Spatial span) and mental rotation (Letter rotation). On imagery tests, MG was impaired on one test (Tails test); while DR was impaired on two of the three imagery tests conducted (Tails, Colours test).

Table 4.9. *Overview of ancillary cognitive deficits*

Cognitive test (*no of measures) / Patient ID	Visual neglect (number of measures: 1)	Imagery (number of measures: 3)	Mental rotation (number of measures: 1)	Visuospatial memory (number of measures: 4)	Visual memory (number of measures: 2)
EH	✓	✓	X	XXX	X
MG	✓	X	X	XX	XX
DR	✓	XX	✓	✓	X

no=number; **Visual neglect measure: OCS Hearts Cancellation; **Visual imagery measures**: Colours test, Big/Small test, Tails test; **Mental rotation measure**: Letter rotation task; **Visuospatial memory measures**: Location learning – Immediate Recall, Delayed Recall; Spatial span - forward, backward; **Visual memory**: Shapes test: Immediate Recall, Delayed Recall.*

*✓ Indicates good performance on a single measure; **X** indicates impaired performance on a single measure. The number of ✓ or X is indicative of performance on more than one test within that domain or when multiple facets of the same test (e.g.: forward and backward span performance, immediate and delayed recall) are measured. Therefore one 'X' indicates impairment in one measure of the cognitive domain, two 'XX' indicates impairment in two measures of the domain and so on.*

Thus, these results support the third hypothesis since each RN patient showed deficits in one or more ancillary cognitive abilities involving visual memory, visuospatial working memory, imagery and mental rotation.

4.4 Discussion

The study identified three patients with RN using the novel and supplementary tasks. As hypothesized, the patients showed dissociations in RN manifestation based on type of representation (topological: DR, non-topological: MG) and time of acquisition of representation (pre-stroke: MG, post-stroke: DR). In addition, patient EH showed RN across both topological (Mall, Map) and non-topological (Clock Cueing) measures as well as pre-(Clock Cueing, Map) and post-stroke (Mall) information. Given that each patient had unexpected cerebellar lesions, the second *revised* hypothesis predicting a mixed profile of ipsilesional and contralesiona deficits was also supported, i.e. DR showed left sided RN, contralesional to his right cerebellar lesion while EH and MG showed ipsilesional right sided RN. Finally, as per the third hypothesis, all three patients showed deficits in ancillary cognitive tests with a common shared deficit in visual memory. DR showed a relatively more intact cognitive profile than EH and MG who had deficits in most cognitive domains tested.

(i) Do the novel measures contribute to RN literature?

Most importantly, the novel methods were useful in identifying patients with RN. DR and EH showed deficits in the Shopping Mall task; and EH and MG showed deficits in the Clock Cueing task.

Along with double dissociations between topological and non-topological RN based on DR and MG's performances, the Mall task also helped to identify dissociations *within* topological RN. In most previous studies, biases in representations are elicited by combining object reports across perspectives and then comparing number of items reported for the left side to the right side (e.g., Guariglia et al., 2013; Rode et al., 2010). When combining object reports across perspectives, the side of the representation is always considered contingent upon the perspective in which the layout is being imagined. However, if a patient was unable to rotate his/her mental representation either due to poor attention allocation to the layout or due to discrete mental rotation deficits, then the assumption that their perception of the layout has changed with perspective shifting is incorrect. Hence, in this study, viewer-dependent LQs were also calculated i.e. where the 'left' side of representation is always considered to be on the left from a canonical perspective, regardless of the perspective taken in imagery. Thus, while DR (who did not show mental rotation impairment in ancillary test battery) showed viewer-independent topological RN for the left side of the Mall's representation, EH (who was impaired on the mental rotation task) showed viewer-dependent topological RN for the right-hand side of the Mall's representation.

This dissociation can be explained using existing theories of RN. For example, DR's pattern of deficits in the Shopping Mall task was similar to Della Sala's proposition of lateralised visuospatial working memory deficits (Della Sala et al., 2004), i.e. that while the patient would be unable to hold and manipulate objects satisfactorily in the left side of imagery space, there would be no significant loss of information during mental rotation of the layout. However, information that had been previously learnt well from the right side of the layout would be lost when rotated and imagined as being on the left. In accordance with this theory, for both SId and SIdLoc scores, DR reported fewer shops from the left side of his representation. These few shops were not lost to report during mental rotation of the Mall to assume the opposite perspective. However, for shops that he had initially reported from the right side of imagery, mental rotation of the Mall led him to forgetting shops when he perceived them as being on his left. It must be noted that DR reported only up to a maximum of 50% of the learnt shops in each perspective, likely on account of his visual memory deficits observed on the ancillary test battery. Hence, the amplitude of laterality based differences is not large.

On the other hand, EH's RN deficit could have been modulated by deficits in mental rotation and/or lateralized spatial attention. In prior studies, changing vantage points to elicit imagery based recall might have been the most logical way to identify whether lateralized deficits were not solely on account of poor memory for the represented layout. However, in patients with difficulties in mental rotation, such as in the case of EH (refer to his Letter Rotation task performance), it is imperative to explore viewer-dependent scores and assess memory for the layout separately. Importantly, if the viewer-dependent representational bias was not investigated, EH's biases would not have been identified. For example, on the Map description task (Table 4.6), on viewer-independent scoring, EH scored an LQ of 0. This indicated symmetrical performance in reporting landmarks from both sides. However, only when considering viewer-dependent scoring, the extreme LQ of 100 became obvious showing that he had severe difficulties reporting cities from the right side of representational space. Thus, in his case, his specific type of RN would have been missed and masked if only traditional scoring methods based on perspective shifts were to be considered.

Lateralized attentional deficits can also be helpful in explaining EH's viewer -dependent topological RN. According to Della Sala et al. (2004), when a patient does not attend to or explore items on one side of imagery space sufficiently, he/she would lack the attentional resources required to mentally transform a poorly explored representation.

While there were no apparent lateralized spatial attention deficits for *visual* space observed in EH's Hearts cancellation performance, he did show lateralised attentional deficits for the right side of *imagery* space as observed in his Clock Cueing performance. This task required patients to use attention exploration processes while maintaining the clock's representation in mind. EH showed significantly slower response times to trials when his attention was required to be disengaged and switched from the right side of imagery space to the left side of visual space, as compared to when no such switching was required (RVE). This deficit cannot be explained as being on account of general attention switching related impairments or as being on account of switching from imagery space to visual space. This is because EH did not show any significant deficits in switching attention from the left side of imagery space to the right side of visual space, as compared to left valid trials (LVE). This finding is also in keeping with Bartolomeo et al.'s (2005) observation that RN patients may be able to form representations for both sides of imagery space but may explore one side inefficiently due to attentional biases.

The Shopping Mall task is also the first RN task to allow a quantitative assessment of memory and ratings of familiarity for the represented layout. Familiarity with shops was not seen to distinguish DR and EH's performance on the task from controls. However, recognition memory was seen to play a role in contributing to topological RN. Task-based recognition memory performance in addition to both patients' deficits in the Shapes test in the ancillary test battery proposes a plausible association between visual memory and RN. However, it is possible that the relation between memory and RN is contingent on whether pre-stroke or post-stroke memory is being represented and on differences between recognition and recall memory (Aggleton & Shaw, 1996; Holdstock, Mayes, Roberts, Cezayirli, Issac, O'Reilly, & Norman, 2002). For example, EH had symmetrical free *recall* of cities in the Map task testing *pre-stroke information*, but his *recognition* of shop locations was impaired for the right side of the Mall's layout learnt *post-stroke*.

To summarize, the Mall and Clock Cueing tasks contributed to the identification of patients with topological (DR) and non-topological (EH, MG) RN deficits. DR and EH not only showed dissociated performance based on type of layout, but also dissociations within topological RN based on whether viewer-independent or -dependent perspective was being considered. Based on their performance in the RN tasks, visual memory, visuospatial working memory, spatial attention and mental rotation may each play an important role in contributing to RN, although the nature of this contribution requires further investigation in future large scale studies.

(ii) Is RN performance modulated by time of acquisition of memory of the representation?

Time of acquisition of memory for information to be represented was important in two out of three RN patients in the current sample. While DR showed RN only while representing a topological layout learnt post-stroke (Shopping Mall), MG showed RN only when considering an object representation learnt pre-stroke (Clock Cueing). Research with patients with neurological damage and amnesia lends support for dissociations pertaining to time of acquisition of memories. For instance, a study of amnesic patients with damage to areas involved in memory processing has shown dissociations in memory recall for remote and recent memories. Rosenbaum et al. (2005) have shown dissociations in a patient's topographical memory performance after widespread brain damage to both left and right hemispheres post a motorcycle accident. Specifically, the patient showed at least partial or completely intact topographical memory for remote knowledge acquired prior to his injury in structured mental navigation assessments of his neighbourhood (e.g.: recognition of landmarks, sequencing landmarks along a route, estimating distance between landmarks etc.). However, this patient failed to acquire spatial information in a new environment, for both topological information (such as learning a simple new route despite extensive training) and non-topological information (recalling positions of common objects on a board following a short delay).

On the other hand, EH did not show a similar dissociation in RN based on time of acquisition of memory. His results are in line with van Dijck et al.'s (2013) patient GG, who showed RN for memories acquired both pre- and post-stroke. While one apparent commonality between EH and GG is that they both showed an extensive profile of cognitive deficits on neuropsychological testing that may have contributed to a more pervasive profile of RN in these patients, it is difficult to reliably indicate what factors may distinguish EH's RN manifestation from DR and MG, given the case study approach. For example, each patient's demographic, stroke and pre-morbid cognitive profile could make a unique contribution to their RN performance. The assessment of the impact of these factors on RN performance requires a larger sample of patients with RN and well-suited statistical methods (e.g. involving covariate analyses) to be informative.

Interestingly, none of the patients had non-topological RN impairments for non-topological representations based on newly learnt information post stroke (Object arrays task).

(iii) Brain regions and cognitive mechanisms associated with RN in this sample.

Curiously, despite the dissociations identified in the behavioural data, all three patients had lesions in the right cerebellum. EH also had lesions involving the right frontal and insula regions; but given his right- sided RN deficits, it is more likely that his RN impairments were related to the cerebellar lesion rather than the ipsilateral cortical lesions. This finding of right- sided cerebellar lesions in RN patients is novel given that previous investigations have predominantly reported cortical lesions in frontal, posterior parietal and temporal regions in RN patients (Della Sala et al., 2004; Guariglia et al., 1993; Guariglia et al., 2013; Palermo et al., 2009; Palermo et al., 2010a; Rode et al., 2004), with one recent study specifically implicating the right temporoparietal junction in topological RN assessed using Familiar squares test (Committeri, Piccardi, Galati, & Guariglia, 2015).

Neuroanatomical studies have shown that due to cortico-subcortical loops and mechanisms of cerebello-cortical diaschisis, lesions to subcortical structures can induce behavioural deficits identical or similar to cortical lesions (Botez, Botez, Elie, & Attig, 1989; Nguyen & Botez, 1998; Schmahmann & Pandya, 2008). The cerebellum has reciprocal connections with the association and paralimbic regions of the cerebral cortex such that it receives information from afferent connections through the pons. This information is then processed in the cerebellum and transmitted back to the association cortices via the thalamus and red nuclei. While the cerebellar anterior lobe and part of lobule VI receive afferents from the contralateral motor and premotor cortices, the association areas in prefrontal and the posterior parietal regions are linked to crus I and II of the posterior cerebellum (Allen & Tsukahara, 1974; Schmahmann & Pandya, 2008). All three of the RN patients had lesions impacting the right crus of the cerebellum, even though DR’s lesion affected crus I and EH’s lesion affected crus II (Figure 4.3). Hence, in the context of the current study, one possibility is that RN in these patients was linked to disruption of the pathways connecting the cerebellar crus and the cortical areas implicated in RN.

As mentioned earlier, another interesting finding was that although both DR and EH had right cerebellar lesions and RN on the Shopping Mall task, DR showed deficits for the contralesional side while EH's deficits were ipsilesional. While no previous study has identified the cerebellum as related to impairments in *RN*, studies have shown an association between cerebellar lesions and *visual neglect* for both contralesional and ipsilesional space (Hildebrandt, Spang, & Ebke, 2002; Kim et al., 2008; Silveri, Misciagna, & Terrezza, 2001). Unfortunately, the scans obtained in the study were not suited to and lacked the resolution to explore the neuroanatomical underpinnings of this interesting finding in further detail. However, one speculation is that the dissociation in the side of topological RN could be related to the involvement of the superior cerebellar peduncle. The major output from the cerebellum is via the superior cerebellar peduncle which is the location for the crossing of fibres from the cerebellum to the contralateral cortical hemispheres, i.e. decussation (Catani & de Schotten, 2008; Salamon et. al., 2007; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). This peduncle is considered an important landmark because lesions above the decussation are known to cause contralateral deficits while lesions below it are considered to cause ipsilateral deficits (Marcus, Jacobson & Sabin, 2014).

Although, no one-to-one relationship between the lesions of the patients in the study and cognitive functions served by the cerebellum can be drawn due to lack of adequate sample size and imaging measures, one aspect to consider is the possibility that cerebellar lesions may disrupt some of the specific cognitive functions required to represent and manipulate information in imagery space. Based on patients' performance on the ancillary test battery, visual memory may be considered as important to all types of RN, whereas visuospatial working memory, spatial attention and mental rotation may be important to creating, attending and manipulating the mental representation of a well-known object like a clock.

Previous studies have shown that in patients with damage to the cerebellum, visuospatial organization (Botez et al., 1989), and spatial construction ability involving three dimensional mental folding, was impaired (Fehrenbach, Wallesch, & Claus, 1984) when compared to age- matched controls. Patients with cerebellar lesions have also shown difficulties in tasks requiring processing of complex 2D and 3D figures through use of mental reconstruction and rotation of the objects (Molinari, Petrosini, Misciagna, & Leggio, 2004). Specifically these patients were able to manipulate real objects in visual space but were only impaired when task involved mental assembly and manipulation of objects. Functional magnetic resonance imaging (fMRI) studies with healthy controls have also shown that the cerebellum is involved in tasks requiring motor imagery and mental rotation (Parsons et al., 1995; Vingerhoets, De Lange, Vandemaele, Deblaere, & Achten, 2002). Additionally, each RN patient in this study had lesions involving one or both of lobules VI-VII in the right cerebellum (Fig.4.3), which has been implicated in spatial orienting deficits in patients with acquired or developmental cerebellar abnormalities (Townsend et. al.,1999). The cerebellum is also known to support visuospatial working memory (Baier, Muller, & Dieterich, 2014; Hautzel, Mottaghy, Specht, Müller, & Krause, 2009; Luis et al., 2015). Specifically, Baier et al. (2014) showed in patients with unilateral cerebellar strokes that irrespective of side of lesion, the cerebellum may be related to impairments in executive control, attentional selection and filtering of irrelevant information from entering working memory rather than online maintenance of information.

To summarize, it is possible that the right cerebellum or its remote cortical connections (via the pons and thalamus) might play an important role in representation and manipulation of spatial information in mental imagery. While its exact role in RN is not clear based on the available data, one possibility is that the cerebellar lesions disrupted its connectivity with the posterior and frontal regions of the cerebral cortex, which are frequently implicated in RN. Additionally, cerebellar impairments may cause deficits to key cognitive abilities that are frequently recruited in RN assessments.

However, it must also be noted that not all patients with cerebellar lesions and ancillary cognitive deficits need necessarily develop RN. This is seen in the example of patient NB who had bilateral cerebellar lesions and some of his lesion overlapped with both MG and EH's lesions in the right cerebellum (Fig. 4.5d). However, NB did not show any RN on the novel tasks. Although he did not undergo testing on the ancillary cognitive battery, it is common knowledge that patients with stroke sometimes have a diffuse profile of cognitive deficits which may not necessarily result in RN. On the other hand, despite sharing a similar diffuse pattern of cognitive deficits on the test battery and presence of non-topological RN on the Clock Cueing task, MG did not share EH's deficits in topological RN tasks. Thus, it is more likely that deficits in ancillary cognitive domains may make important contributions and exacerbate the manifestation of RN and its sub-types, rather than be the sole cause of it.

One important shortcoming of this study was that due to the limited number of RN patients identified, the *role* of individual differences between patients that may modulate RN (e.g. age, education, stroke characteristics etc.) could not be reliably assessed. Thus, unfortunately, the case study approach does not allow for generalizations of results to a larger RN sample. Consequently, the results from the current chapter's case studies can be considered specific to the patients identified using the four selected RN tasks.

Hence, future studies would benefit from investigating the role of the cerebellum, cognitive abilities and individual differences contributing to dissociations in RN with larger samples of patients. Such studies may benefit from neuroimaging such as diffusion tensor imaging to help understand the anatomical underpinnings of RN (such as in patients with cerebellar lesions). They may also undertake a more fine-grained study of cognitive mechanisms within the context of the RN task. For example, just as measures of memory and familiarity were obtained from the Mall task, the task paradigm could be used to additionally obtain a more direct assessment of other cognitive processes such as visuospatial working memory and mental rotation. This may in turn facilitate a better understanding of which cognitive processes are impacted and consequently, are key to RN manifestation on the task, for each patient.

In conclusion, RN is a multifaceted disorder that can manifest differently in patients depending on the type of layout being assessed and time of acquisition of memory for the layout. These findings emphasize the need for a comprehensive battery of RN tests in research and clinical settings. For example, patient DR's topological RN for newly learnt layouts would have been missed if he was assessed only with the Familiar squares task as is done in many RN studies. Similarly, the complete profile of EH's RN would not have emerged if only the Familiar square or Geographical map or o'Clock task had been conducted. Furthermore, by using tasks like the novel RN methods described in this thesis, information on the role of cognitive abilities such as visual memory and spatial attention can be obtained, which may help in planning remediation strategies for RN. However, since the current investigation was a pilot, even in their current form, both the

Shopping Mall and Clock Cueing tasks would benefit from use in larger scale research studies to further evaluate their strengths and limitations with more patients and rigorous statistical analyses, before being recommended for use in clinical settings.

CHAPTER 5 - Effects of contralesional Transcranial Magnetic Stimulation in Visual Neglect patients

5.1 Introduction

Non-invasive brain stimulation using Transcranial Magnetic Stimulation (TMS) has shown potential in rehabilitating visual neglect in animals (Lomber, Payne, Hilgetag, & Rushmore, 2002; Payne & Rushmore, 2004; Rushmore, DeSimone, & Valero-Cabré, 2013; Rushmore, Valero-Cabré, Lomber, Hilgetag, & Payne, 2006; Sprague, 1966) and stroke patients (Brighina et al., 2003; Cazzoli et al., 2012; Fu et al., 2015; Kim, Chun, Kim, & Lee, 2013; Kim, Jung, & Shin, 2015; Koch et al., 2008, 2012; Lim, Kang, & Paik, 2010; Nyffeler, Cazzoli, Hess, & Müri, 2009; Shin et al., 2012; Shindo et al., 2006; Song et al., 2009). All the above patient studies have demonstrated the therapeutic potential of repetitive Transcranial Magnetic Stimulation (rTMS) to rehabilitate egocentric neglect (*spatial neglect*); with one study also including allocentric neglect (*object neglect*) (Kim et al., 2015).

As discussed in Chapter 1, rTMS draws on the framework of Kinsbourne's interhemispheric rivalry theory to modulate neglect (Kinsbourne, 1970). It is postulated to play a role in reinstating interhemispheric balance by either suppressing activity of the non-lesioned hemisphere (e.g.: Brighina et al., 2003; Cazzoli et al., 2012; Kim et al., 2015; Nyffeler et al., 2009; Shindo et al., 2006; Song et al., 2009) or by facilitating activity in the lesioned hemisphere (Kim et al., 2013) to aid neglect recovery. At least thirteen (published) rTMS studies have attempted to remediate visual neglect with a sample size ranging from two to thirty four patients across investigations (see Chapter 1, Table 1.1 and Jacquin-Courtois, 2015; Müri et al., 2013 for summary of studies)

To summarize, seven of the thirteen rTMS studies used sham control (Cazzoli et al., 2012; Fu et al., 2015; Kim et al., 2013; Kim, Kim, Chun, Yi, & Kwon, 2010; Koch et al., 2012; Nyffeler et al., 2009; Oliveri et al., 2001). All thirteen studies reported improvements in visual neglect and used inhibitory protocols; with nine using 0.5/ 1 Hz stimulation (Brighina et al., 2003; Kim et al., 2013; Kim et al., 2010; Kim et al., 2015; Koch et al., 2008; Lim et al., 2010; Oliveri et al., 2001; Shindo et al., 2006; Song et al., 2009) and four using continuous Theta Burst Stimulation (cTBS) (Cazzoli et al., 2012; Fu et al., 2015; Koch et al., 2012; Nyffeler et al., 2009) to the contralesional parietal lobe (P3, P5). In two of the thirteen studies, excitatory protocols to the *ipsilesional* parietal lobe (P4) were also used alongside (Kim, Kim, Shin & Kim, 2010; Kim et al., 2013), with only one showing evidence of improvement in neglect with excitatory stimulation (Kim et al., 2013).

It is difficult to directly compare results from any two studies due to the wide variability in methodological parameters and outcome measures employed. For example, time since stroke was a highly variable factor with patient inclusion ranging from sub-acute (one week - six months) to chronic stage (> six months) between studies as well as a wide interval of recruitment between patients within a study. Similarly, it remains to be definitively established how many sessions are required to observe improvements in neglect. While just a single session has been reported to lead to improvements in neglect (Koch et al., 2008; Nyffeler et al., 2009; Oliveri et al., 2001), so did twenty sessions (Koch et al., 2012) and any number of sessions ranging between one and twenty (Brighina et al., 2003; Kim et al., 2013; Kim et al., 2010; Lim et al., 2010; Shindo et al., 2006; Song et al., 2009). However, higher number of sessions were shown to be better than a single session in a recent study where ten sessions of inhibitory rTMS improved neglect (spatial and object) as compared to a single session (Kim, Jung, & Shin, 2015).

Along with differences in rTMS methodological parameters, there was also variability in the outcome measures used across studies. It has been noted that tests of neglect have variable sensitivity and neglect diagnosis can depend on the nature of the test and complexity (Azouvi et al., 2006). Additionally, the behavioural assessment of neglect in daily life (ADL) has been reported to be more sensitive than any other single measure of neglect and recommended for use in therapeutic trials (Azouvi et al., 2006). However, to date only three rTMS studies have used ADL (Barthel Index, Catherine Bergego scale (CBS)) as an outcome measure (Cazzoli et al., 2012; Kim et al., 2013; Shindo et al., 2006).

From a review of the above studies, a broad consensus can be derived that inhibitory rTMS to the contralesional P3 or P5 at 80-100% of the motor threshold has the potential to rehabilitate visual neglect as measured by varied outcome measures including ADL. However, it is unclear whether any benefit of rTMS stimulation noted in the short term is sustained in the longer term, e.g., at six months. The longest follow-up post rTMS was conducted by Shindo et al. (2006) at six weeks. However, this study recruited only two patients in the chronic stage and no control/ sham patients for comparison. Given that spontaneous recovery has been shown to plateau after three months post stroke (sub-acute stage) (Nijboer, Kollen, & Kwakkel, 2013; Stone, Patel, Greenwood, & Halligan, 1992), it is surprising that very few studies have attempted to study the long term contributions of rTMS in this stage. Of the three studies that targeted rTMS in sub-acute neglect patients, one showed benefits immediately post rTMS (Kim, Chun, Kim, & Lee, 2013) while two others showed improvements up to 2-3 weeks post intervention (Cazzoli et al., 2012; Song et al., 2009). Here, to investigate this further, effect of rTMS intervention provided in the sub-acute stage (<3 months post stroke) was studied on neglect performance up to 6 months.

Object neglect performance was also evaluated. To date, only one of the thirteen studies has explored the effect of rTMS on object neglect (Kim et al., 2015). However, Kim et. al.'s (2015) study neither employed a sham/ control group nor did their behavioural measure, i.e. Ota's task, use cut-offs to identify object neglect impairments. Thus, their study only informed about *changes* in Ota's task performance rather than changes in object neglect per se. Additionally, without a sham group, it cannot be reliably concluded that the change in performance over time was contingent upon rTMS intervention. Hence, the current study uses both, a standardized outcome measure with cut-offs as well as includes a sham group to explore any significant effects of rTMS on object neglect.

Finally, most previous rTMS explorations have restricted the scope of their study to the effects on neglect. However, deficits in non-spatially lateralized domains such as sustained attention, selective attention and spatial working memory frequently accompany lateralized visuospatial neglect deficits and exacerbate its presentation (Duncan et al.,1999; Husain & Rorden, 2003; Malhotra et al., 2005; Robertson et al., 1997; Van Vleet & DeGutis, 2013b). Even at the chronic stage, work using the BCoS cognitive screen (Humphreys, Bickerton, Samson, & Riddoch, 2012) has shown that prediction of long term performance (nine months post stroke) in spatial attention was improved when taking into account tests of sustained attention and executive function (Bickerton et al., 2015). Hence, in the current study, measures of auditory sustained attention and executive function were included as outcome measures to explore if there was any association between neglect improvement post rTMS and these other potentially related, but non-spatially lateralized domains.

I hypothesize that both spatial and object neglect would improve post rTMS and these improvements would be retained at six months in the intervention group, but not in the sham group. Additionally, the improvements in spatial neglect will be accompanied by improvements in the non-neglect measures in the intervention group, but not in the sham group.

5.2 Methods

5.2.1 Participants

Stroke survivors in the sub-acute stage of stroke were screened for inclusion at two community hospitals in Oxfordshire (Abingdon Community hospital and Witney Community hospital) between August 2013 and August 2015. Patients were approached for the study if (i) they demonstrated spatial and/or object neglect as identified by the asymmetry scores on the Hearts Cancellation test of the Oxford Cognitive Screen (OCS) (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015); (ii) neglect diagnosis was confirmed by the multi-disciplinary team (MDT) comprising of doctors, therapists and optometrist at the hospital; (iii) were between one week and within six months of the stroke event; (iv) were medically fit; (v) able to comprehend instructions and provide informed consent as per the opinion of the MDT; (vi) able to concentrate for 20-30 minutes as judged by the MDT; (vii) had no co-morbid psychological or neurological disorders (e.g.: depression, dementia) as judged by the MDT; (viii) had no contra-indications for rTMS administration upon administering a screening questionnaire (e.g.: history of epilepsy, major head trauma or fainting spells, presence of metal in the skull or implanted devices such as pacemakers, cochlear implants, etc.). All patients underwent conventional rehabilitation at the hospitals during the course of the rTMS sessions.

Informed consent was obtained in keeping with the ethical protocol approved by the U.K National Research Ethics Committee and the guidelines set out in the Declaration of Helsinki.

5.2.2 Procedure

Computer based randomization was used to allocate a patient in the trial to the IG (Intervention Group) or CG (Control Group). A battery of cognitive tests (see Section 5.2.3) was administered at baseline testing a few weeks prior to rTMS intervention. Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, Wales UK) connected to a figure of eight coil was used to deliver rTMS. The resting motor threshold was defined as the lowest intensity of stimulation required to elicit five visible motor twitches in the relaxed right hand's first dorsal interosseous muscle, in response to ten consecutive stimuli. To identify this threshold, the optimal 'hotspot' in each patient's motor cortex was identified and stimulated (Rossini et al., 2015). rTMS was then provided at 90% of this identified resting motor threshold. The IG received twenty minutes of rTMS at 1 Hz (1200 pulses) to the left inferior parietal lobe (P3) of the intact hemisphere. The CG was stimulated with the same parameters at the vertex. Each participant received six sessions of rTMS in total, on alternate days spread over two weeks (three sessions per week). This alternate day protocol has been applied in two previous studies that showed improvements in spatial neglect post stimulation, that lasted for up to two and six weeks respectively (Brighina et al., 2003; Shindo et al., 2006). Follow-up testing on the same cognitive test battery as at baseline was conducted both in the short term, i.e. less than one month post rTMS and in the long term, i.e. at 6 months or more post rTMS.

5.2.3 Outcome measures

Figure 5.1 provides details of the number of participants tested at each time point (screening, baseline, before and after each rTMS session, short term follow-up < 1 month post rTMS, long term follow-up > 6 months post rTMS) and outcome measures used at each time point. The Hearts Cancellation task from the OCS (Demeyere et. al., 2015) was used multiple times during the study, including before and after each rTMS session. In order to restrict practice effects, *six parallel versions* of the task were created and administered in random order to each patient across test sessions. While administering parallel versions may not eliminate the likelihood of increased preparedness and familiarity with the task, both groups were matched in the number of times they were exposed to this task and its multiple versions, to enable unbiased inter-group comparisons. A more detailed cognitive test battery incorporating other tests measuring neglect, sustained attention, executive function and Quality of Life test (QoL) was administered at baseline, < 1 month and > 6 months post rTMS.

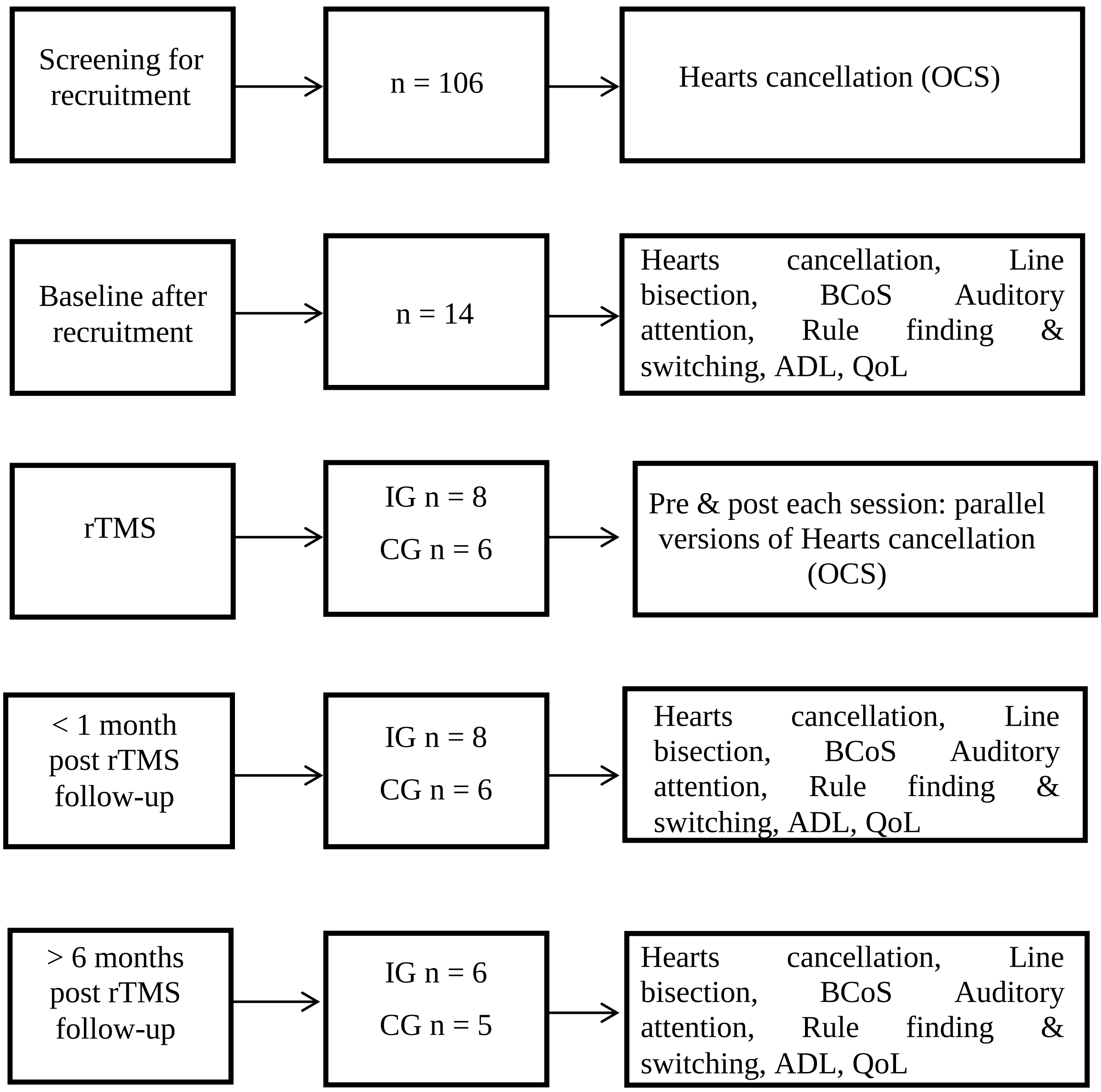

Figure 5.1. Number of participants tested and outcome measures used at each time point of the study

IG=Intervention Group; CG= Control Group, OCS: Oxford Cognitive Screen, BCoS: Birmingham Cognitive Screen, ADL: Activities of Daily Living, QoL=Quality of Life
Patients were tested at the following intervals: screening, baseline, before and after each rTMS session, < 1 month post rTMS and > 6 months post rTMS. The Hearts Cancellation task of the OCS was administered at each time point while other tests of neglect, non- spatial tests and QoL were administered at baseline, < 1 month post rTMS and > 6 months post rTMS.

