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Action and rehabilitation in hemispatial neglect

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A thesis submitted in fulfilment of the requirements for the Degree

of Doctor of Philosophy

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Abstract

Milner and Goodale (1995, 2006) propose a model of vision that makes a distinction between 'vision for perception' and 'vision for action'. Regarding hemispatial neglect, they, somewhat contentiously, hypothesize that this disorder is better explained by damage to a high-level representational structure that receives input from the ventral visual stream, but not from the dorsal-stream. Consequently, they postulate that neglect patients should code spatial parameters for action veridically. Another strong claim of the model is that the dorsal stream's control of action is designed for dealing with target stimuli in the 'here and now', yet when time is allowed to pass and a reaction has to be made on the basis of a visual memory, the ventral stream is required for successful performance. One prediction from this is that neglect patients should be able to perform immediate actions, but should present specific impairments when the action is delayed.

In Part I of this thesis the pattern of spared and impaired visuomotor abilities in patients with neglect, as specifically predicted by the perception and action model (Milner & Goodale, 1995, 2006), was investigated. In Chapter 1, the performance of patients with and without neglect after right hemisphere stroke was compared with that of age-matched controls. Participants were asked to point either directly towards targets or halfway between two stimuli (gap bisection), both with and without visual feedback during movement. No neglect-specific impairment was found in timing, accuracy or reach trajectory measures in either pointing or gap bisection. In Chapter 2, I tested whether

neglect patients would be unimpaired in immediate pointing, yet show inaccurate pointing in a condition where a delay is interposed between the presentation of the stimulus and the response signal. Similarly to Chapter 1, it was found that neglect patients showed no accuracy impairments when asked to perform an immediate action. Conversely, when pointing towards remembered leftward locations they presented specific accuracy deficits that correlated with neglect severity. Moreover, an **initial** voxel-based lesion-symptom analysis further revealed that these deficits were associated with damage to occipito-temporal areas which were also mostly damaged in the neglect group.

Furthermore, training of grasping the centre of rods (visuomotor feedback training) has been shown to improve neglect (Robertson, Nico & Hood, 1997; Harvey *et al.*, 2003). It is postulated that by using the spared visuomotor abilities in these patients it is possible to 'bootstrap' their perceptual deficits through some 'dorsal-to-ventral recalibration'. Hence, in Part II the immediate and long-term effects of visuomotor feedback training were explored on neglect conventional measures, as well as in daily life tasks. I found that this technique improves neglect symptoms and crucially that these improvements were long lasting, as they were present even after 4-months post-training. Importantly, I also show that the training effects generalize to the patient's daily lives at follow-up. These findings are very encouraging for the rehabilitation of neglect as this condition has been shown to be the best single predictor of poor recovery after stroke and very difficult to treat.

Declaration

I declare that this thesis represents my own work except unless indicated in the text and that it does not include work forming part of a thesis presented for another degree.

_____

Stéphanie Rossit

Para o avô Aldo Rossit

(de quem toda a família Rossit sente muita falta)

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The findings reported in Chapter 1 are in press:

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The findings reported in Chapter 2 have been published or in press:

Rossit, S., Muir K., Reeves, I., Duncan, G., Birschel, P. & Harvey, M. (2009). Immediate and delayed reaching in hemispatial neglect. *Neuropsychologia*, *47*, 1563-72.

Rossit, S., Malhotra, P., Muir, K., Duncan, G., Reeves, I. Birschel, P. & Harvey, M. (in press). The neural basis of visuomotor deficits in hemispatial neglect. *Neuropsychologia*, DOI:10.1016/j.neuropsychologia.2009.04.015

In addition, this research has been presented at the annual meetings of the Vision Sciences and Cognitive Neuroscience Societies in 2008 and subsequently published as abstracts:

Harvey, M., Muir, K., Reeves, I., Duncan, G., Livingstone, K., Jackson, H., Castle, P. & Rossit, S. (2008). Pointing and bisection in open and closed loop reaching in patients with hemispatial neglect. *Journal of Vision*, *8*, 305.

Rossit, S., Muir, K., Duncan, G., Reeves, I., Livingstone, K., Clark, H., Castle, P., & Harvey, M. (2008). Pointing to the past in patients with hemispatial neglect. *Supplement of the Journal of Cognitive Neuroscience*, *68*.

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Part I: Action in hemispatial neglect

General Introduction

Symptomatology and incidence of hemispatial neglect

Around the world more than 15 million people suffer from a stroke each year and hemispatial neglect affects up to 70% of such patients (e.g., Bowen, McKenna & Tallis, 1999; Stone *et al.*, 1993). This disorder is classically defined as an inability to spontaneously report, respond or orient towards events on the contralesional side of space with either eye or limb movements. Moreover, the disorder cannot be attributed to sensory (i.e., hemianopia) or motor (i.e., hemiplegia) dysfunctions (Heilman, 1979). For example, severe neglect patients may behave as if the left side of the world ceased to exist (Mesulam, 1981), failing to eat food on the left side of their plate and ignoring people or objects on their left. It has been shown that this disorder is more persistent and severe amongst right hemisphere damaged patients (e.g., Stone *et al.*, 1992). Additionally, it has also been reported that hemispatial neglect is the single best predictor of poor functional recovery from stroke and is notoriously difficult to rehabilitate (Buxbaum *et al.*, 2004; Gillen, Tennen & McKee, 2005; Katz *et al.,* 1999).

Several subtypes of neglect have been described, which are not mutually exclusive and may vary from patient to patient (for a recent review see Heilman, Watson & Valenstein, 2002; and see Vallar, 1998 for a proposed taxonomy). Neglect may affect the contralesional body (personal neglect),

contralesional space within reaching distance (peripersonal neglect), or space beyond the reaching space (extrapersonal neglect). Spatial neglect may occur in all three axes of space (horizontal, vertical, radial) and occur in different frames of reference (body-centred, object-centred or environmentally-centred). Also, neglect may be accompanied by a number of other associated phenomena like anosognosia (denial of symptoms), anosodiaphoria (indifference to illness or disability) and extinction of contralesional stimuli. Additionally, non-lateralized deficits (e.g., in sustained attention, phasic alerting, spatial working memory) may be prominent and have an important influence on neglect severity and persistence (Husain & Rorden, 2003). Hence it is not surprising that, nowadays, hemispatial neglect is viewed as a complex heterogeneous syndrome, and not as a single condition (e.g., Husain & Rorden, 2003; Milner & McIntosh, 2005; Robertson, 2001).

Anatomy of hemispatial neglect

Numerous studies have examined the neural basis of neglect in humans, but this matter has recently become the subject of much controversy (Marshall *et al*., 2002; Karnath & Himmelbach, 2002). Heilman *et al.* (1983) were the first to conduct an anatomical study using computerized tomography (CT) scans with 10 neglect patients. It was observed that the overlap of the lesions was located in the inferior parietal lobule (IPL; see Figure 1) and temporo-parietal-occipital (TPO) junction. In a later study Vallar and Perani (1986), who analysed 16 CT scans of neglect patients found that in six patients the lesions were centered in the parietal-occipital junction and in eight patients the overlap was in the supramarginal gyrus of the IPL. These findings have been replicated by other

subsequent investigations (Halligan *et al.*, 2003; Leibovitch *et al.*, 1998, 1999; Perenin, 1997; Samuelsson *et al.*, 1997; Vallar, 1993, 2001). However, recently the traditional view that neglect is more common after damage at the TPO junction has been challenged by a controversial study carried out by Hans-Otto Karnath and his research group (Karnath, Ferber & Himmelbach, 2001). These authors argued that previous investigations included patients who presented concomitant primary defects in their visual field and thus the lesions overlapped posteriorly. Karnath, Ferber and Himmelbach (2001) reported that the maximum overlap in 25 'pure' left neglect patients (i.e., without concomitant visual field deficits) laid in the middle part of the superior temporal gyrus (STG; see Figure 1) and not in the TPO junction area (when compared to lesions of 25 patients without the condition). Moreover, they then compared the lesions of 11 patients with both neglect and hemianopia to the ones of four control patients with visual field deficits, but without neglect. In line with their hypothesis they found that the centre of lesion in these patients was in the IPL involving the TPO junction area and that this damage was affected in both neglect and non-neglect patients.

Mort *et al.* (2003) criticized Karnath, Ferber and Himmelbach (2001)'s approach by arguing that their inclusion of only 'pure' neglect patients biased the results towards more anterior damage. To that end, they used higher resolution lesion mapping methods and compared magnetic resonance imaging (MRI) scans of an unselected sample of 35 stroke patients (19 with neglect and 16 without the condition). They observed that although some of their patients presented superior temporal damage, the most critical region associated with neglect was located in the angular gyrus, on the lateral surface of the IPL, and in the parahipppocampal gyrus. Nonetheless, in a later large-group study

Karnath *et al.* (2004) refuted Mort *et al.* (2003)'s conclusions. In their study Karnath *et al.* (2004) included a large unselected sample of 140 stroke patients, 78 with neglect and 62 control patients without the disorder. In agreement with their previous study, Karnath *et al.* (2004) found that the region of maximal overlap in neglect patients was located in the right superior temporal cortex, the insula and subcortically the putamen and the caudate nucleus.

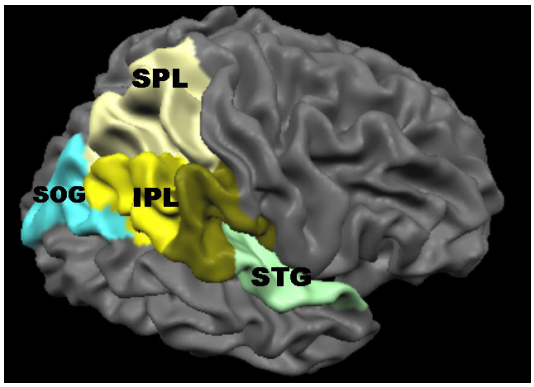

Figure 1. Right hemisphere of the human brain, with the different brain areas located nearby neglect-associated sites coloured. Abbreviations: SOG-superior occipital gyrus; SPL-superior parietal lobe; IPL-inferior parietal lobe (composed of the supramarginal gyrus, which surrounds the lateral sulcus, and the angular gyrus, which is inferior to the intraparietal sulcus and is located at the end of the superior temporal sulcus); STG-superior temporal gyrus. The Brain surface was created with Brainvoyager Brain Tutor free software.

The lack of agreement between these different studies could be due to a number of factors such as different proportion and types of neglect patients included, and differences in the measures used for neglect diagnosis (e.g., Milner & McIntosh, 2005). For example, whereas Karnath *et al.* (2004) used cancellation tasks, Mort *et al.* (2003) additionally applied line bisection. Moreover, very recently Committeri *et al.* (2007) observed that different forms of neglect are associated with different lesion sites in a sample of 52 stroke

patients. Whereas personal neglect was associated with lesions in the right IPL, neglect within reaching space was associated with lesions including the STG.

There is no doubt that most neglect patients present extensive brain damage affecting more than one brain lobule and this might explain why individual patients show different patterns of neglect, depending on the distribution of damage. Therefore, further research is necessary to clarify which lesion location is most related to each form of neglect. Importantly, nowadays, new and free software tools are available to allow a more precise localization of damage than ever before (see Rorden & Karnath, 2004 for a review). Previous anatomical studies (e.g., Heilman *et al.*, 1983; Vallar & Perani, 1986) used paper-and-pencil procedures like the so-called Damasio templates (Damasio & Damasio, 1989). At present, the entire lesioned area of an individual can be used for a high-resolution analysis in Talairach space (Rorden & Brett, 2001; Talairach & Tournoux, 1988), which is also used in functional imaging studies. Therefore, in the present experiments I will take advantage of these new lesion-mapping techniques.

Theories on hemispatial neglect

Research into hemispatial neglect has expanded vastly over the last 30 years, but the causes behind this perplexing syndrome are still largely unknown. Three main theoretical hypotheses have been proposed to explain neglect, more specifically the directional motor, representational and attentional accounts (see Heilman, Watson & Valenstein, 2002 for a review). In brief, the directional motor account (e.g., Heilman & Valenstein, 1979) argues that although right hemisphere patients with neglect might perceive stimuli to their left, they have a

difficulty in initiating eye or limb movements in that direction. In this line, neglect patients have been reported to present several forms of 'action-intention' deficits: a failure to act on the contralesional space (hemispatial akinesia); a slowing of movements towards the contralesional space (directional hypokinesia); and a reduced ability to sustain an action in or towards the contralesional space (directional impersistence). Representational accounts of neglect emphasize a deficit in the stored neural representation of space, in that many patients with neglect fail to report items that appear on the contralesional side of a scene that they imagine (e.g., Bisiach & Luzzatti, 1978). In addition, some attentional models argue that neglect patients present an ipsilesional attentional bias (e.g., Heilman & Valenstein, 1972; Kinsbourne, 1970; Watson *et al.*, 1973, 1974) or are unable to disengage from stimuli in ipsilesional space and shift contralaterally (e.g., Posner *et al.*, 1984).

It is important to note that none of these explanations can fully account for the panoply of deficits presented by patients with hemispatial neglect and that they may not be mutually exclusive. Moreover, as pointed out by Husain and Rorden (2003), only a small number of studies have attempted to localize the brain regions responsible for these different deficits. Notably, the focus of recent research has been to understand if a particular deficit is indeed neglect-specific or lesion-location specific, rather than just reporting the presence or absence of a single behavioural symptom (e.g., Himmelbach, Karnath & Perenin 2007; Husain & Rorden, 2003). In other words, researchers have included control patients without neglect to test if these patients also present the pathology observed and map the neural basis behind the symptoms. This will be the approach that I will use in this thesis.

The perception and action model

More than 20 years ago Ungerleider and Mishkin (1982), stipulated a two-pathway model for visual processing in the cerebral cortex. In their pivotal paper (Mishkin, Ungerleider & Macko, 1983), the visual discrimination ability of monkeys with lesions in the inferotemporal cortex (ITC) was compared with the one of animals with damage to the posterior parietal cortex (PPC). Monkeys with ITC damage presented a profound impairment in visual pattern recognition whilst the ones with PPC damage were impaired in a landmark discrimination task. They argued that whilst lesions in the ITC perturbed the ability of the animal to perceive objects, lesions in the PPC disturbed their ability to perceive spatial relationships between those objects. Furthermore, they suggested the existence of a ventral stream projecting from the primary visual cortex (V1) to the ITC, and a dorsal stream projecting from V1 to the PPC. According to these authors the ventral stream mediates object vision, enabling the monkey to identify an object ('what' stream), while the dorsal stream mediates spatial vision, enabling the monkey to locate the object ('where' stream).

In the past, studies of visual processing were mainly concerned with object recognition, and there was little interest in how actions to objects might be effected (Goodale & Humphrey, 1998). This fascination with what and how we 'see' has meant that many other functions of vision have either been ignored or been assumed to depend on the same mechanisms that support sight (Goodale & Humphrey, 1998). Nowadays, this perspective has been altered and there has been a shift towards an understanding of how visual information is used to control and access actions to objects, in addition to comprehending recognition processes.

This shift of interest from perception to action has its roots in an influential paper by Goodale and Milner in 1992 and in two subsequent books published by these authors (Milner & Goodale, 1995, 2006). Based on evidence from neuropsychological observations in humans, as well as electrophysiological and behavioural studies in the monkey, they reviewed the argument of Ungerleider and Mishkin (1982) by focusing on the outputs the two visual streams serve. Rather than emphasizing differences in the visual information handled by the two streams, Milner and Goodale (1995, 2006)'s account focuses on the difference in the requirements of the output systems that each stream of processing serves. While their model also postulates the existence of dorsal and ventral streams for the processing of visual information in the human brain, it proposes different functions from Ungerleider and Mishkin (1982). In particular, the dorsal occipito-parietal stream is thought to process visual information dedicated to the guidance of actions ('how' stream) and the ventral occipital-temporal stream computes visual information for the purpose of perceptual tasks ('what' stream; see Figure 2). In other words, they suggest that the reason there are two visual streams is that each must transform incoming visual information for different purposes – 'vision for perception' and 'vision for action'.

According to Milner and Goodale (1995, 2006)'s perception and action model, the ventral stream provides the visual contents of our perceptual experience and codes information in an abstract form suitable for storage and for deploying on cognitive processes like imagining, recognizing, and planning. On the other hand, the dorsal stream serves the much more immediate function

of guiding our actions from moment-to-moment, and therefore needs to code information in a quick, ephemeral and viewer-specific form.

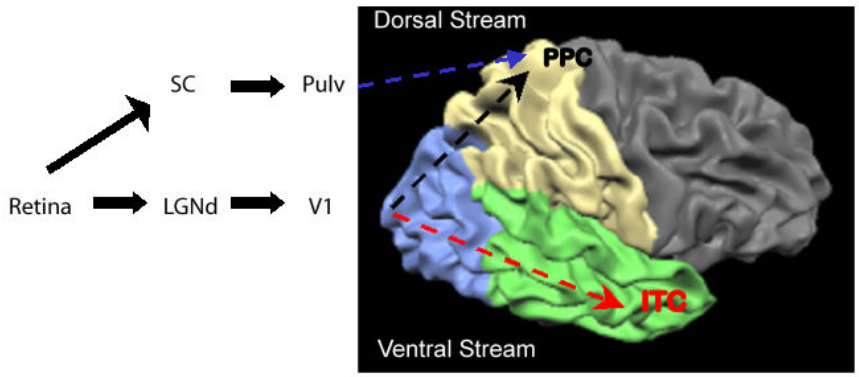

Figure 2. Diagram of the dorsal and ventral visual streams (adapted from Milner & Goodale, 1995, pp. 68). The figure shows the cortical projections on the right hemisphere of the human brain (in blue is the occipital lobe, in green the temporal lobe; in yellow the parietal lobe and in grey the frontal lobe). Abbreviations: LGNd-lateral geniculate nucleus (pars dorsalis); SC-superior colliculus; Pulv-pulvinar; PPC-posterior parietal cortex; ITC-inferior-temporal cortex. Brain surface was created with Brainvoyager Brain Tutor free software.

In addition, they suggest that the contents of the dorsal stream are probably not accessible for cognitive elaboration or conscious monitoring and that the on-line control of action requires frequently updated knowledge of the stimulus position and motion with respect to the observer. It is suggested that the dorsal stream codes the spatial location of objects in egocentric coordinates (i.e., with respect to the observer's eye, head, body or limb) in which the absolute sizes of objects are represented. In contrast, they argue that storing the position of an object in relation to the observer at one moment would not be useful for purposes of recognition or action at a later time. According to them, the most reliable form of spatial coding for such longer-term purposes would be

one that allows the triangulation with respect to stable landmarks in the environment (based on allocentric coordinates), which would depend on ventral visual stream processing. In other words, processing within the ventral stream allows us to recognise an object, while processing within the dorsal stream provides critical information so that we can accurately reach out and grasp it. Thus, their model predicts that both streams process information about object attributes, such as size, shape, orientation and spatial location, but for different purposes.

To address the question of which functional mechanisms are involved in the two visual streams, neuropsychological researchers have studied individuals who have sustained brain damage that spares one of these systems but not the other, analysing their performance in various 'perception' and 'visuomotor' tasks. Patients with bilateral dorsal stream damage are unable to reach accurately towards visual targets that they unequivocally report seeing (e.g., Perenin & Vighetto, 1988) a disorder termed optic ataxia. In contrast DF, a famous patient with visual form agnosia after bilateral damage to ventral stream areas, can reach perfectly to visual targets, but is unable to make accurate perceptual judgements (Goodale *et al.*, 1991; Milner, *et al.*, 1991; Milner & Goodale. 1995, 2006). Therefore, optic ataxia and visual form agnosia have been proposed to constitute a double dissociation, which provides the main argument for the anatomical distinction between a ventral and a dorsal visual stream and their functional distinction for perception and action. Furthermore, the evidence of intact 'action' in DF has been used to motivate the shift of interest from visual recognition processes towards the understanding of how visual information is used to control and access actions to objects.

The perception and action hypothesis for hemispatial neglect

What is compelling about Milner and Goodale's (1995, 2006) model is that it allows specific predictions to be made regarding different aspects of visuomotor control and that these in turn should be differentially affected by hemispatial neglect.

The predictions derived from the perception and action model to hemispatial neglect are mainly driven by the fact that visual information on the neglected side does not reach conscious awareness. As already mentioned, according to their model, it is the ventral visual stream that provides the contents of our visual awareness. Hence, Milner and Goodale (1995, 2006), somewhat contentiously, propose that the perceptual distortions found in patients with neglect might reflect a failure in a high-level representational structure where the products of the ventral stream processing are integrated and made use of. That is hemispatial neglect is a consequence of a disruption of an elaboration of ventral visual stream processing, rather than dorsal (Milner, 1995; Milner, 1998a, b; Milner, 1997).

Another prediction from their model is that many patients subject to distortion of spatial perception should nevertheless code spatial parameters veridically when programming goal-directed movements, since that would be accomplished by dorsal stream structures, which are presumably spared in neglect patients (Milner, 1995; Milner, 1998a,b; Milner, 1997). In agreement with these suggestions, some authors have even argued for the existence of a double dissociation between optic ataxia and hemispatial neglect (e.g., Perenin & Vighetto, 1988; Perenin, 1997). More specifically, it has been suggested that the superior part of the PPC including the intraparietal sulcus (damaged in

patients with optic ataxia) is involved in short-living, unconscious spatial representations required for specific on-line visuomotor computations. On the other hand, the lower part of the PPC, as well as the adjacent occipitotemporal regions (damaged in neglect patients), is involved in the more enduring and conscious representations underlying spatial cognition and complex spatially oriented behaviour (Perenin, 1997). Also in line with these hypotheses is that the dorsal visual stream terminates superiorly in the posterior parietal cortex (Milner & Goodale, 1995, 2006), whilst the neglect-associated lesions overlap maximally over superior temporal lobe areas (e.g., Karnath *et al.*, 2004).

Furthermore, Milner and Goodale' (1995, 2006; Milner, 1995; Milner, 1998a,b; Milner, 1997) suggest that a disruption of spatial allocentric representations, after object identification is at the core of the neglect symptomatology. Accordingly, given the known properties of both streams, this disruption could, more conceivably, be accounted for by visual inputs from the ventral stream, as this stream is thought to be the one responsible for allocentric coding (Murphy, Carey & Goodale, 1998; Schenk, 2006). In contrast, they claim that the visual dorsal stream is relatively spared (Milner, Harvey, & Prichard, 1998; Milner & Goodale, 1995, 2006) and that consequently patients have fewer problems with information coded in purely egocentric coordinates.

Moreover, another strong claim of the perception and action model is that the two streams present different timescales in that while the dorsal visual stream is involved in immediate target-directed actions, the ventral stream is important for actions towards memorized objects or locations. These suggestions are derived from the findings that DF can no longer perform accurately when a delay is interposed between viewing and grasping (Goodale,

Jakobson & Keillor, 1994) and that optic ataxia improves after a delay (Milner *et al.*, 1999). Once again, Milner and Goodale (1995, 2006)'s hypothesis that the ventral visual stream takes over when the action is delayed, allows another specific prediction to be made regarding hemispatial neglect. That is, whilst neglect patients should be able to reach to targets in the 'here and now', they should nevertheless be impaired when the visuomotor action depends on processing carried out by the ventral visual stream (Milner, 1995; Milner & Harvey, 2006). In particular, if hemispatial neglect is better explained by ventral (rather than dorsal) stream damage (Milner, 1995; Milner, 1998a,b; Milner, 1997) than one would expect such patients to be impaired in delayed reaching, similarly to patient DF.