5.2.3.1 Neglect Assessment

Please refer to Chapter 2, section 2.21 for details of the visual neglect measures, OCS Hearts Cancellation (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015), Line bisection (adapted from Behavioural Inattention Test, Wilson et al., 1987) and neglect- specific Activities of daily living (ADL) tasks (Eschenbeck et al., 2010), used in this study.

5.2.3.2 Non-neglect assessment

The BCoS Auditory attention and BCoS Rule finding and concept switching tests were used as measures of sustained attention and executive function respectively (Humphreys et al., 2012).

5.2.3.2.1 BCoS Auditory attention (Humphreys et al.,2012)

Details of this task are provided in Chapter 2, section 2.2.2.

5.2.3.2.2 BCoS Rule finding and concept switching (Humphreys et al., 2012)

Participants were shown a six by six grid of squares with a black marker at their midline. Of these squares, two squares were red, two were green and the rest were grey in colour. With each page turned in the test material, the marker was shown to move within the grid in a lawful manner. The participant had to learn this rule and predict its next move based on this rule. The movement of the marker was also subjected to three rule switches, i.e. when the marker switched in direction of movement, when the marker moved between same coloured squares and when the marker moved between different coloured squares. The participant had to adapt to this concept switch and continue predicting the marker’s movement based on the new rule. Total number of responses and number of rules correctly identified were used to score performance.

5.2.3.3 Quality of Life (QoL)

The Stroke specific QoL scale (Williams et. al., 1999) was used to ask patients to rate the amount of help/ability to perform/agreement with a statement on a scale of 1 (total help required/unable to perform) to 5 (no help needed/no trouble performing). The scale assessed the patients' self-report in relation to feeling energetic, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision and productivity. A low score was indicative of lower self-rated quality of life.

5.2.4 Data Analyses

To determine if the intervention (IG) and sham control groups (CG) were comparable, age, time since stroke, time interval between different assessment time points and neglect tests' scores at baseline assessment were compared between groups using independent t-tests.

The first hypothesis required assessing significant differences in neglect performance between groups over time. This could be assessed using:

(i) ANCOVA: to answer what is the effect of the rTMS on post-test scores that is not conditional on pre-test scores?

(ii) T-test: to answer what is the effect of rTMS on *change* in performance from pre- to post- intervention?

The outcome measures for neglect performance were spatial asymmetry, object asymmetry, centre of cancellation (CoC) (obtained from Hearts Cancellation task), line bisection average deviation and ADL total scores.

Analysis of Covariance (ANCOVA) was conducted where assumptions were met **(**Chapter 2, Section 2.3.4) with pre-rTMS scores as covariate, group as independent variable (IV) and post-rTMS scores as dependent variable (DV). Note that inter-session Hearts Cancellation performance obtained from before and after each individual rTMS session were planned to be explored further *only* if the main ANCOVA analyses comparing pre rTMS session 1 and post rTMS session 6 scores was significant.

Two things to note with regard to the cancellation scores in this dataset: Firstly, for any analysis involving cancellation scores, pre-rTMS scores implies scores obtained immediately prior to the first rTMS session. For line bisection and ADL tests, pre-rTMS scores imply scores from the baseline testing session conducted several days prior to the rTMS onset. Secondly, given multiple data points for the Cancellation task, spontaneous change in performance (baseline - pre rTMS session 1) was considered as an additional covariate for the Cancellation tests. However, spatial and object asymmetry as well as CoC indices have positive and negative signs in their scoring to indicate directionality of neglect. Thus, change scores calculated from these indices would not allow for accurate interpretation, i.e. an asymmetry score of -3 at baseline that spontaneously improved to 0 at rTMS session 1 implying resolution of neglect would translate to a spontaneous change score of -3 (-3-0=-3), which in fact does not reflect this improvement in performance. Using absolute scores would have been ambiguous since the +/- sign was necessary to estimate whether the change score indicated an improvement or deterioration in cancellation performance over time. Hence, spontaneous change in performance between baseline and session 1 could not in fact be used as a covariate in the analyses in involving the selected cancellation measures. For this same reason, change score analyses from pre to post rTMS using t-tests (Chapter 2, section 2.3.2 for assumptions testing), could be conducted only with ADL scores, but not with the asymmetry or line bisection deviation scores.

Although ANCOVA was the preferred analysis method to explore significance of between group variability on performance, the small sample in this study may not be amenable to its many rigorous constraints. Hence, *where ANCOVA was not possible,* difference in neglect performance between groups was assessed using mixed ANOVA with group as between subjects variable and session (pre rTMS, post rTMS) as within subjects variable (Refer to Chapter 2, 2.3.3 for assumption testing details).

All results were assessed for significance only after correcting for multiple comparisons using Bonferroni correction.

For the non-neglect cognitive tests (BCoS Auditory Attention, BCoS Rule finding and concept switching) where impairments could be identified based on age- appropriate cut-offs (Humphreys et al., 2012), very few patients had both neglect *and* were impaired on the BCoS task in question. Hence, no statistical comparisons were made; instead the raw score profile of each individual patient in these tasks is depicted in figures in Appendix C, Figures 5a-5c. For QoL, both ANCOVA and change score analyses were considered.

5.3 Results

One hundred and six sub-acute stroke patients were screened for inclusion in this trial over two years. Of these, a total of 53 patients had neglect with 28 (26%) having only spatial neglect, eight (7.5%) having only object neglect and 17 (16%) having both spatial and object neglect as assessed by the OCS Hearts cancellation task (Demeyere et al., 2015). Fourteen patients who met the inclusion criteria were recruited. Of the 39 who were excluded, the neglect spontaneously resolved prior to trial onset in six patients, six patients had inadequate comprehension and could not give consent, five patients had contraindications to brain stimulation, five patients were medically unfit, five patients had co-morbid dementia, four patients died before trial onset, four patients declined to participate, three patients were discharged before consent could be obtained and one patient withdrew from the trial due to fatigue.

Based on computerized randomization, the 14 included patients were assigned to the intervention group (IG, n = 8, *mean age* = 75. 2, *SD* = 8.5; *females* = 3, *left handed* = 1) or sham control group (CG, n = 6, *mean age* = 80.08, *SD* = 7.1; *female*s = 1, *left handed = 1*). One patient from the CG passed away before 1 month follow-up assessment (C1) and two patients from the IG passed away before 6 month follow-up could be completed (I5, I8). Two of these patients passed away due to stroke related complications (chest infection: C1, recurrent stroke: I8) and one passed away on account of a new, unrelated medical condition (I5). Hence, for six month follow-up data, the sample size for IG was six patients and for CG were five patients. Patients who participated in the study did not complain of any uncomfortable rTMS related side-effects.

Table 5.1 provides demographic and clinical information about participants. Screening was done on average 19 days (*SD* = 9 days) after stroke for IG and 27 days (SD = 21 days) after stroke for CG. This difference in time between stroke and screening was not significantly different between groups, $t(12) = -1.05$, $p = .32$, *Cohen's d* = 0.53. Please also note that although the short term follow up is labelled as < 1 month, all patients except C2 (who was unwell during the scheduled follow up period) were followed up within 15 days of the last rTMS session.

The IG and CG were comparable for age, *t*(12) = -1.47, *p* = .27, Cohen's *d* = 0.58, time between stroke and baseline testing, *t*(5.34) = -1.39, *p* = .22, *Cohen's d* = 0.80, time between baseline testing and start of rTMS, *t*(12) = 1.48, *p* = .17, *Cohen's d* = 0.85, time between end of rTMS and post rTMS 1 month follow-up, *t*(12) = -0.58, *p* = .58, *Cohen's d* = 0.30), time between end of rTMS and 6 months follow-up, *t*(9) = -0.91, *p* = .39, *Cohen's d* = 0.53, and number of hours of physiotherapy and occupational therapy received, *t*(12) = -0.078, *p* = .94, *Cohen's d* = 0.04 (Table 5.1).

Table 5.1. *Clinical and demographic data of study participants (n=14)*

Patient	Age (yrs)	Sex	Type of stroke	Previous stroke	Hemianopia	Therapy hours	Time between stroke and baseline	Time between baseline & rTMS start	Time between rTMS end & follow-up	Time between rTMS end & 6 month follow-up
					Intervention Group					
I1	78	F	Haemorrhage (R Parietal)	Yes	No	77	17d	59d	10d	6mth,18d
I2	75	F	Haemorrhage (R Basal ganglia)	No	No	74	18d	35d	1d	6mth,10d
I3	60	M	Infarct (R MCA & PCA)	No	Complete left hemianopia	25	22d	10d	14d	6mth
I4	88	M	Infarct (R MCA)	No	No	23.5	26d	12d	4d	6mth
I5	81	M	Haemorrhage (R TAC)	No	No	45	30d	10d	2d	n.a
I6	79	M	Infarct (R MCA)		Left inferior homonymous quadrantanopia	48	35d	16d	11d	7mth,29d
I7	68	M	Infarct (R MCA)	No	Left inferior quandrantanopia	39	34d	23d	3d	8mth,6d
I8	71	F	Infarct (R MCA)	Yes	Complete left homonymous hemianopia	10	37d	4d	6d	n.a

Patient	Age (yrs)	Sex	Type of stroke	Previous stroke	Hemianopia	Therapy hours	Time between stroke and baseline	Time between baseline & rTMS start	Time between rTMS end & follow-up	Time between rTMS end & 6 month follow-up
					Control Group					
C1	82	M	No clear lesion in scan/ possible TIA	No	No	17	22d	11d	6d	n.a
C2	90	M	Infarct (R MCA)	Yes	Left inferior homonymous quadrantanopia	15	91d	7d	22d	6mth,30d
C3	78	F	Infarct (R TAC)	Yes	Left inferior homonymous quadrantanopia	26	16d	15d	6d	6mth,23d
C4	85	M	Infarct (R TAC)	Yes	No	40	40d	5d	3d	11mth,24d
C5	74	M	Infarct (R MCA)	No	Left homonymous superior quadrantanopia	43	24d	16d	7d	6mth,1d
C6	71	M	Haemorrhage (R frontoparietal)	No	No	123.5	98d	5d	5d	6mth,16d

R = right, MCA = middle cerebral artery, PCA = posterior cerebral artery, TAC = Total anterior circulation stroke, TIA = Transient Ischemic Attack, M = Male, F = Female, M = months; yrs = years; mth = months, d = days; n.a = not applicable because patient passed away; Hemianopia diagnosis based on optometrist report included in medical notes at baseline; therapy hours were obtained with the help of the therapists from the Sentinel Stroke National Audit Programme.

Table 5.2 provides a cognitive profile of each patient's impairments at screening across various domains of the OCS based on published cut-offs (excluding neglect) (Demeyere et al., 2015). One patient in the IG (I3) did not show any impairment in any tasks other than the Hearts Cancellation. Other than that, both groups had patients who were impaired on similar number of OCS domains, i.e. both groups had a patient each who was severely impaired on 8 domains (I8, C2) while there were others who were impaired on fewer, in both groups.

All eight patients in IG and six patients in CG had left-sided spatial neglect while five patients in each group also had co-existing left-sided object neglect. Baseline neglect severity was comparable between the two groups for spatial asymmetry scores, $t(12) = -1.22$, $p = .25$, *Cohen's d* = 0.67, object asymmetry scores, $t(8) = -1.3$, $p = .23$, *Cohen's d* = 0.82, line length based deviation in line bisection, $F(2,24) = 0.04$, $p = .96$, $\eta_p^2 = 0.003$, line placement based deviation in line bisection, $F(1,12) = 0.005$, $p = .95$, $\eta_p^2 = 0$, and for ADL scores, $t(11) = -.59$, $p = 0.6$, *Cohen's d* = 0.33.

Table 5.2. *Cognitive profile of each patient on the OCS at screening (n=14)*

Domain	IG								CG						Total patients impaired per domain
	I1	I2	I3	I4	I5	I6	I7	I8	C1	C2	C3	C4	C5	C6	
Picture naming		i		i	i	i			i	i	i			I	8
Semantics															0
Orientation				i	i	i		i				i			6
Left visual field				i		i	i	i			i	i	i		7
Sentence reading						i	i		i		i	i			5
Number writing	i	i		i			i	i		i		i			7
Calculation	i			i				i		i					4
Imitation					i		i		i	i		i			5
Verbal recall	i				i			i		i					4
Recall + recognition	i				i			i	i	i					5
Episodic recognition	i							i		i			i		4
Executive task				i		na	i	na		i	i		i		5
Total domains impaired per patient	5	2	0	6	5	5	5	8	4	8	4	5	3	2	

IG: Intervention Group; CG: Control Group; i = impaired, na = could not perform; Cells not marked mean that patient was unimpaired.

5.3.1 Neglect assessment

Please refer to Supplementary material (Appendix C, Table 5a) for average line bisection and cancellation based average spatial asymmetry, object asymmetry and CoC scores for each group and session. The results from the ANCOVA and ANOVA are provided in Tables 5.3 and 5.4 respectively.

Due to the limited sample size, most planned ANCOVA analyses could not be conducted due to violation of the test's assumptions (Table 5.3). As can be seen, only ADL scores could be analysed for each time point using an ANCOVA while for all other tests, mixed ANOVA was conducted, but *without any significant results* (Table 5.4). The only significant results were pertaining to ADL and hence, only these will be expanded upon in this section, for the sake of relevance and brevity.

Table 5.3: *List of results from ANCOVA analyses on cancellation, line bisection, ADL and QoL measures*

Test	Measure	Dependent variable	Independent variable	Covariate (s)	Result/ Reason not done
Cancellation	Spatial asymmetry	Post rTMS session 6	Group (Intervention, Control)	Pre rTMS session 1 scores **$F(1,11)=19.63, p=0.001, \eta_p^2=0.64$**	$F(1,11)=4.14, p=0.07, \eta_p^2=0.27$
		<1 month post rTMS			*1,4,5
		>6 months post rTMS			*4
	Object asymmetry	Post rTMS session 6	Group (Intervention, Control)	Pre rTMS session 1 scores	*3
		<1 month post rTMS			*1,4,5
		>6 months post rTMS			*1,3,4
	CoC	Post rTMS session 6	Group (Intervention, Control)	Pre rTMS session 1 scores	*2
		<1 month post rTMS			*5
		>6 months post rTMS			*4
Line Bisection	Average deviation	<1 month post rTMS	Group (Intervention, Control)	Pre-rTMS average deviation scores **$F(1,11)=5.34, p=0.04, \eta_p^2=0.33$**	$F(1,11)=3.62, p=0.08, \eta_p^2=0.25$
		>6 months post rTMS			*1,3
ADL	Total scores	<1 month post rTMS	Group (Intervention, Control)	Pre-TMS total scores **$F(1,10)=17.46, p=0.002, \eta_p^2=0.64$**	**$F(1,10)=7.23, p=0.02, \eta_p^2=0.42$**
		>6 months post rTMS		**$F(1,7)=8.38, p=0.02, \eta_p^2=0.55$**	$F(1,7)=1.44, p=0.27, \eta_p^2=0.17$
QoL	Total scores (non-neglect measure)	<1 month post rTMS	Group (Intervention, Control)	Pre-rTMS QoL scores	*2
		>6 months post rTMS			*1,4,5

**Assumptions not met: 1: Linearity assumption; 2: Homogeneity of regression slopes; 3:Normality of residuals; 4:Homoscedasticity of residuals; 5: Homogeneity of variance; Results in bold were significant after Bonferroni correction. Significant effect of covariate on outcome measure is highlighted in bold in the 'Covariate(s) column.*

Table 5.4: *List of results from two way mixed ANOVA analyses on cancellation, line bisection and QoL measures*

Test	DV	Between groups IV	Within groups IV	Result/ Reason not done
Cancellation	Spatial asymmetry	Group (Intervention, Control)	Time of assessment (Pre sess 1 rTMS, Post sess 6 rTMS, <1 month post rTMS, >6 months post rTMS)	$F(3,27) = 1.62$, $p = .21$, $\eta_p^2 = 0.15$
	Object asymmetry			$F(3,24) = 0.71$, $p = .56$, $\eta_p^2 = 0.08$
	CoC			$F(2, 17) = 0.68$, $p = .50$, $\eta_p^2 = 0.07$
Line Bisection	Average deviation	Group (Intervention, Control)	1)Time of assessment (Baseline, < 1 month post rTMS, > 6 months post rTMS) 2) Line length (Long, medium, short) 3) Line placement (Left, right)	$F(4,36) = 0.86$, $p = .5$, $\eta_p^2 = 0.09$
QoL	Total scores (non-neglect measure)	Group (Intervention, Control)	Time of assessment (Baseline, < 1 month post rTMS, > 6 months post rTMS)	$F(1, 10) = 1.93$, $p = .2$, $\eta_p^2 = 0.18$

Note: Only group related interactions are reported in the table.

One patient could not perform the ADL task at baseline, resulting in 7 patients in the IG for analysis involving < 1 month follow up scores. As seen in Table 5.3, along with a significant effect of the covariate (baseline ADL scores) on the post rTMS ADL performance, $F(1,10)=17.46$, $p=0.002$, $\eta_p^2=0.64$, a significant main effect of group was also found after covariate adjustment for <1 month post rTMS ADL scores, $F(1,10)=7.23$, $p=0.02$, $\eta_p^2=0.42$; adjusted *mean* for IG (*SE*)=7.55 (0.41), adjusted *mean* for CG (*SE*)= 5.94 (0.44). Post rTMS ADL scores were significantly higher for the IG than for the CG (adjusted *mean difference* =1.61, 95% *CI*: 0.28-2.95, $p=0.02$). To identify if the ADL score change was on account of IG or CG performance, paired t-tests were conducted to compare the pre-rTMS and the <1 month post rTMS session's mean scores for each group. There was a significant improvement in the average ADL scores pre and post rTMS for the IG, $t(6)=-3.03$, $p=0.02$, *Cohen's d*=1.06; *mean* baseline scores (*SD*)= 6.07 (2.05), *mean* post rTMS scores (*SD*)=7.71 (0.76), but not for the CG $t(5)=-0.52$, $p=0.62$, *Cohen's d*=0.11, *mean* baseline scores (*SD*)=5.5 (2.35), *mean* post rTMS scores (*SD*)=5.75 (2.36).

A further reduced sample was available for ADL at 6 months, i.e. IG=6, CG=4 patients. ANCOVA on this reduced sample did not show any significant between group effects, $F(1,7)=1.44$, $p=0.27$, $\eta_p^2=0.17$, adjusted *mean* for IG(*SE*)=6.83(0.49), adjusted *mean* for CG(*SE*)=5.89(0.6), adjusted *mean difference*=0.94, 95% *CI*:-0.9-2.78, $p=0.27$, although the covariate baseline performance was seen to significantly contribute to ADL performance even at the 6 months follow up ($F(1,7)=8.38$, $p=0.02$, $\eta_p^2=0.55$).

Change score analyses on the ADL task revealed no significant differences between the IG and CG when comparing performance between baseline and < 1 month post rTMS, $t(11) = 1.89$, $p = .09$, *Cohen's d* = 1.06, and between baseline and > 6 months post rTMS, *t*(8) = 0.54, *p* = .61, *Cohen's d* = 0.31. Although not significant, IG showed relatively greater improvement from baseline to < 1 month post rTMS of 1.6 points in comparison to controls' 0.25 points and an improvement of 1.17 points from baseline to > 6 months post rTMS while CG showed a smaller improvement of 0.13 (See Figure 5.2).

For individual patient's change in performance for each ADL sub-task from baseline to < 1 month and baseline to > 6 months, please refer to Appendix C, Table 5b.

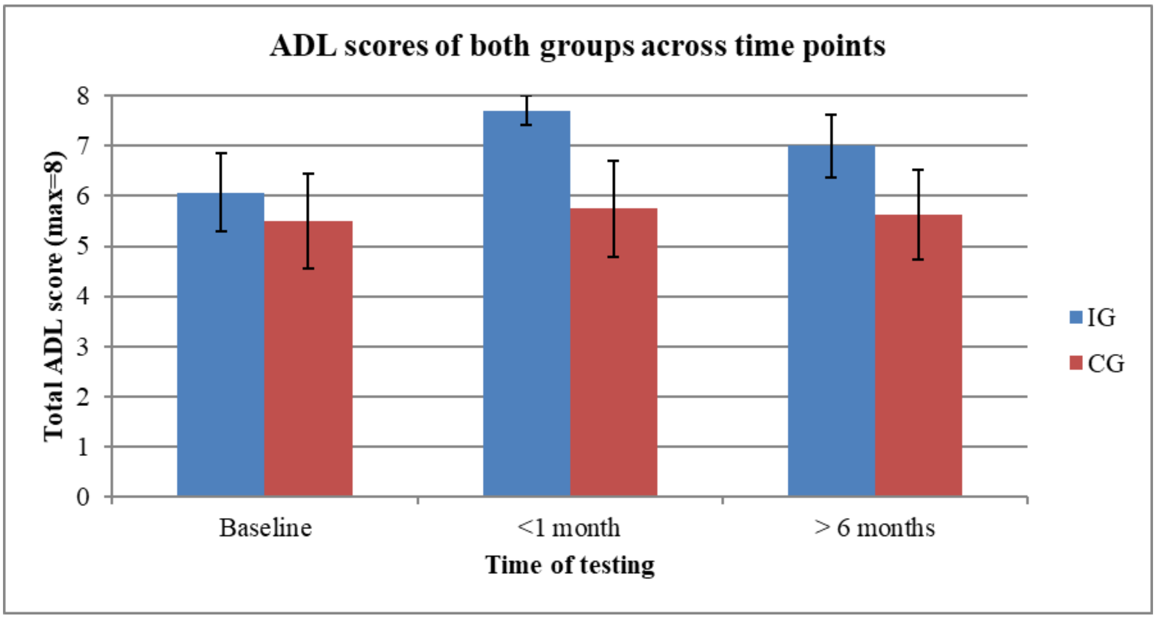

Figure 5.2. ADL scores of both groups across time points

IG: Intervention Group; CG: Control Group
Higher scores on this task imply better ADL
Error bars depict standard error
Change scores between baseline and < 1 month as well as between baseline and > 6 months using unadjusted means was not significantly different between groups.

5.3.2 Non-neglect assessment

5.3.2.1 BCoS tasks

While group data on these tasks is reported in Table 5.5, figures depicting each impaired patients' performance on the BCoS Auditory attention and BCoS Rule finding and concept switching tasks is included in Supplementary material since this data has no direct scope of advancing the study's findings (Appendix, Figures 5a-5c). It must also be noted that since no between groups statistical comparisons were made, it is not possible to comment on the significance of changes in these tests pre and post rTMS.

Table 5.5. *Average scores for IG and CG on supplementary non-neglect tests*

	IG			CG		
Test	Baseline Mean(SD)	< 1 month Mean(SD)	6 months Mean(SD)	Baseline Mean(SD)	< 1 month Mean(SD)	6 months Mean(SD)
BCoS Auditory attention						
Sustained attention index (SAI)*	1.17(3.2)	-0.17(0.4)	-1(1.2)	1.6(1.9)	2.33(0.6)	1.25(1)
BCoS Rule finding & switching						
Total score (max=18)	5.86(6.3)	8.14(7)	7.33(6.4)	8.17(6.3)	4.8(4)	3(2.9)
No. of rules correct (max=3)	0.86(1.2)	1.29(1.3)	1.17(1.3)	1.5(1.4)	0.6(0.9)	0.25(0.5)
QoL						
Total score (range=0-245)**	179.7(39)	183.9(33)	178(35)	186.3(49)	185(69)	122.1(88)

**Sustained attention index = no. correct in block 1 - no. correct in block 3. Hence, for sustained attention index, a negative score implies better performance in block 3 than block 1.*

***QoL: higher score implies better QoL*

5.3.3 QoL

Table 5.5 provides average QoL ratings for each group and at each assessment session. ANCOVA assumptions were not met for this data (Table 5.3), hence ANOVA was conducted (Table 5.4). Self-rated QoL scores were not significantly modulated by an interaction between group (IG, CG) and time of testing (baseline, < 1 month post rTMS, > 6 months post rTMS), $F(1, 10) = 1.93$, $p = .2$, $\eta_p^2 = 0.18$. Independent t-tests for change in QoL scores between groups did not show any significant changes between baseline and < 1 month post rTMS, $t(10) = 0.93$, $p = .37$, *Cohen's d* = 0.56, and baseline and > 6 months post rTMS, $t(9) = 1.54$, $p = .16$, *Cohen's d* = 0.9.

To summarise the results, significant difference between groups in the neglect-specific ADL task was seen only in the short term (<1 month) post rTMS (but not in the long term 6 month follow-up) when the patients' baseline performances on the task were taken into account. Specifically, after adjusting for the covariate, patients who had received rTMS to the intact parietal lobe showed a significant improvement of 1.6 points on the neglect-based ADL task post intervention when compared to the sham control group. With regard to object neglect, the sample size was limited and did not reveal any significant effects between groups. Thus, the first hypothesis is only partially accepted since not only was the neglect specific improvement in the ADL task restricted to the 1 month follow up, but also because no significant between group changes were seen for object neglect. The second hypothesis stating that rTMS based improvements will extend to non-neglect measures, could not be comprehensively evaluated on account of limited data.

5.4 Discussion

The study's main objectives were to investigate the role of rTMS in improving spatial and object neglect, as well as related non-neglect measures at ~one month and six months post rTMS. Despite limited patient recruitment, this study revealed three interesting results. Firstly, in comparison to vertex stimulation in the sham control group, six sessions of rTMS to the contralesional inferior parietal lobe over alternate days was related to neglect-based ADL improvement in sub-acute stroke patients. The between group differences were significant only in the short term (<1 month post rTMS) and were not retained in the long term (>6 months post rTMS). Secondly, neither of the two classical paper-pencil tests (cancellation, line bisection) revealed any significant neglect related results in the short or long term. Finally, rTMS did not result in any significant object neglect related improvements in the IG as compared to the sham group.

(i) rTMS efficacy in improving neglect-based ADL performance in the short term (< 1 month), but not in the long term (> 6 months).

The current study was able to show that improvement in the IG's ADL performance post intact parietal lobe rTMS was greater than that afforded by spontaneous recovery and/or placebo effect in the sham group, at least in the short term. Surprisingly, these significant differences in performance were not extended to the longer term follow up. One obvious explanation for this was the small sample of patients that were available for the six months follow up. Only four CG patients could be tested on the ADL task at 6 months as compared to six IG patients. Although the power of the analyses was improved on account of the covariate's inclusion, these results cannot be generalized to the population without replication in a larger sample.

In addition to the sample size limitation, a second possible explanation could be that the rTMS protocol was not optimal for generation of long term benefits. rTMS effects from a single session have been shown to last for approximately 60 minutes (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Ridding & Rothwell, 2007; Thut & Pascual-Leone, 2010; Valero-Cabré, Pascual-Leone, & Rushmore, 2008). While conventional plasticity based neural effects from a single session may not extend to sessions interspersed by long (24/ 48 hour) intervals, research suggests that it is in fact *metaplastic* changes in the brain that may be responsible for accrual effects from multiple rTMS sessions (Abraham, 2008; Cohen et al., 2010; Valero-Cabré et al., 2008). In other words, plasticity based effects from each rTMS session may influence behaviour in the immediate offline period up to 60 minutes. However, metaplastic changes from rTMS application, i.e. the ability of the targeted neurons and synapses to facilitate further plasticity in its networks, may make the stimulated region and its interconnections more susceptible to modify activity levels when re-exposed to future sessions of neuromodulation. Thus, multiple sessions of rTMS may facilitate the *ease* with which a particular behavioural effect is achieved rather than be related to any single session's prolonged effect on neglect performance. This was demonstrated by Valero-Cabre et. al. (2008) in their study with two feline subjects whose visuospatial orientation performance was studied immediately and 24 hours after each of 30 daily, 20 minutes, 1 Hz rTMS sessions to the posterior parietal cortex. They showed that cumulative sessions induced a greater magnitude of effect on visuospatial behaviour peaking at ~20 sessions although the effects post each rTMS session were not seen beyond 60 minutes or after 24 hour interval. Thus, metaplasticity based benefits may underlie the accrual effects on neglect performance that have been reported in 1 Hz rTMS studies employing both daily (Kim et al., 2013; Kim, Jung, & Shin, 2015; Lim, Kang, & Paik, 2010) and alternate day (Brighina et al., 2003; Shindo et al., 2006) stimulation protocols.

Interestingly, Valero-Cabré et. al. (2008) also reported that when both cats underwent 1 Hz rTMS in a last (31^{st}) session after a 7 day stimulation-free period, their behavioural performance was comparable to when measured at the height of rTMS facilitation. In humans, some research on maintenance rTMS/reintroduction of rTMS sessions in depression patients has revealed that adjunct sessions helped to reinstate symptomatic benefits and/or lower or delay further relapse in the long term; this was especially the case in those who responded positively to the initial intervention but relapsed subsequently (Dunner et al., 2014; Fitzgerald, Grace, Hoy, Bailey, & Daskalakis, 2013; Philip et al., 2016; Richieri et al., 2013). Thus, in order to explore the potential of metaplasticity in the long term, it may be worthwhile to assess the utility of providing periodic rTMS maintenance sessions to patients, especially if they responded well to the initial intervention. The periodic stimulation could be especially relevant given that at six months post rTMS, opportunities for purposeful training of behaviour in cognitively enriching environments may have diminished post discharge from rehabilitation units (Cecatto & Chadi, 2007).

(ii) rTMS benefits seen for ADL task, but not for conventional paper-pencil measures.

Another interesting result in this study was that the short term benefits of rTMS were seen for the neglect based ADL task, but not the classical cancellation and line bisection tasks. ADL testing has been found to be more sensitive to neglect identification than any single conventional test and comparable to the use of a whole paper-pencil conventional test battery (Azouvi et al., 2002). Functional assessments using ADL tasks in rehabilitation trials with neglect patients were found to be sensitive to change and useful in tracking patient progress after intervention (Cazzoli et al., 2012; Kim et al., 2013; Samuel et al., 2000). These tasks also improved detection sensitivity by allowing for identification of impairments that may only be apparent in the context of completing complex tasks that require higher resources and multitasking (Bowen, McKenna, & Tallis, 1999). Despite the importance of ADL assessment, surprisingly, only three of the studies assessing rTMS effects on neglect have included ADL as a test measure (Cazzoli et al., 2012; Kim et al., 2013; Shindo et al., 2006). Of these, only two showed rTMS related improvements in ADL (Cazzoli et al., 2012; Kim et al., 2013) and none showed dissociation between ADL and paper-pencil tests.

The dissociation between ADL and conventional tests, and increased sensitivity of ADL tasks, could be because these tasks require *automatic* orienting of attention to stimuli in environment while conventional paper-pencil tests rely on *voluntary* orientation of attention (Azouvi et al., 2002, 2006). Secondly, in the current study, performance on the paper-pencil tasks may have lost sensitivity due to practice effects on these tasks in comparison to ADL. The cancellation task was performed not only at baseline and at follow up post rTMS, but also before and after each rTMS session. Additionally, the occupational therapists at the rehabilitation sites also used the Behavioural Inattention test (BIT) (Wilson et al., 1987) which includes versions of both cancellation and line bisection in order to monitor the patients' neglect. ADL test used in the current study was relatively new and involved activities like hair combing, face creaming, telephone dialling, address copying etc. that were likely to have higher personal relevance and ecological validity. In contrast, the conventional tests may capture lateralized bias but not its translation to the functional domain (Chen, Hreha, Fortis, Goedert, & Barrett, 2012).

(iii) No significant effects of rTMS on object neglect in the short or long term.

In the current study, no improvements were observed in object neglect performance between groups and across time points. This finding is not surprising given the analysis was underpowered with a small sample of 5 patients each in each group. One previous study has revealed benefits to object neglect using rTMS to the contralesional parietal lobe (P3) in chronic stroke patients (Kim et al., 2015). In addition to the limited sample size, one other primary difference between the current study and Kim et al.'s study (2015) was the outcome measure used for object neglect (OCS Hearts Cancellation vs Ota's task). Although both tasks are cancellation measures, the OCS task only required identification of targets amidst distractors while Ota's task required identification of both targets and distractors which may have encouraged patients to explore the available space more completely. Additionally, the OCS cancellation task had a denser stimulus array and a time limit whereas Ota's task did not. Thus, the overall difficulty of the OCS Hearts Cancellation task was different from the Ota's task. These task-based differences might also account for the difference in object neglect related findings between studies.

With regard to QoL, no significant improvement in self-report ratings were identified for the IG group patients relative to sham group, across sessions. One reason could be that this scale was not specific to neglect-related QoL. Hence, creation and use of a neglect-specific QoL, similar to the neglect-specific ADL task used in the current study, would be beneficial. Additionally, the scale was indicative of self-report based on subjective feelings of adequacy which might not necessarily correlate with ability. Hence, measurement of anosognosia in future studies would also help to substantiate findings from both neglect tests and QoL self-report.

Overall, given that the ultimate goal of cognitive rehabilitation is to enable patients to lead better-adjusted lives and facilitate functional independence, the relative improvement of IG as compared to CG in ADL activities, is an important finding indicative of a meaningful improvement of neglect, at least in the short term. Eschenbeck et. al.'s (2010) ADL test used in the current study has several advantages over the questionnaire based ratings of ADL that are typically used in research studies. For example, commonly used ADL measures in neglect literature like the Barthel Index (Mahoney & Barthel., 1965) and the Functional Independence Measure (Granger, Hamilton, Keith, Zielezny, & Sherwin, 1986) cover a wide range of activities which are not neglect-specific and not sensitive enough to identify subtle improvements in neglect performance on daily life functioning (Chen et al., 2012; Kerkhoff & Schenk, 2012). The

Catherine Bergego scale (Azouvi, 1996) although neglect-specific and facilitates testing of anosognosia, is not applicable to bedridden patients and is limited in its standardization of task administration and scoring (i.e. based on clinical observations). In comparison, Eschenbeck et. al.'s (2010) ADL task requires patients to perform everyday life activities in their natural environment, but in a structured format. While both Catherine Bergego scale and Eschenbeck's task assessed neglect in different spatial frames (personal, peri personal, extra personal), the former uses the rater's subjective Likert ratings to determine neglect severity, while the latter provides graded scoring guidelines based on number of target outcomes (partially/ completely) achieved. Thus, the ADL test used in the current study was able to assess subtle effects based on objective scoring criteria, which may have increased its sensitivity for neglect detection.

This study also demonstrated the importance of using covariates in statistical analyses to account for the impact of uncontrollable individual differences between patients on test performance. In patient studies, it is impossible to find uniformity in variables such as impact of illness on behavioural performance. Hence, using baseline scores as covariates increased statistical power to detect true and significant intervention related effects even in a relatively small sample. Thus, accounting for at least some variability contributing to neglect performance helped to ascertain the potential of rTMS in benefitting ADL. A larger sample could have afforded the use of more covariates in the analyses.

The primary limitation of this study was a small sample which was heterogeneous in stroke related factors and cognitive profile of deficits. To increase inclusivity and avoid selection bias, I did not exclude patients with recurrent strokes or control for baseline cognitive functioning. However, both these factors are related to aspects of recovery. This limitation also emphasizes the relative benefits of using a randomized crossover design (e.g. Cazzoli et al., 2012) where the patient serves as their own control. Such a design would help to control for patient heterogeneity and improve power of the study. However, one must consider the possibility that brain stimulation based plasticity may have an enduring impact as well as be time-sensitive (Cramer et al., 2011). Hence, if rTMS intervention is applied before sham, then the enduring effects of rTMS based plasticity may extend into the measurement of neglect even in the sham phase. On the other hand, if the patient undergoes sham before multiple sessions of 1 Hz intervention, the delay between stroke and intervention must be controlled for. Alternatively, use of cTBS is advocated since these protocols are quicker (< 1 minute), patient-friendly and can be easily used in crossover designs. Research using cTBS protocols has shown that additional trains of stimulation applied before the effect of the initial train wears off, disproportionately extends neglect related improvements. Thus, the additional sessions may take advantage of ongoing neuroplasticity induced in the initial cTBS session. For example, Nyffeler et. al. (2009) showed that while two trains of cTBS separated by 15 minutes improved neglect for up to 8 hours as compared to baseline, two additional trains administered at 60 and 75 minutes respectively after the first, extended the behavioural benefits for up to 32 hours. Cazzoli et. al. (2012) used the same protocol but extended it to eight trains administered over two days and reported significant improvements in neglect patients' ADL performance using the Catherine Bergego scale, lasting for up to three weeks.

Another limitation of the current study was that the timing between baseline testing and rTMS was not rigorously controlled. Administering a comprehensive battery of tests with severely impacted neglect patients in a rehabilitation hospital setting was penalized by a trade-off that testing occurred over multiple sessions. Hence only the test with the least administration time (cancellation) was given to the patient immediately prior to the first rTMS session to acquire the most recent baseline measure possible, for at least one of the tasks. Unfortunately, the use of spontaneous recovery scores prior to intervention could not be used as a covariate in statistical analyses for this chosen neglect measure, i.e. cancellation based asymmetry and CoC indices used negative signs in scoring to indicate directionality and were not amenable to calculation of change scores. Future larger sample studies using tests amenable to measurement of spontaneous recovery, can assess if rTMS benefits are significantly different between those who demonstrate spontaneous recovery prior to intervention versus those who do not.

There were a few other drawbacks of the current study. Long term follow-ups increased the likelihood of medical health related complications and general well-being in an elderly sample which could have affected their cognitive test performance. Additionally, sub-acute stroke patients were accessed from inpatient rehabilitation hospitals in Oxford rather than from hospitals providing care at the acute stage of stroke. This implies that the sample in this study precluded mild stroke patients who are frequently discharged home after acute stage care. By extension, it may indicate that the patients recruited in the current study may have had more severe strokes requiring sub-acute stage care in a rehabilitation facility. Individuals with severe stroke have been reported to show slower and less significant functional gains during inpatient rehabilitation (For review, see Pereira et al., 2012). Hence, factors such as stroke severity and extent of brain damage are relevant to assessing the rehabilitation potential of rTMS and should be included in future studies.

Findings from the study indicate need for future work exploring the efficacy of multiple closely spaced cTBS sessions as well as maintenance rTMS sessions in extending neglect improvements to the long term. Additionally, future studies would benefit from identifying patient-related factors that may contribute to inter-individual variability in response to rTMS such as age, stroke severity, cognitive reserve, etc. Optimising protocols for these factors may help to augment neglect related benefits. Finally, the relationship between rTMS based neglect improvement and changes in potentially related non-neglect domains such as sustained attention could not be adequately explored in the current study and need further exploration in a study with larger sample of patients and use of cognitive paradigms with higher sensitivity to subtle deficits.

In the next chapter, I have attempted to investigate if rTMS induces changes in functional brain activity that may help to explain neglect recovery.

CHAPTER 6 - An investigation of attention related modulation of occipital lobe activity in neglect patients as a function of rTMS

6.1 Introduction

Stroke causes structural damage to a brain region, but the consequent lesion may impair other important remote nodes of a functional brain network, by long-distant effects termed diaschisis (Carrera & Tononi, 2014; Feeney & Baron, 1986; Jackson, 1884). These changes in functional activity can be both intrahemispheric and interhemispheric and can have consequences on cognitive functioning. For example, a stroke restricted to a focal region in the ventral attention network can alter physiological functioning of the dorsal fronto-parietal attentional regions, which in turn could decrease the top-down modulation of the visual cortex and reduce its responsiveness (Corbetta & Shulman, 2011). Additionally, in the weeks following stroke, increased activity has been noted in distant brain regions connected to the stroke regions including the contralesional hemisphere (Cramer, 2008). One interpretation of the increase in contralesional hemisphere activity is that it reflects a stroke-related reduction of interhemispheric inhibition (Cramer, 2008) which has also been hypothesized to be related to deficits such as the neglect syndrome (Kinsbourne, 1974).

The top down disruption of visual processing in neglect patients was demonstrated in a study manipulating attention load at fixation with two focal parietal lobe lesioned neglect patients (Vuilleumier et al., 2008). In this investigation, both patients underwent functional Magnetic Resonance Imaging (fMRI) when they passively watched a string of coloured letter stimuli at fixation (low attention load) and whilst monitoring the central stream of letters, were required to respond to a red letter target (high attention load). The investigators found reduced activation of occipitotemporal cortex in the right hemisphere related to high rather than low attention load in response to contralateral checkerboards across both unilateral and bilateral conditions. This attention load paradigm was further adapted to replace checkerboards with visual objects in a behavioural study with a larger sample of six neglect patients (Vuilleumier et al., 2008). Results were in line with the fMRI study and showed that object recognition in the left visual field was worse in these patients under high attention load than low load. Thus, parietal lesions can be related to attention-dependent disruptions in functional activity in the visual cortices of neglect patients.

Concurrent TMS-fMRI studies of healthy controls receiving TMS to the parietal lobe while in the scanner while passively watching bilateral moving stimuli (as compared to a blank display) has shown that parietal TMS can modulate activity in the visual cortex (Ruff et al., 2008). Furthermore, Plow et al. (2014) showed in a sample of ten healthy controls that 1 Hz repetitive TMS (rTMS) to the left intraparietal sulcus disrupted contralateral performance in a visual tracking task and changes in functional activation of the parietal, temporal and occipital lobes. Specifically, in the targeted left hemisphere, the inferior parietal lobe and middle occipital gyrus showed lowered activation whereas the superior parietal and middle temporal lobe as well as the superior occipital gyrus showed higher activation. This pattern of activation was reversed in the homologous regions of the un-stimulated right hemisphere. Based on these results, they suggested that the transient decrease in attention related task performance due to a ‘virtual’ parietal lesion was related to disruption of network-wide interhemispheric processes including the occipital cortex (Plow et al., 2014).

Hence, recovery from attentional deficits may also be reflected in restoration of functional activity in these interacting disrupted areas (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Cramer, 2008; Nudo, 2013). Corbetta et al. (2005) demonstrated a ‘push-pull’ pattern in the dorsal parietal cortex in 11 unilateral stroke patients with neglect/extinction when performing a Posner cue priming attention paradigm (Posner, Walker, Friedrich & Rafal, 1984): at the acute stage the right hemisphere showed no activation but reactivated at the chronic stage, while the left hemisphere's activation in this region was stronger at the acute than chronic stage. Similarly, regions of interest in ventral and dorsal occipital cortex showed relative reactivation in the right hemisphere at the chronic stage compared to the acute stage (Corbetta et al., 2005).

One use of rTMS has been in its role as a non-invasive brain stimulation technique to remediate visual neglect in stroke patients (for recent review, see Jacquin-Courtois, 2015). Changes to motor threshold and in motor evoked potential (MEP) amplitudes have been typically used as indicators of brain stimulation induced changes to cortical excitability and related improvements in motor functions (Fregni et al., 2006; Khedr, Abdel-Fadeil, Farghali, & Qaid, 2009). MEPs have also been used to study the effects of brain stimulation to regions participating in attention; such as using paired pulse rTMS to the posterior parietal cortex (PPC) and motor cortex (M1) of the contralesional hemisphere (Koch et al., 2008). The extent of hyperexcitability in PPC-M1 correlated with neglect severity in these patients. The investigators also did a follow up experiment where 600 pulses of 1 Hz rTMS to left PPC at 90% resting motor threshold was seen to bring down the left hemisphere's M1 hyperexcitability in ten of these patients to be comparable to five control patients. This was also associated with an impact on neglect, reducing left sided omissions on a visual chimeric naming task (Koch et al., 2008). In a subsequent study, Koch et al. (2012) replicated these findings using two weeks of continuous Theta Burst Stimulation (cTBS) to the left PPC instead of a single session of 1 Hz rTMS. Both the above studies provided evidence that non-invasive brain stimulation has the potential to produce changes to functional connectivity in the hyperactive left parietofrontal circuits and this correlated with improvement in neglect measures.

It must be noted that MEPs allowed for an investigation of changes in the left hemisphere's activity *but did not explore the effect on the lesioned hemisphere*. Hence, the study in this chapter aimed to explore the role of rTMS in a sample of neglect patients by assessing behavioural task performance and functional modulation of activity in *both the lesioned and non-lesioned hemispheres, pre- and post-rTMS*. Previous rTMS studies have shown benefits of rTMS in improving neglect in patients at both the sub-acute (Cazzoli et al., 2012; Kim, Chun, Kim, & Lee, 2013; Song et al., 2009) and chronic stages (Brighina et al., 2003; Kim, Jung, & Shin, 2015; Shindo et al., 2006). However, the functional changes in the brain in sub-acute and chronic neglect patients, pre- and post- rTMS rehabilitation, have not been previously examined or compared.

Thus, the primary questions were:

i) Do patients with neglect on behavioural tasks but with different lesion profiles and stage of stroke (sub-acute, chronic) show abnormal patterns of functional activity as compared to controls?

ii) Does rTMS help to redress any observed abnormal functional activity in patients assigned to the Intervention Group?

The task chosen was an adaptation of a paradigm that has been used successfully with young controls (Schwartz et al., 2005) as well as with stroke patients to study effects of attention modulation at fixation, on the visual cortex (Vuilleumier et al., 2008). The task adaptation was first tested as a behavioural pilot with one sub-acute and one chronic neglect patient (see Appendix D for details). In the main experiment, the adapted task was used with healthy elderly controls to elicit significant regions of functional activity.

In order to account for the uniqueness of each patient's lesion, stage of stroke and assignment to group (Intervention or Sham), each patient was treated as a case study and their results compared to the elderly controls at baseline and post rTMS separately.

I hypothesized that at baseline, the results from Vuilleumier et al.'s (2008) study would be replicated such that each patient would show hypoactivation in the right hemisphere relative to controls. The second hypothesis was that post rTMS, the Intervention Group patients would show a resolution of this abnormal functional activity observed at baseline, to be more comparable to controls post rTMS. This resolution would also be reflected in improvement in neglect behaviourally.

6.2 Method

For details of the behavioural pilot, please refer to Appendix D.

6.2.1 Participants

Recruitment of patients to the study was unfortunately limited; only four patients (WM, LG, BR, SW) were eligible and consented to the study despite the multiple recruitment centres. The inclusion criteria for patients in the study were the same as Chapter 5 except in this study stroke survivors were recruited regardless of time since stroke. Visual neglect has been shown to benefit from rTMS even in the chronic stage (Brighina et al., 2003; Lim, Kang, & Paik, 2010; Shindo et al., 2006). Since chronic stage patients were recruited from the Cognitive Neuropsychology Centre (CNC) at University of Oxford, no medical team was recruited to confirm their neglect diagnosis, unlike for sub-acute patients recruited from Abingdon and Witney community hospitals.

Fifteen healthy controls who were aged more than 60 years and had no contraindications to fMRI scanning were recruited from the CNC. Of the controls, one participant was excluded due to high rate of false alarms in the fMRI task. The average age of the group of remaining controls was 70 years (*SD* = 5.2 years, *Range* = 61-79 years, *Males* = 7, *Right-handed* = 7). Patient demographic and clinical data are given in Table 6.1.

Informed consent for patients was obtained in keeping with the ethical protocol approved by the U.K National Research Ethics Committee and the guidelines set out in the Declaration of Helsinki. Informed consent for controls was obtained in accordance with an ethical protocol approved by the Central University Research Ethics Committee at the University of Oxford.

Table 6.1. *Clinical and demographic data of study participants*

Patient	Stage of stroke	Age (yrs)	Sex	Type of stroke	Hemianopia	Time bw stroke & baseline cognitive testing	Time between baseline cognitive testing & fMRI	Time bw baseline fMRI and rTMS sess 1	Time bw rTMS sess 6 & post rTMS fMRI	Time bw post rTMS fMRI & follow up cognitive testing
					Intervention Group					
WM	Sub-acute	60	M	Infarct (R MCA & PCA)	Yes	22 d	9 d	3 d	14 d	2 d
BR	Chronic	88	M	Infarct (R MCA)	No	10 m, 13 d	9 d	10 d	11 d	10 d
					Sham Group					
LG	Sub-acute	74	M	Infarct (R MCA)	Yes	24 d	13 d	3 d	27 d	7 d
SW	Chronic	73	F	Haemorrhage (R lobar intracerebral)	No	11 m, 8 d	1 m, 8 d	2 d	3 d	3 d

R = right, MCA = middle cerebral artery, PCA = posterior cerebral artery, M = Male, F = Female, m = months; yrs = years; d = days, n.a = not applicable, bw = between, sess = session

6.2.2 Procedure

The procedure (including rTMS stimulation parameters) was identical to that in Chapter 5, section 5.2.2. Each patient underwent baseline fMRI scanning at the earliest appointment available post baseline testing. This was followed by six sessions of rTMS followed by a repeat fMRI scan at the earliest available appointment post rTMS and follow up cognitive testing.

6.2.3 Tasks

6.2.3.1 Behavioural Tasks

Please refer to Chapter 2, section 2.2.1 for test and scoring descriptions of the OCS Hearts Cancellation, Line Bisection and neglect-specific ADL tasks.

6.2.3.2 fMRI Task

The task was an adaptation of one that has been previously used to study changes in functional activity for attention load based modulation in the visual cortex in two neglect patients (Vuilleumier et al., 2008). In the original study, two task loads, no load and high load were used in two successive experimental runs. The participants in that study were two parietal stroke patients with neglect, one at two months post stroke and the other at five months post stroke. In the current study, the task was not intended to measure functional activity changes based on attentional load. Rather, the rationale was to compare activation for only the condition of the task that engaged high attentional load at fixation and compare any changes in functional activity in task performance as a function of rTMS stimulation. Some other adaptations were also made to the task to suit the sample of sub-acute stroke patients who were observed to fatigue easily during cognitive testing sessions.

The task used in the current study consisted of 4 pseudorandom epochs of checkerboards flickering at 8 Hz in the participant's Left visual field (LVF), Right visual field (RVF), Bilateral visual field (BVF) or not flickering as in the Control (Ctrl) condition. Each epoch lasted 20 seconds each and was split over two runs. Each run started with a blank grey screen for 20 seconds. Participants were instructed to fixate on a central white '+' and whilst ignoring the peripheral checkerboards, press a button on a response box whenever the '+' changed colour to red. The occurrence of the red '+' was distributed equiprobably across conditions. The task lasted ~6 minutes in total.

The original study had used retinotopic mapping with their patients (Vuilleumier et al., 2008). However, retinotopic mapping was not conducted in the current study given that in the original study, each of areas V1-V4 of the visual cortex showed a reduction in the right occipital lobe for both patients.

6.2.4 fMRI Acquisition Parameters

Blood oxygen level dependent (BOLD) fMRI images and an anatomical T1 image were acquired using 3T Siemens MR scanner. fMRI data was acquired using echo planar imaging, *repetition time* = 2.8 secs, *echo time* = 30 ms, *flip angle* = 90 degrees, *Field of Vision* = 192 x 192 mm^2, *matrix size* = 64 x 64 mm^2, thus giving a *voxel size* = 3 x 3 x 3 mm^3. The fMRI scan resulted in a total of 100 volumes; each composed of 51 axial slices and acquired over two blocks (see Section 6.2.3.2). An axial T1 anatomical image was also acquired for each participant, *repetition time* = 2.04 secs, *echo time* = 4.7 ms, *flip angle* = 8 degrees, *Field of Vision* = 192 x 192 mm^2, *matrix size* = 192 x 192 mm^2, *voxel size* = 1 x 1 x 1 mm^3 to enable co-registration of the functional images with the structural image.

6.2.5 Data Analysis

6.2.5.1 Behavioural analysis

It is important to note that behavioural neglect tasks and performance on the fMRI task cannot be directly compared. The fMRI task required peripheral checkerboards to be ignored whilst in the neglect tasks, no such explicit instructions were given, allowing for symmetrical opportunities for exploration of both visual fields during task performance. Additional factors for consideration were time interval between behaviour testing and fMRI scans, as well as fluctuations in neglect performance from session to session based on factors such as alertness and spontaneous recovery. Hence, neglect tasks were considered only to inform about presence or absence of neglect at different stages of testing and the fMRI behavioural results were only used to ensure that the patient was being attentive.

6.2.5.1.1 Neglect Tasks

For neglect-specific performance, scores on OCS Hearts cancellation spatial asymmetry, average deviation on line bisection and total scores on the ADL task have been used to comment on neglect performance at baseline (pre rTMS) and post rTMS. Control norms were only available for spatial asymmetry scores, whereas line bisection and ADL performance have been evaluated as pre-post measures.

OCS Hearts Cancellation (Demeyere et al., 2015):

When screened for inclusion to the study, all patients met the inclusion criteria of impaired spatial asymmetry scores. However, the scores used as baseline in the current study on the cancellation task are from subsequent testing after screening.

Spatial asymmetry = Number of targets cancelled in right columns – left columns

Impairments were noted if patient's spatial asymmetry score was < -2 or > 3 (Demeyere et al., 2015). Thus, a positive spatial asymmetry score > 3 would indicate left neglect.

Line Bisection (adapted from Wilson et al., 1987):

Mean deviation on long length lines was computed as

$$\textit{Line Bisection Deviation} = \frac{\textit{marked left side distance - true half length}}{\textit{true half length}}$$

A score of -1 indicated maximum leftward deviation and a score of +1 indicated maximum rightward deviation.

ADL (Eschenbeck et al., 2010):

For each of the 8 ADL tasks, a score each of 1, 0.5 or 0 was given depending on whether the patient was able to successfully complete, partially complete or could not complete the task. Thus, a maximum total score of 8 implied perfect performances on all the ADL sub-tasks.

6.2.5.1.2 **fMRI Task**

The proportion of targets accurately detected across the whole task and separately for LVF, RVF and BVF was calculated for each patient. Each patient's proportion correct for pre and post rTMS scans was compared to the controls average using Crawford and Howell's t-test (Crawford & Howell, 1998).

6.2.5.2 fMRI Analysis

fMRI analysis was conducted using FSL v5.0.8 provided by the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FMRIB, www.fmrib.ox.ac.uk/fsl).

Pre-processing included brain extraction using BET (Brain Extraction Tool) (Smith, 2002) to remove non-brain structures, followed by motion correction to account for participant's head motion during the scan using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). Spatial smoothing using a 5 mm Gaussian kernel of full-width at half maximum was applied to account for functional and anatomical variability between participants and to improve signal to noise ratio. The whole 4D data set was normalized using a single scaling value ('grand mean scaling'; FSL sets mean at ~100^2 in each voxel) so that higher-level analyses comparisons between subjects was valid. High pass filter with a 100 seconds cut off was used to remove low frequency drifts. Functional data was registered to the respective participant's structural image and MNI 152 standard space using FLIRT (FMRIB's Linear Registration Tool) (Jenkinson et al., 2002; Jenkinson & Smith, 2001).

This pre-processed data was analysed using a general linear model (GLM) approach in FSL's FEAT v6.0 using FILM (FMRIB's Improved Linear Model) autocorrelation correction. The hemodynamic response function was modelled as a gamma function, a normalisation of the probability distribution function of the gamma distribution with zero phase, standard deviation of 3 seconds and a mean lag of 6 seconds. Six head motion regressors were modelled as variables of no interest and were orthogonalized with regard to the rest of the design matrix. In addition to these, four explanatory variables (EVs) of interest were modelled into the design corresponding to checkerboard presentation in the LVF, RVF, BVF and Ctrl. The blank screen used at the start of each run was used as the resting baseline in FSL. All EVs were modelled with their temporal derivatives. FEAT was used to fit the model to the data, elicit parameter estimates for each of the main EVs against the resting baseline and contrast the parameter estimates against each other. For controls, statistical activation maps were obtained for average activation across conditions (LVF, RVF, BVF and Ctrl), LVF>RVF, RVF>LVF and BVF>RVF. Of these, the key contrast of interest to left neglect was LVF > RVF and subsequent comparisons between each neglect patient and elderly controls', concentrated on this contrast. The resultant Z statistics images (Gaussanized T) were thresholded using clusters determined by Z > 2.3 and a significance threshold of $p \leq 0.0001$.

First level analysis was done for each patient and control wherein data of each run in the session was analysed separately using the above parameters. At the second level, output from the first level was averaged across the two experimental runs for each participant in each session using fixed effects modelling to account for within session variances. Third level analyses was done *only for controls* where data of all 14 subjects was averaged with mixed effects analyses using FLAME (FMRIB's Local Analysis of Mixed Effects). Mixed effects analysis at this level modelled variance from both within sessions (fixed effects variance), as well as from between sessions and participants (random effects variance), in order for the controls' results to be representative of the population. For both second and third level analyses, one sample t-test was used to identify if subject/group average activation was significantly greater than zero. Note that patient data was not averaged since each patient was assigned to a unique category based on time since stroke and Intervention/ Sham group assignment.

Within patient whole brain changes from pre to post rTMS analysis could not be performed due to lack of appropriate comparative control group. While the limited number of patients in the study did not provide for an appropriate sham control group, healthy controls were only scanned once and could not provide for measures of change in activation over time. Hence, only between subjects' analyses was conducted to compare each individual patient's data to elderly controls, separately at baseline and post rTMS for the LVF> RVF contrast. The statistical analysis used by FSL for these comparisons was a special case of the two sample unpaired t-test, i.e. prediction interval test. This test is used when one of the two groups only has a single subject, such as in the comparison of a single patient to a group of controls in this study. However, FSL is sensitive to normality assumptions required to use the parametric two sample t-test; in the case of a single patient sample in one of the groups, the normality assumption is unfortunately violated. Consequently, results from this study cannot be generalized to other neglect patients.

For each comparison, both Patient>Controls and Controls>Patient contrasts were investigated to identify relative hyperactivity and hypoactivity in patients' data in comparison to controls. Clusters of activation were labelled using the Harvard-Oxford cortical and subcortical structural atlases in FSLView. Note that although whole-brain statistical analyses were conducted between each patient and the controls, discussion of between group results for the LVF> RVF contrast will be meaningfully constrained *only to the regions identified as significant to the task based on the controls' results.*

Lastly, in order to visualize the extent and direction of BOLD signal change from resting baseline in the significant clusters identified for the LVF>RVF contrast, regions of interest (ROIs) were created from the statistical activation maps obtained from each analysis (henceforth referred to as contrast-based ROIs). Note that since the ROIs were chosen *for* their significance in whole brain analyses, any further ROI based statistical comparisons of signal change would also be significant (Poldrack, 2007). Hence, the ROI-extracted data signifying percentage of BOLD signal change (% BSC) was used to inform about *patterns* of signal change in each patient's pre and post rTMS data when compared to controls.

For a particular cluster that was significantly activated in the whole- brain between subjects' analysis, the corresponding Z statistics' activation map's threshold was adjusted using FSL's 'fslmaths' script to extract the significant ROI and binarize it. Since the cluster/ROI was also intended to be anatomically constrained to the regions identified based on controls' activation for LVF>RVF (see above), an anatomical ROI was created using FSLView's Harvard Oxford cortical atlas. Thus, the final ROI combined the contrast-based and anatomical binarized ROIs so as to extract information on % BSC from the functionally significant and anatomically pertinent cluster of interest. The % BSC for each ROI was extracted for each patient and control using FSL's 'featquery' script.

6.3 Results

6.3.1 Behavioural results

6.3.1.1 Neglect Tasks

Each patient showed impairment in *at least one* of the neglect tasks at baseline. Figure 6.1 shows lesion and behavioural data on neglect tests for each patient. The lesions were drawn manually using the best scan available for visualizing them. Lesions for all four patients showed an involvement of the parietal cortex. BR's lesion additionally included frontal and temporal regions while SW's lesion included frontal and occipital regions.

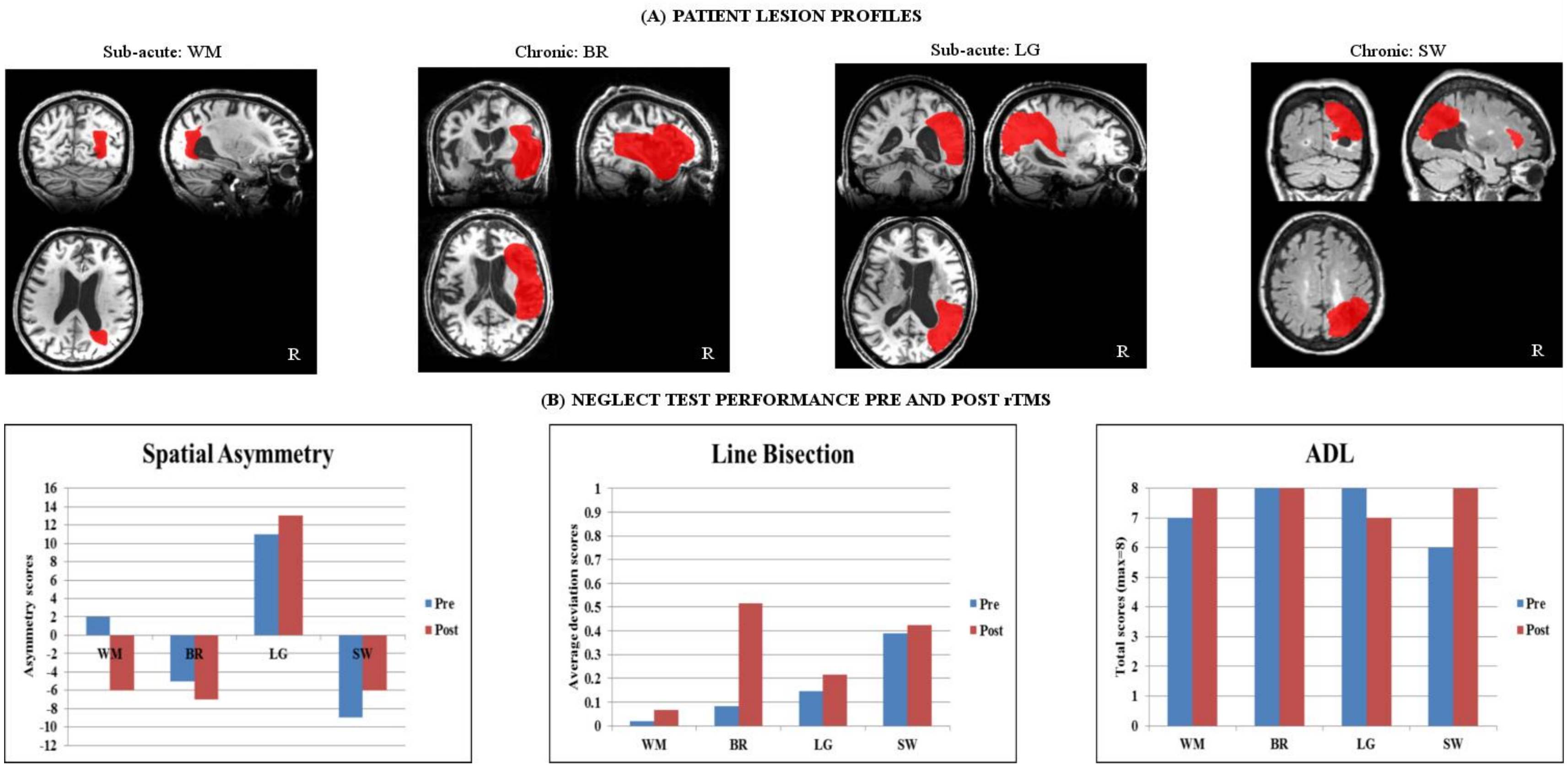

Figure 6.1. Lesion data and neglect test performances for each patient

(A) Lesion profile of each patient is depicted. All patients had lesions inclusive of the posterior parietal lobe. Chronic patient BR's lesion extended to fronto- temporal regions while SW's lesion extended to frontal and occipital regions. Lesions were manually drawn on the best structural scan available for the patient at baseline.