The action debate in hemispatial neglect

Harvey, Milner and Roberts (1995) found that neglect patients make rightward errors when asked to bisect horizontal lines at their midpoint and present a leftward bias in the landmark task (i.e., the patient is asked to judge which end of the line is closer to a central landmark). Furthermore, Milner and Harvey (1995) and Milner, Harvey and Pritchard (1998) observed that neglect patients judge the leftward of two horizontal lines or rectangles on the left hemispace to be shorter than two identical stimuli on the right. Similarly, when asked to perform manual judgements of size, neglect patients underestimate the size of target cylinders when they are placed on their left (e.g., Milner & Harvey, 1995; Milner, Harvey, Roberts & Forster, 1993). Based on these observations several authors have suggested that many patients with left sided neglect under-perceive the visual extent of the left side of space (e.g., Harvey, Milner &

Roberts, 1995; Milner *et al.*, 1993; Miner & Harvey, 1995; Milner, Harvey and Pritchard, 1998; Pritchard *et al.*, 1997). In fact, while the perceptual deficits associated with this syndrome have been extensively studied, the motor behaviour of these patients has not yet received the equivalent degree of attention. In addition, whether or not goal-directed movements of left neglect patients are affected by the rightward bias found in 'perception' tasks (like line bisection) has been controversially discussed for more than a decade.

Very briefly, it has been found that reaction and movement times towards points and objects located in the contralesional hemispace are generally increased in patients with hemispatial neglect (Heilman *et al.*, 1985; Husain *et al.*, 2000; Mattingley, Bradshaw & Philips, 1992; Mattingley, Philips & Bradshaw, 1994; Mattingley *et al.*, 1998b). Moreover, Goodale *et al.* (1990), Harvey, Milner and Roberts (1994) and also Jackson *et al.* (2000) reported rightwardly curved trajectories in the pointing movements of right hemisphere lesioned and recovered neglect patients. What is less clear though is whether these biases are indeed neglect-specific. Karnath, Dick and Konczak (1997) tested acute neglect patients and right hemisphere lesioned patients without neglect and found no evidence of a rightward bias in the reach trajectory or the terminal accuracy on both patient groups (when compared to healthy controls), findings later repeated by Harvey *et al.* (2002), Himmelbach and Karnath (2003) and McIntosh *et al.* (2002). In fact, Himmelbach and Karnath (2003) argue that even patients with severe spatial neglect in the acute stage of their stroke, can reach accurately to a target and they can do so in both left and right hemispace.

Nevertheless, in a recent controversial review Coulthard, Parton and Husain (2006) concluded that many patients with hemispatial neglect are

impaired when reaching towards the contralesional side of space. Their arguments were based on previous findings that such patients take more time to initiate and/or complete an action towards the contralesional side of space (Heilman *et al.*, 1985; Husain *et al.*, 2000; Mattingley, Bradshaw & Philips, 1992; Mattingley, Philips & Bradshaw, 1994; Mattingley *et al.*, 1998b) and/or present increased rightward curved trajectories (Goodale *et al.*, 1990; Harvey, Milner & Roberts, 1994; Jackson *et al.*, 2000).

In a later paper, Himmelbach, Karnath and Perenin (2007) strongly contested Coulthard, Parton and Husain (2006)'s paper by arguing that the studies reviewed contrasted the performance of neglect patients against healthy age-matched controls, a comparison that does not clarify whether these biases are neglect-specific. They suggest that the critical comparison is between patients with and without neglect, as the motor abnormalities observed in neglect patients may simply be a consequence of '*a phenomenon occurring with (so far not further identified) brain damage*' (pp. 1980). In other words, the presence or absence of such deficits may not depend on the presence of neglect, but rather, more generally, on the extent of damage to the visuomotor control network. In keeping with this, studies that have included patients without neglect after right-hemisphere lesions have failed to find any neglect-specific temporal or spatial inaccuracies in reaching or grasping (Harvey *et al.*, 2002; Himmelbach & Karnath, 2003; Karnath, Dick & Konczak, 1997; Konczak & Karnath, 1998). In a final reply, Coulthard, Parton and Husain (2007) clarified their conclusions by agreeing that the reaching deficits observed in neglect may not be specific to the condition.

Outline of the present experiments

Therefore, whether the visuomotor behaviour of neglect patients is necessarily subject to lateral biases and whether their dorsal visual stream is relatively spared is still a matter of debate in the literature. Furthermore, the present thesis intends to address the pattern spared and impaired visuomotor abilities in patients with hemispatial neglect, as specifically predicted by the perception and action model (Milner & Goodale, 1995, 2006).

It is important to highlight the differences between Milner and Goodale (1995, 2006)'s hypotheses of dissociated perceptual and visuomotor processing in neglect and earlier suggestions of a dissociation between perceptual and pre-motor (or motor directional) contributions to neglect. According to the later view the perceptual neglect deficits may result from either a spatial bias in the processing of sensory inputs or, alternatively, from spatial biases in the selection and execution of motor acts and special techniques have been used to disentangle these aspects of neglect (see Mattingley & Driver, 1997 for a review). In contrast, the perception and action model is concerned with the differential processing of visual information for different purposes and this is orthogonal to the distinction between perceptual (input) and pre-motor (output) neglect. In particular, Milner and Goodale (1995, 2006) suggest that the visual processing that gives rise to conscious visual awareness may be independent from the neural mechanism that process the same sensory inputs for the guidance of automatic goal-directed actions. It is therefore crucial to state from the outset of the thesis that my experiments are not concerned with the distinction between input and output biases or, in other words, in classifying neglect patients in perceptual and pre-motor categories as proposed by

Heilman and Valenstein (1979). Instead of pursuing this distinction, I will adopt Milner and Goodale's approach (1995, 2006; Milner & McIntosh, 2002; McIntosh *et al.*, 2004b) and investigate whether parallel visual pathways may be differentially affected by the perceptual biases that neglect patients frequently exhibit.

In Chapter One I will test the hypothesis that visuomotor control is spared in neglect patients by examining their temporal and accuracy performance when reaching towards targets on both sides of space and with or without visual feedback about the target and hand position during movement. Chapter Two will address the specific hypothesis that patients with hemispatial neglect suffer from ventral stream-related motor deficits, rather than dorsal. That is, I will test the claim that such patients can guide their actions to visible targets even if these are placed in left space, yet fail to do so if a delay is introduced between stimulus and response. Moreover, in both chapters I will compare the performance of neglect patients with that of two control groups, one of healthy controls and one of patients without the condition. This will allow testing whether the motor abnormalities are neglect-specific or result from damage to the visuomotor control network. Furthermore, I will use the recently developed voxel-based lesion-symptom analysis (Rorden, Karnath & Bonilla, 2007) to conduct an **initial** exploratory investigation of the lesioned brain areas potentially associated with the temporal and spatial visuomotor abnormalities observed after right-brain lesions.

Chapter 1

The influence of visual feedback in target-directed reaching and gap bisection in patients with hemispatial neglect

Introduction

Everyday we make rapid, goal-directed movements to interact with the environment and visual information plays a significant role in the precise and efficient control of such actions. A daily example of our dependence on visual feedback for reaching accuracy is when we miss the light switch when reaching for it in darkness.

A number of researchers have focused on the extent to which visual feedback is required for the accurate control of action. This has been investigated using a variety of manipulations that have included withdrawing of vision of the limb and/or environment (Prablanc *et al.*, 1979a, b). In healthy participants, preventing vision of the hand during movement has been shown to cause a reduction in accuracy (e.g., Jakobson & Goodale, 1991; Prablanc *et al.*, 1979a), produce a greater curvature in the reaching paths (e.g., Sergio & Scott, 1998) and slowing of the movement time (e.g., Connolly & Goodale, 1999).

More than a century ago, Woodworth (1899) suggested that the control of target-directed movements involves the central planning prior to movement initiation and the processing of sensory information to correct errors during

execution. Furthermore, many researchers (for review see Jeannerod, 1988) have suggested that the acceleration phase, is essentially ballistic, bringing the hand to the vicinity of the target and is associated with open loop processing, in that there is no opportunity to use on-line sensory feedback. On the other hand, the deceleration phase is thought to be more dependent on sensory feedback and closed loop processing to allow adjustments of trajectory to hit the target. However, whether visual feedback is used for actions in a continuous or intermittent manner remains a subject of debate in the literature (e.g., Desmurget & Grafton, 2000; Saunders & Knill, 2003).

As discussed in the General Introduction, it is still unclear if patients with hemispatial neglect are specifically impaired in their visuomotor abilities when compared to right-brain damaged patients without the condition. One particular question that has been debated over the last two decades is if neglect patients use visual feedback efficiently in the guidance of their actions. To investigate this matter researchers have compared the performance of patients in open loop conditions, in which no visual feedback is available during movement, with conditions in which visual feedback is available throughout the reach (i.e., closed loop).

In a seminal paper Goodale *et al.* (1990) studied recovered hemispatial neglect patients with right hemisphere lesions, but who at the time of testing no longer showed evidence of neglect in clinical tests. Nine patients and 13 age-matched controls were asked to perform a target-directed pointing task and an analogue of the line-bisection task, in which they had to place their right index finger at the point perceived to be midway between two light emitting diodes (LEDS; a task now referred to as gap bisection). Both tasks were performed in

closed loop conditions and the reaching trajectories were analysed visually. It was found that patients with right hemisphere damage made large rightward errors in the gap bisection task, but not when pointing directly at the target. Moreover, patients were making large rightward deviations from the outset of the reach on both tasks. However, these deviations were corrected in the pointing task, so that the final rightward errors were much smaller than those observed in the gap bisection task. The authors argued that a detailed analysis of reach to point movements can reveal subtle deficits that may not be apparent from clinical assessment in patients with unilateral brain lesions. Furthermore, they suggest that future experiments should include a condition where vision of the moving hand is removed, as perhaps without this information patients might fail to make any corrections in the pointing task.

Indeed that is exactly what Harvey, Milner and Roberts (1994) investigated in a later study. They analysed the performance of 12 patients with unilateral right hemisphere lesions and 12 with unilateral left hemisphere damage (all with no signs of neglect; except two who had recovered from the condition) when compared to 12 age-matched controls. Participants were asked to perform the same pointing and gap bisection tasks as Goodale *et al.* (1990) but this time with and without visual feedback of the hand whilst reaching. In stark contrast with Goodale *et al.* (1990), Harvey, Milner and Roberts (1994) observed that only when no visual feedback was available did the right-hemisphere damaged patients present rightward trajectory biases and large rightward terminal errors on both tasks (albeit more in the gap bisection condition). This asymmetry was present regardless of the hand used and was consistent across all three target positions (left, center, right). Also, right-brain

damaged patients presented overall longer reaction times when compared to the healthy control group.

So why were Goodale *et al.* (1990)'s patients trajectories curved in closed loop and Harvey *et al.* (1994)'s patients not? Goodale *et al.* (1990) speculated that the deficits in their patients resulted from the presence of subtle neglect, but this interpretation is not convincing for Harvey, Milner and Roberts (1994)'s data as most patients in their sample never experienced neglect. To account for this discrepancy Harvey, Milner and Roberts (1994) argued that the ipsilesional deviations documented by Goodale *et al.* (1990) might reflect fronto-parietal damage, irrespective of the presence of neglect. In addition, they discussed the presence of a premotor bias or a subclinal optic ataxia in their patients to account for the rightward bias in open loop reaching.

To clarify if the observed deficits in closed loop reaches were indeed an expression of subtle neglect Karnath, Dick and Konczak (1997) were the first to directly compare the performance of five acute neglect patients with five patients without neglect after right-brain damage, as well as six healthy controls on a simple target-directed pointing task. The task was performed under normal room light and in complete darkness to prevent vision of the hand during the movement. The authors did not find any deviation of the hand trajectory that specifically occurred when patients had neglect. In fact, both patient groups presented similar curvatures and end-point errors to healthy controls for all target positions and lighting conditions. The only difference was found for movement time, in that both patient groups took significantly longer to complete their movements when compared to healthy participants. Karnath, Dick and Konczak (1997) argued against Goodale *et al.* (1990) proposing that the failure

of neglect patients to explore the contralesional part of space does not induce a spatial bias in hand trajectory formation during goal-directed arm movements. Furthermore, they suggested that such deviations of pointing movements toward the ipsilesional side rather seem characteristic of patients with optic ataxia. In a later and complementary study, Konczak and Karnath (1998) studied in detail the velocity patterns of pointing movements, in the same patients and tasks as Karnath, Dick and Konczak (1997), and observed that movement times were longer in both patient groups due to prolonged phases in both acceleration and deceleration (in both open and closed loop). In addition, the velocity profiles of the neglect patients were not direction-specific. This evidence seems to suggest no impairment in using on-line visual feedback for the guidance of movement in both patients with and without neglect.

However, more recently Jackson *et al.* (2000) found curvature biases in three right-brain damaged patients (two of them who presented neglect and one recovered patient) in a closed loop reaching task. Their study consisted of three target-directed pointing conditions: vision/vision (the target locations were defined visually); vision/proprioception (with no visual cues of the targets which were defined proprioceptively); and proprioception/proprioception (identical to the vision/proprioception trials with the exception that the subjects had no visual information about the moving limb). Now, similarly to Goodale *et al.* (1990), the patients only presented rightwardly curved trajectories when visual feedback of target and hand were available. However, no biases were found when targets were defined proprioceptively, which led the authors to conclude that their patient's misreaching was not due to impairment of motor control *per se*, but

rather to a spatial distortion in the visual representation of space used to plan and control movements.

Harvey *et al.* (2002) were the first to study the influence of visual feedback in the grasping abilities of neglect patients. To do this they compared the performance of four right-brain damaged patients with neglect, three without the disorder and five healthy controls. Participants were asked to grasp objects, located in either right or left space, at near and far distances both under normal vision and without visual feedback of the hand and target during movement. The authors observed that neither of the two patient groups differed from the healthy participants in terms of maximum grip aperture or grip orientation nor the time to reach maximum grip aperture. In terms of path trajectory, right-brain damaged patients showed the same amount of path curvature in open and closed loop conditions, whereas the trajectory of healthy controls proved straighter in the closed loop condition. Thus, like in Goodale *et al.* (1990) and Jackson *et al.* (2000)'s studies the curvature of the patients was increased (relative to healthy participants) when movements were made under visual feedback. However, no curvature differences could be found between the patients with and without neglect. Furthermore, both patients groups proved markedly slower in movement time and peak velocity when compared to controls, but again no difference was obtained between the two patient groups and this slowness was not direction-specific. Finally, whereas the healthy participants spent less time decelerating under normal vision, this difference was not present for the patients. To account for their results Harvey *et al.* (2002) suggested that after right-brain damage the patients might be less efficient when using visual feedback to home in on the target, requiring longer time to decelerate under

closed loop conditions and producing more curved trajectories. However, they state that this impairment in goal-directed behaviour is not confined to hemispatial neglect.

In another attempt to clarify if patients with right-brain damage present increased ipsilesional curvatures Himmelbach and Karnath (2003) analysed the terminal accuracy and several hand path curvature measures of target-directed movements with room lights turned on and in darkness. They tested 17 patients with right hemisphere lesions (six patients with neglect, four patients who had already recovered from neglect and seven patients who never showed neglect) as well as nine age-matched healthy controls. No systematic bias of terminal accuracy or hand path curvature was found that could be specifically attributed to neglect. Additionally, these authors found that although there was a higher absolute curvature in neglect patients when compared to healthy subjects (but when compared not patients without the condition), in the closed loop condition, this difference was not direction-specific, in contradiction to the results obtained by Jackson *et al.* (2000). On the basis of their results, the authors suggested that spatial neglect is not specifically associated with a systematic bias of goal-directed hand movements towards the ipsilesional side.

In sum, the results regarding the influence of visual feedback on the visuomotor abilities of neglect patients have been most inconclusive. Whilst Goodale *et al.* (1990) reported that recovered neglect patients, when compared to healthy controls, presented large rightward deviations in gap bisection (but not pointing) with visual feedback, Harvey, Milner and Roberts (1994) found rightward biases in both pointing and gap bisection only for open loop reaches (in right hemisphere lesioned patients without neglect). Moreover, Jackson *et al.*

(2000), found large rightward deviations in neglect patients when pointing to visually-defined targets, but again others have not replicated this neither for target-directed pointing nor object-directed grasping (Harvey *et al.*, 2002; Himmelbach & Karnath, 2003; Karnath Dick & Konczak, 1997). Unfortunately, the results from these studies cannot be easily compared, as researchers have used different patient groups, measures of accuracy and hand path curvature, as well as different tasks and lighting conditions.

Based on this controversy, the present experiment examined the visuomotor performance of a significant sample of right hemisphere lesioned patients with and without hemispatial neglect, as well as a group of healthy subjects, in both pointing and gap bisection, both with and without visual feedback. As discussed in the General Introduction, if Milner and Goodale (2006) are correct in claiming that the dorsal stream is relatively spared in hemispatial neglect, then neglect should not specifically affect pointing in either open or closed loop conditions, even when reaches are made towards the left side of space.

Regarding the gap bisection task, one could assume that neglect patients should show a rightward bias in this task as these patients typically show a bias in line bisection (e.g., Harvey, Milner & Roberts, 1995; Milner & Harvey, 1995). However, and in contrast to Goodale *et al.* (1990)'s claims, this hypothesis has been elegantly refuted by McIntosh *et al.* (2004a). The first experiment of McIntosh *et al.* (2004a) showed that left neglect patients curiously present smaller rightward errors in gap bisection when compared to the bisection of filled lines. In their second study they assessed the cause of this error reduction by applying an explicit coloured cue manipulation to the line and

gap bisection tasks. Under these matched cueing conditions they found the same level of performance on both line and gap bisection, suggesting that the reduction in bisection error is a result of cueing effects. Thus, in the present experiment it is predicted that neglect patients will not present a specific bias in the gap bisection condition, even those with a rightward error in line bisection.

Finally, although it is hypothesized that there is no neglect-specific impairment in action control, I expect that some patients will present deficits in the tasks, especially if their brain damage extends to crucial nodes in the visuomotor control network. Therefore, another aim of this study is to clarify the neural basis of motor deficits after right-hemisphere damage, a topic also hotly debated in the literature. Previous studies (e.g., Bisiach *et al.*, 1990; Tegner & Levander, 1991) have reported that frontal and basal ganglia lesions produce motor abnormalities in neglect patients, but the mapping methods used did not allow a precise localization of the site of damage. Other studies argue instead that injury to the right posterior-inferior parietal cortex is associated with increased reaction times to left stimuli (Husain *et al.*, 2000; Mattingley *et al.*, 1998*b*). In addition, as pointed out by Rorden and Karnath (2004) anatomical conclusions drawn without a comparison to a control group of patients who also suffer from a brain lesion, but do not show the pathological behaviour, may simply reflect brain injury. The recent development of voxel-based lesion-symptom analysis (Rorden, Karnath & Bonilla, 2007) thus provided a unique opportunity to conduct an **initial** exploratory investigation of the lesioned brain areas in right-brain damaged patients potentially associated with temporal and spatial visuomotor abnormalities.

Method

Participants

Eleven patients with left hemispatial neglect after right hemisphere damage participated in the study (RH+; mean age 66.8, SD 7.7). Nine patients with right hemisphere damage without neglect (RH-; mean age 67.2, SD 7.8) and 10 healthy participants (mean age 71.0, SD 4.8) served as control groups. The groups were age-matched and all participants were right-handed (Annett, 1967). The healthy participants had normal or correct-to normal visual acuity. On average patients took part in the experiment eight months after stroke onset and there were no differences in onset times between the two patient groups.

Patients were included in the RH+ group if they scored below the cut-off on the conventional sub-tests of the BIT (Behavioural Inattention Test; Wilson, Cockburn & Halligan, 1987) or presented a significant rightward bisection error (Harvey, Milner & Roberts, 1995) or were impaired in a lateralized manner in the sub-test B of the Balloons test (Edgeworth, Robertson & McMillan, 1998). Patient MMG was included in the neglect group despite scoring above the cut-off on the neglect assessment measures, because she showed typical signs of neglect as reported by family members and therapists/clinical staff (e.g., bumping into objects on the left). Importantly, none of the RH- patients ever showed signs of neglect on these tests.

Hemianopia and extinction were formally assessed using computerized perimetry and extinction tests (adapted from Walker *et al.*, 1991), on a laptop with a 285 by 214mm screen with stimuli at a viewing distance of 60cm

approximately. On both tasks a central fixation cross appeared for 1000ms and was extinguished 100ms before the target was presented, leaving a blank screen on to which targets were displayed for 100ms. For the perimetry task, a black stimulus (circle with 2mm of diameter) appeared on one of 36 possible positions on a white background. The distance between the stimuli was fixed (6.5˚ in x-axis and 4.8˚ in the y-axis). Patients were first asked to fixate on the central cross and after fixation offset they were asked to press a key when they detected target appearance. A total of 106 trials (including 10 practise and 24 catch trials) were presented, two per target position. In the extinction test, squared stimuli (black 2 x 2mm) were presented on a white background, unilaterally to either the left or the right of the screen or simultaneously on both sides (located at 2.9˚ or 5.7˚ from the centre of the screen). Patients were asked to report the number of squares they detected (i.e., left, right, both or none). A total of 70 trials (including 7 practise and 10 catch trials) were presented, 10 for each condition and eccentricity. In neglect patients AB, DF, FH and NF extinction could not be assessed in a meaningful way as these patients were unable to report the presence of a single leftward stimulus. Demographic and clinical data of all patients are presented in Table 1.

In addition, to assess the general cognitive status the following sub-tests of the Wechsler Adult Intelligence Scale - Revised (WAIS-R; Wechsler, 1981) were administered to all patients: picture completion, vocabulary, block design, information, digit span and object assembly. An analysis of variance with group (RH+ and RH-) as the between factor was performed on the scaled scores of each sub-test. This revealed that neglect patients were significantly impaired on all performance sub-tests when compared to RH- patients, [block design: $F_{(1,18)}$

= 19.15, $p < .001$; picture completion: $F_{(1,19)} = 10.34$, $p < .01$; object assembly: $F_{(1,17)} = 20.98$, $p < .001$]. This finding is almost certainly due to reduced processing of information on the left of the stimulus displays. No differences between the two groups were obtained for information, digit span and vocabulary scaled scores.

Ethical approval was granted by the South Glasgow University Hospitals Trust and the study was carried out according to the Declaration of Helsinki. All participants gave their informed consent prior to participation in the study and were reimbursed for their travel expenses.

Table 1 - Demographic and clinical data of the right-brain damaged patients.