(B) Each patient's performance on the neglect test battery is shown. Based on normative data, none of the patients improved in their spatial asymmetry scores. On long length line bisection although all patients showed worsening of deviation performance, BR showed worse deviation than WM, LG and SW post rTMS. On ADL, WM in the Intervention Group and LG in the Sham group improved and declined by one point respectively; however SW in the Sham group improved on the task by two points.

OCS Hearts Cancellation

At baseline, three out of four patients (BR, LG, SW) showed impaired spatial asymmetry on this task based on normative cut-offs (Demeyere et al., 2015). Post rTMS, all patients including WM showed impaired spatial asymmetry performance. Importantly, neither the Intervention Group (WM, BR) nor Sham group (LG, SW) patients showed resolution of neglect on this task post rTMS. Overall, none of the four patients improved in their spatial asymmetry scores and were each below cut-off post rTMS.

Line Bisection

At baseline, all patients showed a rightward ipsilesional bias on this task. Post rTMS, each patient's bias was seen to worsen regardless of whether they were in the Intervention or Sham group. Interestingly, BR, despite being assigned to the Intervention Group showed a relatively bigger shift in ipsilesional deviation post rTMS indicating worsening of neglect as compared to baseline. The magnitude of the deviation cannot be assessed as significant or not without norms. However, overall, each of the Intervention and Sham group patients showed an ipsilesional bias in line bisection and worsening of the bias indicating that their neglect had likely not resolved on this task.

Neglect-specific ADL

At baseline, of the 2 Intervention Group patients (WM, BR), WM showed difficulty in completing one of the eight ADL sub-tasks. However, post rTMS his performance on the ADL task improved to ceiling. BR, the other Intervention Group patient, performed at ceiling at both time-points.

In the Sham group, no improvement in task performance was expected. This was supported by LG's task performance where in fact, post rTMS, he failed to perform one of the ADL sub-tasks adequately. However, surprisingly, SW, the chronic Sham group patient showed a two point improvement from pre to post rTMS. Since her two point improvement was greater than the one point increase (WM) or decrease (LG) in ADL performance, this result will be considered in more detail in the Discussion.

Overall, none of the patients showed any significant improvement in neglect post rTMS, except SW, who despite being in the Sham group showed a marginal improvement on the ADL task as compared to the other included patients. For the remaining three patients (WM, BR, LG), neglect did not improve post rTMS regardless of their assignment to the Intervention or Sham groups or time since stroke (sub-acute, chronic).

6.3.1.2 fMRI Task

Average proportion of targets detected by controls was 0.989 (*SD* = 0.02).

Table 6.2 shows proportion of targets correctly detected in the fMRI task and results from the Crawford and Howell's analysis. All patients showed an improvement in target detection from baseline to post rTMS. BR was the only patient who despite making an improvement, continued to be impaired post rTMS when compared to elderly controls. SW performed at ceiling both at baseline and post rTMS.

Table 6.2. *Proportion of central targets correctly detected by each patient across all conditions at baseline and post rTMS*

Patient	All targets		LVF		RVF		BVF	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
WM	1	0.98	1	1	0.92	1	0.83*	1
BR	0.7*	0.83*	0.67*	0.75*	0.67*	0.75*	0.92	0.92
LG	0.91*	1	1	1	0.75*	1	0.92	1
SW	1	1	1	1	1	1	1	1

**Significantly lower target detection than controls at $p < 0.001$ using Crawford and Howell's t-test.*

6.3.2 fMRI Imaging results

i) Healthy controls

Average activation across conditions irrespective of peripheral stimulation showed significantly active clusters in the left and right occipital poles. Table 6.3 lists the clusters significant at $Z > 2.3$ and $p \leq 0.0001$. The table also lists the peak MNI co-ordinates, along with size and strength of the activation. Figure 6.2 depicts these significant clusters of activation for the contrasts explored, graphically.

Table 6.3. *Main effects of visual stimulation in controls across all conditions for contrasts explored*

Hemisphere-Areas	Co-ordinates			Z value	Size (voxels)
	X	y	Z		
		Average activation			
L- Occipital pole	-30	-92	-16	4.35	745
- occipital fusiform gyrus					
R- Occipital pole	24	-92	-12	3.73	513
		LVF > RVF			
R- Occipital pole	16	-92	-20	5.93	7986
- lateral occipital cortex					
		RVF > LVF			
L- Occipital pole	-12	-96	-2	5.94	4442
- lingual gyrus					
-occipital fusiform gyrus					
		BVF > RVF			
R- Occipital pole	18	-92	-20	5.85	7698
-lingual gyrus					
-occipital fusiform gyrus					

L=left hemisphere; R=right hemisphere.
All clusters were significant at p≤0.0001.Clusters in italics indicate significant sub-clusters.

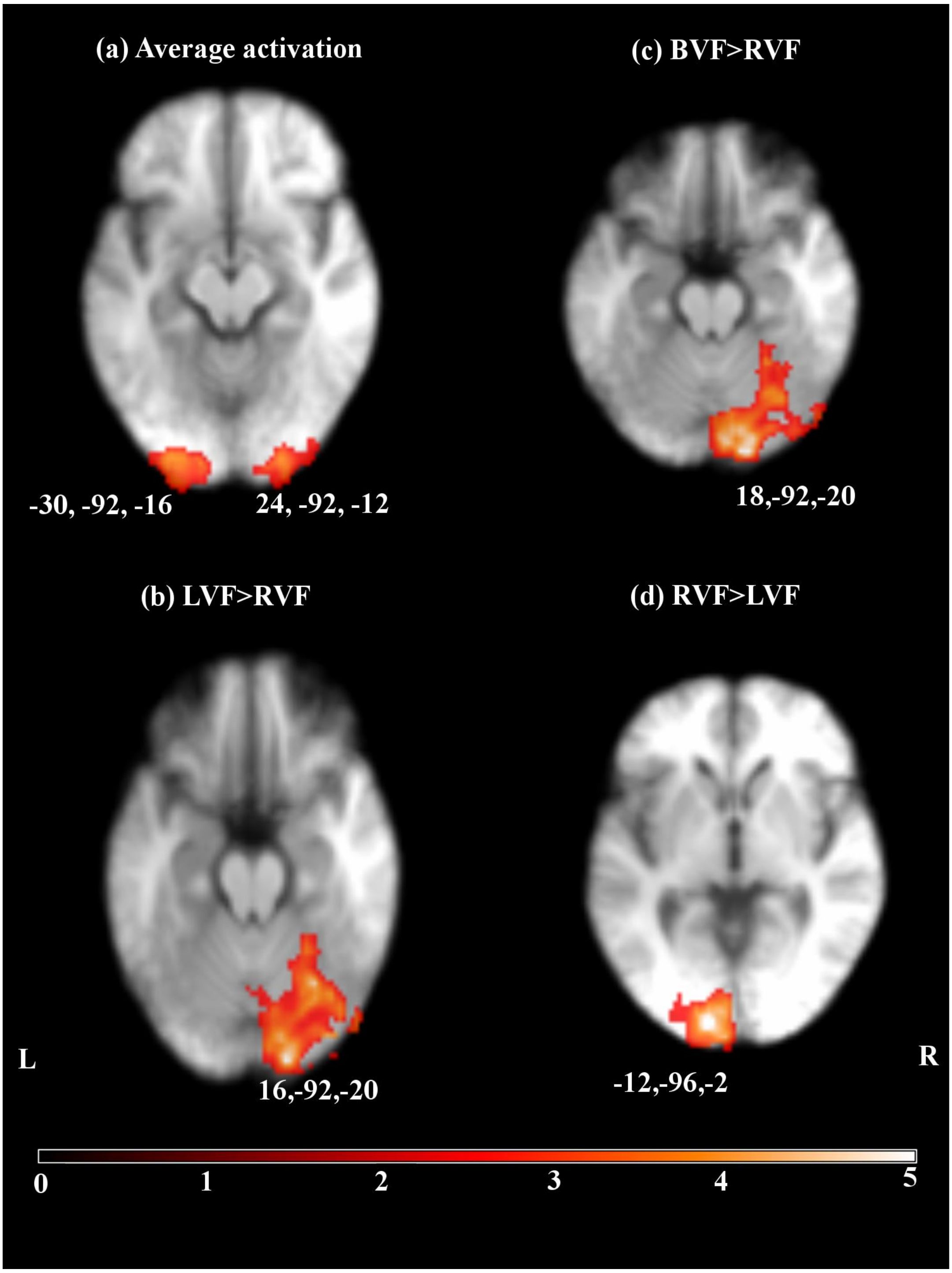

Figure 6.2. Significantly active clusters for controls across contrasts

L = Left hemisphere; R = Right hemisphere; LVF = Left visual field; RVF = Right Visual Field; BVF = Bilateral Visual Field

This figure shows significant clusters thresholded at Z >2.3 at p $\leq$ 0.0001 for different contrasts using controls data. MNI peak co-ordinates of activation are depicted next to the cluster.

(a) Average activation across all conditions irrespective of visual field showed significant activation in bilateral occipital poles;

(b) For the contrast BVF > RVF, significant activation was seen in the right occipital poles;

(c) For LVF > RVF, controls showed significant activation in contralateral right occipital pole, and

(d) For RVF > LVF, controls showed significant activation in the contralateral left occipital pole.

It was seen that the comparison of the contrast combining activation across all conditions (LVF, RVF, BVF, Ctrl) against the resting baseline showed left occipital pole activation (peak cluster $Z = 4.35$, $p \leq 0.0001$) involving sub-clusters in the occipital fusiform gyrus. For the same contrast, the right occipital pole was also seen to be significantly active (peak cluster $Z = 3.73$, $p \leq 0.0001$).

For the contrast of LVF > RVF, controls showed significant contralateral occipital lobe activation (peak cluster $Z = 5.93$, $p \leq 0.0001$, Table 5.3) involving the *right* occipital pole, with one of the sub-clusters involving the lateral occipital cortex. For the reverse contrast of RVF > LVF, controls showed significant activation in contralateral *left* occipital lobe (peak cluster $Z = 5.94$, $p \leq 0.0001$, Table 5.3) with sub-clusters localized to left occipital pole, occipital fusiform gyrus and lingual gyrus.

This high versus low attention modulation paradigm has been previously tested with *younger controls* in a single study (Schwartz et al., 2005). The current study was different from Schwartz et al.'s (2005) study in its use of only the high load task. Additionally, it was more similar in task requirements to Vuilleumier et al.'s (2008) study which was conducted with *elderly patients*. However, some comparisons can be made across Schwartz et al.'s (2005) study and the current study as both these used control participants.

For both LVF > RVF and RVF > LVF contrasts, the areas of activation observed in the contralateral occipital lobes overlapped with the findings from Schwartz et al.'s (2005) study with younger controls. The key difference between the results presented here and the original study was that Schwartz and colleagues also found significant activation in the parietal lobe for LVF > RVF (superior parietal lobe, posterior intraparietal sulcus) and for RVF > LVF (inferior parietal cortex, posterior intraparietal sulcus) when combining both low and high attention loads.

Finally, for the contrast BVF > RVF, areas involving the right occipital pole, lingual gyrus and occipital fusiform gyrus showed activation (peak $Z = 5.85$, $p < 0.001$, Table 5.3). Similar to the unilateral stimuli condition (LVF > RVF), the main cluster of activation for the bilateral checkerboard stimulation remained in the right occipital pole.

ii) Patient case studies

The lesion characteristics of the patients differed from the study by Vuilleumier et al. (2008). Although each patient in the current study had lesions involving the right inferior parietal lobe, the chronic patients also had lesions in in the right frontal lobe with BR's lesion further including the temporal lobe and SW's lesion involving the visual cortex. Additionally, both sub-acute patients had hemianopia at baseline (although without lesion involvement of primary visual cortex), unlike in the original study where neither patient showed any visual field deficits. Since the patient characteristics differed along the above parameters, stage of stroke and their assignment to Intervention or Sham group, each patient was treated as a separate case study.

The only significant clusters identified in controls after thresholding were in the occipital lobes. Hence, patient data will also be discussed in the context of the occipital lobes. However, I have reported all significant clusters of activation in the tables for completeness. Each patient's imaging data at baseline and post rTMS was compared separately to controls' for the key contrast of LVF>RVF. The contrast RVF > LVF was not explored since the results would be an exact reversal of the contrast LVF > RVF (i.e. LVF > RVF, patient > controls contrast = RVF > LVF, controls > patient). Both patient

$>$ controls and controls > patient comparisons were explored to test for hyperactivation and hypoactivation in patients compared to controls.

Table 6.4 reports the significant clusters of activation obtained from comparing each patient to controls, at baseline and post rTMS, for the LVF>RVF contrast. All clusters reported were significant at $p \leq 0.0001$. In some cases, no significant clusters were found and these results held even after examining the data at $p \leq 0.05$. Occipital lobe activations are highlighted in red.

Table 6.4. Details of significant clusters for LVF > RVF when comparing each patient's data to controls

Comparisons	Hemisphere –Areas	Co-ordinates			Z value	Size (voxels)
		x	y	z		
Patient baseline vs Controls'						
WM Patient > Controls	L- Occipital pole	2	-96	-10	5.5	1490
	R -Brain stem	2	-40	-72	5.05	1894
	R- Postcentral gyrus	36	-24	60	4.28	1148
	R- Postcentral gyrus	14	-32	52	3.95	1065
Controls > WM Patient	R -Occipital pole	28	-102	0	4.43	2164
	L -Temporal pole	-40	6	-46	4.28	849
BR Patient > Controls	L- Occipital pole	-10	-94	-2	4.34	2558
	L- Frontal pole	-16	40	-24	3.76	723
Controls > BR Patient	R- Postcentral gyrus	62	-6	28	3.68	700
	R- Occipital pole	14	-94	16	3.99	559
LG Patient > Controls	N.S					
Controls > LG Patient	R- Occipital pole	10	-94	-2	4.81	5045
SW Patient > Controls	L- Occipital pole	-4	-102	8	4.51	1653
Controls > SW Patient	R -Occipital pole	14	-96	14	4.49	4220
Patient post rTMS vs Controls'						
WM Patient > Controls	L- Occipital pole	0	-94	-12	5.31	1015
Controls > WM Patient	R- Occipital pole	10	-94	-2	4.64	5057
BR Patient > Controls	L- Occipital pole	-12	-94	-2	5.01	3453
	L- Frontal pole	-20	38	32	3.75	1582
	R- Cerebellum	18	-58	-52	3.59	654
	L- Superior parietal lobule	-26	-42	66	3.78	537
Controls > BR Patient	R- Occipital pole	16	-94	20	4.68	1524
LG Patient > Controls	N.S					
Controls > LG Patient	R- Occipital pole	12	-94	2	4.75	5327
SW Patient > Controls	L- Occipital pole	-4	-102	10	4.58	4764
	L- White matter	0	26	26	3.69	2354
	R- Intracalcarine cortex	6	-82	10	5.83	1781
	R- Frontal orbital cortex	38	26	-14	3.62	1029
Controls > SW Patient	R- Occipital pole	8	-96	14	4.42	1774

N.S: Not significant; L=Left hemisphere; R= Right hemisphere; Occipital activations highlighted in red.

For each of the significant occipital lobe clusters identified in the above table, ROIs were created. Although 14 of the ROIs incorporated the occipital pole, each ROI was unique and individually created to incorporate the exact voxels for which a patient's activation significantly differed from controls' for the LVF>RVF contrast.

Figure 6.3 presents the percent of BOLD signal change (% BSC) from rest in each unique contrast-based ROI for the LVF>RVF contrast. For controls, an average of % BSC from rest was obtained in the same ROIs as each patient. It was noted that across comparisons with each patient (except LG who did not show significant activation in the left occipital pole for Patient>Controls comparison), controls hypoactivated the left occipital pole and activated the right occipital pole in comparison to rest, for the LVF>RVF contrast. None of the patients showed this pattern of % BSC either pre or post rTMS.

Please note that while % BSC can be compared between patients' and controls at each time point, within patients' comparisons of signal change from pre to post rTMS cannot be made. Given rTMS's role in inducing network based changes in activity, the occipital lobe changes in functional activation from pre to post rTMS cannot be meaningfully interpreted without accounting for changes in other parts of the attention network.

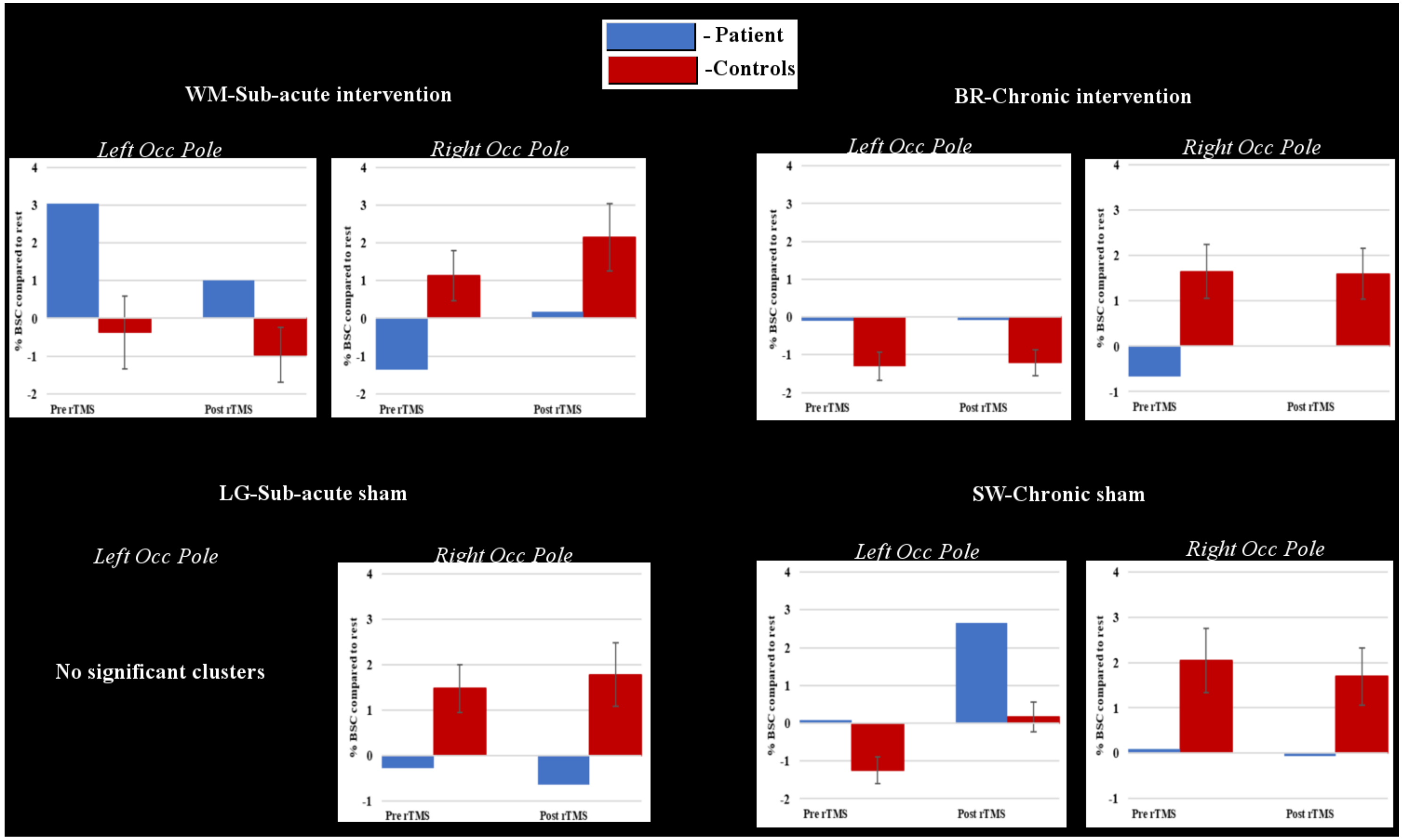

Figure 6.3: Patients' and controls' percentage of BOLD signal change in occipital ROIs for LVF>RVF contrast

Occ: Occipital; % BSC: percentage of BOLD signal change (from resting baseline); Error bar reflects standard deviation.
Controls hypoactivated the left occipital and activated the right occipital pole for the LVF>RVF contrast relative to their resting baseline. Both Intervention group patients' (WM, BR) % BSC in the right occipital pole was significantly lesser than controls at baseline. This pattern was not reversed significantly to match controls' level of activation even after rTMS, even though the direction of activation in the right occipital pole was seen to be more aligned to controls' for WM, post rTMS.

Thus, while Table 6.4 provides relative whole-brain hyper and hypoactivation of voxels in patients in comparison to controls' for the LVF>RVF contrast, ROI extracted values in Figure 5.3 depict the pattern of activation in the contrast-based ROIs for each patient and controls' on average. From whole-brain analyses, it can be concluded that activations in the left occipital pole for the Patient>Controls and in the right occipital pole for the Controls>Patient contrasts were significantly different when cluster thresholded at $p \leq 0.0001$. Details of % BSC related results are reported for each case study separately below.

Patient WM (sub-acute Intervention group) showed hyperactivity in the left occipital pole and hypoactivity in the right occipital pole as compared to controls. Post rTMS, there continued to be a significant difference in his activation from controls for both ROIs. Interestingly, the right occipital pole was seen to be activating post rTMS, albeit much lesser than the controls' (Figure 6.3).

Patient BR (chronic Intervention group) did not show significant hypoactivation of the left occipital pole at baseline or post rTMS as seen in controls. He also showed a relative hypoactivation of the right occipital pole at baseline in contrast to controls' average activation, and this pattern did not change significantly even after rTMS.

Patient LG (sub-acute- Sham group) did not activate any regions significantly more than controls' at baseline or post rTMS. At both time points, LG significantly hypoactivated the right occipital pole in contrast to controls' who on average, activated the right occipital ROI for the LVF>RVF contrast.

Patient SW (chronic- Sham group) showed some hyperactivity in the left occipital ROI at baseline which was significantly different from the hypoactivation of this ROI by controls'. Both SW and controls showed an increase in activation in this ROI post rTMS, although the magnitude of activation was significantly higher for SW than controls. For the right occipital pole ROI, SW's % BSC was significantly lesser than controls both at baseline and post rTMS. Interestingly, for another region in the right occipital lobe, i.e. the intracalcarine cortex, SW showed a significant increase in % BSC post rTMS as compared to controls (Figure 6.4, 6.5). Such a significant difference in activation was not seen in this ROI when comparing her *baseline* performance to controls' average activation in the intracalcarine ROI.

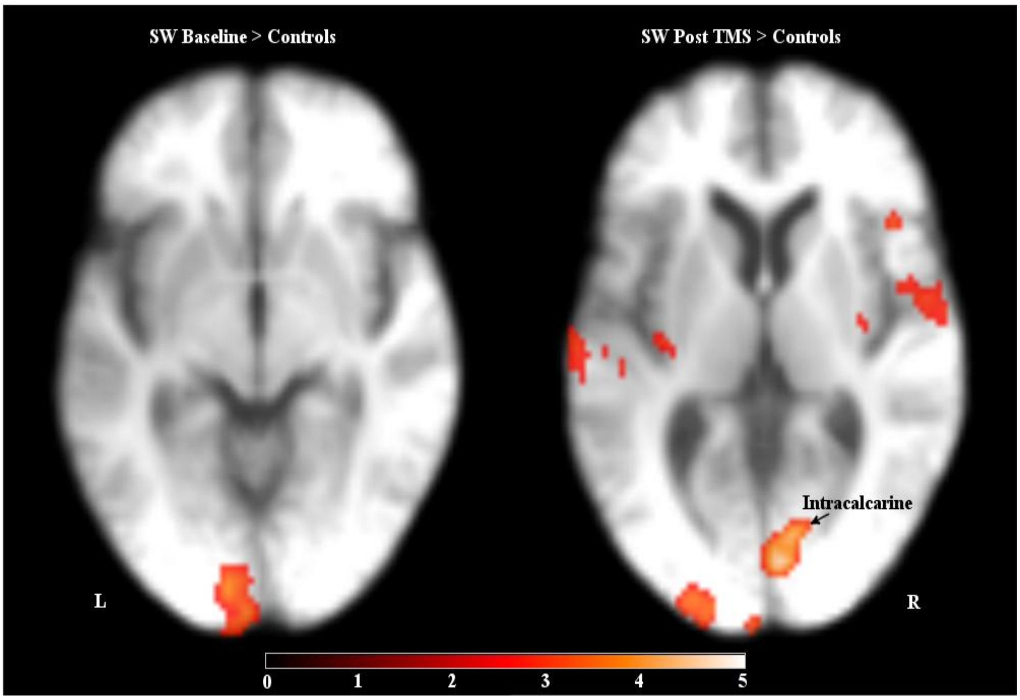

Figure 6.4. Comparison of SW's baseline and post rTMS activations to controls for LVF > RVF

This figure shows significant clusters thresholded at Z > 2.3, p ≤ 0.0001 for the comparison SW > Controls.
At both baseline and post rTMS, SW showed significantly more activation in the left occipital pole than controls for unilateral activation in the LVF. However, post rTMS, SW also showed significant activation in the right intracalcarine cortex as compared to controls.

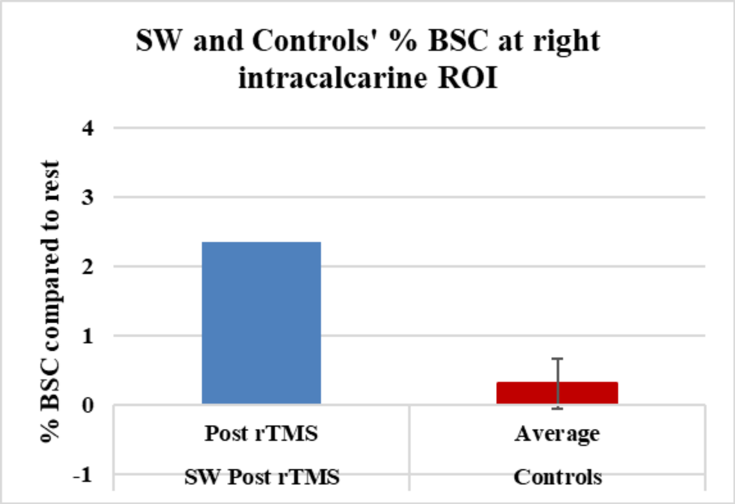

Figure 6.5: Comparison of SW and Controls' % BSC in the right intracalcarine cortex for LVF>RVF

%BSC: Percent BOLD signal change; Error bar reflects standard deviation.
SW's post rTMS % BSC in this ROI was significantly higher than at rest and significantly different from controls' average activation in this ROI.

Overall, every patient in the study showed hypoactivation of the right occipital pole when peripheral visual stimuli were presented in the left visual field, after controlling for activation in response to the right visual field, i.e. for LVF>RVF. Importantly, rTMS did not significantly change the pattern of hypoactivity in the right occipital pole in any of the patients regardless of whether they were sub-acute or chronic stage patients or whether they were assigned to Intervention Group or Sham group.

For individual patients, two additional observations were made:

(i) *SW showed activation in the right occipital lobe's intracalcarine cortex post rTMS, despite being in the Sham rather than the Intervention Group;*

(ii) *LG, who was also assigned to the Sham group, did not show a hyperactivation of the left occipital lobe in the LVF > RVF contrast at baseline or post rTMS when compared to controls.*

6.4 Discussion

This study investigated whether neglect patients showed abnormal patterns of functional activity compared to controls and whether rTMS helped to redress any of the observed abnormal functional activity in the patients assigned to the Intervention group.

(i) Neglect patients right and left hemisphere's functional activity impairments (vs controls)

The imaging data supported the first hypothesis of the study by showing that each patient had a relative hypoactivation of the right occipital lobe at baseline when compared to controls, regardless of their lesion profile or stage of stroke. These results are in line with the findings of Vuilleumier et al. (2008) who used a version of the same task as in the current study, with two neglect patients. Both patients in their study showed hypoactivation of all retinotopically mapped areas of the right occipital lobe for peripheral stimuli in the LVF>RVF contrast, when comparing high and low load conditions. In the current study, I did not use two task loads, so it is difficult to make a direct comparison to the original study. However, when considering my adaptation of the high load condition from their study, each patient showed hypoactivity in the right occipital lobe at baseline when compared to elderly controls, for the LVF>RVF contrast.

Although no retinotopic mapping was conducted, it was noted that the main results in the right occipital lobe referred to the occipital pole which incorporates the early visual cortex areas V1 and V2 (McKeefry, Watson, Frackowiak, Fong, & Zeki, 1997a; Zeki, Watson, Lueck, Friston, Kennard & Frackowiak, 2001). This finding asserts the observation that the attention load in the current study's task adaptation was comparable to the high rather than low load from Vuilleumier et al.'s (2008) study who found reductions in V1-V4 areas of the right occipital regions in response to LVF in unilateral and bilateral conditions. It can be speculated that activation in V4 which is suggested to be involved in colour processing (Bartels & Zeki, 2000; Gegenfurtner, 2003; McKeefry & Zeki, 1997b) was not found in our study as compared to the original study possibly on account of the elimination of use of multi-coloured stimuli at central fixation. However, this finding is only a speculation given that retinotopic mapping was not conducted and hence there was no fine grained examination of the specific visual areas recruited in the patients.

One additional factor specific to patients WM and LG was that they both had co-existing left sided hemianopia which could have had a bearing on activity in the ipsilesional right visual cortex. Previous studies with hemianopia patients with occipital lobe damage have shown reduced functional activity in the lesioned primary visual areas (Nelles et al., 2007; Polonara et al., 2011; Wang, Guo, Sun, Jin, & Tong, 2012). Thus, even though both WM and LG had hemianopia post parietal stroke, it is possible that effective connectivity between the two regions and/or structural connectivity may have contributed to their hypoactivation of the right occipital lobe.

All patients except LG also showed significant difference in activity in the left occipital lobe when compared to controls. This was observed despite the exclusion of activation to RVF in the contrast LVF > RVF. While a relative comparison of activity between hemispheres was done using contrast-based ROIs rather than retinotopic mapping, one postulation is that the difference in patients' left occipital lobe activity when compared to controls may indirectly reflect abnormal activity of left hemisphere frontoparietal networks involved in attention modulation. This has been shown in a study by Koch et al. (2008) who used a twin-coil TMS approach with twelve neglect patients and reported hyperexcitability of their left posterior parietal cortex-motor cortex when compared to other right hemisphere stroke patients without neglect and healthy controls.

(ii) Lack of rTMS related improvement in the Intervention group (vs controls)

rTMS to the left inferior parietal lobe neither significantly increased the activation of the right occipital lobe nor significantly changed the activation in the left occipital pole in either of the two Intervention Group patients (WM, BR) to be comparable to controls'. Hence, the second hypothesis of this study was not supported. These patients did not show an improvement in the behavioural neglect measures either. One possible explanation for these results is that in both Intervention Group patients, the reported extent of stroke was extensive (Table 6.1, Figure 6.1). BR's lesion spanned over frontal, parietal and temporal lobes while WM's stroke involved both middle and posterior cerebral arteries in the right hemisphere, although his lesion seen on the scan did not reveal the magnitude of the stroke as stated in clinical notes. It is possible that the extent of his stroke was not adequately represented in his scan obtained 29 days post stroke. Patients with extensive damage have been known to show poor neglect recovery post standard rehabilitation (Maguire & Ogden, 2002). So it is possible that the extensive stroke related damage in the Intervention group patients could be one of the reasons for not having seen any rTMS related benefits in their visual neglect.

iii) **Spontaneous ADL recovery and concurrent reactivation of right occipital lobe (vs controls)**

An interesting finding was that only the Sham group-chronic stroke patient SW, showed an improvement in the behavioural neglect-specific ADL task performance from baseline to post rTMS. Although this pattern of improvement in ADL was not expected post sham rTMS for SW, her improvement in task performance is likely related to spontaneous recovery in neglect over time. ADL tasks have been found to be sensitive in identifying intervention related changes. For example, improvement in ADL for up to three weeks post rTMS has been previously shown in neglect patients after application of eight trains of continuous Theta Burst Stimulation (cTBS) to the left posterior parietal cortex (Cazzoli et al., 2012). Additionally, the main result from the rTMS trial reported in Chapter 5 of this thesis was a significant improvement in the neglect-specific ADL task in the Interventional group at <1 month follow up, relative to the Sham group when controlling for baseline performance on the task. This improvement was not observed in any of the other neglect tasks for SW which could be reflective of the multifaceted nature of neglect along with the differences in the sensitivity of individual tests of neglect (Azouvi et al., 2002).