Group	Patient	Gender	Age	Scan	Etiology	Lesion location	Lesion volume (cm^3)	TO	VFD	EXT	BIT	Line bisection	Balloons
RH+	AB	F	70	MRI	Infarct	Temporo-occipital	100.7	6	Yes	(-)	131	31	50
	AM	M	63	CT	Infarct	Fronto-temporal-parietal-insular	85.3	7	Yes	Yes	130	11	50
	DS	F	64	MRI	Infarct	Fronto-temporo-occipital	56.5	4	Yes	(-)	91	82	50
	FH	F	80	MRI	Haemorrage	Temporo-parietal	108.6	15	Yes	(-)	103	75	27
	JH	F	56	MRI	Infarct	Fronto-temporo-parietal	189.2	19	Yes	Yes	139	25	43
	JK	F	69	CT	Infarct	Fronto-temporal	50.9	4	No	No	141	15	44
	JM	M	55	MRI	Infarct	Fronto-parietal	169.5	7	Yes	Yes	117	11	43
	JS	M	76	MRI	Infarct	Temporal, insular cortex and periventricular white matter	105.2	28	Yes	Yes	129	9	36
	MM	F	72	CT	Infarct	Fronto-temporal-insular	18.0	4	No	No	128	0	50
	MMG	F	63	MRI	Infarct	Dorsal frontal, parietal, corona radiata	61.6	2	No	No	142	3	59
	NF	F	67	MRI	Infarct	Fronto-temporo-parietal	268.8	7	Yes	(-)	143	6	29
RH-	AMI	M	60	CT	Infarct	Lentiform nucleus	1.4	2	No	No	146	3	50
	AW	F	64	MRI	Infarct	Basal ganglia	2.6	6	No	No	145	-2	50
	DM	M	78	MRI	Infarct	Fronto-temporal	59.6	3	No	No	145	1	50
	JC	F	76	CT	Infarct	Fronto-temporal	9.4	9	No	No	146	3	53
	JST	M	56	CT	Infarct	Dorsal frontal, posterior temporal, parietal	49.0	5	Yes	No	146	1	53
	LS	M	60	CT	Infarct	Caudate nucleus	1.8	7	No	No	144	5	50
	MP	F	66	MRI	Infarct	Basal ganglia	0.7	5	No	No	146	1	53
	RM	M	73	CT	Infarct	Lentiform nucleus	0.2	2	No	No	141	6	46
	SC	M	72	CT	Infarct	Frontal	16.2	13	No	No	140	3	54

TO = time since injury onset (months); VFD = visual field defect; EXT = extinction; BIT = Behavioural Inattention Test conventional sub-tests score (cut-off = 129); Line bisection represents the average error (in mm) obtained with 20 lines (200mm length), no sign is equivalent to a rightward error and a negative sign is equivalent to a leftward error (cut-off = 6mm, Halligan, Manning & Marshall, 1990); Balloons represents the lateralized index score in sub-test B (patient is impaired when this index is lower than 45%); (-) unable to diagnose extinction.

Stimuli and procedure

Targets were white circles (diameter 7mm) projected (HITACHI CP-X345 Multimedia LCD Projector, refresh rate of 60Hz) onto a horizontal Perspex box (77cm width/ 97cm length/ 30cm height) via a reflection mirror (3mm thick, 60 x 60cm). The box was placed on top of a wooden table at which the subjects were comfortably seated (see Figure 3). The target surface was 77cm wide and 49cm long. Targets were visible only when illuminated and no tactile information of their locations was available. The central target was located 40cm in front of the start trigger and aligned with the centre of the box. At the start of each trial, the participant's right index finger rested on the start trigger, aligned with the subject's sagittal midline. Eye movements were unrestricted. The room was slightly darkened so that the targets were clearly visible when illuminated.

Figure 3 – Front and side views of the reaching platform.

The design was adapted from Goodale *et al.* (1990). In the pointing condition, the target appearance was triggered by press of the start trigger. Participants were asked to press the start trigger for 1000ms after which a tone (800Hz for 500ms) cued the subjects to initiate the movement. The target remained visible until the end of the trial and participants were instructed to point to the target as quickly and as accurately as possible. In this condition, subjects were presented with three targets illuminated one at a time located at -10cm (left hemispace), 0cm (central) and 10cm (right hemispace). In the gap bisection condition, on pressing the start trigger two identical circles were presented simultaneously for 1000 ms after which a tone (800Hz) cued the subject to point midway between these two circles as quickly and accurately as possible. In this case the two circles were presented simultaneously at three different positions, either in left (-15 and -5cm), centrally (-5 and 5cm) or right hemispace (5 and 15cm). The dots varied randomly in location from trial to trial although the distance between them was fixed (10cm). Note that the true midpoints in the gap bisection task were identical to the locations of the targets used in the pointing task (-10, 0 and 10cm) and all movements were made with the right arm and hand.

As in Harvey, Milner and Roberts (1994), all participants reached under closed loop conditions first, yet the order of the bisection and pointing tasks was counterbalanced across participants. In the closed loop condition the room light permitted full vision of the arm and hand during the movement. In the open loop condition, subjects wore shutter glasses (PLATO Model S-3, Translucent Technologies Inc., Toronto, Canada), which prevented vision of the arm, hand and target during movement as the shutters closed as soon as the start trigger

was released (e.g., Harvey *et al.*, 2002). These manipulations resulted in four blocks of trials: closed loop pointing; closed loop gap bisection; open loop pointing; and open loop gap bisection. Each block contained six practise trials (2 for each target position) and 36 experimental trials (12 for each target). Calibration coordinates were obtained at the end of the each session, by continuous illumination of each target, one by one, allowing the subjects to adjust their terminal fingertip position until they felt they had perfectly occluded the target. There were three calibration trials per target (-10, 0, 10cm) and three for the start position.

Pointing responses were recorded by sampling the position of a magnetic marker, attached to the tip of the right index finger, at a rate of 108HZ, using an electro-magnetic motion analysis system (Minibird, Ascension Technology Inc., Burlington, USA). The start trigger, the shutter glasses, the on-line recordings and the stimuli presentation were simultaneously controlled and timed by a PC, by means of a Virtual Instrument generated with LabView software (National Instruments, Newbury, UK).

Behavioural analysis

Data obtained from the recordings were analysed off-line. The start and end of each movement were defined by a velocity-based criterion of 40mm/s and 50mm/s respectively. First, a trial-by-trial analysis was performed to exclude any trials in which participants did not follow the instructions (i.e., did not wait for the beep to start moving, did not home in on target). A mixed analysis of variance was performed on the number of trials analysed with group (healthy controls, RH- and RH+) as between factor and task (pointing, gap bisection) and visual

feedback (open loop and closed loop) as within factors. This revealed no effects of group or task or an interaction between group and task or visual feedback. However, the effect of visual feedback was significant [$F_{(1,27)} = 16.86$, $p < .001$] in that open loop trials were more error prone (in pointing open loop 7.9% of collected trials were excluded and in gap bisection open loop 7.7% were excluded), when compared to closed loop reaches (only 1.5% of trials were excluded in both closed loop pointing and gap bisection).

The terminal accuracy variables were absolute and signed angular error, relative to the ideal reach either to the target (pointing) or to the location midway between the two targets (gap bisection). The absolute angular error was defined as the unsigned constant angular error relative to the ideal reach. This angular error was calculated for each trial based on the subtraction of each participant's movement angle by the ideal reach angle. The ideal angles were obtained from individual calibration coordinates of x and y positions at the start trigger and at the different target positions. In addition, the directionality of this angular error in terms of right and leftward (-) deviations from the ideal reach angle was also computed.

To analyse the movement trajectory the cumulative hand path curvature index was computed (e.g. Himmelbach & Karnath, 2003). First, the mean x coordinates for each 1mm y coordinate were obtained for each subject, per target position and condition. Secondly, the deviations in the x-axis of the subject's trajectory from a perfectly straight trajectory to the target were also computed. This was obtained individually for each participant based on the calibration coordinates. Finally, the deviations of the trajectories at each y data point were added up using the sign to denote the direction of curvature. This

cumulative value was then divided by the distance between movement start and end in the y-axis, providing a sensitive measure of systematic direction-specific changes. Finally, reaction and movement times were also analysed.

Lesion analysis

Lesion data were available for all twenty patients (11 MRI scans and 9 CT scans; MRI scans could not be obtained for all patients due to clinical constraints). The extent and location of each patient's lesion was visualized and defined using the MRICRO software package (Rorden & Brett, 2000; www.mricro.com). For each patient, the area of damage was determined by inspection of the digital brain image, slice by slice, by a clinical neurologist, who was blind to the design, group assignment and purpose of the experiment. Lesions were drawn on 11 axial slices of a T1-weighted template, corresponding to the Talairach z coordinates of -24, -16, -8, 0, 8, 16, 24, 32, 40, 50, 60mm using the identical or closest matching transverse slices for each patient.

In Figure 4A and B the overlap of the reconstructed lesions for the RH+ and RH- patients is presented. However, the lesions overlaps of neglect and non-neglect patients (Fig 4A and 4B) do not differentiate between loci of lesion associated with neglect and those areas most likely to be damaged by vascular insult. Thus, it is important to subtract the lesions of neglect patients by lesions of patients without the condition. The power of this subtraction technique is that common lesions that are damaged with equal incidence in both groups (presumably due to the vulnerability of this region) are not highlighted (Karnath *et al.*, 2004).

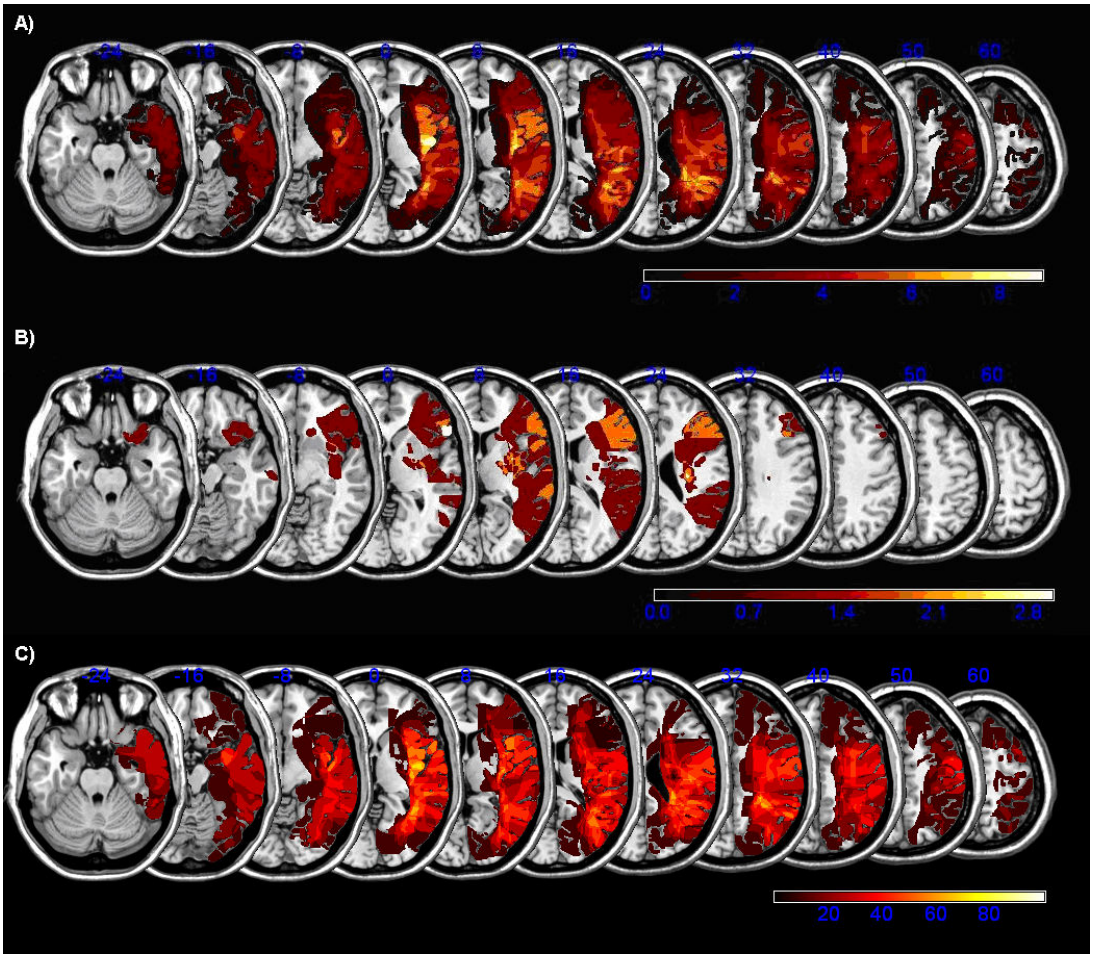

Figure 4 - Lesion overlap map summarising the degree of involvement for each voxel in the lesions of neglect patients (N = 11; A) and patients without neglect (N = 9; B); the range of colour scale derives from the absolute number of patient lesions involved in each voxel. (C) Lesions of neglect patients minus those of RH- control patients; the range of the colour indicates the percentage of areas mostly damaged in patients with neglect.

The regions that were mostly damaged in patients with neglect are presented on Figure 4C. The foci that were maximally damaged in patients with neglect (71%) were located in the gray matter of the superior temporal gyrus (Talairach coordinates: 47, -10, 0), the insula gray matter (Talairach coordinates: 43, -7, 0) and its surrounding white matter (Talairach coordinates: 45, -8, 0) and the white matter nearby the claustrum (Talairach coordinates: 37,

-8, 0). Consistent with previous studies, the lesions of neglect patients were significantly larger in volume than those of the non-neglect group [$F_{(1,19)} = 14.03$, $p = .001$, see Table 1].

Finally similarly to recent papers (e.g., Sarri *et al.*, 2009), whenever a behavioural impairment was observed, the voxel-based lesion-symptom mapping statistical approach was implemented using MRICROn software (Rorden, Karnath & Bonilla, 2007; www.sph.sc.edu/comd/rorden/mricron/). This analysis was performed with voxel-based maps of the Brunner-Munzel non-parametric statistic (BM; Brunner & Munzel, 2000; Rorden, Bonilla & Nichols, 2007). The BM test is a rank order test which relates lesioned voxels to behavioural performance in a continuous fashion without pre-categorizing patients into RH- or RH+ groups. Thus it takes the behavioural data from all patients and asks which voxels, when lesioned, are associated with that behavioural characteristic. Therefore, this test provides a relatively assumption-free measure of whether or not damage at each voxel is associated with a particular deficit (Rorden, Bonilla & Nichols, 2007). For each voxel, patients are divided into two groups according to whether they did or did not have a lesion affecting that voxel and the behavioural scores are compared for these two groups (damaged/non-damaged). The BM statistic tests if the difference in behaviour between the two groups is significant and thus provides a Z score for each voxel. Multiple comparisons were controlled by using the false discovery rate (FDR; $p < .05$).

Throughout this thesis, the voxel x-, y-, and z- Talairach-space coordinates (in mm; Talairach & Tournoux, 1988) are reported for significant results that survived FDR thresholding. For each significant brain area, the

voxel position which obtained the highest (peak) Z score, within the BM range, is presented.

Results

Means for each participant were computed per condition for each variable and target position. All variables were analysed with a 3 x 2 x 2 x 3 mixed analysis of variance with group (healthy, RH- and RH+) as a between-factor and visual feedback (closed loop, open loop), task (pointing, gap bisection) and target (left, centre and right) as within-subject effects. Post-hoc comparisons were made with the Bonferroni adjustment ($p < .05$).

Terminal accuracy

The descriptive statistics for absolute angular error per visual feedback, target and group are presented for the pointing and gap bisection tasks in Tables 2 and 3 respectively. The analysis of variance on absolute angular error revealed a significant main effect of target [$F_{(2,54)} = 8.51$, $p = .001$] and pairwise comparisons showed that overall participants were less accurate in their leftward reaches when compared to centred (mean difference = 0.4˚, $p < .01$) and rightward reaches (mean difference = 0.5˚, $p = .01$). No differences in accuracy were found between centred and rightward reaches. The main effect of visual feedback was also significant [$F_{(1,27)} = 97.47$, $p < .001$], in that overall participants were less accurate when reaching without visual feedback during

movement. The main effect of task was not significant and participants were similarly accurate in gap bisection and pointing.

Table 2 - Means and standard errors (in parenthesis) of absolute angular error (in degrees) for the pointing condition per group, visual feedback and target position.

	Pointing closed loop			**Pointing open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	0.5 (0.0)	0.4 (0.0)	0.4 (0.0)	2.2 (0.4)	2.0 (0.5)	2.3 (0.6)
RH-	0.4 (0.0)	0.4 (0.0)	0.4 (0.0)	4.5 (0.9)	2.7 (0.6)	2.1 (0.3)
RH+	0.4 (0.0)	0.4 (0.0)	0.4 (0.0)	3.6 (0.5)	2.6 (0.5)	2.6 (0.5)

Table 3 - Means and standard errors (in parenthesis) of absolute angular error (in degrees) for the gap bisection condition per group, visual feedback and target position.

	Gap bisection closed loop			**Gap bisection open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	0.6 (0.1)	0.7 (0.1)	0.6 (0.1)	2.2 (0.4)	1.8 (0.3)	2.4 (0.3)
RH-	0.6 (0.1)	0.6 (0.1)	0.7 (0.1)	3.8 (0.6)	2.3 (0.4)	2.2 (0.4)
RH+	0.9 (0.1)	0.7 (0.1)	0.8 (0.1)	3.8 (0.4)	3.6 (0.5)	2.6 (0.4)

In addition, there was significant interaction between target and visual feedback [$F_{(2,54)}$ = 9.00, p < .001] and post-hoc tests demonstrated that only in the open loop condition were participants less accurate in their leftward reaches when compared to centred (mean difference = 0.8˚, p < .001) and rightward reaches (mean difference = 1.0˚, p < .001). In contrast, in the closed loop condition there was no difference in the reaching accuracy between target positions.

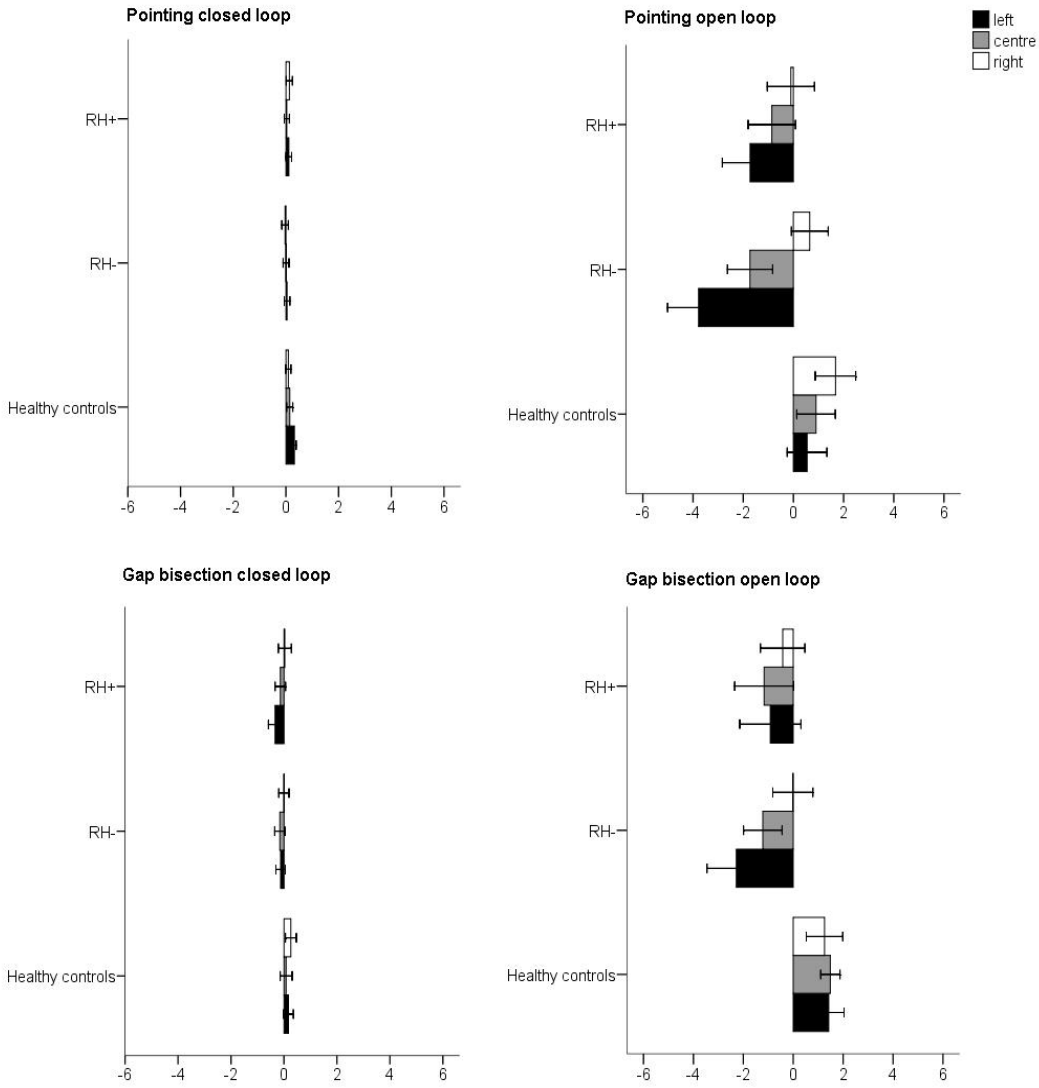

Figure 5 - Mean directional angular error (in degrees) in the open loop pointing and gap bisection per group and target position. Error bars represent standard errors.

The main effects of group and condition were not significant and the interactions between group and visual feedback and group and task were also not significant. However, there was a significant interaction between group and target [$F_{(2,54)}$ = 3.15, p < .05] which was further qualified by the group, visual feedback and target interaction [$F_{(2,54)}$ = 3.69, p = .01]. Pairwise comparisons revealed that only for leftward targets, and only in the open loop condition, were

RH- patients less accurate when compared to healthy controls (mean difference = 1.9˚, $p < .05$). Interestingly, neglect patients (RH+) were as accurate as the healthy or RH- control groups (mean difference = 1.5˚ and -0.4˚ respectively). In terms of directionality, as can be seen in Figure 5, the signed angular errors of the patients without neglect in response to left stimuli were overshoots.

To investigate which brain areas were critically associated with the reduced accuracy in the open loop pointing and gap bisection towards the left, the voxel-based lesion analysis was performed on the mean absolute angular error for both tasks for the leftward reaches. As can be seen in Figure 6, this revealed that several cortical and subcortical areas were significantly associated with the impaired open loop reaching ($Z > 2.16$, $p < .05$; BM range = -6.96, 6.88). The lesion mainly associated with poor accuracy was located subcortically in the lentiform nucleus [peak Z = 6.88 (21, -9, 0)].

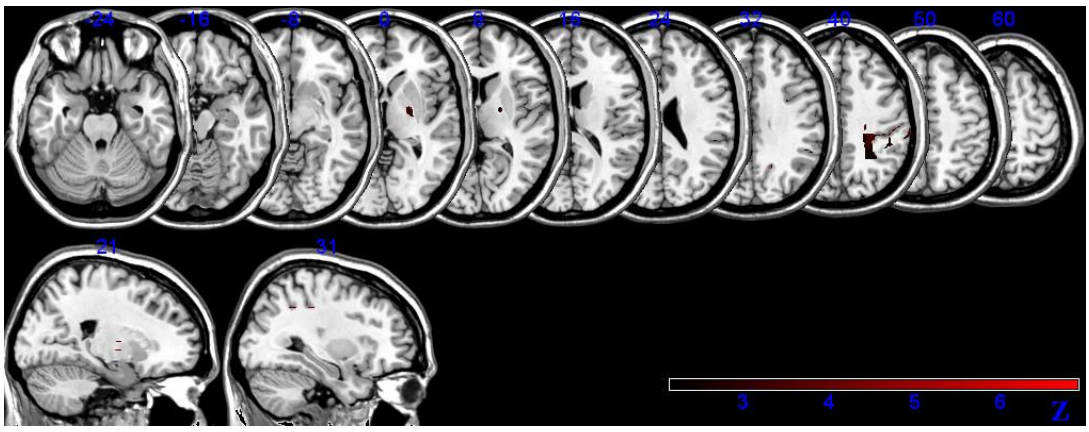

Figure 6 - Voxel-based lesion statistical map (in axial and sagittal view) revealing the right-brain damaged areas significantly associated with increased terminal error in leftward open loop pointing and gap bisection. The legend (and coloured areas) represents the range of Z scores that survived FDR threshold of $p < .05$.

Cortically, several occipito-parietal-frontal areas were associated with this deficit: the occipito-parietal white matter near the precuneus [peak Z = 3.46 (19, -58, 32; 26, -42, 40)], the inferior parietal lobe gray [peak Z = 3.46 (42, -29, 40)] and surrounding white matter [peak Z = 3.46 (32, -52, 40)], the parietal white matter near the post-central gyrus [peak Z = 3.46 (31, -32, 40)] and the pre-central gyrus gray matter [peak Z = 2.41 (60, -12, 32)]. Importantly, lesion volume did not significantly correlate with poor accuracy.

Hand path curvature (HPC)

On Figure 7 and 8, the mean trajectories of the index finger in the x by y plane were reconstructed for the pointing and gap bisection tasks (respectively) per visual feedback, condition and group. Although overall the trajectories seem more variable in the open loop condition, no differences are apparent between the groups.

In terms of the cumulative hand path curvature index, the analysis of variance revealed a main effect of target [$F_{(2,54)}$ = 9.59, p < .001]. Pairwise comparisons revealed that reaches were straighter towards the central position when compared to rightward and leftward reaches (p < .001). No differences in curvature were obtained between leftward and rightward reaches and there was also no main effect of visual feedback. The main effect of task was also significant [$F_{(1,27)}$ = 4.19, p = .05], in that the reaching paths were more curved in the pointing condition when compared to the gap bisection. Both these effects were further qualified by significant interactions between target and visual feedback [$F_{(2,54)}$ = 11.26, p < .001], target and task [$F_{(2,54)}$ = 11.75, p < .001] and target, task and visual feedback [$F_{(2,54)}$ = 10.92, p < .001]. A breakdown of these

interactions revealed that leftward and centred closed loop pointing trajectories were more curved than leftward and centred gap bisections (mean difference leftward = 5.6mm , $p < .001$; mean difference centre = 2.1mm, $p = < .01$), whereas no difference was observed for rightward reaches. Moreover, in open loop no curvature differences were observed between target positions or task.

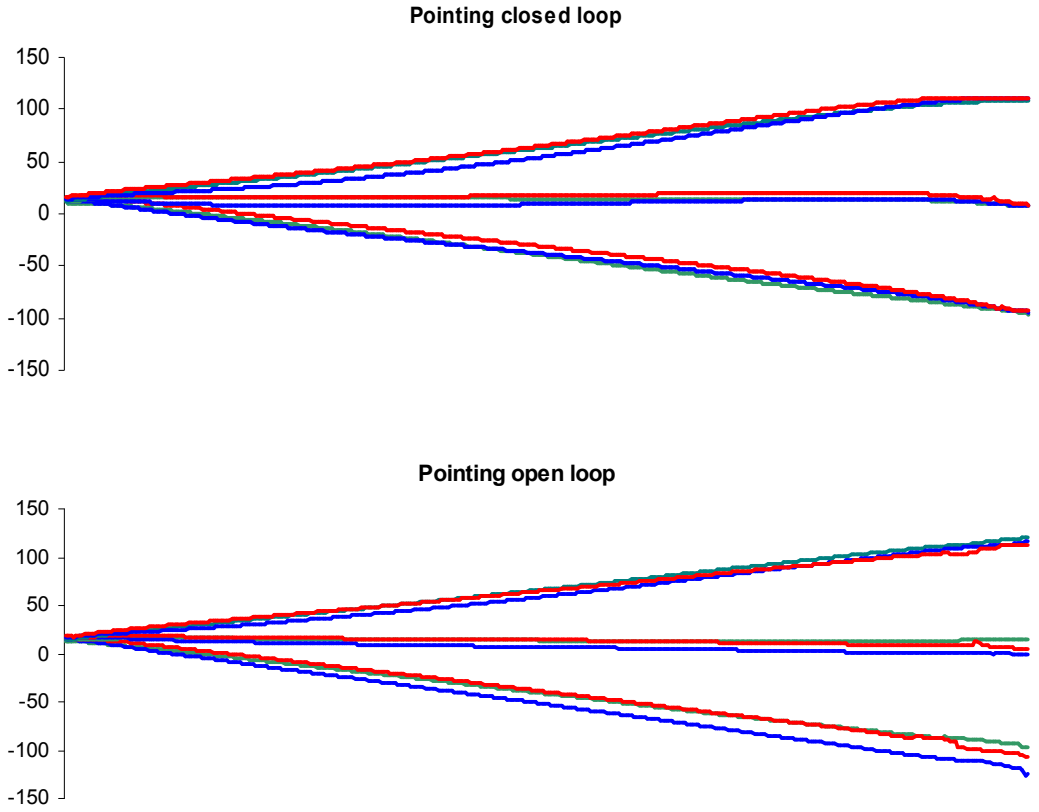

Figure 7 – Mean reaching trajectories (in the x-y plane) of the RH+ patients (red line), the RH- patients (blue line) and the healthy controls (green line) in target-directed pointing in closed and open loop per target position (represented in the y-axis in mm).

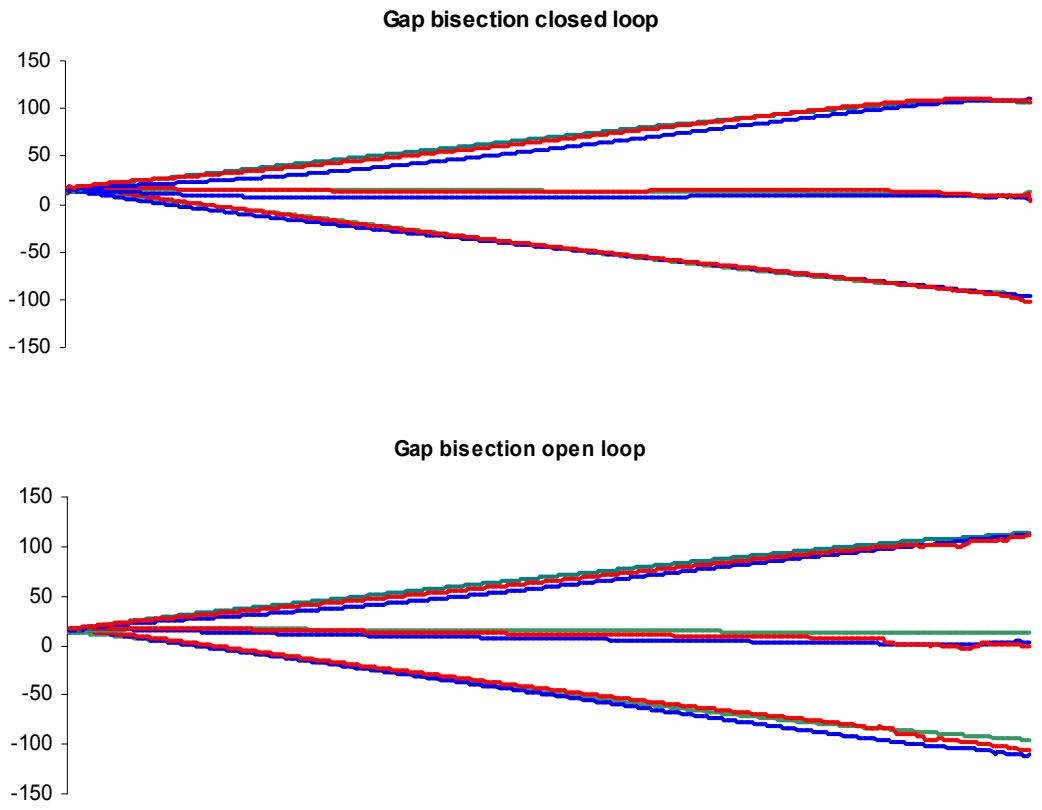

Figure 8 – Mean reaching trajectories (in the x-y plane) of the RH+ patients (red line), the RH- patients (blue line) and the healthy controls (green line) in gap bisection in closed and open loop per target position (represented in the y-axis).

These observations indicate that the participant's hand paths were straighter when they bisected the space between two LEDs (in left and centred positions), when compared to when they had to point towards a single target. Moreover, this advantage for gap bisection was only present when visual feedback was available. It is important to note however that the analysis on terminal accuracy revealed that participants were less accurate in open loop reaching when compared to closed loop. Thus, although participants presented high pointing curvatures in closed loop for some target positions, the availability of visual feedback might have allowed them to correct their hand path so that

their terminal errors were much smaller in the closed loop condition, when compared to their accuracy when no visual feedback was available.

Moreover, there was no significant main effect of group. Thus, right-brain damaged patients with or without neglect did not show increased curvatures when compared to the healthy subjects, even when the target was presented in left space (see Tables 4 and 5 for descriptive statistics of HPC). In addition, as for the terminal accuracy analysis, RH+ patients' reaches were not significantly more curved than the ones of RH-.

Table 4 - Means and standard errors (in parenthesis) of cumulative HPC index (in mm) for the pointing condition per group, visual feedback and target position.

	Pointing closed loop			**Pointing open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	13.3 (2.7)	9.1 (2.1)	9.9 (1.9)	12.2 (3.7)	9.2 (3.5)	15.0 (4.6)
RH-	15.0 (1.7)	4.0 (1.8)	4.8 (2.7)	0.9 (3.9)	0.0 (1.2)	7.7 (2.2)
RH+	20.8 (2.4)	9.8 (2.1)	12.4 (1.5)	9.2 (3.5)	5.7 (4.5)	10.6 (4.4)

Table 5 - Means and standard errors (in parenthesis) of cumulative HPC index (in mm) for the gap bisection condition per group, visual feedback and target position.

	Gap bisection closed loop			**Gap bisection open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	10.7 (2.8)	8.5 (1.9)	14.0 (2.3)	9.5 (4.1)	10.1 (2.8)	14.7 (4.7)
RH-	9.9 (1.4)	1.7 (1.3)	5.5 (2.4)	5.0 (3.5)	1.5 (3.1)	7.2 (2.6)
RH+	11.7 (2.6)	6.3 (2.0)	12.3 (2.0)	8.3 (5.1)	2.7 (4.7)	10.4 (3.9)

Reaction Time

In Table 6 and 7, the descriptive statistics for the reaction times of the pointing and gap bisection conditions are presented respectively. This time, the analysis

of variance did not reveal any main effect of target, task or visual feedback and the interaction between these factors was also not significant. Although there was no main effect of group, the interaction between group and target was significant [$F_{(2,54)}$ = 4.46, p < .01]. Pairwise comparisons revealed that only for leftward reaches neglect patients had increased reaction times when compared to healthy controls (mean difference = 126ms, p < .05), yet were no different from patients without neglect (mean difference = 38ms).

Table 6 - Means and standard errors (in parenthesis) of reaction time (in ms) for the pointing condition per group, visual feedback and target position.

	Pointing closed loop			**Pointing open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	301 (58)	314 (54)	308 (55)	271 (19)	275 (15)	293 (21)
RH-	319 (25)	295 (24)	285 (21)	400 (32)	415 (43)	409 (23)
RH+	460 (79)	399 (84)	370 (65)	391 (28)	384 (24)	377 (18)

Table 7 - Means and standard errors (in parenthesis) of reaction time (in ms) for the gap bisection condition per group, visual feedback and target position.

	Gap bisection closed loop			**Gap bisection open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	286 (44)	313 (50)	297 (45)	270 (20)	286 (22)	293 (22)
RH-	329 (38)	323 (32)	325 (38)	429 (24)	410 (30)	434 (37)
RH+	394 (60)	338 (35)	350 (40)	386 (27)	380 (28)	361 (28)

To investigate if this increase in latency was related to neglect severity, Pearson correlation analyses were run between the BIT, the bisection errors, the lateralised index of the Balloons test and the mean reaction times for

leftward reaches for all right-brain damaged patients. However no significant correlations were found. Furthermore, the correlation analysis between the mean reaction times for leftward reaches and the percentage of stimuli detected on the left side of the screen in the computerized perimetry test or the percentage of bilateral stimuli detected on the extinction task was also not significant. These observations suggest that the increased reaction time for leftward reaches was not significantly associated with the presence of neglect or hemianopia or extinction.

Once more to investigate which brain areas were critically associated with the increased reaction times for leftward reaches, the voxel-based lesion analysis was implemented (see Figure 9). Several cortical and subcortical brain areas were significantly associated with the increased times for leftward movement initiation ($Z > 2.00$, $p < .05$; BM range = -4.14, 12.73). The most strongly associated voxels were located around the parietal-occipital fissure, affecting white matter regions near the precuneus [peak Z = 12.73 (16, -56, 32)] and superior occipital gyrus [Z = 3.13 (34, -73, 24)], the inferior parietal lobe [peak Z = 12.73 (62, -38, 32)] and the frontal white matter near the posterior cingulate gyrus [peak Z = 12.73 (21, -34, 32)]. In addition, this deficit was also associated with damage to the middle and superior temporal gyri [peak Z = 6.53 (59, -45, 0; 61, -59, 16) and surrounding white matter [peak Z = 6.53 (47, -70, 16); peak Z = 3.85 (50, -32, 16)]. Subcortically, the statistical map revealed that lesions in the white matter surrounding the lentiform nucleus [peak Z = 6.53 (32, -3, 0)], the caudate [peak Z = 4.25 (35, -15, -8)] and nearby white matter [peak Z = 4.25 (35, -17, -8)], the white matter close to the claustrum [Z = 4.25 (33, -

12, -8)] and the thalamus [Z = 4.25 (23, -16, 8)] were also associated with this deficit.

To a lesser extent, damage to the white matter near the inferior temporal gyrus [Z = 3.16 (64, -50, -16)] and to the gray and white matter areas at the border between fusiform gyrus [Z = 3.16 (34, -75, -16)] and the temporal lobe [Z = 3.16 (52, -66, -16)] were also related with this impairment. Finally, also associated with this, were lesions in the inferior frontal gyrus gray [Z = 2.42 (57, 42, 8)] and surrounding white matter [Z = 2.42 (50, 29, 0)].

Again lesion volume did not significantly correlate with increased leftward reaction times.

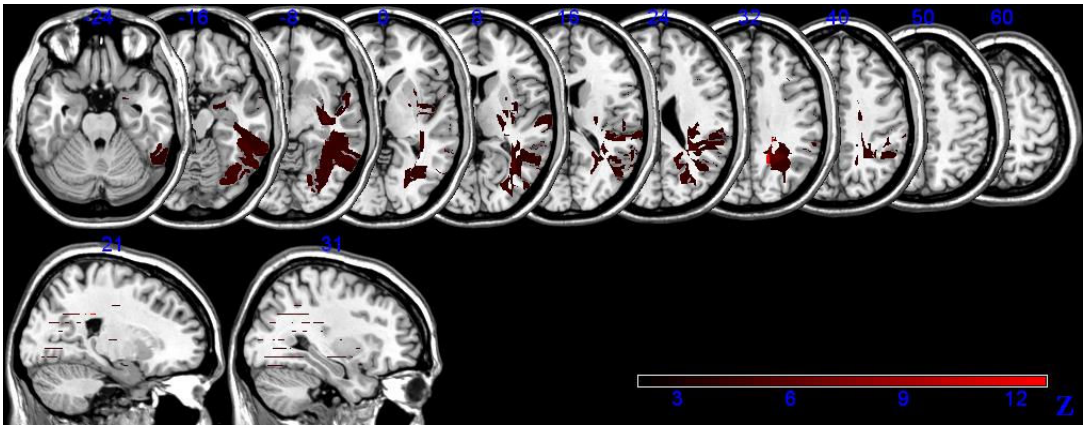

Figure 9 - Voxel-based lesion statistical map (in axial and sagittal view) revealing the right-brain damaged areas significantly associated with increased reaction time to initiate a movement towards a leftward location. The legend (and coloured areas) represents the range of Z scores that survived FDR threshold of $p < .05$.

Movement time

There was a significant main effect of side [$F_{(2,54)} = 101.82$, $p < .001$], and post-hoc tests revealed that participants presented a gradient increase in movement

time from rightward, to centre and leftward targets (p < .001 for all comparisons). The effect of visual feedback [$F_{(1,27)}$ = 49.44, p < .001] was also significant, in that participants took longer to complete their movements without visual feedback of their hand and target during movement, when compared to the closed loop condition. Finally, there were no effects of task or group, and neither patient group took longer to complete their movements when compared to healthy controls, for all target positions (see Table 8 and 9 for movement time descriptive statistics).

Table 8 - Means and standard errors (in parenthesis) of movement time (in ms) for the pointing condition per group, visual feedback and target position.

	Pointing closed loop			**Pointing open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	613 (33)	576 (32)	563 (36)	725 (46)	700 (47)	679 (50)
RH-	652 (22)	615 (23)	608 (22)	810 (40)	767 (38)	729 (38)
RH+	725 (34)	664 (30)	652 (26)	801 (47)	756 (48)	710 (43)

Table 9 - Means and standard errors (in parenthesis) of movement time (in ms) for the gap bisection condition per group, visual feedback and target position.

	Gap bisection closed loop			**Gap bisection open loop**		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Healthy controls	650 (41)	611 (36)	589 (39)	733 (54)	705 (51)	672 (53)
RH-	692 (26)	648 (28)	633 (24)	861 (43)	781 (36)	763 (43)
RH+	727 (39)	684 (39)	654 (32)	814 (50)	753 (51)	728 (56)

Discussion

The current study aimed to clarify whether, compared to right hemisphere lesioned patients without neglect, patients with hemispatial neglect were impaired, when reaching towards the contralesional side of space with or without visual feedback of the hand and target position. Furthermore, computerized lesion-mapping techniques were used to further identify the set of brain regions potentially related to the motor abnormalities observed after lesions in the right hemisphere.

No evidence for neglect-specific deficits in reaching after right-hemisphere lesions

As expected, no neglect-specific impairment was found on either reaching or gap bisection, even when movements were made without visual feedback, and even when stimuli were presented on the left side of space. In fact, only the patients without neglect were less accurate than the healthy controls in open loop reaches towards the left side of space. These findings are in agreement with Harvey, Milner and Roberts (1994). However, in terms of directionality no rightward biases in the terminal errors were found, as these patients presented overshoot errors with respect to the ideal reach for both open loop tasks (see Figure 5).

In addition, and as reported by Karnath, Dick and Konczak (1997), neither patient group differed from healthy controls in terms of the hand path curvature. In particular for gap bisection, this finding is remarkable since eight

out of the 11 neglect patients presented a significant rightward bias for line bisection (see Table 1). However, the current data agree with McIntosh *et al.* (2004a)'s findings that the advantage for gap bisections over line bisection is deemed to result from cueing effects. This could also explain the observation that my participants presented less curved trajectories in gap bisection when compared to when they had to point to a single LED.

In a similar vein, Robertson, Nico and Hod (1995) found that the rightward errors made by left neglect patients when pointing to the centre of a horizontal rod decreased when the instruction was to pick up the rod at its middle, a finding later replicated by Robertson, Nico and Hod (1997). Interestingly, Edwards and Humphreys (1999) reported that in one neglect patient the improvement found in the grasping task, when compared to the pointing task, only occurred when on-line visual feedback was available and that the decrease in the rightward error only emerged late in the movement trajectory. In line with this, I also found that for all participants the advantage of gap bisection over pointing in terms of HPC was only present when visual feedback was available.

The present data is also consistent with the dissociation reported by Pritchard *et al.* (1997). They found that though a neglect patient systematically underestimated the size of objects presented on the left (relative to those presented on the right), she was able to reach out and grasp the same objects with ease. In later studies, McIntosh *et al.* (2002) showed that a wider sample of neglect patients could perfectly grasp leftward objects and Harvey *et al.* (2002) also found no neglect-specific impairment for grasping in open loop.

In keeping with this, it is well established that neglect patients do not show the gross misreaching to visual targets that is observed in patients with optic ataxia. Lesions in these patients were classically assigned to the parietal lobes, including the intraparietal sulcus and inferior and/or superior parietal lobules (Perenin & Vighetto, 1988). Karnath and Perenin (2005) recently used lesion subtraction analysis to clarify the parietal foci involved by contrasting the lesions in patients with parietal damage with optic ataxia against lesions in parietal patients without the condition. They found that optic ataxia was commonly associated with lesions in the precuneus, in the superior-occipital gyrus near the parieto-occipital junction and in the superior parietal lobe. Indeed, these areas are thought to be part of the dorsal stream (for a review see Culham, Cavina-Pratesi & Singhal, 2006; Culham & Valyer, 2006; Milner & Goodale, 2006). In patients with left neglect, the site of maximum lesion overlap is usually located in the right inferior parietal lobe (Mort *et al.*, 2003) or the superior temporal cortex (Karnath, Ferber & Himmelbach 2001; Karnath *et al.*, 2004), which might suggest that visual dorsal stream is relatively spared in neglect (Milner & Goodale, 1995, 2006).

Moreover, it has also been suggested that neglect patients are unimpaired in reaching due to the existence of a double dissociation within the PPC: while more superior regions seem to be involved in rapid on-line visuomotor control, more inferior areas, like the ones damaged in neglect, seem to subserve longer-lasting, explicit multimodal representations (e.g., Himmelbach *et al.*, 2007). In line with these claims, other studies have further demonstrated that neglect patients are also able to avoid obstacles on the neglected side whilst reaching (McIntosh *et al.*, 2004b; Milner & McIntosh,

2003), a finding that contrasts with the observation that patients with optic ataxia are impaired in such tasks (Schindler *et al.*, 2004).

Regarding latency, patients with neglect demonstrated increased reaction times towards contralesional stimuli when compared to healthy controls, but were no different from patients without neglect. This observation again suggests that this deficit is not specific to neglect and in fact this latency increase did not correlate with neglect severity. Furthermore, I also did not find an increase in movement time after right-brain damage, as both patient groups did not even differ from healthy controls. A number of studies have already shown that there are no neglect-specific impairments in reaching (Himmelbach & Karnath, 2003; Konczak *et al.*, 1999; Konczak & Karnath, 1998) and that is exactly what was replicated here for both open and closed loop pointing and gap bisection.

Nonetheless the present findings contradict those of Mattingley *et al.* (1992, 1994, 1998*a*, 1998*b*), who found increased latencies specific to neglect. However, I would argue that display complexity might explain the observed differences: in Mattingley *et al.*'s tasks, displays containing competing stimuli were used and so, the increased latencies observed for neglect patients may be a result of impaired stimulus selection rather than a deficit in motor planning and execution.