In addition to improved ADL performance post rTMS, SW was also the only patient to show a significant activation of the right occipital lobe in the intracalcarine cortex post rTMS when compared to controls (Figure 6.4, 6.5). The calcarine fissure has been shown to carry projections from the parietal association areas to the primary visual areas V1 and V2 in correspondence to representation of the peripheral visual field in macaque monkeys (Borra & Rockland, 2011). Despite significant variability in retinotopic mapping of specific visual areas, a general agreement is that area V1 extends over the calcarine fissure in humans (Aine et al., 1996; Tootell et al., 1998). Thus, this partial improvement in neglect as seen by SW's ADL result could be explained as a potential spontaneous improvement in visual processing, facilitated by increased activation of a part of the right occipital lobe that receives projections from the parietal lobe.

Spontaneous improvement in neglect performance and an associated reactivation of networks involved in attention processing has been previously demonstrated (Corbetta et al., 2005). These researchers reported that neglect recovery at the chronic stage in eleven neglect patients with lesions to frontoparietal regions was correlated with rebalancing of activity in the dorsal parietal lobe in addition to reactivation of bilateral parietal operculum, superior and middle occipital regions and dorsolateral prefrontal cortices. Rehabilitation based neuroimaging studies have shown that neglect recovery as seen by improvements in behavioural task performance is associated with increased activity in bilateral brain regions including the occipital lobe. In an intervention study using a single session of prism adaptation with seven neglect patients, improvements in line bisection and visual search tasks post adaptation were associated with increased activation in bilateral parietal, frontal and occipital regions (Saj, Cojan, Vocat, Luaute & Vuilleumier, 2013). In another intervention trial using three weeks of alertness training with seven chronic neglect patients, short term improvement in behavioural tests of neglect (up to one day post training) was associated with an increase in bilateral hemispheric activity in the frontal, cingulate, parietal and occipital cortices (Thimm, Fink, Küst, Karbe, & Sturm, 2006). Thus, reactivation of activity in regions participating in attention modulation has been repeatedly shown to relate to improvements in neglect performance. However, it must be acknowledged that in view of the case study approach employed in the current study, the interpretation of these results must be considered cautiously while acknowledging the associated probability that the results could be on account of inter-session differences in behavioural performance as well as functional activity in the brain.

iv) Limitations of the study

The most important limitation of this study was the small sample size of patients. A review of the ROI extracted % BSC for the left occipital pole showed that even within a small group of patients, disruption of functional activity in the brain post stroke has substantial inter-individual variability (Figure 6.3). For example, comparison of WM, BR and SW's activation at baseline compared to controls shows significant, but different patterns and levels of abnormal activation in their respective left occipital pole ROIs as compared to controls. A larger sample size while enabling the use of more robust statistical analyses, would also help to understand the nature of individual differences in functional activation and changes therein post rTMS on account of the patient's age, stroke related factors, neglect severity, cognitive state during testing, pattern of recovery etc. Another limitation of this study was that the time between neglect assessment and neuroimaging was inconsistent and sometimes separated by long intervals providing scope for spontaneous recovery of neglect during this period. Hence, future studies would benefit from conducting neglect assessments on the day of the scan and scanning patients closer to the completion of rTMS. In appreciating the individuality of each patient (demographics, medical history, etc.) and differences in time between behavioural testing and scanning, the results from this study are not considered generalizable.

Overall, the study showed a potential relation between spontaneous neglect recovery and increase in right hemispheric activation, based on SW's results. However, given the case study approach, this finding is speculative and needs replication in future studies with a larger sample of neglect patients. Additionally, since neither of the Intervention group patients improved significantly on behavioural neglect measures, the role of rTMS in facilitating behavioural and functional activity related changes in neglect patients could not in fact be assessed in this study. Hence, a larger sample of patients in a future study will help to re-explore this question more substantially.

CHAPTER 7 - Cognitive predictors of spatial and object neglect in sub-acute stroke

7.1 Introduction

Cognitive retraining is a classic rehabilitation method used to ameliorate spatial neglect (Bowen et al., 2013; Bowen, Lincoln, & Dewey, 2007). The restorative approach to retraining involves identifying cognitive disorders in patients based on neuropsychological testing, disassembling the deficit to identify ‘core’ cognitive mechanisms underlying these disorders and systematically training them to improve the disorder (Ben-Yishay & Diller, 1993; Diller & Gordon, 1981). In this regard, even though neglect is known as a heterogenous disorder, it is predominantly treated as a disorder of visuospatial attention impairments (Bartolomeo, Schotten, & Chica, 2012; Charras et al., 2012; Corbetta & Shulman, 2011; Li & Malhotra, 2015). Consequently, techniques such as visual scanning training, eye patching and non-invasive brain stimulation are frequently used to alleviate lateralized spatial attention deficits, with *short lasting* benefits (Azouvi, Jacquin-Courtois, & Luauté, 2017a; Bowen et al., 2013; Manly, 2002; Pierce & Buxbaum, 2002; Yang, Zhou, Chung, Li-Tsang, & Fong, 2013).

One potential reason for the lack of stronger and longer lasting benefits of cognitive retraining may be because it does not address the range of cognitive processes that may be integral to neglect manifestation across individuals. Given the multifaceted nature of the syndrome, neglect patients do not show a unitary pattern of deficits upon neuropsychological testing (Azouvi et al., 2002, 2006; Ferber & Karnath, 2001; Rengachary, D’Avossa, Sapir, Shulman, & Corbetta, 2013) which can be on account of individual differences in patient characteristics (Gottesman et al., 2008; Ringman, Saver, Woolson, Clarke, & Adams, 2004), stroke/ lesion related factors (Cassidy, Bruce, Lewis, & Gray, 1999; Chechlacz et al., 2012; Corbetta et al., 2015; Farnè et al., 2004; Husain & Kennard, 1996; Karnath, Rennig, Johannsen, & Rorden, 2011; Levine, Warach, Benowitz, & Calvanio, 1986), test sensitivity (Azouvi et al., 2002; Bonato, 2012;

Rengachary et al., 2013), neglect severity (Gottesman et al., 2008; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017) and important to this chapter, damage to varied cognitive mechanisms that may contribute to neglect (Rorden, Fruhmann Berger, & Karnath, 2006; Toba et al., 2018).

For example, cancellation performance in neglect patients appears to be modulated by several non-spatial and spatial components such as alertness, sustained attention, speed of processing, selective feature processing, spatial working memory, spatial remapping, planning, organizing and perseveration (Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2014; Doricchi & Incoccia, 1998; George, Mercer, Walker, & Manly, 2008; Husain & Rorden, 2003; Pisella & Mattingley, 2004; Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009; Ten Brink, van der Stigchel, Visser-Meily, & Nijboer, 2016; Van Vleet & DeGutis, 2013b). Establishing whether some of these cognitive mechanisms are *fundamental* (independent of individual differences pertaining to patient and stroke related factors) to spatial or object neglect is especially relevant given there is a need for evidence based guidelines to support emerging trends of 'combined' rehabilitation techniques to benefit neglect amelioration (Azouvi et al., 2017a; Kerkhoff & Schenk, 2012; Saevarsson, Halsband, & Kristjansson, 2011; Saevarsson, Kristjansson, & Halsband, 2010; Takeuchi & Izumi, 2015).

One approach to this problem is to develop sophisticated methods to obtain multiple indices reflective of discrete cognitive processes engaged in a task (e.g. Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2014; Habekost & Bundesen, 2003; Kraft et al., 2015). However, an alternative method of extracting information on shared cognitive processes underlying a disorder is by evaluating its relationship with other disorders that may engage the same cognitive mechanisms (de-Wit & Wagemans, 2015). Thus, shared deficits in cognitive mechanisms may explain co-occurrence between neglect and other cognitive disorders post-stroke (Hier, Mondlock, & Caplan, 1983; Linden, Samuelsson, Skoog, & Blomstrand, 2005; Maguire & Ogden, 2002; Massa et al., 2015).

Biased attention mechanisms

Attentional bias, favouring ipsilesional over contralesional space, is considered a cognitive hallmark of the neglect syndrome (Bartolomeo & Chokron, 2002; Driver & Mattingley, 1998; Heilman & Valenstein, 1979; Kinsbourne, 1970; Posner, Snyder, & Davidson, 1980). However, biased spatial attention has also been implicated in extinction with one proposal characterising extinction as a milder form of neglect (Çiçek, Gitelman, Hurley, Nobre, & Mesulam, 2007; Hillis et al., 2006; Karnath, 1988; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994). These observations of biased ipsilesional performance in neglect and exinction patients raise the possibility that they may share a stronger attentional shift towards ipsilesional stimuli due to disinhibition of intact hemisphere (Kinsbourne, 1970) or competition for limited attention resources (de Haan, Karnath, & Driver, 2012; Desimone & Duncan, 1995; Duncan, Humphreys, & Ward, 1997; Mattingley, Driver, Beschin, & Robertson, 1997) or due to difficulty disengaging attention from ipsilesional to contralesional space (Posner, Walker, Friedrich, & Rafal, 1984).

Global/ Local processing of elements in space

Another process that may be shared by patients such as those with neglect and constructional apraxia is an impairment in selective processing of global and local features in space (Chechlacz et al., 2014; Chechlacz, Mantini, Gillebert, & Humphreys, 2015; Christie et al., 2012; Delis, Robertson, & Efron, 1986; Doricchi & Incoccia, 1998; Halligan & Marshall, 1994; Peru & Chelazzi, 2008). Local/ global processing is commonly assessed using hierarchical figures like the Navon task paradigm and overlapping figures (Chamberlain, McManus, Riley, Rankin, & Brunswick, 2013; Chamberlain, Van der Hallen, Huygelier, Van de Cruys, & Wagemans, 2017; Delis et al., 1986; Lamb, Robertson, & Knight, 1990; Navon, 1977; Peru & Chelazzi, 2008; Robertson, Lamb, & Knight, 1988) and in some studies, using cancellation (Doricchi & Incoccia, 1998) and complex figure copy performance (Chechlacz et al., 2014; Chechlacz et al., 2015; Kuschner, Bodner, & Minshew, 2009; Wilson & Batchelor, 2015).

Typically, healthy controls show precedence of global over local feature processing and interference of global processing on local processing (e.g. Navon, 1977; Navon & Norman, 1983; Proverbio, Minniti, & Zani, 1998; Shedden & Reid, 2001). Spatial neglect patients have been reported to show a reverse pattern of hyperattention towards processing local details of hierarchical figures such that they are unable to sustain a representation of the global form (Bultitude & Woods, 2010; Delis et al., 1986; Doricchi & Incoccia, 1998; Halligan & Marshall, 1994). Fewer studies have explored the processing of features in object neglect, but have found that each hemisphere may conduct contralesional local processing of object features independent of hemifield (Christie et al., 2012; Kleinman et al., 2007).

Spatial relationships between visual elements

In conjunction with attention related deficits, impaired internal representation of visual elements and their spatial relationships may also contribute to neglect. One demonstration of this is allochiria, i.e. spatial transposition of stimuli from the neglected side to the ipsilesional side, frequently observed in drawing/ copying tasks (Di Pellegrino, 1995; Halligan, Marshall, & Wade, 1992a, 1992b). Patients have also been shown to demonstrate difficulties pertaining to size estimation (Milner & Harvey, 1995) and space compression (Halligan & Marshall, 1991) providing additional evidence for distortions in internal spatial representation in neglect. Distortions in copying performance, along with severe spatial disorganisation and gross alterations of spatial relations between figures has been reported in patients with right hemisphere injury, both with and without neglect (Gainotti & Tiacci, 1970). Importantly, such deficits occur in both constructional apraxia (Chechlacz et al., 2014; Russell et al., 2010; Smith & Gilchrist, 2005) and neglect (Behrmann & Plaut, 2001; Pisella & Mattingley, 2004).

Sustained attention

One important non-spatially lateralised cognitive ability that has been associated with neglect is sustaining attention over time (Sarter, Givens, & Bruno, 2001) and space (Malhotra, Coulthard, & Husain, 2009). The ability to sustain attention is required to support processing in several different cognitive domains (Corbetta et al., 2015; Massa et al., 2015) with deficits therein implicated in exacerbation of neglect (Husain & Rorden, 2003). Sustained attention deficits in neglect patients have often been studied by asking patients to identify transient, infrequent and randomly occurring stimuli that are presented auditorily, with some paradigms involving delineation of target stimuli from non-target distracters (Hjaltason, Tegnér, Tham, Levander, & Ericson, 1996; Robertson, Manly, Beschin, et al., 1997; Samuelsson et al., 1998). Within a neglect assessment measure such as cancellation, the imposition of a time limit has been known to reduce neglect severity likely due to an increase in tonic alertness/ sustained attention (George et al., 2008). Improvements in neglect have also been associated with improvements in sustained attention (Samuelsson et al., 1998). Hence, the relationship between spatial and sustained attention has been further explored in rehabilitation efforts where training sustained attention has shown improvements in spatial neglect measures (DeGutis & Van Vleet, 2010; Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995; Thimm, Fink, Küst, Karbe, & Sturm, 2006; Van Vleet & DeGutis, 2013a).

While the literature above summarizes the potential of shared cognitive mechanisms in contributing to multiple disorders, it must be noted that individual differences between patients may modulate their role in neglect. Such differences may in turn explain dissociations observed between neglect, extinction, constructional apraxia and sustained attention deficits occurrence that have been noted in some studies (Barbieri & De Renzi, 1989; Farné et al., 2004; Luukkainen-markkula & Tarkka, 2014; Vallar & Perani, 1986; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994; Vossel et al., 2011). For example, age (Oken, Kishiyama, & Kaye, 1994), sex (Pletzer, Scheuringer, & Scherndl, 2017; Roalf, Lowery, & Turetsky, 2006), mood (Gasper & Clore, 2002; Huntsinger, Clore, & Bar-Anan, 2010) in addition to the hemisphere of injury (Fink et al., 1996; Lamb et al., 1990; Peru & Chelazzi, 2008; Robertson et al., 1988) have been known to modulate the role of global and local processing of features in space. Similarly, most studies show that sustained attention deficits in neglect patients may be restricted to those with right hemisphere strokes (DeGutis & Van Vleet, 2010; Hjaltason et al., 1996; Robertson et al., 1995; Samuelsson et al., 1998; Van Vleet & DeGutis, 2013a). Hence, an investigation of whether these cognitive processes are pervasive in the neglect syndrome, surpassing such individual differences between patients, was performed in this study.

Specifically, I assessed if there is a relationship between performance on selected tests available from the BCoS (Birmingham Cognitive Screen) test battery that was administered to a large sample of stroke patients as part of the Birmingham University Cognitive Screen trial (Humphreys et al., 2012). Consequently, original/ modified scores from tests used in the battery to assess visual and tactile extinction (double simultaneous stimulation), constructional apraxia (complex figure copy) and sustained attention (auditory sustained attention) were used to determine the relative importance of potentially shared cognitive mechanisms in predicting spatial and object neglect occurrence.

Please note that the modification for the BCoS task scores in relation to the double simultaneous stimulation paradigm and complex figure copy was modelled after previously published studies. To elaborate, Chechlacz et al. have used a similar scoring modification for the BCoS tasks to study the neural correlates of visual and tactile extinction (Chechlacz et al., 2013) and of global/ local processing and spatial relations between elements that contribute to drawing performance (Chechlacz et al., 2014; 2015). These studies were conducted in a sample of patients extracted from the same dataset as is used in the current study.

The scores obtained from the BCoS tests were used in a multivariate blocked logistic regression model after factoring out the effects of individual differences in patient and stroke characteristics in a separate block. The regressions were conducted separately for spatial and object neglect (identified using cancellation task performance) since several studies assert that the two sub-types of visual neglect are distinct syndromes (Heinke & Humphreys, 2003; Humphreys, 1998; Humphreys & Riddoch, 1994; Rorden et al., 2012) with separate underlying anatomical correlates (e.g. Chechlacz et al., 2010; Medina et al., 2009; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010).

Five main hypothesis were tested:

(i) Presence of visual and tactile extinction will each be associated with higher likelihood of spatial and object neglect occurrence.

(ii) High scores on global feature processing based on the complex figure copy task will be associated with low odds of spatial neglect occurrence.

(iii) High scores on local feature processing based on the complex figure copy task will be associated with low odds of object neglect occurrence.

(iv) High scores indicative of efficient depiction of spatial relationships between visual elements in the complex figure copy task will be associated with low odds of spatial neglect occurrence.

(v) High scores on sustained attention task (indicative of impairment) will be associated with high odds of both spatial and object neglect occurrence.

7.2 Methods

7.2.1 Participants

The BCoS test was administered to a total of 771 stroke survivors as part of the Birmingham University Cognitive Screen (BUCS) trial (Humphreys et al., 2012). Patients were included in the BUCS trial from hospitals across West Midlands (for details, see Bickerton et al., 2015) based on the following inclusion criteria: (i) they were medically stable; (ii) within 3 months of stroke (i.e. at sub-acute stage); (iii) able to understand conversational English; (iv) able to give informed consent; (v) able to concentrate for ~35-40 minutes as judged by a multi-disciplinary clinical stroke team at the hospital; (vi) had no history of premorbid conditions affecting their cognitive state (e.g., dementia) based on clinical notes. All participants were tested in a quiet room in the hospital by trained examiners using the Birmingham Cognitive Screen (BCoS) (Humphreys et al., 2012). The BUCS trial was approved by the South Birmingham

Central Research Ethics committee and was carried out in accordance with the principles of the Declaration of Helsinki.

Note that data used was pre-collected by Prof Humphreys' research team during the BUCS trial and used for this chapter with permission from the team involved in the creation of the database. The total number of patients included in this study reflected those for whom both visual neglect test scores were complete and CT scans were available to enable inclusion of lesion side and volume. Thus, of the 771 patients included in the trial, data for visual neglect and key variables of interest were available for 613 patients at the sub-acute stage. Of these patients, only 274 patients had CT scans with visible lesion(s). Hence, the final sample included at sub-acute stage was 274 patients.

7.2.2 Test measures

Test measures were extracted from the Birmingham Cognitive Screen (BCoS, Humphreys et al., 2012).

7.2.2.1 Test of spatial and object neglect

Please refer to Chapter 2, section 2.2.1. for details of the BCoS Apple Cancellation tests used to identify spatial and object neglect.

In the current study, patients with both left and right-sided neglect were included. Neglect scores were binarized as impaired or unimpaired based on age-appropriate cut-offs, for the logistic regression.

7.2.2.2 Tests of extinction

Both visual and tactile extinction were tested using double simultaneous stimulation. For testing visual extinction, the examiner placed themselves approximately one meter opposite to the participant and at their midline. The examiner would hold up either their left or right index finger on either side of their head for unilateral trials or both fingers together for bilateral trials at approximately 20 cm from their nose. Participants were instructed to look at the examiner's nose and respond by pointing as to which finger/ fingers the examiner moved (by two brief bending movements) during the trial. The time provided for a response was 15 seconds per trial. For the tactile extinction task, the examiner asked the participant to place both their hands on their knees and close their eyes. Participants had to indicate which hand(s) had been touched (by two gentle tapping movements) by the examiner.

For each task, there were four unilateral left, four unilateral right and eight bilateral trials. The BCoS manual only provides cut-offs for unilateral and bilateral trials separately which were not thought adequate for identifying extinction. Hence, a modified Extinction index was calculated (Chechlacz et al., 2013) and data from the 100 controls were used to identify those impaired. This modification to the index involved multiplying the unilateral asymmetry score by 2 before subtracting the bilateral score from it. Thus, this index accounted for the difference in the number of unilateral (n = 4) and bilateral trials (n = 8) for each side.

*Extinction index = (unilateral trial score * 2) - bilateral trial score*

An extinction index was calculated separately for left and right sided trials. A positive extinction index score implied difficulties in bilateral trials more than unilateral trials whereas a score of zero could be indicative of either a visual field defect (if participants did not respond to any of the trials) or no difference in performance on a particular side for unilateral or bilateral trials. Thus, while a positive score exceeding cut-off implied extinction, negative scores or a score of zero implied no extinction related impairments on the task. The maximum impairment was indicated by a score of 8. The cut-offs for visual extinction at > 95th percentile were > 0 for both sides' extinction indices (≤ 64 years), > 1 for both sides' extinction indices (65-74 years) and > 0 for both sides' extinction indices (≥ 75 years). For tactile extinction, the cut-offs were > 1 for left tactile extinction and > 0 for right tactile index (≤ 64 years), > 0 for both sides' extinction indices (65-74 years) and > 1 for both sides' extinction index (≥ 75 years).

Extinction scores were binarized using cut-offs for inclusion in the logistic regressions (impairment=1, no impairment=0). Given the ambiguity in the interpretation of the extinction index score of 0 as a visual field deficit or as no difference in unilateral and bilateral trial performance, a binarized scoring system using cut-offs was thought better suited to aid interpretation of results.

7.2.2.3 Test of constructional apraxia

Constructional apraxia in the BCoS was measured using the Complex figure copy test (Figure 7.1). The figure had elements presented centrally and also to the left and right of the midline. The number of elements to the left and right of the centre were balanced to account for the probability of left and right neglect. Participants were provided a maximum of 5 minutes to copy the figure. Scoring considered organisation and neglect by accounting for presence/absence of elements, shape/proportion of elements and correct placement of elements. The scores were further divided into scores for the middle set of elements, left-sided elements and right-sided elements.

Similar to a previous study that used the complex figure copy task (Chechlacz et al.; 2014, 2015), the scores from the test were manipulated to extract two parameters to represent spatial relationships and global/local processing of elements respectively. For spatial relationship scores, total number of elements *correctly placed* in the drawing was included in the regression model, with perfect placement of features scoring a maximum of 27 points. For the global/local processing scores, the global features included the middle square, left rectangle, right rectangle and the main diagonal while the local features comprised of features within the left rectangle (the top left parallel bar, bar parallel to the top bar, left horizontal bar, left circle, left end of diagonal/ three parallel bars), middle square (left curve, arrow, right curve, the cross) and right rectangle (double dot, right side of triangle, left side of triangle, right horizontal bar, right diagonal end/ curved 's' shape). Thus, depending on the presence of these features in the patient's drawing, the maximum global feature score possible was 4 and local feature score was 14. The scores were entered separately and as continuous measures in the logistic regression model.

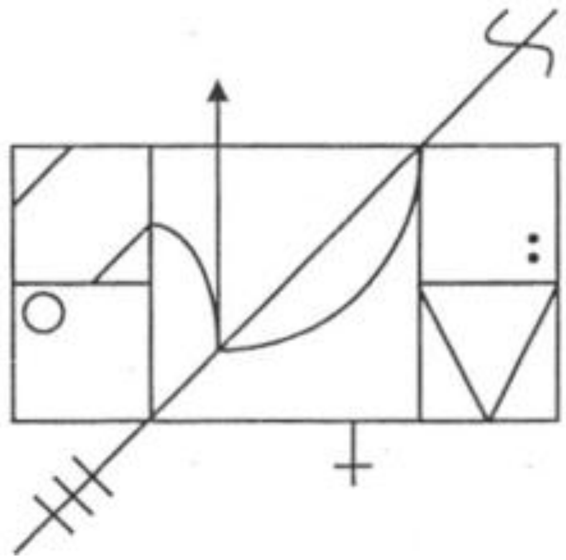

Figure 7.1. BCoS Complex figure copy test

In this task, participants were presented with this figure at midline and asked to copy it onto a blank sheet. Scoring took into consideration the correct placement of all the elements relative to one another (spatial positioning) and the correct reproduction of four global (middle square, left and right rectangles, main diagonal) and fourteen local features (left rectangle's top left bar, bar parallel to top left bar, left horizontal line, left circle, left diagonal end/ three parallel bars, middle square's left curve, right curve, arrow, cross, right rectangle's double dot, left and right sides of triangle each, right horizontal bar and right end of diagonal/ curved 's' shape) of the drawing.

7.2.2.4 Test of sustained attention

Please refer to Chapter 2, section 2.2.2 for details of the BCoS Auditory attention task that was used to measure sustained attention.

Sustained attention index scores were entered in the regressions as a continuous measure.

7.2.2.5 Other variables included in the study

Demographic variables (age, sex, years of education), type of stroke based on clinical notes, lesion volume, side, time between stroke and BCoS assessment, orientation at time of testing assessed using BCoS Orientation sub-test (orientation to time, space and personal information) and mood at assessment using the Hospital Anxiety and Depression test (HADS) (Zigmond & Snaith, 1983) were included in the regression models as covariates.

Age, years of education and time between stroke and BCoS assessment were continuous measures whereas gender (1 = female, 0 = male), lesion side (1=left, 2=right, 3=bilateral) and type of stroke (1 = transient ischemic attack: TIA, 2 = subarachnoid haemorrhage, 3 = intracerebral haemorrhage, 4 = ischemic stroke, 5 = other/unknown) were included as nominal variables. Lesion volume was calculated using an in-house Python script (Van Rossum, 2000; https://www.python.org/) using the Nibabel module (2.1.0) (http://nipy.org/nibabel/). For both orientation and mood, test scores across sub-tasks were combined to give a unitary measure. Thus, the maximum score possible for orientation implying well- oriented was 14. HADS scores ranged between 0 and 42 with a score of 0 implying no mood related problems.

7.2.3 Data Analysis

Participants included had completed all cognitive tests of interest. However for covariates, the average of the group was used when there was missing data for these participants. The maximum number of missing values for which the average was substituted was for the variable of mood (n = 12).

Binomial logistic regressions were conducted using IBM SPSS v24. Logistic regression was chosen because the aim of the study was to investigate the likelihood of identifying cases of spatial and object neglect based on values of multiple independent variables. Cognitive scores that are found to significantly predict neglect occurrence in this sample can shed light on key cognitive processes contributing to neglect *after* controlling for effects of confounding variables of no interest. For details of regression assumption testing, please refer to the data analysis methods section of Chapter 2 (2.3.5).

Two separate sets of hierarchical blocked logistic regressions were conducted to identify cognitive predictors of neglect performance at the sub-acute stage, one each for spatial and object neglect. Within each of these sets, regressions were done separately for models involving the two complex figure copy scores (global/local processing, spatial positioning) to account for multicollinearity between these variables (refer to Appendix E, Table 7a for correlation matrix). The regressors were entered hierarchically in a blocked fashion, with the first block including the covariates, i.e. age, sex, education, stroke type, lesion volume, lesion side, time since stroke at testing, orientation and mood at testing and the second block adding the cognitive variables of interest. Using hierarchical blocks can thus help to evaluate the relative contribution of individual blocks of predictors and in the context of the current study, evaluate the role of the cognitive variables in predicting neglect after factoring out the effects of demographic and stroke related variables in the preceding block.

The overall significance of the model, the variance in the DV explained by the model, the sensitivity and specificity of the model to distinguish between neglect cases and non-cases, and the cognitive variables that contributed significantly to the predictive ability of the model were obtained as outcome measures from the regressions. Variables were identified as significant after adjusting for multiple comparisons using False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995). Even though FDR is traditionally considered as a method for estimating the proportion of wrongly rejected *null* hypotheses (Benjamini & Hochberg, 1995), it has been argued as applicable to control for Type 1 errors and to improve statistical power even for studies *with planned hypotheses* (Frane, 2015), such as in the case of the current study. Furthermore, the FDR correction has been suggested to be more appropriate than Bonferroni correction (Bonferroni, 1936) for use in research studies with a relatively large number of hypotheses (Glickman, Rao, & Schultz, 2014; Pike, 2011), as in the case of the current chapter.

7.3 Results

The percentage of included patients who were impaired in each disorder is given in Figure 7.2. The cut-offs used to calculate impairments were based on normative data obtained from 100 healthy controls (Humphreys et al., 2012). In the included sample at the sub-acute stage, the incidence of spatial and object neglect was comparable with 26% showing spatial neglect and 27% showing object neglect. Relative to neglect, a higher incidence of deficits was seen on the constructional apraxia (57%) and sustained attention (35%) tests while a lower incidence was seen on visual (18%) and tactile extinction (20%) tests.

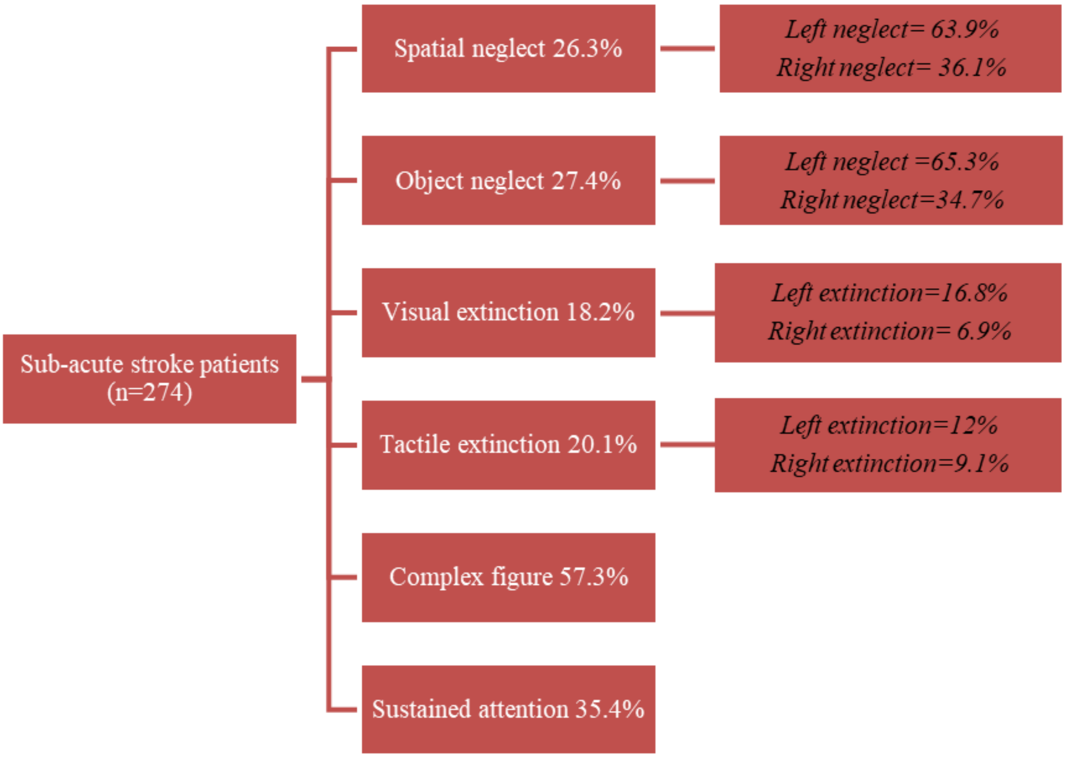

Figure 7.2. Percentage of patients impaired in each domain at sub-acute stage

The above figure depicts the number of patients included in the analysis at sub-acute stage. Number of patients impaired in each domain at each stage were identified based on cut-offs obtained from data of 100 age-matched controls.

Descriptive and cognitive test data for the participants at the sub-acute stage are provided in Table 7.1. On average, the patient included in the database was ~69 years of age with 11 years of education. The majority of the patients were male, had ischemic stroke and right hemisphere lesions, and their cognitive assessment was conducted within a month post stroke on average.

Tables 7.2 and 7.3 show regression results from these separate models; one model included global and local processing while the other included spatial relations.