Alternatively, the finding that neglect patients were not specifically impaired in reaching could be related to the auditory tone which cued the subjects to start the movement. This might have increased the patient's alertness and ameliorate their spatial bias. Indeed, nonspatial warning sounds have been shown to improve the perception of visual events on the left side of

space relative to right events in neglect patients (e.g., Robertson *et al.*, 1998). However, in Himmelbach and Karnath (2003)'s study no auditory cue was used to cue movement start and still no neglect-specific differences were observed in reaching performance.

In addition, another possibility could be that wearing the shutter goggles could have cued the patients about the type of trial that was about to unfold. However, Jakobson and Goodale (1991) have showed that if open and closed loop trials are randomly interleaved rather than blocked healthy participants treat all trials as open-loop trials. Blocking the trials thus allows the visuomotor system to anticipate the reliable presence (or absence) of visual feedback and, thus, to program the reach accordingly (Connolly & Goodale, 1999).

Motor deficits after right-hemisphere damage

Interestingly, right-hemisphere damaged patients (irrespective of neglect) presented increased reaction times for all leftward reaches as well as reduced accuracy in open loop leftward reaching. It has been suggested that in darkness the motor system cannot rely on visual feedback and is presumably operating in an open-loop mode, which requires that large parts of the trajectory reflect the motor plan designed before execution (Harvey, Milner & Roberts, 1994). Thus the present findings indicate that the early motor planning and/or programming processes (i.e., target selection and/or target localization and/or computation of the motor command), are frequently impaired after right hemisphere damage. However, I would argue that once the coordinates of a specific target have been acquired, the subsequent execution of the reach is functional, as no abnormalities were observed in the closed loop condition.

Moreover, the finding that RH- were only impaired in accuracy when no visual feedback was available suggests that this group used visual feedback to normalize spatial accuracy and that on-line correction is relatively spared after right-brain damage. Conversely, it also indicates that this group of patients are more dependent on visual feedback than healthy controls. Alternatively, since participants have to hold the target location in the mind during the open loop phase, errors in this condition could be simply related to a deficit in spatial working memory. This has previously been demonstrated for neglect patients and even right hemisphere patients without neglect, who perform worse than healthy controls (Malhotra *et al.*, 2004, 2005; Vuilleumier *et al.*, 2007).

Target location is usually determined from visual information, but the sense of hand position can be localized in space through both vision and proprioception. The present study did not separate the effects of preventing visual feedback about limb position from preventing vision of target position. Thus it is impossible to know what type of information the patients are particularly dependent on for their end-point accuracy. Also relevant would have been to manipulate the timing at which visual feedback is available (e.g., no feedback, feedback during either the first or last portion of the trajectory, feedback during the entire trajectory) as this would reveal when the presence of visual information is crucial for optimizing the reaching accuracy of right-brain damaged patients.

Contribution of visual information to the on-line control of arm movements has also been studied using the so-called double-step paradigm, where the target is displaced at movement onset. In young adults, a target location change at the outset of a pointing movement elicits a fast on-line

correction to accurately reach the target without requiring the programming of a new motor output (e.g., Goodale, Pélisson & Prablanc, 1986). Interestingly, fast corrections in response to target displacements have been found not to require awareness of the location shift and under certain circumstances participants are even unaware of their own limb modifications (e.g., Pélisson *et al.*, 1986). Recently, it has also been shown that these corrections are so fast that they can prevail in spite of an instructed stop response and this is taken as evidence for a strong 'automatic pilot' of the hand, believed to be mediated by neural structures of the PPC (Pisella *et al.*, 2000; Gréa *et al.*, 2002).

Farnè *et al.* (2003) studied seven patients with right-brain lesions (four with neglect) in a double-step grasping task. They found that while their performance was close to that of healthy controls in the right side of space, they did not show positional tuning of grip formation, nor fast corrections of their movements when acting in the left hemispace. Importantly, and in agreement with the present data, this impairment was not specific to neglect. The small number of patients included in Farnè *et al.* (2003)'s investigation did not allow a precise location of the damage associated with these deficits, albeit six out of the seven patients had frontal lobe damage. Haaland *et al.* (2004) studied double-step reaching with and without visual feedback of the arm in 17 left and 15 right hemisphere lesioned patients. It was observed that left hemisphere damaged patients presented increased latencies and trajectory deficits. On the other hand, in accordance with the present findings, they found that the final error of the right-brain damaged patients was greater in the open loop condition and when the target location was perturbed. Thus, these studies indicate that although neglect patients are also not specifically impaired when performing on-

line corrections in response to target jumps, some right-brain damaged patients might present impairments in this ability. As a result, future studies could combine lesion-symptom mapping to assess the neural basis of deficits in on-line corrections in patients with right hemisphere lesions.

Brain regions potentially associated with motor deficits

The present findings suggest that both right-hemisphere lesioned patients with and without neglect might be impaired when reaching towards the left side of space. What remains to be clarified is the anatomical basis of these deficits. While a more refined anatomical study would require a larger number of patients, here an **initial** exploration of this matter via voxel-based lesion-symptom analysis was performed.

The lesion subtraction analysis revealed that areas in the superior temporal gyrus, insula and claustrum were most frequently damaged in the neglect group. What is remarkable is that none of these areas were associated with the reduced accuracy for open loop reaches, which is in line with the claim that this deficit is not neglect-specific. Instead, the accuracy impairment was associated with damage to the basal ganglia (lentiform nucleus), the occipito-parietal areas near the precuneus and the parietal-frontal areas located in the inferior parietal lobe and post- and pre-central gyri. Similarly, increased reaction times to the leftward targets were also associated with damage near the lentiform nucleus, to parieto-occipital areas near the superior occipital gyrus and precuneus and parietal-frontal areas (inferior parietal lobe, posterior cingulate and inferior frontal gyrus).

Of potential interest is the robustly highlighted basal ganglia region as it corroborates previous findings that lesions in this area are related to the motor aspects of neglect (Bisiach *et al.*, 1990; Tegner & Levander, 1991). Moreover, in a recent anatomical study Sapir *et al.* (2007) investigated the neural basis of directional hypokinesia in 29 neglect patients. Patients were classified as having directional hypokinesia when they showed slowing in the ability to detect contralesional targets when reaching in a leftward direction, compared with a rightward direction. In the six patients who showed the motor bias Sapir *et al.* (2007) found that the maximum lesion overlap was in the lentiform nucleus (putamen), the claustrum, followed by the white matter in the pre-central gyrus, the inferior frontal gyrus, the frontal operculum and the anterior insula. Like Sapir *et al.* (2007) I also found that increased reaction times were associated with damage to the basal ganglia and inferior frontal gyrus.

Another cluster of voxels that was strongly associated with the motor abnormalities was located in the vicinity of the parietal-occipital fissure involving the white matter near the superior occipital gyrus and precuneus. This observation supports the neural underpinnings of optic ataxia (Karnath & Perenin, 2005). Although, the parietal-occipital voxels reported here are located more inferiorly than the ones reported in this previous study, the present data would suggest that areas surrounding the parietal-occipital fissure are involved in the visuomotor computations for reaching.

In line with these suggestions, several neuroimaging studies (e.g., Astafiev *et al.*, 2003; Connolly, Anderson & Goodale, 2003; Prado *et al.*, 2005), with healthy individuals, have provided evidence that parieto-occipital areas mediate the mechanisms involved in action planning and control. Indeed,

Connolly, Anderson and Goodale (2003) found activation in a region located along the medial surface of the superior aspect of the parietal cortex in the precuneus that responded preferentially when subjects planned to point rather than make a saccade to a remembered location. They argued that this region appears homologous with the monkey parietal reach region, coding the visuomotor intention to make an arm movement to a particular location. In a more recent fMRI experiment, Culham *et al.* (2008a) investigated the role of the superior parietal occipital cortex (SPOC; which includes the superior end of the parieto-occipital sulcus as well as regions in the cuneus and precuneus) in reaching. Interestingly, the anterior intraparietal sulcus was actived for to the grasping component regardless of whether a reach was required, but the SPOC was much more activated when actions were executed toward an object requiring arm extension. In the second study they found that the SPOC showed preferential activation for objects within a reachable space, when compared to a condition where the object was in a position beyond the reach. In the final experiment they observed that SPOC activation was modulated by gaze distance and argued that this area might provide the dorsal visual stream with information about object distance important to guide the reach towards a target.

Several transcranial magnetic stimulation (TMS) studies have also implicated PPC areas in feed-forward planning and feedback control. For instance, in Desmuget *et al.* (1999)'s study participants were asked to 'look and point' with their right hand to peripheral visual targets that jumped in some trials and single TMS pulses were applied over the left PPC. They found that when TMS was applied subjects were still able to correctly reach to the stationary target, but were unable to correct the aiming trajectory in the jumping target

trials. Importantly, when, subjects used their left hand and were stimulated on the left PPC no effect of TMS was observed, which suggests that TMS did not perturb target localization. Desmuget *et al.* (1999) suggested that left PPC seems responsible for updating the motor plan on the basis of visual feedback, in that it mediates the estimation of hand position, the computation of the motor error and the corrective signal. In a later sudy, Vesia *et al.* (2008) applied single-pulse TMS over the dorsal-lateral PPC (a site over a part of the angular gyrus and close to the posterior part of the IPS) while varying visual feedback of the hand (full vision; final vision; initial and final vision; middle and final vision). They found that left parietal stimulation significantly increased end-point variability, whereas right parietal stimulation produced a significant leftward shift in both visual fields. However, these effects were only observed in the final vision of hand condition. In line with Desmurget *et al.* (1999), they argued that TMS over the PPC does not disrupt the internal representation of the visual reach goal, but rather the reach vector (target location – hand position) or the sense of initial hand position that is used to calculate this vector.

Thus, there is growing evidence in the literature that areas in the PPC cortex play an important role in both the planning and on-line control of visually-guided reaching. Indeed, very recently Blangero *et al.* (2009) conducted a meta-analysis on 15 fMRI studies in reaching and found four bilateral foci of activation in the vicinity of the intraparietal sulcus: parieto-occipital junction, precuneus, middle part of the intraparietal sulcus and anterior part of the intraparietal sulcus. In line with this, I found that damage to occipito-parietal voxels in the vicinity of the precuneus and inferior parietal lesions were related to increased latencies needed to initiate the reach and to a higher dependence on visual

feedback whilst reaching (as evidenced by increased terminal errors in open loop).

Nevertheless, not only PPC lesions were involved with the motor deficits observed here. In particular, I also found that damage to parieto-frontal areas located in the post- and pre-central gyrus were associated with poor accuracy in open loop reaching and that lesions to areas near the posterior cingulate gyrus were related with increased reaction time to leftward targets. In line with these observations, Astafiev *et al.* (2003) also found that pointing (but not looking or attending) preparation selectively activated a fronto-parietal brain network involving the anterior cingulate cortex, the inferior and superior parietal lobe, the precuneus, the dorsal pre-central gyrus (i.e., dorsal premotor area) and the posterior superior temporal sulcus. Also in line with the fronto-parietal areas reported here, is the study by Beurze *et al.* (2007). They found activation in the posterior parietal cortex (intraparietal sulcus), premotor cortex, the medial frontal cortex (anterior cingulate and superior frontal sulci) and the insular frontal cortex in a task that involved the integrative processing of target and arm information to establish the reach plan. Beurze *et al.* (2007) concluded that the posterior parietal cortex and the dorsal premotor cortex are involved in the computations necessary for reach planning in that they specify both the spatial location of a target and the effector selected for a forthcoming action.

In addition, damage to the thalamus was also implicated in increased reaction time, which is in line with anatomical studies that report the existence of several neural pathways which run through the thalamus to anterior cortical areas and play a role in action generation and monitoring (see Sommer, 2003 for a review). Interestingly, Paus (2001) reviewed evidence which suggests that

an important source of input to the cingulate cortex comes from the thalamic nuclei, which might mediate the arousal-related changes in cingulate cortex activity. Perhaps this might be related to the finding that neither lesions to the cingulate or the thalamus were related to the errors in open loop and were only associated with increased reaction times.

One surprising finding was that damage to temporal areas (superior, middle and inferior temporal gyri) was also associated with increased reaction time. One might argue that because the hotspot of damage in the neglect patients is also in the superior temporal gyrus than this might indicate that this deficit is neglect-specific. Indeed, damage to the claustrum was also associated with increased reaction time. However, the behavioral analysis would disagree with this view point, as the increased reaction time did not correlate with neglect severity and neglect patients were not significantly different from RH- controls. Instead, I would propose that damage to the superior temporal areas alone may not be the single cause of the increased reaction time, as some patients without neglect may also present increased reaction times to leftward targets. In addition, it has been suggested that the occipital lobe has direct connections with the frontal lobe through a white matter tract (the inferior fronto-occipital fasciculus; IFOF), which runs deeply in the temporal lobe (see Doricchi *et al.*, 2008 for a review). Urbanski *et al.* (2008) recently employed diffusion tensor imaging tractography in four stroke patients with right hemisphere lesions (two with neglect) and found that in the neglect patients it was not possible to track the IFOF in the right hemisphere. These findings led the authors to suggest that lesions in this particular white matter tract may contribute to neglect by impairing top-down modulation of visual areas from frontal cortex or the transmission of

visual input to frontal areas important for arousal. Thus, the association between temporal damage and increased reaction time in the present study could represent the effect of disconnection rather than temporal damage *per se*.

It is important to note that I do not claim that damage to one of these regions alone is responsible for visuomotor deficits after right-brain damage. Instead it is proposed that these deficits are not a consequence of damage to neglect-associated areas alone, but result from additional lesions to key nodes of the visuomotor control network. In particular, the consistent association of reaction time and terminal error deficits with damage to the basal ganglia nuclei, occipital-parietal areas and parieto-frontal lobe regions suggests that these are the critical regions for the reaching deficits after right-brain damage. In line with this view, it has been found that basal ganglia lesions associated with neglect cause abnormal perfusion of the superior temporal gyrus, inferior parietal lobe and inferior frontal gyrus (Hillis *et al.*, 2005; Karnath *et al.*, 2005). Furthermore, it is well established that the PPC has critical white matter connections to the frontal lobe, the cerebellum and the basal ganglia (e.g., Rizzolatti & Luppino, 2001) and that it is well positioned to receive both visual and somatosensory input and to send output to premotor and motor areas in the frontal cortex. Thus, even a small lesion in a location where several antero-posterior connections traverse, might be sufficient to disrupt the visuomotor modules in both frontal and parietal cortices (Bartolomeo, Thiebaut de Schotten & Doricchi, 2007). Future work with a larger group of patients will be required to corroborate and refine the present findings.

Conclusion

The current study shows that neglect *per se* does not produce impairments either in planning or execution of actions, which is in line with the proposal that the dorsal visual stream for on-line visuomotor control is relatively spared in these patients (Milner & Goodale, 1995, 2006). Moreover, I showed that motor deficits do emerge after right-hemisphere damage, but irrespectively of the presence of neglect. Voxel-based lesion-symptom analysis revealed that such deficits are associated with damage to the basal ganglia as well as to occipital-parietal and frontal areas, structures that are often associated with but not critical for hemispatial neglect (Karnath *et al.,* 2004; Mort *et al.,* 2003). Thus, these results confirm the current view that neglect is not a single condition, but a complex syndrome of multiple deficits, which vary depending on the specific networks damaged (Husain & Nachev, 2007).

In the following chapter I will examine the possibility that there are different forms of actions (on-line and off-line) and that neglect might only affect actions thought to depend on off-line processing presumably carried out by the ventral visual stream (Goodale, Westwood & Milner, 2004; Milner, 1995; Milner & Harvey, 2006; Milner & Goodale, 2006). In particular, the next chapter will examine the performance of neglect patients in delayed actions when compared to immediate actions.

Chapter 2

Immediate and delayed reaching in patients with hemispatial neglect

Introduction

As reviewed in the General Introduction, Milner and Goodale (1992, 1995, 2006, 2008) proposed a model of vision that made a distinction between 'vision for perception' and 'vision for action' outlining, a new way of looking at the functional organization of the visual ventral and dorsal streams. Nonetheless, according to their model not all actions depend exclusively on the visuomotor modules of the dorsal stream, as another key assumption of this model is that the two visual streams operate under different time constraints and frames of reference.

The visual world around us is quite unstable, in that the object and observer locations may change quite rapidly. Milner and Goodale (1995, 2006) propose that in order to ensure accuracy, the action system must provide constantly updated visual information about the target object in coordinates relative to the observer (i.e., in an egocentric frame of reference). Consequently, they suggest that the dorsal stream uses on-line computations so that retinal inputs are transformed at the time the action is about to be executed. So, according to these claims, my dorsal stream ensures that the visual input about this thesis remains both relevant and accurate, so that I can grab it whilst I am

moving to another room. On the other hand, they suggest that the ventral visual stream retains information over a much longer period of time and within an allocentric (i.e., scene based) frame of reference. They argue that it does so to allow object characteristics to be maintained and thereby aiding object recognition across different timings, contexts and viewing conditions. That is, my ventral stream will allow me to recognize this thesis many months, even years, after I have submitted it.

If this temporal dissociation between the two streams exists then movements directed to memorized objects (termed delayed actions) might be expected to look rather different from movements directed to objects that remain visible. Indeed, in an early study, Elliot and Madalena (1987) found that healthy subjects exhibited greater errors in their movement amplitude after 2s period of vision occlusion prior to movement initiation. In a similar vein, Gnadt, Bracewell and Anderson (1991) also showed that saccades towards a present target are quite different from saccades towards remembered targets in both humans and monkeys.

In a pivotal paper, Goodale, Jakobson and Keillor (1994) carried out a series of experiments to investigate the differences in the visual control of pantomimed and natural grasping movements. In their first experiment they asked healthy participants to perform immediate grasps or 2s delayed grasps towards one of 3 objects. In addition, they also investigated a third condition in which immediate and delayed trials were randomized rather than blocked. As expected, they found that delayed actions reached lower peak velocities, tended to last longer and were less accurate when compared to immediate grasps, regardless of the expectation of the subject about the trial type that was about to

unfold. Goodale, Jakobson and Keillor (1994) hypothesized that the visuomotor modules operate in real time, but the stored information during delayed actions must depend on another system that represents object locations for long periods of time. In addition, they speculated that this system might be the same as the perceptual system presumed to mediate object recognition.

To test the hypothesis that the ventral stream might mediate pantomimed actions, Goodale, Jakobson and Keillor (1994) further investigated visual form agnosia patient DF, whose ventral stream shape-processing system is destroyed (James *et al.*, 2003). She was asked to perform both immediate and 2s delayed grasping movements when compared to 10 age-matched controls. It was found that although DF fails to discriminate between the objects in perceptual testing (Goodale *et al.*, 1991), when she reaches out to pick up these objects her hand preshapes in-flight in a manner that reflects normal sensitivity to their dimensions. However, when a delay is imposed between object viewing and movement initiation, all evidence of anticipatory hand shaping disappears in DF. The authors argued that DF has lost all information about object size needed to preshape her hand in-flight in the delayed condition as she has no 'percept' of the object in the first place and thus cannot fall back on the stored information that was available to normal controls. In other words, they suggest that the visuomotor mechanisms responsible for the control of actions towards visible objects do not appear to retain (in memory) information about the target object or the grasping movement it affords. Visual memory for object features instead appears to depend on the perceptual mechanisms that reside in the ventral stream.

In agreement with Goodale, Jakobson and Keillor (1994)'s findings, it was also later reported that when asked to point to targets in real time DF's accuracy is excellent, however when a 10s delay is introduced, she makes errors twice as large as those of three age-matched control participants (Milner, Dijkerman & Carey, 1999). Although, Goodale, Jakobson and Keillor (1994)'s hypothesis is attractive it is nevertheless based on a single dissociation. Patient DF performed normally on the immediate pointing task and very poorly in the delayed task, but such a pattern could simply reflect task difficulty, which is presumably greater in delayed than immediate actions. On the other hand, if their hypothesis is correct it should be possible to observe the converse pattern of results in patients with damage to the immediate visuomotor system of the dorsal visual stream.

Indeed, that is exactly what Milner *et al.* (1999) investigated in a later study. They compared the performance in immediate versus delayed reaching in a patient with optic ataxia to that of three age-matched controls. They studied patient AT who suffered from bilateral parietal damage extending to the upper part of the occipital lobes and slightly to the medial part of the right premotor cortex. At the time of testing this patient presented severe optic ataxia for targets in her peripheral visual field. In the immediate condition participants were asked to point to one of the presented LEDs after a viewing period of 2s while maintaining fixation on a central light. In the delayed condition, the LED was presented for 2s, but participants had to wait for a tone presented 5s later before pointing to the remembered target location. Paradoxically, but according to their predictions, they found that their patient showed significantly smaller terminal errors and decreased latencies in the delayed condition when

compared to immediate reaches. These results are even more astonishing when compared to the performance of healthy controls, who performed worse in the delayed condition. The authors suggested that the improvement of AT with delay reflects the sparing of her temporal lobes. This sparing could partially compensate for her parietal damage by retaining information about relative locations of the target with respect to the fixation point, thus enabling improved pointing under delayed conditions. Milner *et al.* (1999) argued that there are two systems for spatial representation in the brain specialized for two broadly different purposes: one is dedicated to the immediate guidance of actions in space, uses spatial information coded in egocentric coordinates and is located in the superior parietal lobe; the other one is designed for the longer-term coding of spatial relationships for perceptual and cognitive purposes and may lie in a more inferior (parieto-temporal) location in the brain. Furthermore, they suggest that this later system could operate allocentrically in the delay task by computing target location relative to the fixation point and may receive information about spatial relationships through occipito-temporal visual areas.

Importantly, these results have been further replicated with other optic ataxic patients. Milner *et al.* (2001) studied patient IG, who suffered from bilateral occipito-parietal infarction and who, like AT, was impaired in immediate pointing towards peripheral targets. In a first session, Milner *et al.* (2001) asked IG to perform perceptual matching (i.e., manual size estimate), delayed pantomime grasping (i.e., pretend to grasp an object they had seen 5s earlier) and delayed real grasping (i.e., a condition in which the object remained present before and after the delay; equivalent to immediate grasping). They found that IG was within the normal range in the perceptual matching task, but failed to

perform delayed real grasps towards the same objects. However, and in line with previous results reviewed above, her grasping performance improved in the 5s delay condition (i.e, delayed pantomime), when compared to an immediate task. Furthermore, after practise IG became able to scale her handgrip when grasping a real target object that she had previewed earlier, presumably by using a pantomiming strategy. In a second experiment, they investigated which sources of visual information IG was using during delayed real grasping by elegantly interposing catch trials in which the object was changed during the 5s delay period. Indeed, they found that she was using a memory-based route to bypass her on-line visuomotor deficits. In particular, she was opening her hand widely when the wide object had been previewed, even when reaching out to grasp the narrow object. This pattern of results was not observed in healthy participants as they just grip scaled according to the object that was facing them, regardless of the object that had been seen previously. Milner *et al.* (2001) argued that their results indicate that networks independent of the dorsal visual stream can provide off-line visuomotor guidance.

Revol *et al.* (2003) also found an accuracy improvement in a delayed reaching task with an optic ataxic patient (OK) who had posterior parietal damage in the right hemisphere. In addition, Rossetti *et al.* (2005) set out to investigate both IG and AT in immediate, delayed and delayed real pointing tasks. They also included some incongruent trials in delayed real pointing by changing the target's location during the delay. They replicated their previous results (Milner *et al.*, 2001), in that the patients' performance improved in delayed conditions. In addition, they again found that in the delayed real pointing incongruent trials, patients initiated their movements towards the

previously viewed target location rather than the one facing them. They argued that optic ataxic patients relied on off-line processing to remedy their impaired access to on-line visual information.