Table 7.1. *Demographic, clinical and cognitive characteristics of patients*

Variables	***Sub-acute (n=274)***
Sex	Female: 119; Male: 155
Stroke Type	TIA: 3; Subarachnoid haemorrhage: 2; Intracerebral haemorrhage: 45; Ischemia: 221; Other: 3
Lesion side	Left: 104; Right: 126; Bilateral: 44
Age	69 years (13 years)
Education (number of years)	11 (2.89)
Time since stroke at assessment	24 days (21 days)
Lesion volume	31 cm^3 (56.46 cm^3)
Orientation (max 14=well oriented)	12 (2.34)
Mood (HADS) (range 0-42, 0=no impairment)	12 (7.9)
Left Visual Extinction Index*	0.5 (1.7)
Right Visual Extinction Index*	0.04 (0.8)
Left Tactile Extinction Index*	0.5 (1.9)
Right Tactile Extinction Index*	0.01 (1.3)
Complex figure (global processing max=4)	3.6 (0.9)
Complex figure (local processing max=14)	12.4 (2.7)
Complex figure (spatial relations max=27)	20.8 (6.8)
Sustained attention index$	2.08 (3.4)

Scores reflect Mean (SD), TIA: Transient ischemic attack
**For each extinction index ((unilateral score*2)-bilateral score), scores ranged between -8 and +8 such that positive scores implied impairments in identification of targets on bilateral trials> unilateral trials.*
$ Sustained attention index (no. correct block 1- block 3) ranged between -18 and +18 with positive scores implying worse performance in block 3 than 1, i.e. poor sustained attention over time.

Table 7.2. *Multivariate analyses based significant predictors of spatial and object neglect at sub-acute stage (with local/global processing)*

Cognitive regressors of interest	Model coefficient χ^2 (df=18)	Nagelkerke's R^2	Overall percentage of cases correctly classified by model	Percentage of correctly classified events by model	Percentage of correctly classified non-events by model	Significant variables of interest	Wald statistic	Odds Ratio (95% Confidence Interval)
Spatial neglect								
Visual extinction; Tactile extinction; Global processing; Local processing; Sustained attention index	70.65	0.33	81.4%	45.8%	94.1%	Visual extinction	11.8	3.94 (1.8-8.6)
						Tactile extinction	7.9	2.9 (1.4-6.2)
						Local processing	12.4	0.7 (0.6-0.9)
Object neglect								
Visual extinction; Tactile extinction; Global processing; Local processing; Sustained attention index	74.67	0.35	81%	42.7%	95.5%	Visual extinction	8.1	3.1 (1.4-6.8)
						Local processing	15.7	0.6 (0.5-0.8)

df=degrees of freedom

Both model coefficients $\chi2$ values were significant at $p<0.001$. Wald criterion based cognitive variables were significant at $p<0.05$ post False Discovery Rate (FDR) correction. Classification of cases was based on a cut-off of 0.5.

Table 7.3. *Multivariate analyses based significant predictors of spatial and object neglect at sub-acute stage (with spatial relations)*

Cognitive regressors of interest	Model coefficient χ^2 (df=17)	Nagelkerke's R^2	Overall percentage of cases correctly classified by model	Percentage of correctly classified events by model	Percentage of correctly classified non-events by model	Significant variables of interest	Wald statistic	Odds Ratio (95% Confidence Interval)
				Spatial neglect				
Visual extinction; Tactile extinction; Spatial relations; Sustained attention index	66.54	0.32	79.9%	43.1%	93.1%	Visual extinction	10.8	3.6 (1.7-7.7)
						Spatial relations	12.1	0.9 (0.9-1)
				Object neglect				
Visual extinction; Tactile extinction; Spatial relations; Sustained attention Index	59.1	0.28	79.9%	40%	95%	n.s		

df=degrees of freedom, n.s: not significant

Both model coefficients χ2 values were significant at p<0.001. Wald criterion based cognitive variables were significant at p<0.05 post False Discovery Rate (FDR) correction. Classification of cases was based on a cut-off of 0.5.

In terms of assumptions testing (refer to Chapter 2, section 2.3.5.1), all continuous predictor variables were found to be linearly related to the logit of the DV using the Box-Tidwell approach (Box-Tidwell, 1962). Additionally, multicollinearity between the cognitive predictors was assessed by reviewing the correlation matrix (Appendix E, Table 7a), variance inflation factor (VIF) and tolerance values (Appendix E, Table 7b). Predictors were not considered multicollinear if the correlations between them was <0.8, VIF for each variable was < 10 and the tolerance values were > 0.1 (Field, 2009). Since spatial relations and local processing of features obtained from the complex figure copy tests were highly correlated (r=0.85, p<0.05), these were included in separate regression models.

In terms of the main regression results (Tables 7.2-7.3), the significance of the cognitive predictor model as a whole, in predicting neglect is depicted by the $\chi 2$ value at p<0.001 (Tables 7.2-7.3, column 2). The relative variance explained by the overall model in the Dependent variable (DV, neglect) is assessed using Nagelkerke's R^2 (column 3). The model's overall capability to classify neglect cases and non-cases correctly is given in column 4 of the tables while sensitivity and specificity to categorize individual cases of neglect are represented by the percentage of cases correctly classified (column 5) and percentage of non-cases correctly rejected (column 6). The regressions also helped to identify which variables included in the model make a significant contribution (column 7) to the identification of neglect by calculating the Wald statistic (column 8). Finally, the Odds ratio (OR) along with 95% confidence intervals can be used to interpret the 'odds' of having neglect (column 9).

For continuous variables, this is the odds of the DV (i.e. neglect) occurring with each one unit increase in the predictor variable. For categorical variables, the change in odds ratio can be interpreted in reference to the category assigned as 'baseline', i.e. coded as 0 for gender and extinction, and as 1 (TIA) for stroke type and lesion side (left hemisphere). OR values of < 1 indicate a negative relationship between the variables, i.e. decreased odds of neglect occurrence for a one unit increase in the predictor's scores, and vice versa.

7.3.1 Spatial neglect

Multivariate regression revealed that spatial neglect at the sub-acute stage could be predicted by visual and tactile extinction scores (indicative of biased spatial attention processes) as well as by local processing of features from the complex figure copy task (Table 7.2). In the model including spatial relations between features of the complex figure copy, visual extinction and spatial relations were both predictive of spatial neglect (Table 7.3).

For visual and tactile extinction, a positive relationship was seen such that having extinction, increased the odds of spatial neglect. On the other hand, for local feature processing and spatial relations between the features, the odds ratio showed an inverse relationship such that lower scores were related to a higher likelihood of spatial neglect occurrence. Between the two models, 32-33% of the variance in neglect occurrence could be explained by the cognitive variables after controlling for demographic and stroke related factors. Furthermore, the models could classify 79-81% of the data as cases and non-cases of neglect, although the specificity of the models (93-94%) was higher than the sensitivity (43-46%).

7.3.2 Object neglect

For object neglect, both multivariate regression models were significant and added higher prediction value to cases and non-cases of object neglect as compared to the constant-only model and the variables of no interest model (Tables 7.2-7.3). Specifically, the model including local/ global processing of features (Table 7.2) explained a higher amount of variance in the DV (35%) relative to the model including spatial relations between the features (28%) (Table 7.3). The overall percentage of data correctly classified by both models was approximately 80%, with a specificity of ~95% and relatively lower sensitivity ranging between 40 and 43%.

With regard to significant cognitive variables of interest, visual extinction and local processing of features were identified in the first model as significantly contributing to the model's capability of identifying object neglect. The odds ratio showed that the presence of visual extinction was associated with a higher likelihood of object neglect occurrence. Additionally, each unit decrease in number of local features reproduced in the complex figure copy was related to a higher likelihood of object neglect occurrence in the sub-acute stage. Interestingly, while spatial relations between features was a significant predictor of spatial neglect it did not share a significant relationship with object neglect (Table 7.3).

Overall, of the five hypotheses, the results clearly supported three of them, i.e. that:

- the presence of extinction increased the likelihood of spatial and object neglect occurrence.
- high scores implying increased accuracy of reproduction of spatial relations between visual elements was associated with reduced odds of having spatial neglect.
- high scores on local processing of features was found to be associated with lower odds of having not just object neglect as hypothesized, but also spatial neglect.

However, a similar relationship was not found between global processing and spatial neglect. Finally, sustained attention performance did not significantly contribute to the prediction of spatial or object neglect.

7.4 Discussion

This study was conducted to identify cognitive processes that may be considered fundamental to the neglect syndrome across patients with different profiles of demographic and stroke related factors. Overall, models with cognitive predictors were able to classify cases and non-cases of neglect with higher efficiency than models with constant only or with demographic and stroke related factors. Each of the significant results is discussed below.

7.4.1 Biased attention mechanisms as predictor of spatial and object neglect

The presence of extinction increased the likelihood of neglect occurrence. Both visual and tactile extinction scores were able to predict spatial neglect, whereas only visual extinction scores were a predictor of object neglect. (Table 7.2). The relationship between extinction, whether visual or tactile, and spatial neglect suggests that there might be a shared mechanism which is most easily explained as biased orienting of attention to the ipsilesional side.

Theoretically, the Interhemispheric Rivalry theory (Kinsbourne et al., 1970) provides a framework to evaluate the contribution of biased orienting of attention in space that may underlie both neglect and extinction. Posner et al. (1984) have suggested that spatial attentional difficulties in neglect and extinction patients can be broken down into difficulties with disengaging attention from the ipsilesional side, switching attention to the target and engaging the target. In extinction, the ipsilesional bias is elicited only during conditions of bilateral stimulation, when an exaggerated competition occurs between concurrent stimuli for limited capacity of attentional resources. Extinction to the contralesional side is reported to manifest as a consequence of this competition, in light of the disproportionate amount of attention recruited by ipsilesional stimuli (Driver, Mattingley, Rorden & Davis, 1997; de Haan, Karnath, & Driver, 2012; Làdavas, 1990; Mattingley, Driver, Beschin, & Robertson, 1997).

Biases in attention orienting are not restricted to the visual space. In a patient with pure tactile (and no visual) extinction, increasing the salience of contralesional tactile stimuli enhanced tactile discrimination suggesting a role for attentional mechanisms in tactile space (Olson, Stark, & Chatterjee, 2003). Other studies have shown that attention mechanisms operate on a supramodal representation of space and can be modulated cross-modally in extinction patients. For example, in four patients with left tactile extinction and concurrent visual neglect, visual feedback obtained from crossing the left hand over the midline into ipsilesional space speeded up responses to tactile stimuli as compared to when the hand remained in the neglected contralateral space (Sambo et al., 2012). The authors explained that processing of tactile stimuli was enhanced in ipsilesional space where attention was selectively biased post stroke.

Unlike spatial neglect, tactile extinction scores were not predictive of object neglect, but visual extinction scores were. This might be accounted for by differences in the sensitivity of the two extinction tests. Alternatively a multimodal account of attention biases may not be applicable to object representations based on the current data. Why should visual attentional biases predict object neglect? It is possible that attentional biases might operate within an object-based framework as well as a more generalised spatial one (Egly, Driver, & Rafal, 1994). Further work is necessary to investigate this possibility.

7.4.2 Local, but not global processing of elements as predictor of spatial and object neglect

The current results showed that low scores in reproduction of local features from the complex figure copy was related to a higher likelihood of both spatial and object neglect occurrence (Table 7.2). In terms of cancellation task performance, these results may reflect the ability of the patient to focus attention on individual shapes in order to discriminate between targets and distracters. The number of correctly cancelled targets and incorrectly cancelled distracters contributes to the diagnosis of spatial and object neglect respectively in the BCoS cancellation task (Humphreys et al., 2012). Hence, local processing of features may indicate a role for higher visuo-perceptual discriminatory ability of objects/object features, facilitated by focussed attention processes.

This interpretation of the results is supported by previous studies that implicate both attention and perception related mechanisms as underlying impaired processing of features in space (Chamberlain, Van der Hallen, Huygelier, Van de Cruys, & Wagemans, 2017; Lamb, Robertson, & Knight, 1990; Robertson, Lamb, & Knight, 1988). For example, depletion of attention resources in neglect patients was suggested to selectively disrupt focussed or distributed attention affecting processing of local and global features respectively (Peru & Chelazzi, 2008) or disrupt divided attention involved in allocation of available attention between global and local features (Lamb et al., 1990; Robertson et al., 1988). Similarly, perceptual processes that facilitate visual discrimination such as automatic encoding of stimuli features (e.g. spatial frequency, size, density, number of elements etc.), may also underlie differences in global and local feature processing (Robertson et al., 1988).

Anatomically, processing of local and global details has been predominantly attributed to the left and right hemispheres respectively (Delis et al., 1986; Fink et al., 1996; Halligan & Marshall, 1994; Lamb et al., 1990). Patients with right hemisphere lesions have been found hyperattentive to local details which is postulated to interfere with their ability to distribute attention to and maintain representation of the global form (Delis et al., 1986; Doricchi & Incoccia, 1998; Marshall & Halligan, 1995). For example, when shown hierarchical figures such as a large letter/shape comprised of several smaller letters/shapes, i.e. Navon task (Navon, 1977), for reproduction from memory, patients with right hemisphere lesions were unable to reproduce the global structure but were able to produce the local details in a disorganized manner. On the other hand, left hemisphere lesioned patients were able to produce the larger form but not the local details of the drawings (Delis et al., 1986).

Since the current study included left, right and bilaterally lesioned patients, after partialling out the effects of lesion side in the analysis, only local processing was identified as a significant predictor of neglect. One explanation for this observation could be that global processing may be a right hemisphere dominant function, while local processing of features may have a more distributed presence across hemispheres. This suggestion finds support in a study by Peru and Chelazzi (2008) where they found that on a task with overlapping shapes requiring patients to either count the number of shapes (distributed attention) or focus on features of the shapes (focussed attention), both left and right hemisphere patients were impaired in focussing attention to local details. However, only patients with right hemisphere damage *and* severe visual neglect showed global processing deficits.

One other factor that may have affected these results is the use of the complex figure copy task that, unlike the Navon hierarchical figure, draws upon cognitive mechanisms such as planning, organizing, visuomotor ability in addition to attentional and perceptual mechanisms (Chen et al., 2016; Kim, Namgoong, & Youn, 2008; Possin, Laluz, Alcantar, Miller, & Kramer, 2011; Trojano, Grossi, & Flash, 2009). Consequently, the four global features available from the drawing may not have sufficed as sensitive or pure measures of global feature processing ability. This is especially likely if patients' organization ability was relatively intact and they used the global form to organize placement of local features (see Appendix E, Table 7a for evidence of high correlation between global and local processing of features) as is seen in figure copy performance of healthy controls (Wilson & Batchelor, 2015).

7.4.3 Spatial relations between visual elements as predictor of spatial neglect

The scores obtained from placement of visual elements of the complex figure copy test were found to predict the occurrence of spatial neglect. Based on the results, higher scores on spatial positioning of the figure copy elements was related to lesser odds of having spatial neglect (Table 7.3). This indicates that beyond selective attention to locations in space, having an intact spatial representation of the visible visual elements is important to spatial neglect. On the other hand, spatial relationships between features of the complex figure copy were not predictive of object neglect (Table 7.3). This finding is in line with previous research suggesting that spatial coding can be different for within object representations (where elements are coded as parts of an object) and between object representations (where elements are coded as independent objects) (Humphreys, 1998; Humphreys & Riddoch, 1994). Thus, in the context of the cancellation task, an impoverished representation of the contralesional side of the layout in addition to distorted spatial coding of the shapes that constitute the layout may both contribute to poor cancellation performance in spatial neglect patients.

An important mechanism contributing to the integrity of the representation is spatial remapping, i.e. the ability to remap space over saccades to ensure visual integration and updating of visual representations of stimuli (Danckert & Ferber, 2006; Pisella & Mattingley, 2004). According to Pisella & Mattingley (2004), spatial neglect may be a combination of spatial attention and spatial remapping deficits. Spatial remapping deficits have also been implicated in extinction and constructional apraxia (Pisella & Mattingley, 2004; Russell et al., 2010).

Another mechanism that contributes to the integrity of spatial representations is spatial working memory which has been implicated in playing a role in updating spatial representations across saccades, although its exact relationship with spatial remapping is still unclear (Pisella & Mattingley, 2004; Russell et al., 2010). Spatial working memory deficits have been identified in patients with neglect (Husain et al., 2001; Malhotra et al., 2005; Wojciulik, Husain, Clarke, & Driver, 2001) and may work in conjunction with remapping deficits to disrupt the creation of a coherent representation of visuospatial elements across saccades.

Although each of the cognitive mechanisms discussed in the sections above (7.4.1 – 7.4.3) has been identified as important potential contributors to visual neglect, their co-existence may be indicative of shared anatomical substrates, for example in the parietal lobe. Patient studies as well as non-invasive brain stimulation with healthy controls have implicated parietal cortex in modulating interhemispheric spatial attention processes that have been reported to underlie neglect and extinction (Battelli, Alvarez, Carlson, & Pascual-Leone, 2009; Cazzoli, Wurtz, Müri, Hess, & Nyffeler, 2009; Dambeck et al., 2006; Farah, Wong, Monheit, & Morrow, 1989; Losier & Klein, 2001; Posner et al., 1984; Sparing et al., 2009). Similarly, modulation of the selective attention window involved in allocation of attention to local and global features in space has also been ascribed as a function of the parietal lobes (Lamb, Robertson, & Knight, 1989; Robertson et al., 1988; Treisman, 2004). For spatial remapping, researchers have identified that the parietal lobe is crucial in anticipating the retinal consequences of an eye movement and maintenance of cortical target co-ordinates between saccades, thus enabling the visual integration of successful retinal images over time and space (Bultitude, Van der Stigchel, & Nijboer, 2013; Duhamel, Colby, & Goldberg, 1992; Pisella & Mattingley, 2004).

7.4.4 Sustained attention was not a significant predictor of neglect

The parietal lobe has also been implicated in the modulation of sustained attention (Johannsen et al., 1997; Pardo, Fox, & Raichle, 1991; Thakral & Slotnick, 2009). However, sustained attention was not a significant predictor in the current study. The lack of an association between spatial neglect and sustained attention scores is curious given the findings of several previous studies that show a relationship between the two (Hjaltason, et al., 1996; Maguire & Ogden, 2002; Samuelsson et al., 1998, DeGutis & Van Vleet, 2010; Robertson, et al., 1995; Thimm, et al., 2006; Van Vleet & DeGutis, 2013a).

One explanation for this observation is that the BCoS Auditory Attention task is not a pure measure of sustained attention. The task draws upon working memory (hold target words in mind when processing incoming auditory information) and selective attention abilities (distinguishing between targets and distracters), in addition to sustained attention capacity (Humphreys et al., 2012; Bickerton et al., 2015). This is dissimilar to other studies that reported a significant relationship between the two domains by using a task like tone counting (Robertson et al., 1997; Samuelsson et al., 1998) that does not target any other non-spatial abilities when measuring sustained attention. Hence, the

BCoS auditory attention task may be limited in its potential to capture the relationship between neglect and sustained attention.

7.4.5 Applications and evaluation of study

Taken together, results from this study indicate the importance of utilizing knowledge of neglect-related cognitive processes at the sub-acute stage in tailoring rehabilitation efforts. In addition to biased attentional processes frequently seen to manifest as ‘neglect’ of contralesional space, difficulties in focussed attention and integration of visuospatial information across saccades are also suggested to be integral to neglect.

Consequently, both spatial and object neglect patients would potentially benefit from:

(i) rehabilitation/ retraining to address biased attentional mechanisms, especially difficulties in disengaging attention from ipsilesional side and encouraging exploration of contralesional space;

(ii) enhancing focussed attention to facilitate perceptual processes such as visual discrimination of elements in space.

Spatial neglect would additionally benefit from:

(iii) rehabilitation focused on enhancing spatial remapping and spatial working memory processes to help integrate elements into a coherent spatial representation across saccades.

While several rehabilitation techniques have been used to improve spatial attention related processes (Barrett et al., 2006; Bowen et al., 2013; Jacquin-Courtois, 2015; Saevarsson et al., 2011), prism adaptation holds particular promise in addressing each of the mechanisms identified above, i.e. decreasing ipsilesional bias and enhancing contralesional exploration (Jacquin-Courtois et al., 2013; Rode, Pisella, Rossetti, Farnè, & Boisson, 2003), improving visual search (Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009), altering global/ local processing (Bultitude, Rafal, & List, 2009; Bultitude & Woods, 2010) and enhancing spatial remapping (Bultitude et al., 2013). In addition, recent proposals suggest combining rehabilitation methods to address the multifaceted nature of cognitive deficits that may contribute to neglect (Brem, Unterburger, Speight, & Jäncke, 2014; Looi et al., 2016; Saevarsson et al., 2011, 2010).. Based on these guidelines, future explorations could assess the efficacy of targeting multiple cognitive processes involved in neglect, during retraining. The suggestions for rehabilitation provided here are based on sub-acute stage data and hence, are of particular relevance to rehabilitation undertaken at this stage to supplement spontaneous recovery post stroke (Nijboer, Kollen, & Kwakkel, 2013; Stone, Patel, Greenwood, & Halligan, 1992).

The current study had several limitations. Despite a relatively large sample of patients, the prediction accuracy of neglect for *individual patients* was inadequate, likely due to insufficient number of patients with neglect in the overall sample (< 50%) and due to individual variability in the patients that remain unaccounted for (e.g. stroke and neglect severity). Importantly, since the data were collected as part of the creation of a cognitive battery catering to clinical assessment, its potential to evaluate specific cognitive components was relatively coarse. Future studies would benefit from the use of more sensitive, fine-tuned experimental cognitive paradigms to measure specific cognitive processes. Finally, to further confirm the role of shared cognitive components across disorders, it would be interesting to assess if the rehabilitation suggestions provided above could additionally benefit other disorders that engage these mechanisms, such as extinction and constructional apraxia, in the sub-acute stage of stroke.

CHAPTER 8 - General Discussion

This thesis focused on two important **types** of neglect (Representational Neglect (RN), Visual neglect) and two important **aspects** of neglect research (assessment, rehabilitation). Chapters 3 and 4 involved design and testing of novel methods intended to overcome limitations of existing RN assessment and encourage evaluation of cognitive processes involved in RN. Chapters 5 and 6 attempted to evaluate the short and long term effects of inhibitory repetitive Transcranial Magnetic Stimulation (rTMS) on neglect and related cognitive domains, as well as on task based functional activity. Finally, Chapter 7 identified cognitive mechanisms that were fundamental to spatial and object neglect after accounting for demographic and stroke related inter-individual differences. These results were used to suggest guidelines for cognitive retraining of neglect at the sub-acute stage.

In the current chapter, I will discuss the *key results* from the thesis, limitations of the research conducted and potential avenues for future work.

8.1 Representational neglect results: Chapters 3 and 4

8.1.1 Summary

In Chapter 3, I created two novel RN methods, The Shopping Mall and Clock Cueing tasks, to assess topological and non-topological RN. The utility of these tasks in assessing RN in chronic stroke patients was studied in Chapter 4. The novel methods improved upon existing methods; The Mall task provided a standardized layout with symmetrical landmarks, measures of visual memory recognition for the layout and familiarity with the landmarks, while the Clock Cueing task provided an estimate of spatial attention assessment, while reducing demands on ancillary cognitive mechanisms like angle judgement and decision making. By using novel (Mall, Clock Cueing) and existing tests (Geographical Maps, Object arrays) in a sample of chronic stroke patients, Chapter 4 was able to identify three patients (DR, MG, EH) who showed different patterns of RN based on type of material (topological, non-topological) and time of acquisition of memory for the layout (pre stroke, post stroke). Specifically DR and EH were impaired on the Mall task (topological layout learnt post-stroke), EH and MG were impaired on Clock Cueing (non-topological layout learnt pre-stroke), while EH was also impaired on the Geographical Map task (topological layout learnt pre-stroke). Thus, EH showed a more pervasive pattern of RN while DR and MG showed dissociations. Additionally, their performance on the ancillary cognitive test battery showed that although a role for visual memory, imagery, visuospatial working memory, spatial attention and mental rotation can be ascribed in RN, their specific role may vary based on the demands of the RN task and need further study in a larger sample. Interestingly, each patient had right cerebellar lesions and the role of the cerebellum in RN would also benefit from study using fine- grained neuroimaging in a larger sample.

8.1.2 Key result: RN is a multicomponent disorder

The main takeaway from these chapters was that as is noted about visual neglect (Bonato, 2012; Husain & Rorden, 2003; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994; Rafal, 1994; Toba et al., 2018), RN can also be considered as a multicomponent syndrome. While most RN research to date has primarily focused on unidimensional explanation for RN as a deficit of mental representation, spatial attention or visuospatial working memory (see Salvato et al., 2014), the current research was able to support emerging trends in RN research that claim that there may be a role for several cognitive factors, both spatially non-lateralised and lateralised, in contributing to RN.

Spatially non-lateralised deficits

Each patient showed an overall difficulty with visual memory performance based on the Shapes test (Baddeley, et al. 1994), which measures memory recall for newly learnt information. While this may suggest that DR and EH's ability to retrieve the newly learnt complex layout of the Mall may have been affected, further evidence for the role for memory in EH's RN was obtained based on his poor recognition of shop locations within the Mall. EH's recognition memory, as well as his recall for shops from imagery, were significantly worse for the right side of space than left. A similar relation between poor memory for objects from the neglected side and RN has been previously reported in a single case study for left-sided objects depicted in a complex picture of a farm scene (Beschin, Cocchini, Della Sala, & Logie, 1997a). However, note that neither DR nor EH showed non topological RN on the Object array task (Della Sala, Logie, Beschin, & Denis, 2004), which also required new learning. Additionally, a relationship between memory and RN was not observed on tasks testing information learnt prior to the stroke that relied on retrieval from long term memory (Clock Cueing, Geographical Map). Both patients with RN on the Clock Cueing task were able to successfully retrieve the clock's layout and depict time involving clock hands to both sides of space prior to performing the task. Similarly, EH had a symmetrical recall of cities from both sides of the UK map when no explicit demands were placed on imagery during recall. Thus, the visual memory deficits seen in the RN patients were seen to be specific to newly learnt topological information.

With regard to imagery ability, Palermo et al. (2010a) reported dissociations such that a patient with topological RN demonstrated impairments for mental generation, inspection and manipulation of imagery tasks pertaining to *place* images while a RN patient with deficits only in non-topological RN showed selective deficits in imagery tasks using *object* images (Palermo, Nori, Piccardi, Giusberti, & Guariglia, 2010a). Although the imagery tests used in the current study were coarse and the tasks were restricted to imagery for individual objects, both DR and MG had significant difficulty in creating and inspecting images of objects on one or more of these tasks, as compared to controls. It is possible that their impaired imagery ability contributed to their RN on the Mall and Clock Cueing tasks respectively.

EH and MG were also impaired in identifying whether presented letters were mirror reversed or straight, indicating a difficulty in mental rotation ability. EH's difficulty in mental rotation is in line with his *viewer-dependent* RN on the topological layouts (Mall and Map tasks) where his performance for right sided landmarks was significantly impaired irrespective of the vantage point, i.e. his asymmetrical landmark report persisted as per the canonical perspective even when mental rotation was requested, indicating that he had likely not engaged in perspective shifting. On the Clock Cueing task, these difficulties may have impacted EH and MG's mental rotation of the imagined clock hands from cued to un-cued locations in invalid trials.

EH and MG were also found to have impairments in non-lateralised visuospatial working memory on the ancillary test battery measured using the Location learning (Bucks & Willison, 1997) and Spatial span tasks (Wechsler, 1987). One speculation is that this deficit may have contributed to potential difficulties in maintaining the clock's mental representation and information from the central digital cue active during task performance.

Spatially lateralised deficits

Several studies have implicated a role for lateralised deficits in visuospatial working memory (Beschin et al., 1997a; Della Sala et al., 2004; Logie, Della Sala, Beschin, & Denis, 2005) and spatial attention in RN (Bartolomeo, Bachoud-Levi, Azouvi, & Chokron, 2005; Loetscher & Brugger, 2007) and a possible synergestic relationship between these two cognitive processes in RN (Rode et al., 2010; Salvato, Sedda, & Bottini, 2014).

The Shopping Mall task scores could be explored similar to Della Sala et al. (2004) who used perspective shifting based report of objects from arrays to explain the involvement of lateralised visuospatial working memory deficits. Specifically, DR showed a relatively impoverished representation of shops for the left side of the Mall. With perspective shifting, this impoverished shop report was not further compromised when the shops were imagined on the right side. However, shops that were originally imagined on the right were forgotten when they were imagined as being on the left (neglected) side after perspective shifting. Based on similar observations in their patients' performance on the Object array task, Della Sala et al. (2004) proposed that the system responsible for holding information active on the left side of imagery may be responsible for this pattern of deficit.

In the case of EH and MG's Clock Cueing deficits, the lateralised bias seen as RN may be more likely associated with impaired allocation of attention resources to the clock's representation. Specifically, EH and MG were significantly slower than controls in disengaging attention when the cued location was to the right side of imagery and the target was on the left side of visual space as compared to validly cued trials (RVE: right validity effect). Such a discrepancy between valid and invalid trial responses was not seen when patients were cued to the left side of imagery space. Hence, these results specifically implicate spatial attention processes involved when engaging with the right side of imagery space (cued side) and left side of visual space (target side). Given that the patients detected each visual target on the left side of the Clock, it is likely that the spatial attention deficits noted were on account of poor attention exploration of the right side of the imagined clock, rather than due to target detection in the left visual field. Lateralised deficits in attention based exploration of imagery space was also implicated in a study by Bartolomeo et al. (2005) where RN patients' took longer to respond to auditorily named landmarks that were imagined on the neglected side of a map despite no asymmetry in accuracy performance (Bartolomeo et al., 2005).

Thus, based on the pattern of cognitive deficits observed on the RN and ancillary battery tasks, a potential role for an interaction between spatial and non-spatial cognitive mechanisms in modulating RN is suggested. Based on the lesion data available for the patients, it is suggested that the right cerebellum plays an important role in RN. The cerebellum has also been seen to play a role in visual neglect in previous studies (Hildebrandt, Spang, & Ebke, 2002; Kim et al., 2008; Silveri, Misciagna, & Terrezza, 2001), but this is the first study that has identified RN in cerebellar stroke. It has been implicated in a wide range of cognitive functions that were recruited in the novel RN tasks such as visuospatial processing, mental rotation, imagery, attention shifting and working memory (Baier, Muller, & Dieterich, 2014; Fehrenbach, Wallesch, & Claus, 1984; Luis et al., 2015; Molinari, Petrosini, Misciagna, & Leggio, 2004; Parsons et al., 1995; Townsend et al., 1999; Vingerhoets, De Lange, Vandemaele, Deblaere, & Achten, 2002). However, in order to enable a more in-depth study of the role of cerebellum in RN and associated cognitive deficits, a larger sample of cerebellar lesion patients with RN as well as a higher resolution of neuroimaging is required.

Based on the current study's design and patient recruitment, it is also not possible to estimate the relative importance of each cognitive process in RN. For example, although MG also showed visual memory recall deficits for newly learnt information in the ancillary test battery similar to DR and EH, her performance on both the Mall and Object arrays tasks that both required new learning, was intact. Also note that MG had a profile of deficits similar to EH in the ancillary test battery, but she did not show topological RN on the Mall task like EH. A larger sample of patients may help to clarify some of these discrepancies. However, it is also likely that factors other than cognitive performance contribute to the manifestation of RN. For example, not all RN patients show deficits in visuospatial working memory (van Dijck, Gevers, Lafosse, & Fias, 2013) or mental rotation (Della Sala et al., 2004; Logie et al., 2005). Additionally, inter-individual differences between patients such as in demographic and stroke profile, severity of the cognitive deficits, effect of cognitive reserve, spontaneous recovery and compensatory mechanisms may also require consideration when attempting to evaluate the importance of cognitive deficits in RN.

It is also important to note that each RN task may vary in its recruitment of cognitive abilities. For instance, it is possible that the Mall task engaged visual memory to a greater extent (retrieval of five shops from each side) than the Object arrays task (retrieval of two objects from each side) which may be a potential explanation for why none of the patients showed RN on the Object arrays task despite impaired visual memory as observed in the ancillary test battery results. Hence, interweaving assessment of discrete cognitive mechanisms within the RN task such that inter-task differences in features, layout and complexity are reduced may aid sensitivity of assessment and understanding of cognitive mechanisms recruited in the RN. This suggestion is discussed in greater detail in section 8.5.

8.2 Visual neglect rehabilitation using rTMS: Chapters 5 and 6

8.2.1 Summary

In Chapters 5 and 6, I assessed the utility of rTMS in aiding neglect recovery in a sample of sub-acute neglect patients. The recruitment of patients in both studies was inadequate and reduced the power of the investigations. The main finding from the behavioural investigations in Chapter 5 was that when using baseline performance as a covariate, a significant difference between post rTMS activities of daily living (ADL) scores was obtained between the intervention (IG=8 patients) and control groups (CG: 6 patients) in the short term (<1 month), but not in the long term (> 6 months). This difference was related to IG's significant improvement from pre rTMS to < 1 month post rTMS while no such significant changes were observed for the CG's performance. No other significant results were obtained on any of the other paper-pencil neglect measures included. Additionally, the number of patients with impaired performance on sustained attention and executive function tests was inadequate and hence any influence of rTMS on these non-spatial task performance could not be assessed.

In Chapter 6, I attempted to study the effects of rTMS on neural activity using functional Magnetic Resonance Imaging (fMRI). The fMRI task attempted to recruit attention-based top down modulation of sensory activity. Due to limited recruitment of patients, I used a case study approach to explore brain activity pre and post rTMS rehabilitation in the four left neglect patients included in the study (Patient WM: sub-acute stage, Intervention Group; Patient BR: chronic stage, Intervention Group; Patient LG: sub-acute stage, Control Group; Patient SW: chronic stage, Control Group) and compared activation in the occipital lobes for each patient to a sample of elderly controls. Results revealed relative hypoactivation of the right occipital pole in all four left neglect patients both pre and post rTMS when compared to elderly controls, for unilateral checkerboard stimulation in the left visual field compared to the right (left > right). Behaviourally, surprisingly, the chronic stage control group patient (SW) improved on the neglect-specific ADL measure while none of the other patients showed a similar level of behavioural improvement post rTMS. In line with the control group patient SW's behavioural improvement on ADL, she showed a reactivation of the right occipital lobe's intracalcarine cortex post rTMS when compared to controls. SW's results were unexpected and could either indicate spontaneous recovery or equally likely, inter-session fluctuations.

8.2.2 Key result: Inclusion of ADL tasks improved detection of subtle intervention effects in neglect patients

Amongst the battery of tests that was used to assess neglect and related performance pre and post rTMS, only ADL scores were seen to improve significantly in the IG relative to the CG. Cazzoli et al. (2012) have also reported significant improvements in ADL performance on the Catherine Bergego scale (Azouvi, 1996) in sub-acute neglect patients for up to three weeks after continuous theta burst intervention (cTBS) to the contralesional posterior parietal lobe as compared to a control group without brain stimulation. However, unlike the current study, Cazzoli et al.'s (2012) patients also improved on other neuropsychological measures of neglect. Prism adaptation intervention studies have shown a mixed effect on ADL performance with some studies showing improved ADL for patients in the sub-acute (Keane, Turner, Sherrington, & Beard, 2006) and chronic stages (Shiraishi, Muraki, Ayaka Itou, & Hirayama, 2010), and some others which did not (Rossi, Kheyfets, & Reding, 1990; Ten Brink et al., 2017). Although note that in both studies reporting ADL improvements after prism adaptation, the sample of patients was small ($\leq$5) and there was no control group to assess the effect of spontaneous recovery (Keane et al., 2006; Shiraishi et al., 2010).

In the current study, one factor affecting the lack of significant results on popularly used paper-pencil tests like cancellation and line bisection could be on account of practice effects (discussed further in section 8.4 as a limitation). On the other hand, ADL tasks have been reported to have higher ecological validity and sensitivity than paper-pencil tests (Azouvi, 2017b; Azouvi et al., 2002). One reason for this is that ADL tasks can elicit neglect in the context of complex, everyday behaviour that require multiple cognitive processes and multitasking unlike in 'artificial' test environments (Bowen, McKenna, & Tallis, 1999). Furthermore, ADL tasks rely on automatic orienting of attention rather than voluntary orienting as in the case of paper-pencil tests (Azouvi, 2017b; Eschenbeck et al., 2010). The test used to measure ADL in this thesis incorporated sub-tasks involving different spatial frames of reference (personal, peri-personal extrapersonal) which may have also increased the range of neglect behaviours studied and consequently sensitivity of the test (Eschenbeck et al., 2010). Despite being a multicomponent test, one unique and important contribution of Eschenbeck et al.'s (2010) ADL task is that it not only provided *neglect- specific* scores but also accounted for *severity of neglect* in scoring. For example, in 7 of the 8 sub-tasks, locating an object on the left side of space required to perform the task along with completing the task with symmetrical attention to both sides of space was each credited separately.

Spontaneous improvement in ADL performance was also seen in chronic neglect patient (SW) included in Chapter 6 (fMRI study), despite her assignment to the sham rTMS condition. SW had lesions involving the frontoparietal network (Chapter 6, Figure 6.1) that have been associated with performance on the ADL task (Eschenbeck et al., 2010; Vossel et al., 2011). Hence, one possibility is that spontaneous improvement on this task post rTMS was accompanied by functional reorganisation in the frontoparietal attention network that modulated improvement in right occipital lobe (intracalcarine) activity. This hypothesis is supported by previous studies that have shown evidence of structural connectivity between the calcarine cortex and parietal lobe (Aine et al., 1996; Borra & Rockland, 2011; Tootell et al., 1998) as well as evidence of top down modulation of functional activity in the occipital lobe (Plow et al., 2014; Ruff et al., 2008). Additionally, across studies using visual scanning, optokinetic stimulation and alertness training rehabilitation, improvements in neglect have been reported to occur with bilateral increases in hemispheric brain activity in frontoparietal, temporal and occipital regions (Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013; Thimm et al., 2009; Thimm, Fink, Küst, Karbe, & Sturm, 2006; Thimm, Fink, & Sturm, 2008). However, given that this observation is based on a single patient who underwent sham rTMS where such an improvement was unexpected, another likely possibility is that the behavioural and functional changes merely reflect inter-session random fluctuations in haemodynamic response function, levels of alertness etc. (for review on benefits and pitfalls of neuroimaging in single case studies, see Danckert & Mirsattarri, 2011). Hence, results from the fMRI study need replication in a larger sample of neglect patients, especially including IG patients who show rTMS related benefits in neglect performance. Unfortunately in the current study, both the IG patients did not show behavioural improvements in neglect post intervention.

8.3 Cognitive predictors of visual neglect: Chapter 7

8.3.1 Summary

Chapter 7 was aimed at identifying cognitive components that are fundamental to spatial and object neglect and could be potentially used to guide cognitive retraining efforts in neglect patients. Data from 274 patients were extracted from a large scale database of sub-acute stroke patients (BCoS trial), inclusive of demographic, stroke and lesion related information, along with cognitive performance on the BCoS visual and tactile double simultaneous stimulation task, complex figure copy and auditory sustained attention tasks (Humphreys et al., 2012). Blocked logistic regression was carried out using this data where the potential for prediction of spatial and object neglect by cognitive scores from the tests was assessed after controlling for demographic and stroke related factors. Significant prediction of neglect based on the BCoS cognitive tests provided the scope to explore the role of shared cognitive mechanisms between the predictor tests and neglect. Based on this rationale, results revealed that spatial attention (based on double simultaneous stimulation performance), focused attention (based on *presence* of local features in complex figure copy) and spatial coding of relations between features (based on *placement* scores of features in complex figure copy) could predict spatial neglect performance at the sub-acute stage. Each predictor except spatial coding of relations between features was also predictive of object neglect at the sb-acute stage.

8.3.2 Key result: Spatial bias and selective attention are core mechanisms in both spatial and object neglect; integrity of spatial coding is important to spatial neglect

Given the heterogeneity in the manifestation of neglect (Azouvi et al., 2006; Binder, Marshall, Lazar, Benjamin, & Mohr, 1992; Ferber & Karnath, 2001; Toba et al., 2018), one recent trend has been to combine and tailor rehabilitation efforts to the neglect patient's specific deficits (e.g. Azouvi, Jacquin-Courtois, & Luauté, 2017a; Saevarsson, Halsband, & Kristjansson, 2011). Individual differences in age, education, gender, mood, lesion characteristics are known to heavily influence cognitive task performance (Damasceno, 2010). The current study's findings after controlling for these potential sources of individual differences revealed that some cognitive mechanisms can be considered more pervasive than others across neglect patients. While results showed that disengaging attention from ipsilesional space to reorient to contralesional space (assessed using double simultaneous stimulation in visual space), was important in the prediction of both spatial and object neglect, attending to local features in space (assessed using complex figure copy) was also important to both types of neglect. However, scores indicating inter-relationships between copied features of the complex figure were only indicative of spatial, but not object neglect. Thus, these results showed that both the magnitude as well as the qualitative aspects of the space explored were important to neglect. This finding has been supported by previous literature that showed that even in ipsilesional space, neglect patients may experience difficulty in filtering out task-irrelevant information (Snow & Mattingley, 2006). Consequently, along with a spatial bias, increasing demands on visual selective attention in neglect patients may compromise the integrity of processing even in the 'good' side (Chokron, Peyrin, & Perez, 2018; Rapcsak, Verfaellie, Fleet, & Heilman, 1989). Finally, the inter-relationships between features in space indicative of integrity of spatial coding was also found to be a significant predictor of spatial neglect. The tendency for distorted spatial relationships has been noted based on figure copy performance in neglect patients (e.g. Di Pellegrino, 1995) and indicates a role for spatial remapping and working memory processes in spatial neglect patients (Husain et al., 2001; Pisella & Mattingley, 2004; Wojciulik, Husain, Clarke, & Driver, 2001).

These deficits have important implications for neglect patients in the real world (e.g. navigation), especially in the context of situations with overwhelming incoming information that require divided and selective attention to achieve task goals. Consequently, rehabilitation efforts focusing on improving attentional selection, spatial remapping and working memory may be useful in improving functional independence in neglect patients.

Spatial orienting of attention has been the focus of rehabilitation in neglect using techniques such as visual scanning while techniques such as prism adaptation, caloric, galvanic and optokinetic stimulation have been used to counteract ipsilesional bias. Each of these techniques has been used to produce at least transient improvements in spatial neglect (For reviews, see Barrett et al., 2006; Kerkhoff & Schenk, 2012; Yang, Zhou, Chung, Li-Tsang, & Fong, 2013). The current study suggests that training to enhance efficient selection of target relevant information and suppression of target irrelevant information may be beneficial to both spatial and object neglect. A recent review of rehabilitation techniques for neglect has shown that, relatively, prism adaptation has been the most effective intervention for visual neglect to date (Yang et al., 2013) with potential to improve both spatial and non-spatial aspects of neglect including spatial attention, visual search, feature processing in space and spatial remapping (Bultitude, Rafal, & List, 2009; Bultitude, Van der Stigchel, & Nijboer, 2013; Bultitude & Woods, 2010; Jacquin-Courtois et al., 2013; Rode, Pisella, Rossetti, Farnè, & Boisson, 2003; Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009).

8.4 Limitations

An important limitation of the research included in this thesis was the limited sample size of patients, especially with regard to the study assessing rehabilitation efficacy of rTMS in neglect patients. The sensitivity and power to detect any significant effect of rTMS on neglect, especially object neglect was insufficient given the sample size.

Furthermore, the effect of rTMS on non-spatial cognitive abilities such as sustained attention and executive function could also not be assessed on this account.

Due to limited sample of patients, two chapters employed a case study approach (Chapter 4: RN and Chapter 6: fMRI). One limitation of this approach was that each case study patient had a unique demographic, cognitive and lesion profile that prevented generalisation of their results to other neglect patients. While the results from the RN studies implied that both spatially lateralised and non-lateralised cognitive mechanisms contribute to RN, their exact role in modulating dissociations as well as the role of neural mechanisms underlying RN could not be ascertained based on a sample of three RN patients.

Additionally the case study approach is not suited to explore neuroanatomical bases of RN. For instance, all three RN patients had right cerebellar lesions and yet showed dissociations in RN performance. The relation between their lesions and each patient's unique cognitive profile could not be ascertained although it is known that the cerebellum is connected through pathways to several key cortical regions in the right hemisphere such as the frontal, temporal and parietal lobes (Allen & Tsukahara, 1974; Schmahmann & Pandya, 2008) which have been previously implicated in RN (Della Sala et al., 2004; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993; Guariglia, Palermo, Piccardi, Iaria, & Incoccia, 2013; Palermo, Piccardi, Nori, Giusberti, & Guariglia, 2009; Rode et al., 2004). Similarly, given that there was only one patient that belonged to each assigned group in the fMRI study, despite having a sample of elderly controls to compare brain activation with for the relevant contrast, the findings from each case study can only be considered specific to the patient and to the scan session, i.e. any changes in fMRI activity from pre to post rTMS cannot be reliably attributed to the intervention or behavioural changes in neglect based on a single patient's performance, especially in view of the time between the different assessment sessions. Hence, the results from chapters employing case study approach while able to characterise individual patients' performances, were predominantly useful in providing avenues for future research with larger samples.

A second set of limitations concerned the design of the rTMS study that has scope for improvement. For example, six sessions of 1 Hz rTMS in addition to an extensive battery of tests and fMRI scan pre and post the rTMS implied that the study extended into several weeks for each patient. The effect of fluctuations in patients' physical and cognitive health and spontaneous recovery in neglect that are seen to occur in the sub-acute stage of stroke (Nijboer, Kollen, & Kwakkel, 2013; Stone, Patel, Greenwood, & Halligan, 1992) could have affected the patients' behavioural performance and response to rTMS. Similarly, the time between behavioural testing of neglect and the fMRI scan was varied based on availability of an imaging appointment. The lack of behavioural measures of neglect from the day of the fMRI scan implied that spontaneous recovery could have continued to occur between the behavioural and imaging test sessions.

Additionally, the choice of rTMS protocol and behavioural tests of neglect could have been better suited to the study. The alternate day interval between the multiple rTMS sessions, although found to be useful in previous studies with neglect patients (Brighina et al., 2003; Shindo et al., 2006), may have been sub-optimal in producing long term benefits in the current study. It is possible that a shorter interval between rTMS sessions ($\leq$ 24 hours) may have strengthened the cumulative effects of the sessions to induce improvements in neglect (Valero-Cabré, Pascual-Leone, & Rushmore, 2008). Similarly, behavioural tests included could have benefited from accounting for the potential role of practice effects. Although parallel forms for the cancellation test were used within the study sessions, patients also underwent testing on the clinically popular cancellation and line bisection tests with the therapeutic staff at the hospitals. Hence, it may have been beneficial to use well-established computerized experimental paradigms instead or in addition to the chosen tests since these are also known to improve sensitivity of neglect assessment (Bonato & Deouell, 2013; Rengachary, D'Avossa, Sapir, Shulman, & Corbetta, 2013).

Finally, the identification of essential cognitive processes in neglect as assessed in Chapter 7 would have benefitted from the use of tasks such as the Navon task (Navon, 1977) to assess local-global feature processing and tone counting (Robertson et al., 1997) to assess sustained attention. These tasks allow for a neater and 'purer' assessment of cognitive processes as compared to some of the clinical tests extracted from the BCoS test battery. For example, the complex figure copy task is known to draw upon several simultaneous cognitive processes such as spatial attention, constructional abilities, executive functioning etc. (see Trojano, Grossi, & Flash, 2009 for review). Although scoring from the task was adapted to extract specific sub-processes from within the complex figure copy, it is unlikely that the scoring was completely isolated from the influence of the other cognitive processes recruited in the task.

8.5 Future directions

Future studies may benefit from assessing the utility and validity of the Shopping Mall and Clock Cueing tasks in assessing RN in a larger sample of patients. Additionally, the ancillary cognitive abilities measured with regard to these tasks in the current study can be attempted to be incorporated within the context of the RN task to increase relevance. For example, The Shopping Mall task can be adapted into a 3D virtual environment such that more features could be included and patients could engage in virtual navigation of the environment. Patients could be tested for their ability to form, imagine and manipulate cognitive maps of the topological representation by asking them to describe the navigational path across different perspectives with respect to a given target reference point. This adaptation would be in line with previous tests that assess similar aspects (Guariglia et al., 2005; Nico et al., 2008). Visual memory recall (instead of recognition) could be tested by adding features to the mall such as prominent décor and people, at midline (to avoid interference from visual neglect), and spread over levels of the mall. This would allow for testing non-lateralized deficits in visual and spatial memory within the same test layout. Additionally, by modulating the time between encoding and recall, this adaptation could inform about short and long term memory in these patients. Other non-spatial cognitive abilities like (visual) sustained attention could be incorporated into the task, for e.g. by asking patients to attend to the Mall for a limited time and pressing a response key every time centrally shown shops or object within the Mall were highlighted at unpredictable intervals during this time period. Such task adaptations would require to be administered to healthy controls to adjust difficulty levels and assess suitability before use with patients. A sufficiently large scale study with measures of RN and performances on selected cognitive measures could be used to identify latent cognitive components using confirmatory factor analysis. This would help to assess the relative role of the various spatial and non-spatial abilities recruited in RN.

A larger sample of patients with appropriate neuroimaging would help to identify the neuroanatomical bases of RN in a future study. Diffusion tensor imaging scans can help to assess connectivity between the cerebellum and cortical regions to provide better understanding of the neuroanatomical correlates of RN dissociations in cerebellar lesion patients. Furthermore, lesion analyses based on data acquired from a large sample of patients would help to understand the involvement of brain regions in contributing to the cognitive components recruited in RN. The Clock Cueing task can be assessed using neuroimaging to explore the recruitment of brain areas in attentional processes in imagery space. Furthermore, a parallel version of the task with arrows as cues instead of numbers can be used to assess differences in functional activity for tasks recruiting attention in visual and imagery space. This kind of comparable task paradigm may help to facilitate an understanding of the relationship between visual perception and imagery as well as dissociations and similarities in visual and RN.

In terms of rTMS based rehabilitation for visual neglect, future work in this area would benefit from incorporating the insights acquired from the current study's sample and design related constraints. Specifically, it may be useful to employ a shorter, patient-friendly protocol such as cTBS that may be effective in producing more substantial effects with shorter stimulation time relative to 1 Hz rTMS (Yang et al., 2015). cTBS has been shown to benefit visual neglect rehabilitation (Cazzoli et al., 2012; Fu et al., 2015; Koch et al., 2012; Nyffeler, Cazzoli, Hess, & Müri, 2009) for up to three weeks post stimulation (Cazzoli et al., 2012). Additionally, given that inter-individual heterogeneity is difficult to control in patient studies (Sunwoo et al., 2013; Ten Brink et al., 2017), cTBS protocols can be easily incorporated into cross over designs that would help to reduce the effect of inter-individual differences when assessing efficacy of the intervention (Cazzoli et al., 2012). Just as maintenance rTMS sessions have been shown to benefit depression patients (Dunner et al., 2014; Fitzgerald, Grace, Hoy, Bailey, & Daskalakis, 2013; Richieri et al., 2013), future studies could also ascertain if there is a role for maintenance sessions to enhance benefits of neglect in the long run. Lastly, since one of the original aims of the rTMS exploration was to assess its effect on non-spatial cognitive functions, computerized assessment methods that simultaneously assess neglect and related non-spatially lateralised cognitive components such as processing speed and working memory can be employed in future studies (Bublak et al., 2005;

Bundesen, 1990; Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2014; Finke, Bublak, Dose, Müller, & Schneider, 2006; Habekost & Bundesen, 2003).

Lastly, although the utility of combining rehabilitation techniques has been previously suggested, no known attempt has been previously made to suggest evidence-based guidelines for combining rehabilitation techniques (for review, see Saevarsson et al., 2011). Thus, a future study needs to evaluate the efficacy of the guidelines generated from the current research's findings in improving spatial and object neglect at the sub-acute stage. Specifically, the study can assess if combining rehabilitation efforts to improve spatial and selective attention deficits, spatial remapping and working memory can benefit neglect patients. For example, the use of non- invasive brain stimulation to improve spatial attention and cognitive therapy directed at the core cognitive components identified herein may aid neuroplasticity by coupling a plasticity-promoting intervention with targeted behavioural reinforcement (Cramer et al., 2011), especially in the sub-acute stage where patients are prone to spontaneous recovery (Nijboer, Kollen, & Kwakkel, 2013; Stone, Patel, Greenwood, & Halligan, 1992).

8.6 Conclusion

Overall, the studies included in the thesis aid theoretical understanding of cognitive mechanisms underlying neglect and a potential role for clinical application of this information in work with patients. Specifically, the thesis highlighted the importance of identifying cognitive mechanisms underlying neglect to aid assessment and rehabilitation efforts.

The work in the thesis provided two novel assessment methods for representational neglect (Chapters 3 & 4: The Shopping Mall and Clock Cueing tasks) that improved upon previous tests and can be used in future research to further examine their characteristics and identify dissociations in RN presentation. The tests also demonstrated their scope for identifying discrete cognitive abilities that contribute to the RN syndrome (e.g. visual memory measure in Shopping Mall, spatial attention in Clock Cueing), although their specific involvement in topological and non-topological RN could not be evaluated in this limited sample. Based on the research in this thesis, RN is suggested to be a multicomponent disorder whose presentation can be modulated by a synergistic combination of spatial and non-spatial cognitive abilities. The RN patients each had right cerebellar lesions which implies a potential role for the cerebellum in modulating these cognitive abilities. Furthermore, the results from the rTMS behavioural study (Chapter 5) revealed that the sensitivity of the assessment method in detecting subtle intervention related effects may be aided by increasing the task's functional relevance along with estimating neglect severity, such as in the ADL based assessment of visual neglect (Eschenbeck et al., 2010). Thus, the research in this thesis helped to identify relevant attributes of assessment methods that can serve to enhance theoretical understanding and sensitive assessment of the neglect syndrome, while also providing interesting avenues for future exploration in a larger sample of patients.

The studies in this thesis also demonstrated the importance of using covariates in statistical analyses to improve detection (Chapter 4) and generalizability (Chapter 7) of neglect related effects. By controlling for heterogeneity in patients' demographic, stroke and lesion profiles, spatial and selective attention were found to be important to both spatial and object neglect. Additionally, the integrity of the spatial representation was also found to be important to spatial neglect. These findings suggest a baseline set of cognitive abilities recruited in neglect, that may benefit from being targeted in rehabilitation efforts.

Finally, the potential of rTMS to influence long term neglect behaviour, as well as the study of functional activity underlying rTMS related changes would benefit from re-exploration in future studies with a larger patient sample and study design-related insights gained from the current thesis.

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Appendices

Appendix A: Chapter 3

Table 3a. Perspective based shop report and LQs for Shop Identity (SId)

Shop identity scores (SId)										
Ctrl No.	Left		Right		Viewer independent scores			Viewer dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
C1	7	10	10	7	17	17	0.00	20	14	17.65
C2	9	10	10	9	19	19	0.00	20	18	5.26
C3	8	8	7	8	16	15	3.23	15	16	-3.23
C4	6	6	5	6	12	11	4.35	11	12	-4.35
C5	10	10	10	10	20	20	0.00	20	20	0.00
C6	9	10	10	9	19	19	0.00	20	18	5.26
C7	10	10	10	10	20	20	0.00	20	20	0.00
C8	9	9	8	8	18	16	5.88	17	17	0.00
C9	5	8	8	7	13	15	-7.14	16	12	14.29
C10	10	10	10	10	20	20	0.00	20	20	0.00
C11	9	10	10	9	19	19	0.00	20	18	5.26
C12	10	9	9	10	19	19	0.00	18	20	-5.26
C13	7	8	10	8	15	18	-9.09	18	15	9.09
C14	8	10	9	8	18	17	2.86	19	16	8.57
C15	7	8	7	7	15	14	3.45	15	14	3.45
C16	6	9	9	6	15	15	0.00	18	12	20.00
C17	7	8	8	7	15	15	0.00	16	14	6.67
C18	9	8	7	9	17	16	3.03	15	18	-9.09
C19	9	10	10	9	19	19	0.00	20	18	5.26
C20	10	10	10	10	20	20	0.00	20	20	0.00
Mean (SD)	8.25 (1.55)	9.05 (1.15)	8.85 (1.46)	8.35 (1.35)	17.3 (2.45)	17.2 (2.5)	0.33 (3.44)	17.9 (2.53)	16.6 (2.85)	3.94 (7.5)

*Ctrl = Control; SD = Standard Deviation; LQ = ((left shops-right shops)/(left shops+ right shops)) *100*

Table 3b. Perspective based shop report and LQs for shop identity + location (SIdLoc)

Shop identity & Location (SIdLoc)										
Ctrl No.	Left		Right		Viewer independent scores			Viewer dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
C1	5	10	6	5	15	11	15.38	16	10	23.08
C2	9	10	10	9	19	19	0.00	20	18	5.26
C3	7	8	6	5	15	11	15.38	14	12	7.69
C4	2	4	4	4	6	8	-14.29	8	6	14.29
C5	8	6	6	8	14	14	0.00	12	16	-14.29
C6	9	8	10	9	17	19	-5.56	18	18	0.00
C7	10	10	10	10	20	20	0.00	20	20	0.00
C8	6	9	8	5	15	13	7.14	17	11	21.43
C9	5	6	6	5	11	11	0.00	12	10	9.09
C10	10	10	10	10	20	20	0.00	20	20	0.00
C11	9	7	8	9	16	17	-3.03	15	18	-9.09
C12	8	9	9	10	17	19	-5.56	18	18	0.00
C13	5	5	8	6	10	14	-16.67	13	11	8.33
C14	3	7	8	5	10	13	-13.04	15	8	30.43
C15	4	6	4	4	10	8	11.11	10	8	11.11
C16	2	5	3	3	7	6	7.69	8	5	23.08
C17	4	6	6	5	10	11	-4.76	12	9	14.29
C18	4	4	2	5	8	7	6.67	6	9	-20.00
C19	9	9	9	9	18	18	0.00	18	18	0.00
C20	6	9	9	7	15	16	-3.23	18	13	16.13
Mean (SD)	6.25 (2.63)	7.4 (2.06)	7.1 (2.47)	6.65 (2.35)	13.65 (4.34)	13.75 (4.58)	-0.14 (8.9)	14.5 (4.27)	12.9 (4.89)	7.04 (12.93)

*Ctrl = Control; SD = Standard Deviation; LQ = ((left shops-right shops)/(left shops+ right shops)) *100*

Table 3c. Recognition memory performance for shop identity and shop location

Ctrl	Shop identity					Shop Location				
	Left	Right	LQ	d’	**c**	Left	Right	LQ	d’	**c**
C1	8	7	6.67	1.84	0.48	7	6	7.69	1.93	0.42
C2	10	9	5.26	2.90	-0.30	8	10	-11.11	2.88	0.29
C3	9	9	0.00	1.98	-0.18	6	7	-7.69	1.40	0.27
C4	10	10	0.00	2.67	-0.72	8	8	0.00	1.62	0
C5	9	10	-5.26	2.81	0.00	9	7	12.50	1.64	0.15
C6	9	9	0.00	1.48	-0.43	10	10	0.00	4.11	0.00
C7	10	10	0.00	3.34	-0.39	8	10	-11.11	2.53	0.12
C8	10	8	11.11	3.16	0.17	9	8	5.88	3.02	0.54
C9	10	10	0.00	3.09	-0.51	8	8	0.00	1.78	-0.08
C10	8	10	-11.11	2.51	0.30	9	10	-5.26	3.46	0.00
C11	10	10	0.00	4.38	0.14	8	10	-11.11	3.46	0.32
C12	8	8	0.00	2.36	0.23	10	7	17.65	2.88	0.29
C13	9	9	0.00	2.21	-0.07	9	7	12.50	1.93	0.00
C14	8	8	0.00	1.23	-0.06	10	7	17.65	2.12	-0.09
C15	9	10	-5.26	2.14	-0.33	7	8	-6.67	2.20	0.29
C16	6	8	-14.29	1.23	-0.06	7	7	0.00	0.76	-0.17
C17	7	6	7.69	1.35	0.47	6	5	9.09	1.02	0.30
C18	7	9	-12.50	1.99	0.04	8	8	0.00	2.35	0.21
C19	9	8	5.88	2.09	0.24	9	10	-5.26	2.77	0.00
C20	7	10	-17.65	2.33	-0.01	10	8	11.11	2.77	0.00
Mean (SD)	8.65 (1.23)	8.9 (1.17)	-1.47 (7.6)	2.4 (0.79)	-0.05 (0.33)	8.3 (1.26)	8.05 (1.5)	1.79 (9.46)	2.3 (0.86)	0.14 (0.19)

Ctrl = Control; SD = Standard Deviation;
*LQ = ((left shops - right shops)/ (left shops + right shops)) * 100*

Table 3d. Familiarity ratings for shops in the Mall and familiarity LQ

Ctrl No.	Left sided shops	Right sided shops	Combined ratings	LQ
C1	1.9	1.1	1.5	26.67
C2	1.9	1.6	1.75	8.57
C3	2	1.7	1.85	8.11
C4	3.2	3	3.1	3.23
C5	1.7	1.4	1.55	9.68
C6	1.5	1.5	1.5	0.00
C7	1.6	1.2	1.4	14.29
C8	1.7	1.8	1.75	-2.86
C9	1.7	1.8	1.75	-2.86
C10	1	1	1	0.00
C11	1.7	1.6	1.65	3.03
C12	3.1	2.2	2.65	16.98
C13	2.4	1.9	2.15	11.63
C14	3	3.1	3.05	-1.64
C15	3.4	3	3.2	6.25
C16	3.6	2.3	2.95	22.03
C17	1.1	1.3	1.2	-8.33
C18	2.4	2	2.2	9.09
C19	2.4	2.7	2.55	-5.88
C20	2.7	3.8	3.25	-16.92
Mean (SD)	2.2 (0.76)	2 (0.77)	2(0.72)	5.05 (10.51)

Ctrl = Control; SD = Standard Deviation;
*LQ = ((left shops - right shops)/ (left shops + right shops)) * 100*

Table 3e. Elderly controls: Clock Cueing reaction time based results

Ctrl No.	Left valid RTs	Left invalid RTs	Right valid RTs	Right invalid RTs	Overall validity effect	Left validity effect	Right validity effect
C1	573.13	615.15	472.82	593.96	81.57	42.01	121.14
C2	456.06	597.22	464.65	530.27	103.39	141.16	65.63
C3	513.42	898.83	519.49	776.51	321.22	385.42	257.01
C4	481.54	582.69	521.15	552.49	66.24	101.14	31.34
C5	479.06	505.19	472.86	500.48	26.87	26.13	27.62
C6	500.68	758.38	473.30	648.59	216.49	257.70	175.28
C7	546.41	1024.03	457.77	950.44	485.14	477.61	492.67
C8	721.27	1168.20	647.19	1056.06	427.90	446.93	408.87
C9	670.75	870.23	642.30	790.22	173.70	199.48	147.92
C10	454.28	484.55	465.86	623.41	93.91	30.28	157.55
C11	375.77	404.15	374.02	392.87	23.62	28.38	18.85
C12	530.70	514.09	628.78	457.51	-93.94	-16.62	-171.27
C13	1007.21	1281.03	1071.58	1327.97	265.10	273.82	256.38
C14	414.89	433.38	420.31	407.70	2.94	18.49	-12.61
C15	733.55	718.16	735.91	787.65	18.17	-15.39	51.74
C16	539.84	468.91	466.07	468.91	-34.05	-70.94	2.84
C17	326.14	581.03	352.27	352.09	127.35	254.89	-0.18
C18	388.21	416.62	399.34	448.11	38.59	28.41	48.76
Mean RT (SD)	539. 61 (161.26)	684.55 (264.21)	532.54 (168.79)	648.07 (259.36)	130.24 (157.84)	144.94 (168.98)	115.53 (159.87)

Ctrl=control, SD= Standard deviation

Note: 1) All RTs shown in msecs; 2) Left invalid trials = when attention had to shift from left side of representational space to right side of visual space to detect target.

Table 3f. Elderly controls: Clock Cueing target detection based results

Ctrl No.	Left valid	Left invalid	Right valid	Right invalid	Overall validity effect	Left validity effect	Right validity effect
C1	1	1	1	1	0	0	0
C2	1	1	1	1	0	0	0
C3	1	1	1	1	0	0	0
C4	1	1	1	1	0	0	0
C5	1	1	1	1	0	0	0
C6	1	1	1	1	0	0	0
C7	0.98	1	1	1	0.01	0.02	0
C8	1	1	1	1	0	0	0
C9	1	1	1	1	0	0	0
C10	1	1	1	1	0	0	0
C11	1	1	1	1	0	0	0
C12	1	1	1	1	0	0	0
C13	1	1	1	1	0	0	0
C14	1	1	1	1	0	0	0
C15	1	1	1	1	0	0	0
C16	1	1	1	1	0	0	0
C17	1	1	0.98	1	0.01	0	0.02
C18	1	1	1	1	0	0	0
Mean (SD)	1 (0.006)	1 (0)	1 (0.006)	1 (0)	0.001 (0.004)	0.001 (0.005)	0.001 (0.005)

Ctrl=control; SD= Standard deviation
Note: Left invalid trials = when attention had to shift from left side of representational space to right side of visual space to detect target.