Taken as a whole, the findings with healthy and brain damaged patients agree with Milner and Goodale (1995, 2006)'s idea that when time is allowed to pass and a reaction has to be made on the basis of a visual memory, the ventral stream is required for successful performance. In this case, visuomotor control in the sense of the guidance of an action to a target, visible at the moment the response is required, is replaced by 'perceptual control' dependent upon a memory trace of the target delivered by the perceptual mechanisms in the ventral visual stream and then used to guide behaviour. In sum, based on this dissociation of temporal characteristics between the two streams, it is argued that there are two modes of control for object-directed action: an on-line mode that depends on the visuomotor networks of the dorsal stream and an off-line mode that depends, at least in part, on the perceptual mechanisms in the ventral stream (for a review see Goodale, Westwood & Milner, 2004).

Returning to the syndrome of hemispatial neglect and the purpose of this thesis, Milner and Goodale (1995, 2006) speculate that a disruption of spatial allocentric representations is at the core of neglect symptomatology. Accordingly, given the known properties of both streams, this disruption could be more conceivably accounted for by damage to an area that receives inputs from the ventral visual stream, as this stream is thought to be the one responsible for allocentric coding (e.g., Murphy, Carey & Goodale, 1998; Schenk, 2006). In contrast, they claim that the visual dorsal stream is relatively spared and that consequently patients have fewer problems with information

coded in purely egocentric coordinates. Indeed, in the previous chapter I have shown that on-line visuomotor control is not specifically impaired in patients with hemispatial neglect. However, as it has been suggested that there are different modes of action control then one might expect that these may also be differentially impaired in neglect (e.g., Milner & Harvey, 2006). In fact it has been hypothesized that neglect will only affect actions which tap into perceptual representations processed and stored by the ventral visual stream (Milner & Goodale, 1995, 2006; Milner & Harvey, 2006). More specifically, it is predicted (Milner & Harvey, 2006) that neglect should affect motor tasks where a choice of actions has to be made, or where an action is used to express a perceptual judgement or input (as in action pantomiming).

Thus, the present study was designed to further test these hypotheses using the immediate versus delayed paradigm previously used with visual form agnosia and optic ataxic patients. To do this, two groups of right hemisphere lesioned patients, one with and one without the presence of hemispatial neglect, as well as a group of healthy subjects were asked to perform both immediate and delayed pointing. According to the perception and action model and Chapter 1's findings, it is predicted that neglect patients should not be specifically impaired in immediate pointing even towards the left side of space. Conversely, it is hypothesized that these patients will show inaccurate pointing in the delayed condition, in particular in left space.

It has been previously shown that neglect patients present an impairment of spatial working memory, which during exploration for visual targets (as in cancellation tasks) may cause the patients to revisit previously detected targets (even on the right side of space) and treat them as if they have

not been seen before (Husain *et al.*, 2001; Wojciulik *et al.*, 2001). Pisella, Berberovic and Mattingley (2004) have reported non-lateralized working memory deficits in judgments of spatial locations, but not for colour or shape, in right parietal patients (but not in patients whom the parietal lobe was spared). They concluded that the parietal cortex is crucially involved in updating ad maintaining spatial representations across saccades. Malhotra *et al.* (2005) tested both patients with and without neglect in a vertical spatial working memory task, which did not require memory for sequence nor manual responses. They found that neglect patients were less able to recall spatial locations than right hemisphere patients without the condition, but importantly they were unimpaired in a verbal working memory span. In addition, this spatial working memory deficit correlated with neglect severity (as measured by cancellation tasks) and was associated with damage to the white matter of the parietal lobe and insula. They argued that spatial working memory deficits can occur when patients (with or without neglect) have damage to those regions. Thus, based on these findings it is expected that poor performance in the delayed pointing task will be related to poor visuospatial working memory performance, as participants must be using visuospatial working memory to bridge the temporal gap between perception and action.

Finally, and as in the previous chapter, I used the recently developed voxel-based lesion-symptom analysis (Rorden, Karnath, & Bonilla, 2007) to conduct an **initial** exploratory investigation of the lesioned right-hemisphere areas potentially associated with the motor impairments. In line with Milner and Goodale's (1995, 2006) proposal I expect that the possible neglect-specific impairments in delayed reaching will be associated with damage to areas in the

superior temporal or inferior parietal cortex. On the other hand, if non-neglect-specific impairments are observed in immediate pointing, based on the anatomical findings of the previous chapter I predict that more anterior or sub-cortical damage will be related to this. In other words, this impairment should not be driven solely by neglect-specific damage.

Method

Participants

Eleven patients with hemispatial neglect (RH+; mean age 66.5, SD 7.9) and 10 control patients without neglect (RH-; mean age 68.8, SD 7.7) after right-hemisphere damage as well as 10 aged-matched healthy participants (mean age 72.1, SD 4.2) took part in this study. On average, patients participated in the experiment eight months after stroke onset and there were no differences in onset times between the two patient groups.

Inclusion criteria, neglect measures and neuropsychological assessment were the same as in Chapter 1. However, in addition to the neglect measures, spatial working memory was also assessed with the perceptual version of the vertical computerized test of spatial working memory developed and kindly provided by Malhotra *et al.* (2005). In brief, patients were asked to make yes/no verbal responses about whether the locations were equal between two sets of vertical sequences of spatial locations separated by 1s delay. Three patients (two RH+ and one RH-) could not follow the instructions in the practice trials so no score could be generated. The patients' demographic and clinical data are

presented in Tables 10 and 11. Note that the majority of patients tested in this study were also tested in the previous study and this is highlighted in the Tables.

Similarly to the previous chapter, an analyses of variance with group (RH+ and RH-) as the between factor was performed on the scaled score of each sub-test of the WAIS-R (Wechsler, 1981). In line with the previous chapter, this revealed that neglect patients were significantly impaired on all performance sub-tests when compared to RH- patients, [block design: $F_{(1,19)} = 24.93$; $p < .001$; picture completion: $F_{(1,20)} = 15.39$, $p = .001$; object assembly: $F_{(1, 18)} = 29.97$, $p < .001$]. No differences between the 2 groups were obtained for information, digit span and vocabulary scaled scores.

Table 10 - Demographic and clinical data of the right-brain damaged patients. Patient's initials are in bold and italic when they also participated in Chapter 1's experiment.

Group	Patient	Gender	Age	Scan	Etiology	Lesion location	Lesion volume (cm^3)	TO	VFD	EXT
RH+	***AB***	F	70	MRI	Infarct	Temporo-occipital	100.7	6	Yes	(-)
	AM	M	63	CT	Infarct	Fronto-temporal-parietal-insular	85.3	5	Yes	Yes
	DS	F	64	MRI	Infarct	Fronto-temporo-occipital	56.5	3	Yes	(-)
	FH	F	80	MRI	Haemorrage	Temporo-parietal	108.6	18	Yes	(-)
	JH	F	56	MRI	Infarct	Fronto-temporo-parietal	189.2	18	Yes	Yes
	JK	F	69	CT	Infarct	Fronto-temporal	50.9	4	No	No
	JM	M	55	MRI	Infarct	Fronto-parietal	169.5	3	Yes	Yes
	JS	M	76	MRI	Infarct	Temporal, insular cortex and periventricular white matter	105.2	28	Yes	Yes
	MJ	M	60	CT	Infarct	Occipital-frontal-temporo-parietal	241.3	9	Yes	(-)
	MM	F	72	CT	Infarct	Fronto-temporal-insular	18.0	4	No	No
	NF	F	67	MRI	Infarct	Fronto-temporo-parietal	268.8	7	Yes	(-)
RH-	***AMI***	M	60	CT	Infarct	Lentiform nucleus	1.4	3	No	No
	AW	F	64	MRI	Infarct	Basal ganglia	2.6	6	No	No
	DM	M	78	MRI	Infarct	Fronto-temporal	59.6	3	No	No
	JC	F	76	CT	Infarct	Fronto-temporal	9.4	10	No	No
	KM	M	60	MRI	Haemorrage	Parietal-occipital	12.6	6	No	No
	LS	M	60	CT	Infarct	Caudate nucleus	1.8	7	No	No
	MP	F	66	MRI	Infarct	Basal ganglia	0.7	6	No	No
	NH	M	79	MRI	Infarct	Fronto-temporo-parietal	70.9	4	No	No
	RM	M	73	CT	Infarct	Lentiform nucleus	0.2	3	No	No
	SC	M	72	CT	Infarct	Frontal	16.2	8	No	No

TO = time since injury onset (months); VFD = visual field defect; EXT = extinction.

Table 11 - Neuropsychological assessment data of the right-brain damaged patients. Patient's initials are in bold and italic when they also participated in Chapter 1's experiment.

Group	Patient	BIT	Line bisection	Balloons	SWM	SWM 1
RH+	***AB***	131	31	50	60	95
	AM	130	11	50	82	95
	DS	91	82	50	79	100
	FH	103	75	27	d.a	d.a
	JH	139	25	43	52	50
	JK	141	15	44	72	95
	JM	117	11	43	46	50
	JS	129	9	36	55	60
	MJ	122	2	43	d.a	d.a
	MM	128	0	50	63	100
	NF	143	6	29	d.a	d.a
RH-	***AMI***	146	3	50	98	100
	AW	145	-2	50	89	100
	DM	145	1	50	69	90
	JC	146	3	53	80	100
	KM	145	2	50	d.a	d.a
	LS	144	5	50	72	100
	MP	146	1	53	78	100
	NH	146	-3	50	84	100
	RM	141	6	46	72	90
	SC	140	3	54	65	100

BIT = Behavioural Inattention Test conventional sub-tests score (cut-off = 129); Line bisection represents the average error (in mm) obtained with 20 lines (200mm length), no sign is equivalent to a rightward error and a negative sign is equivalent to a leftward error (cut-off = 6mm, Halligan, Manning & Marshall, 1990); Balloons represents the lateralized index score in sub-test B (patient is impaired when this index is lower than 45%); SWM represents the total score in the spatial working memory test [max = 100; according to Malhotra *et al.* (2005) cut-off is 78]; SWM 1 represents the SWM score for a single location only [max = 100]; (-) = unable to diagnose extinction; d.a = data absent.

Stimuli and Procedure

The apparatus, stimuli presentation and recording procedure were the same as the one used in the previous chapter. However in this experiment the targets were located at –12, -8 and -4cm (left hemispace) and 4, 8, 12cm (right hemispace) with respect to the central target (0cm). The central target was again located 40cm in front of the start trigger, aligned with the centre of the box. At the start of each trial, the right index finger of the subject rested on the start trigger, aligned with the subject's sagittal midline. Pointing was made in closed loop mode, i.e. with full vision of the hand during movement and participants' eye movements were unrestricted.

The paradigm was adapted from Milner *et al.* (1999). In the immediate pointing condition, subjects pressed the start trigger for 2s after which a tone (800HZ for 500ms) cued the subjects to initiate the movement. In this condition the target remained visible until the end of the trial and subjects were instructed to point to the target as quickly and as accurately as possible. In the delayed pointing condition, on pressing the start trigger the target was again illuminated for 2s, but participants had to refrain from pointing for a further 5s. Following this delay period, the auditory signal (800Hz for 500ms) cued the participants to point to the remembered location and they were instructed to point as quickly and accurately as possible '*as if the target was still there'*. The two conditions (immediate and delayed) were given in separate blocks and block order was counterbalanced across participants. Each block contained 14 practise trials (2 for each target position) and 84 experimental trials (12 for each target) with target positions randomised.

Behavioural analysis

Data obtained from the recordings were analysed off-line. As in the previous experiment, start and end of the movement were defined by a velocity-based criterion of 40 mm/s and 50 mm/s respectively.

First, a trial-by-trial analysis was performed to exclude trials in which participants did not follow instructions (i.e., failing to move, move towards the target before the 5s delay period or pulling back without homing in on target). A mixed analysis of variance was performed on the number of trials analysed with group (healthy controls, RH- and RH+) as between factor and condition (immediate, delayed) as within factor. This revealed a main effect of condition [$F_{(1, 28)} = 12.30$, $p < .01$] in that participants' reaches were more prone to error in the delayed condition when compared to the immediate condition. In addition, there was also an effect of group [$F_{(2, 28)} = 16.56$, $p < .001$], which was further qualified by an interaction between group and condition [$F_{(2, 28)} = 9.94$, $p = .001$]. Post-hoc comparisons showed that neglect patients had significantly fewer trials in the delayed (but not in the immediate) condition than RH- or healthy controls ($p < .001$). In particular, in the neglect group 14% of the trials were excluded from subsequent analysis, whereas only less than 1% of trials were excluded in the healthy and RH- control groups. Most frequently neglect patients failed to initiate a movement when cued to do so (10%). Interestingly, of the trials in which neglect patients did not move, 45% were in response to leftward targets, 14% to centred targets, but also 41% in response to rightward targets.

The dependent variables were absolute and signed angular error, reaction time and movement time. Unfortunately, reaction time could not be analysed for delayed pointing trials as on many of the trials participants

gently lifted their finger from the start trigger before or during the delay period (however without moving towards the target), resulting in a noisy measurement.

Lesion analysis

Lesion data was available for all 21 patients (12 MRI scans and 9 CT scans). The extent and location of each patient's lesion was visualized and defined using the MRICRO software package (Rorden & Brett, 2000) in the same manner as in Chapter 1.

In Figure 10A and 10B the overlap of the reconstructed lesions in the RH+ and RH- patients is presented. The subtraction analysis (see Figure 10C) revealed the following foci as being mostly damaged in the neglect group (82%): superior temporal gyrus gray matter (47, -10, 0) and its surrounding white matter (46, -11, 0), the insula white matter (45, -12, 0) and the white matter nearby the claustrum (37, -8, 0). In addition, the lesions of RH+ patients were significantly larger in volume than those of the RH- group ($F_{(1,20)} = 16.77$, $p = .001$, see Table 10).

Finally, as in Chapter 1, whenever behavioural deficits were observed, the voxel-based lesion-mapping statistical approach was performed using MRICROn software (Rorden, Karnath & Bonilla, 2007).

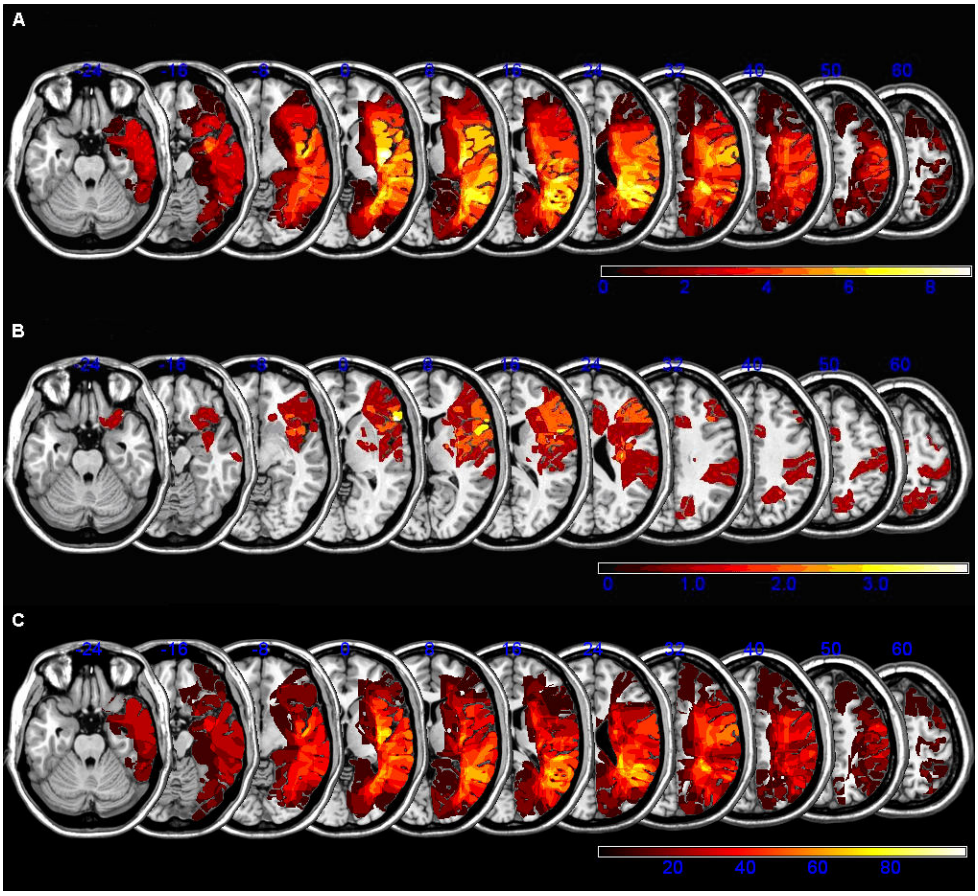

Figure 10 - Lesion overlap map summarising the degree of involvement for each voxel in the lesions of neglect patients (N = 11; A) and patients without neglect (N = 10; B); the range of the colour scale derives from the absolute number of patient lesions involved in each voxel. (C) Lesions of neglect patients minus those of RH- control patients; the range of colour indicates the percentage of areas mostly damaged in patients with neglect.

Results

Means for each participant were computed per condition for each variable and target position. Data for each target position was collapsed across sides: left (-12, -8, -4), centre (0) and right (+4, +8, +12). Reaction time for the immediate condition was analysed with a 3 x 3 mixed analysis of variance with group (healthy controls, RH- and RH+) as the between-subject

factor and target (left, centre, right) as the within subject factor. The remaining variables were analysed with a 3 x 2 x 3 mixed analysis of variance. Group was analysed as a between-factor and condition (immediate, delay) and target (left, centre right) as within-subject effects. Post-hoc comparisons were made with the Bonferroni adjustment ($p < .05$).

Terminal accuracy

The descriptive statistics for the absolute angular error per condition, target and group are presented in Table 12. There was a main effect of side [$F_{(2,56)} = 3.15$, $p = .05$] in that participants made higher errors to the leftward when compared to the rightward targets (mean difference = 0.2°, $p < .05$). No difference in accuracy was found between centred reaches and the reaches made to the other target positions. Furthermore, there was a main effect of condition [$F_{(1,28)} = 51.51$, $p < .001$], in that movements towards remembered locations were less accurate than immediate movements.

Also, there was a main effect of group [$F_{(2,28)} = 7.35$, $p < .01$], which was further qualified by significant interactions between group and side [$F_{(2, 56)} = 2.69$, $p < .05$], group and condition [$F_{(2, 28)} = 5.54$, $p < .01$] and group, condition and side [$F_{(2, 28)} = 2.50$, $p < .05$]. Post-hoc comparisons revealed that RH+ patients presented pathologically increased absolute angular errors when compared to both healthy controls (mean difference = 1.5°, $p = .001$) and patients without neglect (mean difference = 1.2°, $p < .01$), only in the delayed condition, and solely when the target was presented on the left side of space. No difference between the groups was observed for the immediate condition for all target locations. These observations suggest that the impairment in delayed reaching is specific to neglect, as patients without the

condition were as accurate as healthy participants (mean difference = 0.2°). Furthermore, it also indicates that this inaccuracy is direction-specific as no significant impairments were observed when the targets were presented in the centre or on the right side of space.

Table 12 – Means and standard errors (in parenthesis) of the absolute angular error (in degrees) per group, condition and target position.

	Immediate pointing			**Delayed Pointing**		
Target / Group	Left	Centre	Right	Left	Centre	Right
Heatlthy controls	0.5 (0.1)	0.5 (0.1)	0.5 (0.0)	1.0 (0.1)	0.9 (0.1)	1.1 (0.2)
RH-	0.4 (0.0)	0.4 (0.0)	0.4 (0.0)	1.2 (0.1)	1.1 (0.2)	0.9 (0.1)
RH+	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)	2.4 (0.4)	1.7 (0.3)	1.7 (0.3)

To investigate if this decrease in accuracy in the delayed condition was related to neglect severity, Pearson correlation analyses were run between the BIT, the bisection errors, the lateralised index of the Balloons test and the mean absolute error for leftward delayed reaches for all right-brain damaged patients. Interestingly, a significant negative correlation was found between the absolute angular error for leftward targets and the BIT score ($r = -0.84$, $N = 21$, $p < .001$), in that larger error was correlated with poor BIT performance. Moreover, there was also a significant positive correlation between bisection error and movement accuracy to leftward remembered locations ($r = 0.77$, $N = 21$, $p < .001$). That is, higher bisection errors were correlated with higher end-point errors to the leftward target location. However, the correlation between the terminal error and the Balloons test score was not significant.

In addition, I also ran correlation analysis between the mean absolute angular error for left sided delayed reaches, the percentage of stimuli

detected on the left side of the screen in the computerized perimetry test and the percentage of bilateral stimuli detected on the extinction test. This revealed a significant negative correlation in that the worse the performances on the perimetry test ($r = -0.78$, $N = 21$, $p < .001$) and on the extinction test ($r = -0.53$, $N = 21$, $p < .01$), the bigger the error in the delayed pointing to leftward targets. Thus these observations indicate that the terminal accuracy impairment found here is related to both the severity of neglect and/or hemianopia and/or extinction.

Furthermore, correlations between the patients' overall scores on the spatial working memory task and also on their scores for spatial working memory of a single location and the mean absolute angular error for leftward delayed reaches were run, but this was surprisingly not significant. This indicates that there seems to be no relation between the ability to remember target locations in a sequence, for perceptual purposes, and the accuracy of movements towards remembered locations. Thus errors of delayed movements are associated with neglect severity, but not with spatial working memory problems *per se*.

In terms of directionality, as can be seen in Figure 11 the signed angular errors of the patients with neglect were overshoots in respect to left sided targets.

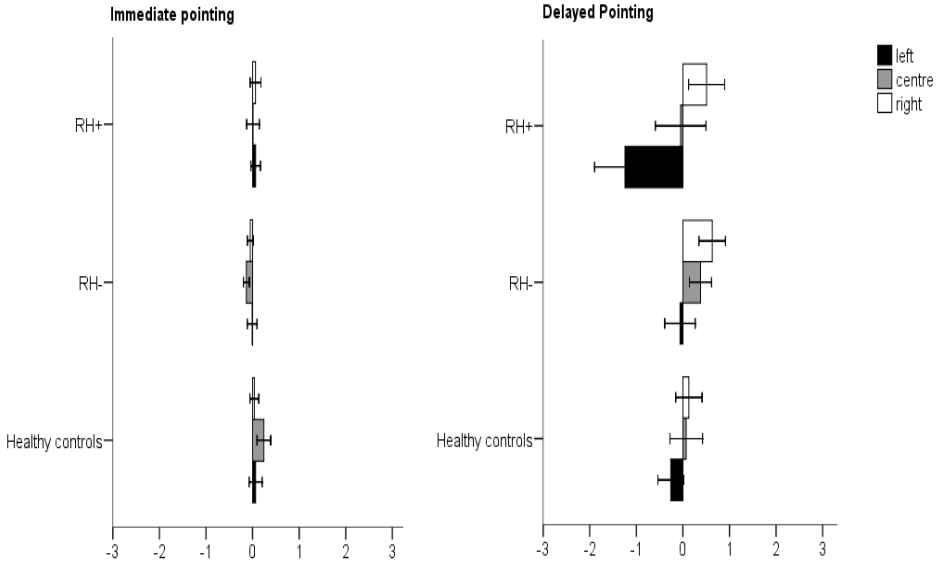

Figure 11 - Mean directional angular error (in degrees) in the immediate and delayed conditions per group and target position. Error bars represent standard errors.

To investigate which brain areas were critically associated with the reduced accuracy for the delayed leftward reaches the voxel-based lesion analysis was conducted on the mean absolute angular error. This revealed that several cortical and subcortical areas were significantly associated with the increased absolute angular error for leftward delayed reaching ($Z > 2.06$, $p < .05$; BM range = -3.82, 15.08; see Figure 12). Poor accuracy was strongly associated with lesions located in several occipito-temporal areas: the white matter near the transverse temporal gyrus [peak Z = 15.08 (34, -35, 8)], the middle temporal gyrus gray [peak Z = 6.27 (65, 0, -8)] and surrounding white matter [peak Z = 15.08 (70, -42, 0)], the superior temporal gyrus gray [Z = 13.43 (64, -26, 0)] and nearby white matter [peak Z = 4.40 (48, -47, 16)], the temporal lobe white matter near the caudate [Z = 15.08 (33, -33, 8)], the middle occipital gyrus gray matter [peak Z = 15.08 (44, -83, 8)] and the fusiform gyrus gray matter [peak Z = 8.22 (24, -68, -8)].

To a lesser extent, the following lesion locations were also related to inaccurate delayed reaching: the occipital lobe white matter near the precuneus [peak Z = 6.81 (28, -73, 16)], the posterior cingulate gray matter [peak Z = 6.81 (28, -65, 16)], the white matter in the vicinity of the inferior temporal gyrus [Z = 6.27 (61, -61, -8)], the parahippocampal gyrus gray matter [peak Z = 6.27 (32, -37, -8)] and nearby white matter [peak Z = 6.27 (28, -36, -8)], the thalamus [Z = 6.27 (18, -32, 8)], the white matter surrounding the lingual gyrus [Z = 6.26 (24, -81, -8)] and the inferior parietal lobe white matter [peak Z = 4.40 (59, -39, 50)]. Importantly, lesion volume did not correlate with poor accuracy.

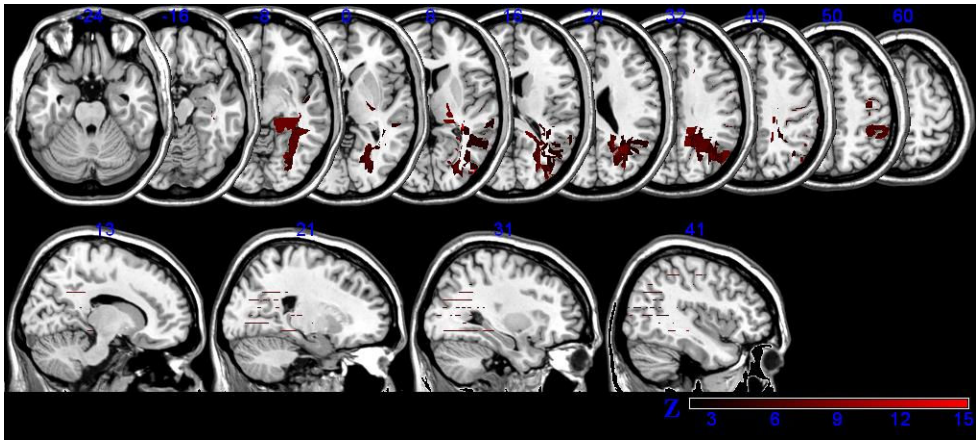

Figure 12 - Voxel-based lesion statistical map (in axial and sagittal view) revealing the right-brain damaged areas significantly associated with increased terminal error in leftward delayed pointing. The legend (and coloured areas) represents the range of Z scores that survived FDR threshold of $p < .05$.

Reaction time

In Table 13, the descriptive statistics for reaction time in the immediate condition are presented. The analysis of variance did not reveal any significant effects of group or target nor an interaction between the main factors. Neglect patients did not take significantly longer to initiate their

movements when compared to healthy controls (mean difference = 94.6ms) or RH- patients (mean difference = 39.6ms).

Table 13 – Means and standard errors (in parenthesis) of reaction time (in ms) for the immediate condition separately per group and target position.

	Immediate pointing		
Group \ Target	Left	Centre	Right
Heatlthy controls	297 (19)	313 (28)	281 (18)
RH-	365 (31)	347 (23)	344 (25)
RH+	397 (31)	379 (53)	399 (50)

Movement time

In Table 14, the descriptive statistics for movement time are presented per group and target position. There was a main effect of condition [$F_{(1,28)}$ = 136.96, p < .001] in that all participants took significantly longer to perform movements in the delayed condition when compared to the immediate condition.

Table 14 – Means and standard errors (in parenthesis) of movement time (in ms) per group, condition and target position.

	Immediate pointing			Delayed Pointing		
Group \ Target	Left	Centre	Right	Left	Centre	Right
Heatlthy controls	612 (29)	575 (32)	564 (29)	748 (30)	713 (26)	702 (32)
RH-	658 (22)	622 (23)	621 (23)	866 (30)	827 (35)	805 (34)
RH+	692 (23)	649 (27)	649 (23)	874 (26)	825 (23)	812 (25)

There was also a main effect of target [$F_{(2,56)}$ = 95.64, p < .001]. Pairwise comparisons showed that all participants presented significantly longer movement times to leftward than to centred or rightward targets (p <

.001). Fastest movement times were obtained when movements were made to right-sided targets, when compared to centred or leftward targets (p = .01 and p < .001, respectively).

Additionally there was a main effect of group [$F_{(2,28)}$ = 4.74, p < .05]. Pairwise comparisons showed that overall neglect patients were significantly slower than healthy controls (mean difference = 97.7ms, p < .05), but were not slower than RH- patients (mean difference = 16.9ms). RH- patients were not significantly slower than healthy controls. The interactions between group and task and/or side were not significant. This data indicates that the increase in movement time in neglect patients is not specific to the disorder, as RH+ patients had similar movement times to RH- patients. In line with this, no significant correlation was found between neglect or hemianopia or extinction severity and the overall movement time.

As for terminal accuracy, to investigate which brain areas were critically associated with the overall increased movement time (collapsed across tasks and target positions), the voxel-based lesion analysis was implemented. This revealed that several regions were significantly associated with these increased movement times ($Z>1.96$, $p<0.05$; BM range=-7.14, 13.43; see Figure 13). The most significantly associated lesioned voxels were located in fronto-parietal regions: the anterior cingulate gyrus [peak Z=13.43 (14, 14, 32)] and its nearby frontal white matter [peak Z=13.43 (12, 12, 40)], the pre-central gyrus [Z=9.20 (58, -19, 40)] and its surrounding white matter [peak Z=4.20 (61, -1, 8)] and the post-central gyrus gray [Z=13.43 (46, -26, 40)] and nearby white matter [peak Z=4.43 (60, -18, 50)].

To a lesser degree, increased movement time was additionally associated with damage to the white matter near the inferior frontal [peak Z=6.60 (47, 15, -8)] and the middle frontal gyri [Z=4.95 (33, 34, 8)], the inferior parietal lobe white matter [peak Z=4.43 (69, -23, 24)], the superior temporal gyrus [peak Z=7.21 (48, 14, -8)] and its surrounding white matter [peak Z=5.95 (48, 7, -8)], the white matter near the middle temporal gyrus [peak Z=2.69 (70, -4, -16)], the claustrum [peak Z=5.77 (28, 21, 16)] and the insula [Z=5.77 (29, 21, 16)]. Again lesion volume did not correlate with increased movement time.

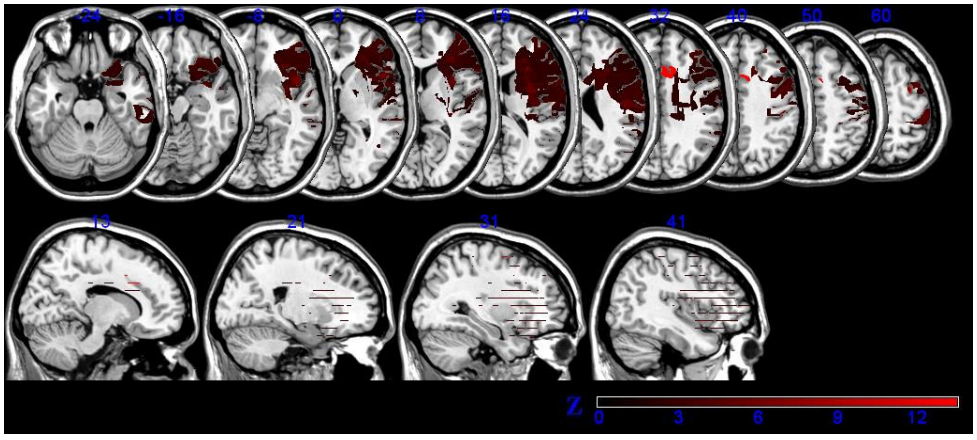

Figure 13 - Voxel-based lesion statistical map (in axial and sagittal view) revealing the right-brain damaged areas significantly associated with increased movement time. The legend (and coloured areas) represents the range of Z scores that survived FDR threshold of $p < .05$.

Discussion

The current study aimed to investigate the reaching performance of right hemisphere lesioned patients with and without hemispatial neglect as well as healthy controls for both immediate and delayed pointing. Furthermore,

lesion-symptom analysis was used to perform an **initial** exploration of the neural anatomy behind the motor deficits observed.

Motor deficits after right-brain damage

As expected no evidence for neglect-specific impairments was found for immediate pointing even when targets were presented on the left side of space. Regarding endpoint accuracy neglect patients did not even differ from healthy control subjects. Indeed the lack of terminal pointing bias in the immediate condition is clearly demonstrated in Figure 11. Furthermore, it is of interest that, unlike for delayed pointing, where neglect patients sporadically failed to initiate a reach altogether, this behaviour was not found for immediate pointing. Thus, it seems that when performing an immediate reach neglect patients do not ignore leftward targets. In terms of latency, I also did not find an increase in reaction time after right-brain damage, as both patients groups did not even differ from healthy controls. The only difference observed was for movement time, in that neglect patients were found to be slower than healthy controls in movement time, on both immediate and delayed conditions. Yet no difference was found in comparison to the RH- group. In addition, this movement time increase was not direction-specific nor did it correlate with neglect severity.

The findings of no neglect-specific abnormalities in immediate reaching agree with the strong claim made by Himmelbach and Karnath (2003) that neglect patients can accurately reach to a single target in both right and left space. As argued before, these observations are also in line with a range of other studies (e.g., Harvey *et al.*, 2002; Himmelbach & Karnath, 2003; Konczak & Karnath, 1998; Konczak *et al.*, 1999).

Nonetheless, the lack of reaction time differences between neglect patients and the other control groups contrasts with numerous other findings that have reported specific initiation impairments to leftward targets in neglect patients (Mattingley *et al.*, 1992, 1994, 1998a, 1998b). However, as argued in the previous chapter, it is likely that task differences come into play here. It is possible that neglect patients have no deficit in initiating a single immediate reach, yet will show lateralized effects when target mapping is more complex either in terms of target competition or off-line processing. Unfortunately, the reaction time measure for the delayed pointing proved too unreliable to be reported here, but I would predict lateralised impairments for this condition.

As argued by Himmelbach, Karnath and Perenin (2007), the critical comparison in reaction and movement times and other kinematic parameters is between brain damaged patients with and without neglect. On this basis they argue that action control is not affected in neglect. Although the present data is in line with this viewpoint, as neglect patients were only impaired in movement time when compared to healthy controls, it is important to note that there are different types of action control and that these may be mediated differently by hemispatial neglect (Milner & Harvey, 2006).

Neglect-specific deficits in delayed reaching

In fact this point came through clearly in the results of the delayed pointing condition, where it was found that neglect patients showed greater endpoint errors when reaching to targets in left space. Moreover, this deficit seemed to be neglect-specific as patients with the disorder were impaired when compared both to healthy and RH- control groups. Additionally, these errors

correlated with neglect severity both in terms of the BIT score and the bisection errors. All these observations suggest that neglect patients do indeed experience problems when a delay is interposed between the presentation of a stimulus and the response. However, unlike patient DF, who also fails on this task, this impairment is specific to contralesional left targets.

To my knowledge, only one other study has investigated the effects of response delay on the motor performance of neglect patients and the results seem to agree with the present findings. Schimodozono *et al.* (2006) used a computerized delayed reaching task with a simple reaction time to dissociate the processes used to detect the target, from those used to initiate a movement and to move towards the target. Their task required a memory-guided response to a target location that was cued before a brief delay period and they tested 22 neglect patients and 31 patients without neglect after right-brain damage, as well as 25 healthy controls. It was found that patients with both neglect and hemianopia were slower to detect a leftward target and to initiate a movement towards it, compared to when the target was on the right side of space. Furthermore, among the patients without hemianopia, target detection was longer for the neglect patients than the patients without the condition or the healthy group. In addition there was no significant difference in the time needed to initiate or complete a reach between the groups. The authors argued that patients with neglect present a specific deficit in target detection, but not in motor initiation or execution. Alternatively, as acknowledged by the authors, the deficits observed could be related to the presence of target distracters or the delay (memory) nature of the task. In fact, I also found that neglect patients failed to initiate a reach

only in the delayed condition. Although end-point accuracy was not investigated in detail by Schimodozono *et al.* (2006)'s study, in line with the present data, they observed that the number of positional errors was greatest in patients with neglect and hemianopia (66.7%), when compared to neglect patients without hemianopia (0%), hemianopic patients without neglect (0%), and patients without neglect or hemianopia (16%).

In terms of directionality, the errors my neglect patients showed towards the leftward targets were effectively exaggerated overshoot errors (see Figure 11). Although this is surprising in light of the fact that hemispatial neglect is essentially defined as atypical rightward orienting, and indeed virtually all the patients showed this bias for line bisection, it seems that the bias does not necessary translate into pointing or grasping tasks. Indeed, in Chapter 1 I also did not find a rightward bias when the patients were asked to bisect a gap between two stimuli. It seems that the rightward bias in neglect is more pronounced when these patients are required to attend to the sizes of objects, but not when reaching or grasping (e.g., Milner & Harvey, 1995; Harvey *et al.*, 2002; McIntosh *et al.*, 2002; Pritchard *et al.*, 1997). Another explanation for the overshoot error would be that the presentation of the leftward target (before the delayed reach) acted as an attentional cue towards the left side of space and may have caused neglect reversal (overextension of the position of the leftward target). In line with this, it has been shown that leftward or bilateral cueing reduces (or even reverses) rightward errors in neglect patients (e.g., Harvey, Milner & Roberts, 1995).

The behaviour of my neglect patients in the delayed task is similar to the one of the visual-form agnosia patient DF (e.g., Milner, Dijkerman, &

Carey, 1999) whose ventral visual stream is damaged (James *et al.*, 2003) and is in stark contrast to that of optic ataxic patients who improve when performing delayed actions (e.g., Milner *et al.*, 1999). Moreover, my observation that neglect patients are specifically impaired in delayed reaching agrees with the view that this condition only affects actions that tap into perceptual representations processed and stored by the ventral visual stream (Milner & Harvey, 2006). Patients with hemispatial neglect could guide their actions to direct visible targets even when these were placed in left space, yet failed to do so when a delay was introduced between stimulus and response.

Nonetheless, it should be noted that recently the evidence that optic ataxia improves in delayed tasks has been somewhat weakened. Himmelbach and Karnath (2005) examined the pointing accuracy of two patients with optic ataxia in four different delay conditions (0, 2, 5 and 10s). Patient US had lesions bilaterally in the parietal lobe, in the left inferior frontal gyrus, occipito-temporal cortex and small lesions in the post and pre-central gyrus. Patient GS presented a unilateral lesion in the left medial parietal cortex involving the precuneus. It was reported that even after a delay these patients were still impaired when compared to healthy controls. Moreover, they observed a gradual increase of pointing accuracy as the delay duration increased rather than an abrupt switch in performance at a specific delay. These observations suggest a gradual change between dorsal and ventral control of reaching behaviour and argue against Westwood and Goodale (2003)'s real time hypothesis that the dorsal stream plays no role whatsoever in delayed actions, and that it is only engaged when the target is visible. However, the present study did not manipulate the

delay intervals making it impossible to know when neglect patients lost the information about target location.

Furthermore, one might argue that the neglect-specific deficit in the delayed task was in the initial coding of the target location. In both the immediate and the delayed pointing tasks, patients had an opportunity to use visual feedback about hand position to modify their reach; although only in the immediate condition could they directly compare the hand position with the target position. Moreover, the accuracy impairments in the delayed leftward reaching were also worst for the neglect patients who presented visual field deficits and extinction, which again might indicate that this deficit is related to the coding of target location. However, a larger sample of right hemisphere lesioned patients without these concomitant symptoms would be necessary to test these observations.

It would have also been useful to test both delayed and immediate movements under open loop conditions. On the other hand, in the previous chapter, I have shown that neglect patients are not specifically impaired in open loop conditions. In fact the patients without neglect were the ones who showed specific impairments when reaching without visual feedback and notably here I have found that these patients were unimpaired when tested in delayed pointing. This indicates that the impairments reported here for delayed reaching cannot be explained simply by the lack of visual information about target position. In agreement with this, is also the finding that in the immediate condition neglect patients did not ignore leftward stimuli, were not slower to initiate their movements and were quite accurate. The same was not true for the delayed condition, as in 10% of trials neglect patients failed to initiate movements altogether. This would suggest that the

deficit found here is probably best explained by a difficulty in maintaining the target location in memory or using it for the execution of a delayed reach. In fact, the observation that the patients never pointed to the right side of space when the targets had been previously viewed on the left indicates that they had at least some notion of its initial location.

Additionally, as outlined in the Introduction, poor performance for the left targets in the delay task was expected to relate to poor visuospatial working memory and I was surprised to find no correlation. Even scores for spatial working memory for mapping a single location, showed no relation between the ability to remember these and the accuracy of the delayed movements towards the left targets. Although ceiling effects might be a distorting influence here, it is clear from single-case analysis that is not the case. In particular, the two neglect patients (JH and JS) with the lowest memory scores did not show large errors to leftward targets and neither are the memory scores of the patients with the largest errors (MJ and DS) particularly low (see Table 11).

One possibility is that the spatial working memory measure and the delayed reaching task tapped into different mechanisms. Indeed, in Malhotra *et al.* (2005)'s study spatial working memory deficits correlated with cancellation tasks, but not with line bisection errors. The authors argued that this observation indicates that spatial working memory deficits affect visual search behaviour, but may not influence other components of the neglect syndrome. In the present study I found that the errors in the delayed condition correlated with line bisection, but not with the Balloons test score. This would suggest that for the delayed pointing task what the patients seem to have the greatest difficulty with, is the coding of the left target as a long-

term perceptual representation that can be accessed for the delayed reach. Whether they can or cannot remember the location of single or even multiple vertical targets amongst distracters does not affect this difficulty. Nevertheless, it would have been relevant to assess the spatial working memory of patients using a 'perceptual' version of the delayed pointing condition. In particular, in the future it would be interesting to test the patients on a task in which a single target is presented in leftward, centred and rightward locations for 2s and then removed for 5s. After this 5s delay a second target could be presented in the same or a different position and patients would be asked to make a same/different verbal judgement about the target positions.

Alternatively, the impairments in the delayed reaching could be related to a deficit in coding the target coordinates in an allocentric frame of reference. That is, participants could have used a strategy of coding the position of the target with respect to the outline of the reaching platform or the start trigger. In other words, the failure of neglect patients to point to a remembered location could be related to their missing ability to use an allocentric frame of reference. Even so, this would still agree with the hypothesis that this deficit is more related to ventral rather than dorsal damage, as the ventral stream seems to be the one responsible for this type of coding (Milner & Goodale, 1995, 2006). In line with this, patient DF has been shown to present deficits in motor tasks that require allocentric coding, but not when an egocentric response is required (e.g., Murphy, Carey & Goodale, 1998; Schenk, 2006; Carey, Dijkerman & Milner, 2009).

Neural basis of visuomotor deficits in neglect patients

In sum, the behavioural analysis revealed that neglect patients present specific increased terminal errors only when performing delayed leftward reaches, but are not specifically impaired in terms of movement times. To investigate this further, I performed an **initial** exploration of the anatomy behind these motor deficits via lesion-symptom analysis.

As expected, damage to the occipito-temporal cortex was robustly associated with reduced accuracy in delayed leftward pointing. The lesions most strongly associated with this deficit were in the superior and transverse temporal gyri and the middle occipital and fusiform gyri. Interestingly, the lesion subtraction analysis also revealed that one of the foci mostly associated with neglect was located in the superior temporal gyrus, which agrees with the claim that this deficit is neglect-specific.

Moreover, the lesion-symptom mapping data also seem to concur with the finding the patient DF, who suffered bilateral damage to the lateral occipital complex (LOC, brodmann areas 18 and 19), is impaired in delayed, but not immediate actions (Goodale, Jakobson & Keillor, 1994; Milner, Dijkerman & Carey, 1999; James *et al.*, 2003). This area is located on the lateral surface of the occipito–temporal junction, along with other areas such as the posterior fusiform sulcus (Cohen *et al.*, 2009), and is believed to mediate object recognition but not object-directed action (e.g., James *et al.*, 2003; Cavina-Pratesi, Goodale & Culham, 2007). Interestingly, I also found that lesions to a cluster of voxels situated in the fusiform and middle occipital gyri (Brodmann area 19) and to the lingual gyrus (Brodmann area 18) were associated with the deficit in delayed pointing.

In keeping with the suggestion that areas in the ventral stream, and especially within the LOC, are important for delayed actions are the results of an fMRI study with healthy participants presented by Singhal *et al.* (2006). They investigated the activation patterns in the LOC and in the anterior intraparietal sulcus (AIP) during three phases of a delayed action paradigm: visual stimulus presentation, delay phase and action execution. It was found that the LOC was activated during stimuli presentation, but interestingly it was again reactivated at the time of the action execution despite the absence of a visual stimulus. In addition, during the delay phase no activation was found in the LOC. AIP also showed greater activation for both the visual presentation and action phases, but in contrast to the LOC, was activated during the delay phase. Singhal *et al.* (2006) suggested that the LOC might process high order information about the target object required by the dorsal stream in order to complete the action after a delay. They further speculate that activity in the LOC may involve the extraction of object properties from memory. Indeed, very recently Monaco *et al.* (2008), presented fMRI data that confirms that the LOC is reactivated after a delay, but regardless of the sensory modality (vision or touch) and that this activation is higher for real actions than imagined actions. This observation suggests that the LOC reactivation is not merely due to the mental imagery processes, but is likely to reflect a general property of memory-guided actions.

Alternatively, DF's deficit in delayed pointing could be related to her additional lesion in the left medial parieto-occipital cortex rather than LOC damage *per se* (James *et al.*, 2003). Indeed, Goodale *et al.* (2008) have investigated a new patient (MC), who also shows impairments for delayed

but not immediate grasping. Like DF this patient has damage to the LOC, but also presents additional bilateral occipital and right parietal lesions (Culham *et al.*, 2008b), making it difficult to know if the LOC alone is the critical area accounting for a dissociation between immediate and delayed actions.