Appendix B: Chapter 4

Supplementary Group Data Analysis

The Shopping Mall Group Analyses: Since the Shopping Mall was administered to patients and controls, a mixed ANOVA was conducted to assess if there was any significant interaction effect of group (controls, patients), scoring method (SId, SIdLoc) and perspective (viewer-independent, viewer-dependent) on LQ scores. This ANOVA did not show any significant interaction effect of group, scoring method and perspective on LQ, F (1, 33) = 0.15, p = 0.7, η_p^2 = 0.005, indicating that at the group level, performance on the task was not significantly different between patients and controls regardless of type of scoring or perspective being considered. The only significant finding from this analysis was an overall effect of perspective on LQ, F(1,33)=7.9, p=0.008, η_p^2 = 0.19 indicating a slight rightward bias in shop report for viewer-independent perspective (LQ *mean* (*SE*)= -1.1 (0.9)) and a left sided bias when reporting shops from imagery for viewer-dependent perspective (LQ *mean* (*SE*)=5.7 (2.1)) (see Chapter 3, section 3.2.6 for discussion on representational pseudoneglect based on elderly controls' shop report).

Clock Cueing Group Analyses: At the group level, a mixed ANOVA was conducted to test if RTs or proportion of targets detected were significantly different based on group (controls, patients) and validity effect indices (OVE, RVE, LVE). The ANOVA showed a significant interaction between group and validity effect index as modulating RTs, F(1,29)= 4.8, p=0.04, η_p^2=0.14 implying that RTs to targets were significantly different for valid and invalid trials between groups, depending on whether overall, right side or left sided cueing in imagery space was being considered. However, independent t-tests did not show any significant difference between controls and patients for OVE, $t(16.4) = -1.1$, $p=0.29$, *Cohen's d*=0.42, RVE, $t(14.1)=-1.5$, $p=0.16$, *Cohen's d*=0.57, or LVE, $t(29)= -0.2$, $p= 0.84$, *Cohen's d*=007. No significant interaction between group and validity effects was seen to modulate target detection, $p>0.05$.

Table 4a. Patient demographics and lesion side

Patient	Lesion hemisphere	Age (years)	Gender	Handedness
DR	**R**	**79**	**M**	**R**
MD	R	73	M	R
EL	R	63	M	R
JB	R	66	M	R
AR	R	76	F	R
MG	**R**	**70**	**F**	**R**
EH	**R**	**67**	**M**	**R**
AT	R	44	M	R
PF	R	73	M	R
LB	L	45	F	R
JH	L	54	F	R
KP	L	88	F	R
RR	L	31	M	R
PH	L	41	M	R
NB	B	54	M	L

L = Left, R = Right, B = Bilateral; M = Male, F = Female; Highlighted patients are those identified with RN on the tasks.

Table 4b. All patients' shop report and LQs for Shop identity (SId)

Shop Identity scores (SId)										
Patient ID	Left		Right		Viewer- independent scores			Viewer- dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
DR	3	4	5	5	**7**	**10**	**-17.65***	9	8	5.88
MD	10	9	10	10	19	20	-2.56	19	20	-2.56
EL	6	9	9	7	15	16	-3.22	18	13	16.13
JB	10	10	10	10	20	20	0	20	20	0
AR	10	9	9	10	19	19	0	18	20	-5.26
MG	6	8	8	6	14	14	0	16	12	14.28
EH	5	6	6	2	**11**	**8**	**15.79***	**12**	**7**	**26.32***
AT	10	9	9	10	19	19	0	18	20	-5.26
PF	4	8	6	8	12	14	-7.69	14	12	7.69
LB	7	8	7	7	15	14	3.45	15	14	3.45
JH	10	10	10	10	20	20	0	20	20	0
KP	9	5	8	6	14	14	0	13	15	-7.14
RR	10	10	10	10	20	20	0	20	20	0
PH	8	9	10	9	17	19	-5.56	19	17	5.56
NB	5	5	5	6	10	11	-4.76	10	11	-4.76
Mean (SD) Ctrls *n*=20	8.25 (1.55)	9.05 (1.15)	8.85 (1.46)	8.35 (1.35)	17.3 (2.45)	17.2 (2.5)	0.33 (3.44)	17.9 (2.53)	16.6 (2.85)	3.94 (7.5)

**p ≤ 0.005 and patient's LQ is worse than the worst control performance being compared to.*
Ctrls = Controls; SD = Standard Deviation
*LQ = ((left shops-right shops)/ (left shops+ right shops)) *100*
Maximum score for each of left and right, top and bottom shop report was 10. Thus, total shops reported from the left and right each for viewer-independent and viewer-dependent scoring was out of 20.

Table 4c. All patients' shop report and LQ for Shop identity+ location (SIdLoc)

Shop Identity + Location scores (SIdLoc)										
Patient ID	Left		Right		Viewer- independent scores			Viewer- dependent scores		
	Top	*Bottom*	*Top*	*Bottom*	*Total left*	*Total right*	*LQ*	*Total left*	*Total right*	*LQ*
DR	2	4	5	4	**6**	**9**	**-20***	9	6	20
MD	10	9	10	10	19	20	-2.56	19	20	-2.56
EL	6	9	9	7	15	16	-3.23	18	13	16.13
JB	10	10	10	10	20	20	0	20	20	0
AR	10	10	10	10	20	20	0	20	20	0
MG	4	4	5	5	8	10	-11.11	9	9	0
EH	0	5	6	1	5	7	-16.67	**11**	**1**	**83.33***
AT	10	9	9	10	19	19	0	18	20	-5.26
PF	2	5	4	3	7	7	0	9	5	28.57
LB	5	8	5	7	13	12	4	13	12	4
JH	10	10	10	10	20	20	0	20	20	0
KP	9	5	6	6	14	12	7.69	11	15	-15.38
RR	10	10	10	10	20	20	0	20	20	0
PH	8	9	10	9	17	19	-5.56	19	17	5.56
NB	3	5	2	6	8	8	0	7	9	-12.50
Mean (SD) Ctrls *n*=20	6.25 (2.63)	7.4 (2.06)	7.1 (2.47)	6.65 (2.35)	13.65 (4.34)	13.75 (4.58)	-0.14 (8.9)	14.5 (4.27)	12.9 (4.89)	7.04 (12.93)

**p ≤ 0.05 and patient's LQ is worse than the worst control performance being compared to*
Ctrls = Controls; SD = Standard Deviation
*LQ = ((left shops-right shops)/ (left shops+ right shops)) *100*
Maximum score for each of left and right, top and bottom shop report was 10. Thus, total shops reported from the left and right each for viewer-independent and viewer-dependent scoring was out of 20.

Table 4d. All patients' Clock Cueing reaction time results

Patient ID	Left cue- left target	Left cue- right target	Right cue- right target	Right cue- left target	All invalid trials	All valid trials	Overall validity effect (OVE)	Right validity effect (RVE)	Left validity effect (LVE)
DR	717.83	759.67	715.28	751.22	755.45	716.56	38.89	35.94	41.84
MD	377.78	473.49	396.56	524.57	499.03	387.17	111.86	128.00	95.71
EL	949.93	1611.00	903.16	1810.10	1710.55	926.55	**784.00***	**906.94***	**661.07***
JB	554.33	777.83	498.24	628.15	702.99	526.29	176.70	129.90	223.50
AR	1073.92	1077.25	624.83	996.09	1036.67	849.37	187.30	371.25	3.34
MG	1445.42	1848.23	1323.20	2461.85	2155.04	1384.31	**770.73***	**1138.65***	402.81
EH	1867.11	2106.49	1229.73	2399.21	2252.85	1548.42	**704.43***	**1169.48***	239.38
AT	394.57	429.79	398.55	458.97	444.38	396.56	47.82	60.42	35.22
PF	635.29	916.44	789.05	1073.67	995.05	712.17	282.88	284.62	281.15
LB	503.59	667.23	505.91	528.13	597.68	504.75	92.93	22.22	163.64
JH	517.24	490.35	575.50	556.02	523.19	546.37	-23.18	-19.48	-26.88
RR	432.08	398.96	447.55	416.51	407.73	439.82	-32.08	-31.04	-33.12
PH	623.07	596.67	678.41	512.50	554.58	650.74	-96.15	-165.91	-26.40
Mean (SD) Ctrls *n*=18	539.61 (161.26)	684.55 (264.21)	532.54 (168.79)	648.07 (259.36)	666.31 (258.49)	536.07 (163.01)	130.24 (157.84)	115.53 (159.87)	144.94 (168.98)

$^*p \leq 0.001$
Ctrls = Control; SD = Standard Deviation
All RTs are in milliseconds.

Table 4e. All patients' Clock Cueing target detection results

Patient ID	Left cue- left target	Left cue- right target	Right cue- right target	Right cue- left target	All invalid trials	All valid trials	Overall validity effect (OVE)	Right validity effect (RVE)	Left validity effect (LVE)
DR	1	1	1	1	1	1	0	0	0
MD	1	1	1	1	1	1	0	0	0
EL	0.98	1	1	1	1	0.99	0.01	0	0.02
JB	1	1	1	1	1	1	0	0	0
AR	0.98	1	0.96	1	1	0.97	**0.03***	**0.04***	**0.02***
MG	1	1	1	1	1	1	0	0	0
EH	1	1	1	1	1	1	0	0	0
AT	1	1	1	1	1	1	0	0	0
PF	1	1	1	0.93	1	1	0	-0.07	0
LB	1	1	1	1	1	1	0	0	0
JH	1	1	1	1	1	1	0	0	0
RR	1	1	1	1	1	1	0	0	0
PH	1	1	1	1	1	1	0	0	0
Mean (SD) Ctrls *n*=18	1 (0.006)	1 (0)	1 (0.006)	1 (0)	1 (0)	1 (0.004)	0.001 (0.004)	0.001 (0.005)	0.001 (0.005)

$*p \leq 0.001$
Ctrls = Control; SD = Standard Deviation

Table 4f. Representational neglect patients' results on the ancillary test battery

Domain	Task	Controls Scores	Patient Score	Stats/Percentile	Interpretation
Visual Neglect	Hearts Cancellation	Controls: *Avg* = 47.94, *SD* = 2.99 *n=15, Avg age (SD)= 69.27 (8.24), 6 males*	EH: 50	$t(14) = -0.306$, NS	Unimpaired
			MG: 49 (1 omission left)	$t(14) = 0.354$, NS	Unimpaired
			DR: 49 (1 omission left)	$t(14) = 0.345$, NS	Unimpaired
Imagery	Colour Task	Controls: *Avg* = 18.79, *SD* = 1.58 *n=19, Avg age (SD)= 70.56 (6.27), 4 males*	EH: 19	$t(18) = 0.130$, NS	Unimpaired
			MG: 19	$t(18) = 0.130$, NS	Unimpaired
			DR: 15	$t(18) = -2.332$, $p = 0.031$	Impaired
	Bigger/ Smaller Task	Controls: *Avg* = 14.72, *SD* = 0.96 *n=18, Avg age (SD)= 71.72 (6.53), 4 males*	EH: 15	$t(17) = 0.282$, NS	Unimpaired
			MG: 14	$t(17) = -0.733$, NS	Unimpaired
			DR: 14	$t(17) = -0.733$, NS	Unimpaired
	Tails Task	Controls: *Avg* = 19.74, *SD* = 1.41 *n=19, Avg age(SD)= 70.56 (6.27), 4 males*	EH: 17	$t(18) = -1.894$, NS	Unimpaired
			MG: 15	$t(18) = -3.277$, $p = 0.004$	Impaired
			DR: 16	$t(18) = -2.585$, $p = 0.019$	Impaired
Mental rotation	Letter Rotation Task	Controls: *Avg* = 18.5, *SD* = 1.51 *n=17, Avg age(SD)= 70 (5.49), 4 males*	EH: 12	$t(16) = -4.188$, $p < 0.001$	Impaired
			MG: 13	$t(16) = -3.544$, $p = 0.003$	Impaired
			DR: 19	$t(16) = 0.322$, NS	Unimpaired

Domain	Task	Controls Scores	Patient Score	Stats/Percentile	Interpretation
Visuospatial memory	Location Learning Test		Norms derived from test manual		
	Immediate Recall		EH: 0.29	35-50	Normal
			MG: 0.46	65 - 75	Above avg
			DR: 0.74	> 98	Above avg
	Delayed Recall		EH: -5	< 2	Impaired
			MG: 0	> 65	Above avg
			DR: 0	> 65	Above avg
	Spatial span task		Norms derived from WMS-R		
	Forward		EH: 6	20	Below avg
			MG: 6	20	Below avg
			DR: 7	44	Normal
	Backward		EH: 3	4	Impaired
			MG: 4	16	Below avg
			DR: 6	62	Normal
Visual memory	Shapes test from Doors & People test battery		Norms derived from test manual		
	Immediate Recall		EH: 6 (age-scaled score)	10 - 25	Below avg
			MG: 5 (age-scaled score)	5 - 10	Below avg
			DR: 8 (age-scaled score)	25	Below avg
	Delayed Recall		EH: 11 (age-scaled score)	75	Above avg
			MG: 9 (age-scaled score)	25	Below avg
			DR: 13 (age-scaled score)	90	Above avg

Avg = Average; SD = Standard Deviation

Appendix C: Chapter 5

Table 5a. Group data on line bisection and cancellation indices

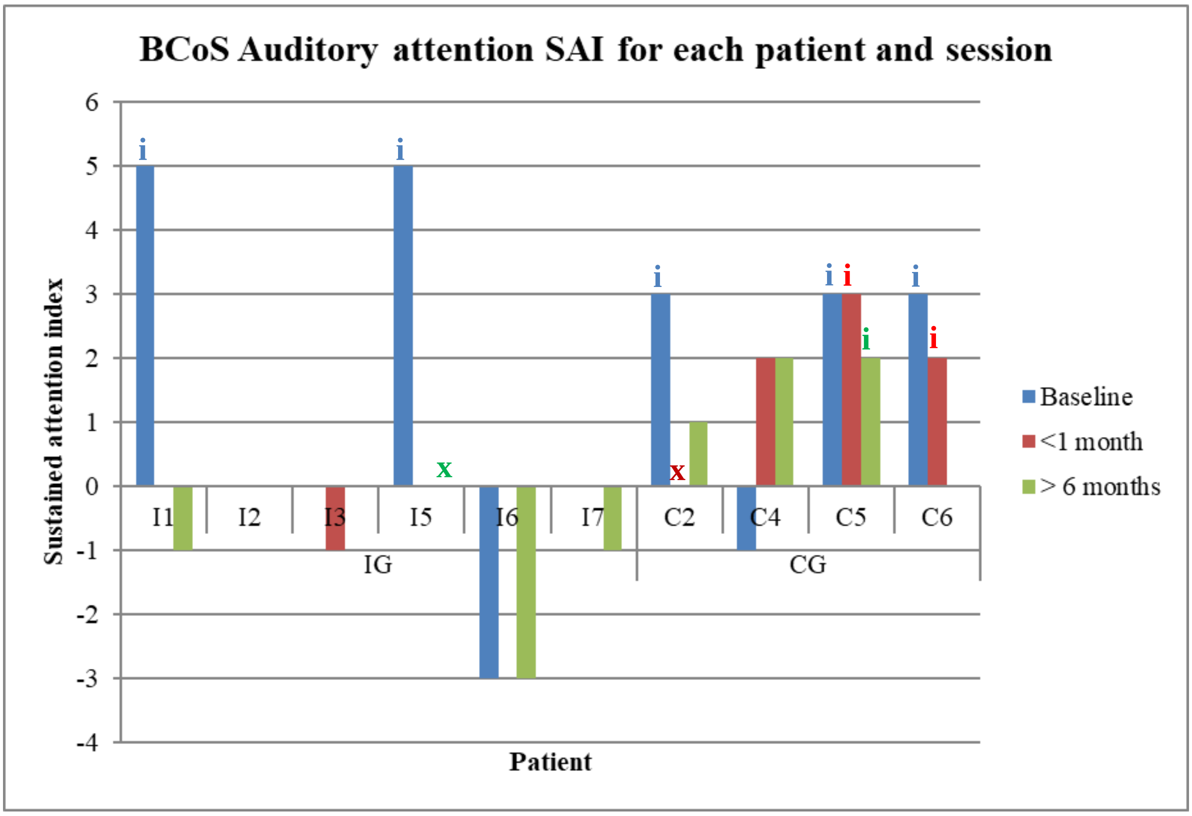
	Intervention Group					Control Group				
	Baseline Mean (SD)	Pre rTMS 1 Mean (SD)	Post rTMS 6 Mean (SD)	< 1 month Mean (SD)	6 months Mean (SD)	Baseline Mean (SD)	Pre rTMS 1 Mean (SD)	Post rTMS 6 Mean (SD)	< 1 month Mean (SD)	6 months Mean (SD)
Line Bisection deviation (range=-1 to +1)										
Long lines	0.1(0.2)	Na	Na	0.09(0.2)	-0.01(0.1)	0.02(0.5)	Na	Na	0.19(0.2)	-0.05(0.5)
Medium lines	0.14(0.4)	Na	Na	-0.04(0.08)	0.01(0.1)	0.04(0.3)	Na	Na	0.11(0.3)	-0.1(0.5)
Short lines	-0.2(0.1)	Na	Na	-0.2(0.2)	-0.12(0.1)	-0.4(0.5)	Na	Na	-0.24(0.2)	-0.34(0.5)
Left lines	0.05(0.1)	Na	Na	0.001(0.09)	-0.02(0.06)	-0.06(0.3)	Na	Na	0.02(0.1)	-0.14(0.4)
Right lines	-0.02(0.1)	Na	Na	-0.1(0.1)	-0.06(0.05)	-0.13(0.3)	Na	Na	0.01(0.2)	-0.19(0.4)
Overall deviation	0.13(0.04)	Na	Na	-0.05(0.08)	-0.04(0.06)	-0.1(0.28)	Na	Na	0.02(0.14)	-0.16(0.41)
Cancellation										
Spatial asymmetry	4.75(7.2)	7(7.4)	7.38(9.7)	2.5(7.8)	5(7.5)	7.83(3.9)	11.33(5.4)	5.33(10.5)	13(2/3)	11(6.5)
Object asymmetry	2.25(2.4)	3.38(5.9)	2.25(3.2)	1.62(2.4)	3.5(8)	5.83(5.5)	3.5(5.6)	2.17(3.9)	5.67(6.1)	4.2(2.6)
Centre of cancellation	0.35(0.4)	0.33(0.3)	0.27(0.3)	0.18(0.3)	0.14(0.2)	0.45(0.3)	0.54(0.3)	0.43(0.4)	0.58(0.1)	0.47(0.3)

Table 5b. Individual patient's change in ADL scores for each sub-domain between time points

		Personal neglect						Peripersonal neglect								Extrapersonal neglect	
	Domain	Face creaming		Hair combing		Address copying		Telephone dialling		Form filling		Tray assembling		Coin counting		Clock reading	
Group	Patient	1m-base	6m-base	1m-base	6m-base	1m-base	6m-base	1m-base	6m-base	1m-base	6m-base	1m-base	6m-base	1m-base	6m-base	1m-base	6m-base
IG	I1	0	0	0	0	+1	0	0	0	0	0	+1	+1	0	0	0	0
	I2	0	0	0	0	+1	+1	0	0	0	0	0	0	0	0	0	0
	I3	0	0	+1	+1	0	0	0	0	0	0	0	0	0	0	0	0
	I4	0	-1	+1	0	0	0	+1	+1	+1	+1	+1	+1	0	-1	0	+1
	I5	0	na	0	na	0	na	0	na	+0.5	Na	0	na	0	na	0	na
	I6	0	0	0	0	+1	0	0	0	+1	+1	+1	+1	0	0	0	0
	I7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CG	C1	0	na	0	na	0	na	0	na	0	Na	0	na	0	na	0	na
	C2	0	0	+1	+1	0	0	-1	-1	0	0	0	0	-1	0	0	-1
	C3	0	na	0	na	0	na	0	na	+1	Na	0	na	0	na	+1	na
	C4	+1	0	-1	0	0	+0.5	0	+1	+0.5	+0.5	0	+1	0	0	0	+1
	C5	0	0	0	0	0	-1	0	0	-1	0	0	0	0	0	0	0
	C6	0	0	0	-1	0	0	0	0	0	+1	+1	+1	0	0	0	-0.5

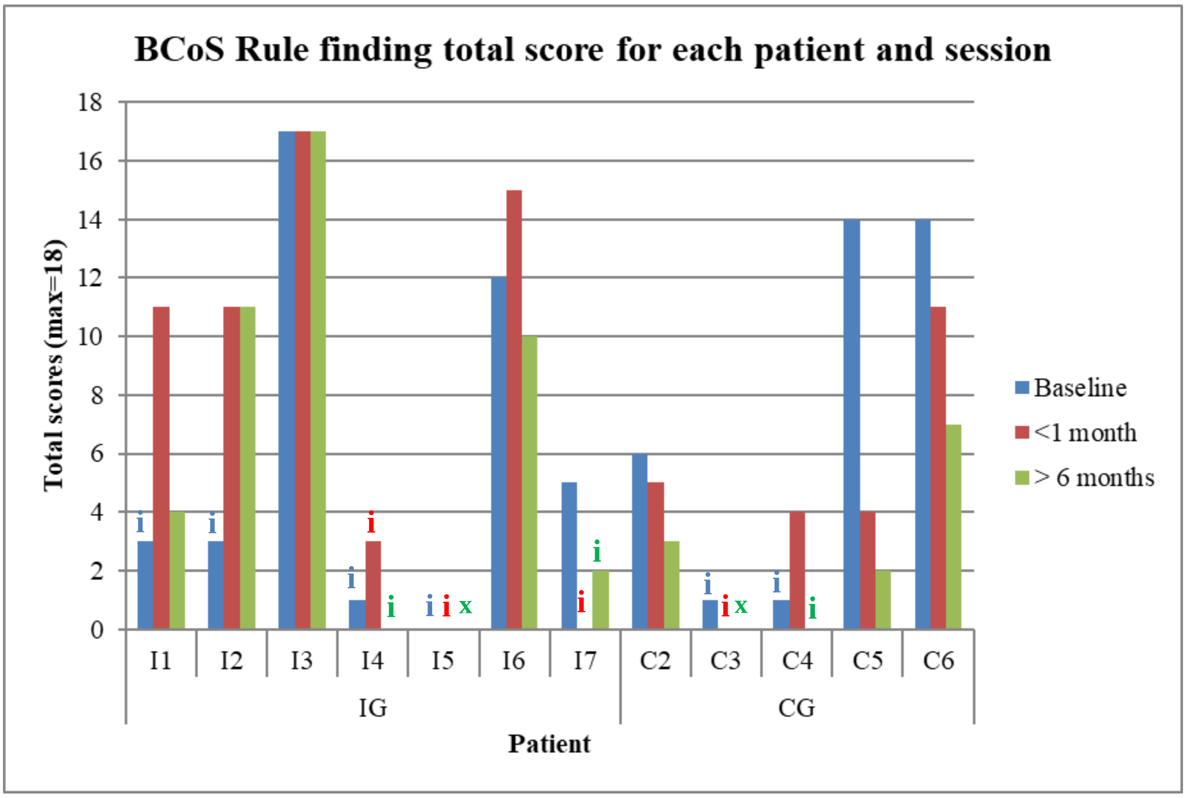
IG: Intervention Group; CG: Control Group; na: Not available as patient passed away; Base: Baseline; 1m: < 1 month; 6m: > 6 months.
This table depicts each patient's change in direction and magnitude of performance between baseline and <1 month and baseline and >6 months for each domain. A positive sign indicates an improvement, 0 indicates no change and negative sign implies deterioration in performance in that sub-domain when compared to baseline.

Figure 5a. BCoS performance on Sustained attention index



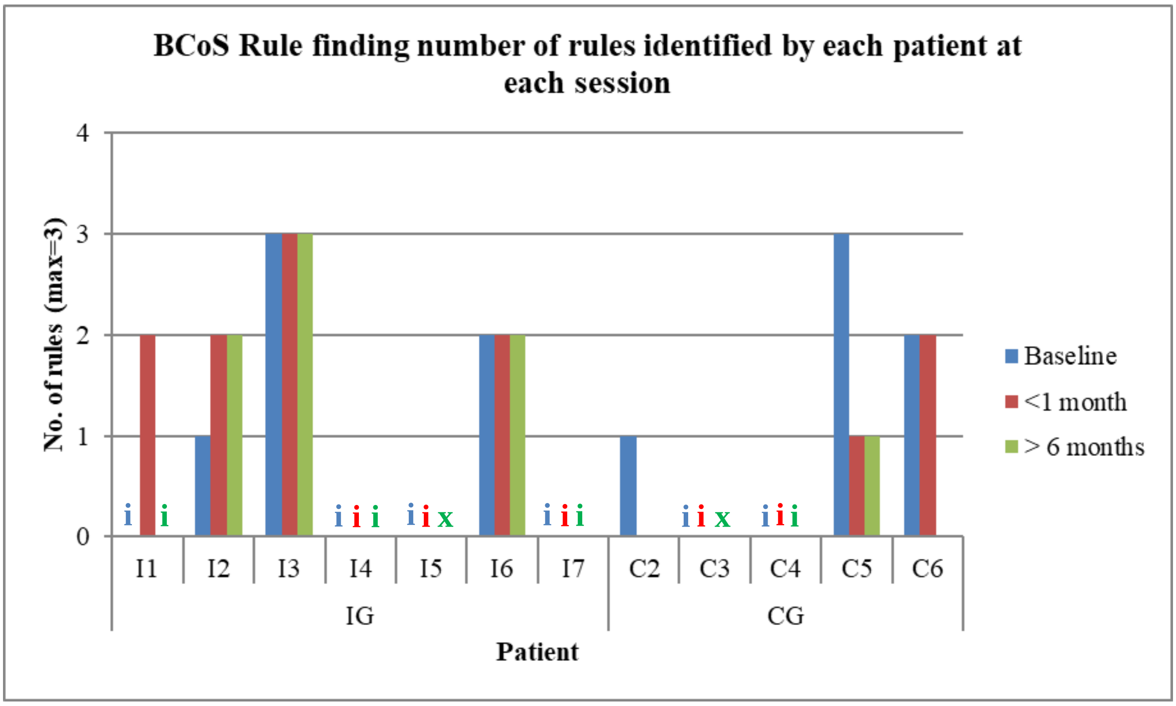
SAI = number correct in block 1- number correct in block 3
IG: Intervention Group, CG: Control Group
When data from the test was unavailable at a certain time point, this is shown by an 'x' in the colour corresponding to the time of testing, i.e. blue=baseline; red=<1 month; green=>6 months.
Scores in the impaired range are shown with similar colour corresponding 'i'; based on BCoS cut-offs (age ≤ 74: > 1, age ≥ 75: > 2)
A negative score in SAI implies that the patient had better performance in the third block than the first.
Both impaired IG patients (I1, I5) improved post rTMS. In CG, 2 of the impaired patients improved > 6 months post rTMS (C2, C6) while 1 patient remained impaired at all time points (C5).

Figure 5b. BCoS Rule finding performance on total scores



IG: Intervention Group, CG: Control Group
When data from the test was unavailable at a certain time point, this is shown by an 'x' in the colour corresponding to the time of testing, i.e. blue=baseline; red=<1 month; green=>6 months.
Scores in the impaired range are shown with similar colour corresponding 'i'; based on BCoS cut-offs age ≤ 64: accuracy < 6; 65-74: accuracy < 5; ≥ 75: accuracy < 4
In the IG, 4 patients were impaired (I1, I2, I4, I5) and of them, 2 improved post rTMS (I1, I2).
In the CG, 2 patients were impaired at baseline (C3, C4) and while 1 patient (C4) improved in the short term, he did not sustain this improvement in the long term

Figure 5c. BCoS Rule finding performance on number of rules identified



IG: Intervention Group, CG: Control Group
When data from the test was unavailable at a certain time point, this is shown by an 'x' , this is shown by an 'x' in the colour corresponding to the time of testing, i.e. blue=baseline; red=<1 month; green=>6 months.
Scores in the impaired range are shown with similar colour corresponding 'i'; based on BCoS cut-off of < 1 rule for all age groups.
In the IG, 4 patients (I1, I4, I5, I7) were impaired at baseline and of them, only I1 improved and that too only at < 1 month post rTMS follow-up.
In the CG, 2 patients were impaired (C3, C4) and neither of them improved in rule finding across sessions

Appendix D: Chapter 6

Behavioural Pilot

In order to test that the task adaptation was appropriate for use in the main fMRI experiment, a behavioural pilot was administered with two neglect patients. Details of the task adaptation are given in Chapter 6, section 6.2.3.2.

Two patients (CN and NJ) were recruited for the pilot. Patient CN was the first case (I1) to participate in the clinical trial reported in Chapter 5. She was a 78 year old woman with right parietal haemorrhage and when conducting the pilot was in the sub-acute stage at 17 days post stroke. Although she completed the behavioural study, she was unable to complete the fMRI scan due to claustrophobia. NJ was a 57 year old male with lesions incorporating right posterior parietal and occipital lobes and was tested 1 year, 5 months post stroke. He declined from participating in the clinical trial, but was happy to complete the behavioural pilot of the task. Both patients gave informed consent in keeping with the ethical protocol approved by the U.K National Research Ethics Committee and the guidelines set out in the Declaration of Helsinki.

CN identified 83% of the ‘red’ targets at fixation accurately, while NJ identified 96% of the targets accurately. Neither patient had any false positive responses during target detection. In comparison, results from the study by Vuilleumier and colleagues, showed that their two participants performed at 96% and 90% accuracy (Vuilleumier et al., 2008).

The behavioural pilot was done to check if the adaptation of the original task engaged attention and was comparable to the behavioural performance of patients from the original study. The current behavioural pilot showed that the task was not too easy for the patients despite the adaptation intended to simplify the task, given that neither patient performed at ceiling. This also implied that the task recruited attentional resources because while there were no false alarms noted, both patients missed targets during monitoring of the central string of stimuli for the ‘red’ target. Hence, the target detection of the two patients with strokes involving the parietal lobe in this study was comparable to the behavioural performance of the two parietal stroke patients in the original study. Based on these behavioural results, this task was considered appropriate for use in the main experiment.

Appendix E: Chapter 7

Table 7a: Correlation matrix of cognitive variables included in the study

Variables	Visual extinction	Tactile extinction	Sustained attention	Global processing	Local Processing	Spatial Relations	Spatial Neglect	Object Neglect
Visual extinction	1	.26*	0.11	-.31*	-.33*	-.35*	.36*	.33*
Tactile extinction	.26*	1	.13*	-.17*	-.17*	-.21*	.26*	.24*
Sustained attention	0.11	.13*	1	-.13*	-.22*	-.26*	0.06	.2*
Global processing	-.31*	-.17*	-.13*	1	.79*	.79*	-.22*	-.23*
Local processing	-.33*	-.17*	-.22*	.79*	1	**.85***	-.34*	-.39*
Spatial Relations	-.35*	-.21*	-.26*	.79*	**.85***	1	-.33*	-.32*
Spatial Neglect	.36*	.26*	0.06	-.22*	-.34*	-.33*	1	.3*
Object Neglect	.32*	.24*	.2*	-.23*	-.39*	-.32*	.3*	1

**p<0.05; Pearson correlations were done for continuous variables and Point Biserial correlations were done where discrete dichotomous nominal variables were involved (visual and tactile extinction, spatial and object neglect). Since local processing and spatial relations of the complex figure copy correlation was >0.8, these variables were used in different regression models.*

Table 7b. VIF and tolerance values to assess multicollinearity between predictors

Cognitive Predictors	VIF	Tolerance
Visual extinction	1.2	0.84
Tactile extinction	1.1	0.91
Global processing	3.2	0.32
Local processing	4.04	0.25
Spatial relations	4.3	0.23
Sustained attention index	1.1	0.91

VIF: Variance inflation factor
For multicollinearity, VIF>10, Tolerance <0.1 (Field, 2009)