In a very recent experiment, Himmelbach *et al.* (2009) were the first to analyse the brain activation patterns associated with immediately executed and delayed reaching movements in a patient with optic ataxia (IG) when compared to 16 healthy participants. In healthy subjects, they observed higher signal increases for movements to visible targets than for delayed movements in the bilateral occipito-parietal junction (POJ), the precuneus and the middle occipital and temporal gyri. However, the reverse contrast did not reveal any significant differences. In IG they also observed indistinguishable activation of intact dorsal occipital (superior occipital cortex) and parietal areas (precuneus) adjacent to the patient's lesions for both types of movements. They argued that dorsal visual stream areas are not only involved in immediate, but also in delayed reaching. This finding thus may explain why even though a delayed movement can ameliorate optic ataxia, the motor performance of these patients still remains suboptimal when compared to that of healthy controls.

Thus both the present findings and the neuroimaging evidence reviewed here suggest that the LOC is not the only area involved in delayed pointing. Alternatively, I would suggest that in conjunction with the LOC (damaged in both DF and MC), areas in the superior temporal cortex might also play a role in memory-guided actions. Indeed Króliczak *et al.* (2007)

found that pantomimed actions were mediated by right-hemisphere activation in the middle temporal gyrus and superior temporal sulcus.

Remarkably no evidence of frontal involvement was found for abnormal delayed reaching, which is in contrast to the results obtained for movement time. It was also observed that occipital damage was unrelated to the impairments in movement time, but was instead associated with the deficits found in delayed reaching. Increased movement times were most robustly associated with anterior damage to fronto-parietal areas (anterior cingulate, pre and post-central gyri). These observations agree with findings that frontal lesions produce motor abnormalities in neglect patients (Bisiach *et al.*, 1990; Sapir *et al.*, 2007; Tegner & Levander, 1991). Thus I would suggest that the slowing observed in the present study is not a consequence of damage to neglect-associated areas alone, but instead results from further parieto-frontal lesions to crucial nodes in the visuomotor network or possibly from a disconnection between its components (e.g., Bartolomeo, Thiebaut de Schotten & Doricchi, 2007).

Conclusion

Taken together, the present findings further support the hypothesis that neglect patients are specifically impaired when performing actions thought to depend on processing accomplished by the ventral visual stream, but not the dorsal (Milner & Harvey, 2006). Moreover, here I have shown that the mediation of such off-line actions may further involve occipito-temporal areas located more anterior than LOC regions. In contrast, movement slowing is not a direct consequence of neglect, but depends on the extent of damage to anterior regions in the frontal lobe. These findings agree with the view that

there might be a functional dissociation within the posterior parietal cortex: while superior areas (usually damaged in optic ataxia) mediate on-line action processes towards visible targets, more inferior areas (like the ones damaged in neglect) may control the processes involved in off-line actions towards memorized locations. In fact, it has been further proposed that parieto-temporal areas, most commonly damaged in neglect patients, may be part of a third stream which receives both dorsal and ventral stream inputs, but depends for much of its visual content on the ventral stream (e.g., Milner, 1995). This last point will be addressed in the General Discussion.

General Discussion

The main objective of Part I was to investigate the visuomotor abilities of patients with hemispatial neglect after right-hemisphere damage. To achieve this, two experiments were carried out to compare their motor abilities to that of right-brain damaged patients without the condition as well as healthy controls. Here I will first summarize the findings from Chapter 1 and 2 and then contrast them. Then I will address their theoretical implications as well as discuss methodological issues and suggest future directions.

The importance of visual feedback for reaching after right-hemisphere lesions

Chapter 1 investigated if neglect patients use visual feedback efficiently to guide their actions. More specifically, the experiment addressed several questions that remained unanswered in the literature: 'Do neglect patients present a rightward bias in gap bisection or pointing and if they do, are these impairments specific to the condition?'; 'Do neglect patients present deficits in open or closed loop condition and if they do is this deficit neglect-specific?'; and 'If motor deficits exist after right-brain damage what is the neural basis behind these?'. It was suggested that the observations from previous studies could not be easily compared as different patient groups were included and different tasks and measures of performance were analysed. To that end, I studied a significant sample of patients with and without neglect, as well as a group of healthy controls, in both pointing and gap bisection and I also manipulated the availability of visual feedback during the reach. Moreover, novel lesion-symptom mapping techniques were

implemented to clarify the neural underpinnings behind the motor deficits observed.

In line with previous findings (e.g., Himmelbach & Karnath, 2003), no neglect-specific impairment was found in terms of latency, hand path curvature or accuracy for either gap bisection or pointing neither in open nor closed loop conditions. However, two observations indicated that patients after right-hemisphere strokes might present deficits in action control. First, it was observed that neglect patients needed longer to initiate a reach towards leftward targets when compared to healthy controls, but were no different than patients without the condition. Based on this, I argued that this deficit was not neglect-specific. The lesion analysis further indicated that this latency increase was most strongly associated with parieto-occipital lesions near the precuneus, as well as damage to the inferior parietal lobe and the posterior cingulate (see Figure 14). Second, the patients without neglect presented increased terminal errors only when reaching in open loop towards leftward targets, when compared to both neglect patients and healthy controls. This observation strongly suggests that this deficit is not neglect-specific and the lesion-symptom analysis indicated that damage to the lentiform nucleus was most strongly associated with this impairment (see Figure 14). Based on these observations I argued that depending on the site of damage some right-brain damaged patients (irrespective of neglect) may present increased reaction times or rely heavily on visual feedback for the successful execution of their movements. Furthermore, I suggested that my neglect patients were not specifically impaired because their damage maximally overlapped in the superior temporal gyrus, insula and claustrum

(see Figure 14) thus relatively sparing the end-points of the dorsal visual stream (Milner & Goodale, 1995, 2006).

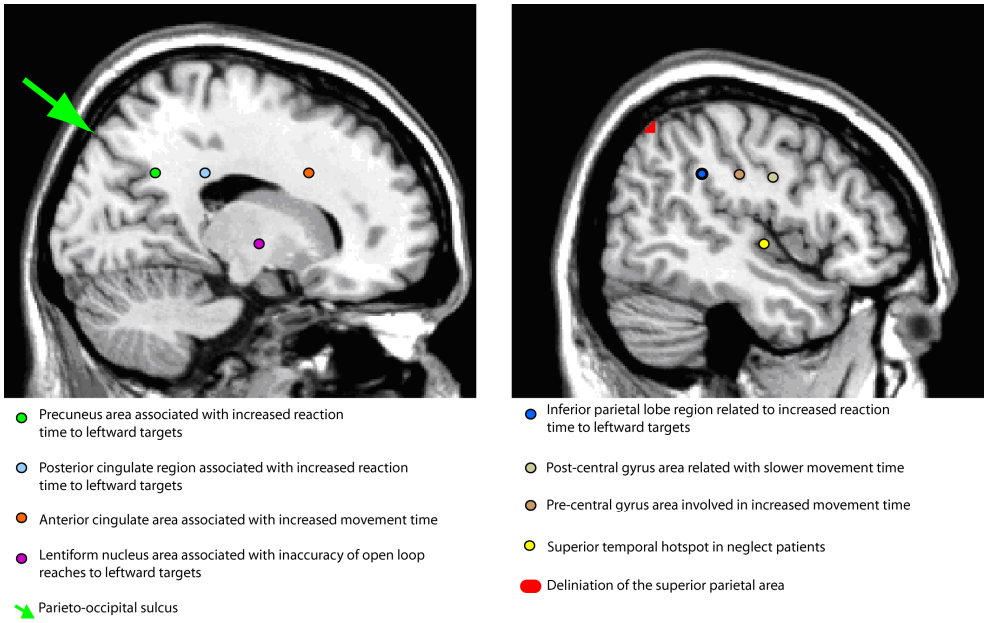

Figure 14. Summary of the lesion analysis results for the non-neglect-specific impairments in reaction time, accuracy in open loop (Chapter 1) and movement time (Chapter 2). For simplicity the areas were mapped in the two sagittal slices (Z = 14 and 47), regardless of their x Talairach coordinate, with MRICROn software (Rorden, Karnath & Bonilla, 2007). The delineation of superior parietal lobe areas was made according to Damasio (2005).

The importance of timing for reaching after right-brain damage

Chapter 2 was designed to test the specific hypothesis that patients with hemispatial neglect will only present deficits in actions which tap into perceptual representations processed and stored in the ventral visual stream, but not in the dorsal stream (Milner & Harvey, 2006). To do this, I compared the performance of RH+ with that of RH- patients and healthy participants in immediate versus delayed reaching. This paradigm had been previously used to dissociate perception and action related-deficits in visual form agnosia and optic ataxia (e.g., Goodale, Jakobson & Keillor, 1994;

Milner *et al.*, 1999). Moreover, I again performed the lesion analysis to understand the neural underpinnings behind the impairments observed.

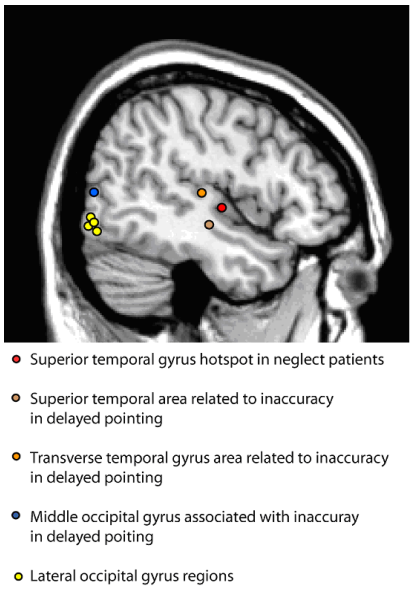

Figure 15. Summary of the anatomical findings regarding the neglect-specific deficit in delayed pointing (Chapter 2). For simplicity the areas were mapped in one sagittal slice (Z = 47), regardless of their x Talairach coordinate, with MRICROn software (Rorden, Karnath & Bonilla, 2007). The delineation of lateral occipital gyrus areas was made according to Damasio (2005).

As predicted by the perception and action model (Milner & Goodale, 1995, 2006), neglect patients only presented specific accuracy deficits in the delayed condition and only for leftward targets. This poor accuracy was highly related to lesions in the temporal lobe, one of the most damaged areas in my neglect patients (see Figure 15). In addition, it was observed that neglect patients were not specifically impaired in either latency or accuracy measures when performing immediate reaches. The only difference observed was in terms of movement time, in that neglect patients took longer to complete their movements towards all target positions when compared to healthy controls, but crucially were not slower than right-brain damaged patients without the condition. I argued that this latency deficit was

not neglect-specific and indeed the lesion-symptom analysis revealed that fronto-parietal lesions located in the anterior cingulate and pre- and post-central gyri were most strongly associated with the slowness in movement time (see Figure 14).

Based on these findings I concluded that the execution of successful delayed actions involves not only the lateral occipital complex (damaged in visual form agnosic patients and activated in healthy subjects for this task; James *et al.*, 2003; Singhal *et al.*, 2006), but also other occipito-temporal areas, in particular in the superior temporal cortex. In addition, I argued that the findings in the immediate condition suggest that on-line action control is spared in neglect patients, yet if their stroke affects fronto-parietal areas they may also be generally slower in the completion of their movements.

Contrasting the two experiments

The findings of no neglect-specific abnormalities in immediate reaching in Chapter 2 are in line with findings reported in Chapter 1, as no neglect-specific impairment was found there either. Nonetheless the behavioural and lesion analysis produced slightly different results.

Chapter 2's observation that neglect patients did not even differ from healthy controls in terms of reaction time for immediate pointing might seem surprising, as in Chapter 1 it was found that patients with neglect presented increased reaction times towards contralesional stimuli when compared to healthy controls. However, one possibility is that in Chapter 2's study participants had 2s to preview the target position whilst in the first experiment they only had 1s. This 1s difference might have given neglect patients enough time to find the target and initiate the reach towards it.

Regarding movement time, although Chapter 2's findings are also in line with the findings reported in the first Chapter, in the first study neglect patients did not even differ from healthy controls in terms of movement time. One possibility is that the inclusion of different patients (and thus different lesions) might explain these differences.

Table 15 - Summary of the results of the lesion-symptom mapping results obtained in Chapter 1 and 2. The Z scores are presented per lobe and particular area for each behavioural deficit, with the highest values in bold.

Lobe	Area	RT	Open loop error	MT	Delayed error
	lingual gyrus	(-)	(-)	(-)	6.26
	superior occipital gyrus	3.13	(-)	(-)	(-)
	fusiform gyrus	3.16	(-)	(-)	8.22
Occipital	middle occipital gyrus	(-)	(-)	(-)	**15.08**
	inferior temporal gyrus	3.16	(-)	(-)	6.27
	middle temporal gyrus	6.53	(-)	2.69	6.27
	superior temporal gyrus*	6.53	(-)	7.21	**13.43**
	transverse temporal gyrus	(-)	(-)	(-)	**15. 08**
Temporal	parahipoccampal gyrus	(-)	(-)	(-)	6.27
	precuneus	**12.73**	3.46	(-)	6.81
	inferior parietal lobe	**12.73**	3.46	4.43	4.40
Parietal	post-central gyrus	(-)	3.46	**13.43**	(-)
	inferior frontal gyrus	2.42	(-)	6.60	(-)
	pre-central gyrus	(-)	2.41	**9.20**	(-)
Frontal	middle frontal gyrus	(-)	(-)	4.95	(-)
	posterior cingulate	**12.73**	(-)	(-)	(-)
Limbic	anterior cingulate	(-)	(-)	**13.43**	(-)
	claustrum*	4.25	(-)	5.77	(-)
	insula*	(-)	(-)	5.77	(-)
	thalamus	4.25	(-)	(-)	6.27
	lentiform nucleus	6.53	**6.88**	(-)	(-)
Sub-lobar	caudate tail	4.25	(-)	(-)	(-)

* = Area mostly damaged in my neglect patients; RT = Increased reaction time to left targets (Chapter 1); Open loop error = inaccuracy in leftward open loop reaching (Chapter 2); MT = Movement time increase (Chapter 2); Delayed error = Inaccuracy in delayed leftward reaching (Chapter 2); (-) = Area not involved in deficit.

In terms of the anatomical findings, what is remarkable is that neither occipital nor temporal lobe lesions were involved for the terminal errors in open loop (see Figure 14 and Table 15). Furthermore, whilst lesions to the middle occipital and to the superior temporal gyri were strongly related to the delayed pathological errors, neither the increase of movement time nor the

accuracy deficit in open loop were associated with damage to the occipital lobe nor were they strongly related to damage in temporal regions (see Table 15). In addition, occipito-temporal lesions were not the strongest lesions associated with the increased reaction time. Furthermore, the non-involvement of the lentiform nucleus in the delayed errors contrasts with its involvement with errors in open loop reaching and increased reaction time to left targets. The absence of lentiform nucleus participation in Chapter 2 might seem surprising since five of the RH- patients included suffered damage to the basal ganglia (see Table 10). In fact, I expected this area to be involved, at least for increased movement time. Nonetheless, this observation points to the different nature behind the deficits in open loop and in delayed conditions.

These observations suggest that occipito-temporal areas seem to be markedly involved in encoding and/or retrieval of target locations for memory-guided reaching. Second, the data also seems to suggest that lesions to these areas seem to be less involved in on-line visuomotor control processes (e.g., target localization and on-line updating of sensory information whilst reaching). In turn, damage to parieto-frontal areas, as well as to the basal ganglia and to the cingulate cortex, are strongly associated with longer reaction times to leftward targets, slower movement times and higher terminal errors for open loop reaching.

Implications for visuomotor control: spared dorsal visual stream in neglect?

The present findings of no neglect-specific deficit in immediate reaching in both Chapter 1 and 2 agree with the view that dorsal visual stream is

relatively intact in these patients (Milner & Goodale, 1995, 2006). In fact, their lesions overlapped maximally in the superior temporal gyrus (Brodmann area 22) and not in the inferior parietal lobule. As reviewed in the General Introduction, Karnath *et al.* (2004) examined the neural correlates of spatial neglect in 140 right-hemisphere stroke patients and, like in the present thesis (although a much smaller number of patients was studied here), they found that the maximum area of overlap was positioned in the superior temporal gyrus (Brodmann area 22) extending into the insula. Nonetheless, other authors have argued that the locus of lesion responsible for neglect is located in the inferior parietal lobe (e.g., Mort *et al.*, 2003). However, these diverging findings could be due to differences in sample selection and size. For example, Mort *et al.* (2003) only included 19 patients with neglect in their sample, potentially leading to inaccurate lesion localization compared to the 74 neglect patients included in Karnath *et al.* (2004)'s sample. Indeed, as Karnath (2001) pointed out, in the group of 67 neglect patients examined by Karnath, Ferber and Himmelbach (2001) and by Samuelsson *et al.* (1997), only three individuals had lesions restricted to the parietal lobe.

Evidence for the involvement of the superior temporal gyrus in neglect also comes from ablation studies in the monkey (Ó Scalaidhe *et al.*, 1995; Luh, Butter & Buchtel, 1986; Watson *et al.*, 1994). Removal of parts of the superior temporal cortex leads to deficits that typically occur in humans with neglect. Conversely, ablation of the monkey inferior parietal lobule does not cause neglect symptoms, but instead produces misreaching for objects and inappropriate orientation of the hand.

Therefore, the present study agrees with the suggestion that the human parietal lobe (but not the temporal) is responsible for the organization

and control of target-directed actions such as reaching, grasping and saccades (for review see Karnath, 2001). Indeed, the non-neglect-specific motor deficits reported here were most strongly associated with lesions in parieto-frontal areas, rather than temporal. Mattingley *et al.* (1998b), have also argued that the inferior parietal lobule has a motor role and the present findings would agree with this view. In fact, lesioned voxels in the inferior parietal lobe were involved in all the deficits and were especially associated with increased reaction times to leftward targets. This finding fits well with the observation that neglect patients with inferior parietal lobe lesions present increased reaction times to leftward targets (e.g., Husain *et al.*, 2000; Mattingley *et al.*, 1998b). Thus, my observations might help explain the diverging findings in the literature and help to solve the debate on the influence of neglect on visuomotor control. In particular, I would suggest that the previous findings of motor deficits in neglect patients result from the extent of their damage to crucial nodes of the visuomotor control network (perhaps to the inferior parietal lobe), and not from damage to the superior temporal gyrus alone. In other words, these deficits are not a direct consequence of hemispatial neglect.

As can be seen in Figure 14, the areas implicated in the motor deficits were located ventrally to the superior parietal lobe. Although, superficially, this might be interpreted against Milner and Goodale's model (1995, 2006), it is important to note that the parietal regions reported here are in line with the areas involved in optic ataxia. In fact, Karnath and Perenin (2005) found optic ataxia to be associated with a lesion overlap that affected the lateral and medial parieto-occipital junction (POJ) in both hemispheres. At the lateral convexity the centre of lesion overlap in such

patients affected the junction between the inferior parietal lobule (IPL), superior parietal lobule (SPL), and the superior occipital cortex (Karnath and Perenin, 2005). The area of lesion overlap further extended via the underlying white matter towards the medial cortical aspect of the hemisphere and included the precuneus close to the parieto-occipital sulcus. Moreover, the present findings also agree with the suggestion that a region in the precuneus, just in front of the parieto-occipital sulcus, could represent the human homologue of the parietal reach region in the monkey as it is strongly activated during planning and control of reaching movements in healthy individuals (Connolly, Anderson & Goodale, 2003; Astafiev *et al.*, 2003; Prado *et al.*, 2005).

Neurophysiological studies in monkeys have also implicated a region in the medial intraparietal sulcus and area V6A (between middle occipital and precuneus regions) in coding arm movement direction and in the transformation of sensory input into reference frames that can be used to guide limb action (e.g. Fattori *et al.*, 2001; Galletti *et al.*, 2003). Thus, my findings agree with the view that the areas in the posterior parietal cortex that play a critical role in on-line control of action, by transforming information about the location of objects into the coordinate frames of the effectors performing these actions, are relatively spared in neglect (Milner & Goodale, 1995, 2006).

The lesion-symptom analysis also helped to pinpoint other cortical areas, outside the posterior parietal cortex, that could potentially cause motor deficits. In particular, I found that lesions in the post- and pre-central gyri, the posterior and anterior cingulate cortex were highly associated with the non-neglect-specific motor abnormalities. These observations are in line

with fMRI studies in healthy individuals (e.g., Astafiev *et al.*, 2003; Beurze *et al.*, 2007) that have consistently found activation in a fronto-parietal network (including the cingulate and pre-central cortex) for reaching tasks. Nonetheless, one could argue that these regions are also commonly associated with neglect. However, a recent study argued that frontal damage is not necessary or sufficient to cause neglect (Mort *et al.*, 2003) and similarly, the occurrence of neglect after cingulate lesions is very rare. In fact, to the best of my knowledge, only two neglect patients with restricted cingulate cortex damage have been reported so far (Heilman & Valenstein, 1972; Klakta, Depper & Marini, 1998). Therefore, I would suggest that lesions in both parietal and frontal lobes are associated with motor abnormalities, such as increased reaction and movement times, in patients with or without neglect. In line with this view, I found that these deficits did not correlate with neglect severity nor were they strongly associated with damage to the superior temporal gyrus (the location where the lesions of my neglect patients maximally overlapped).

At a sub-cortical level, the strong association of lesions to the lentiform nucleus with the high reliance on visual feedback for reaching accuracy indicates that this area might have a potential motor role. However, the lentiform nucleus has also been shown to be the typical sub-cortical structure associated with neglect (Karnath, Himmelbach & Rorden, 2002). In addition areas in the superior temporal gyrus have direct connections with the basal ganglia (Yeterian & Pandya, 1998). This might suggest that the association between lesions in the lentiform nucleus and impairments in open loop reaching could be related to hemispatial neglect. However, the behavioural analysis would strongly suggest that this is not the case, as the

patients without neglect were the ones who were specifically impaired in the open loop condition. Indeed, previous studies have found that lesions to the basal ganglia are associated with the motor aspects of neglect (for a recent review see Fink & Marshall, 2005). Therefore, I would propose that my findings agree with the view that the basal ganglia have a primary role in the control of motor function. Sommer (2003) reviewed evidence that suggests that the basal ganglia pathway, which runs through the thalamus, projects to many motor areas including the frontal eye field, supplementary motor area, primary motor cortex and pre-motor cortex. Furthermore, the conclusion that the basal ganglia plays a role in movement planning and/or control is supported by evidence from patients with Parkinson's disease, in which basal ganglia circuits are disrupted and voluntary movements diminish or disappear (Sommer, 2003).

In conclusion, my observations suggest that on-line visuomotor control is unaffected by neglect, which agrees with the controversial hypothesis that their dorsal visual stream is relatively functional (Milner & Goodale, 1995, 2006). However, some right-brain damaged patients may present reaching abnormalities if their damage extends to crucial nodes of the visuomotor fronto-parietal and cortico-sub-cortical network or causes disconnection between its components.

Implications for visuomotor control: a ventral stream related impairment in hemispatial neglect?

In Chapter 2 I found that not only were my neglect patients exclusively impaired in leftward delayed reaching, but that this deficit was highly associated with superior temporal cortex damage and highly correlated with

neglect severity. This observation fits well with David Milner's proposal that the areas damaged in neglect form part of a third stream which receives input from both streams, but largely depends on the processing carried out in the ventral stream (Milner, 1995, 1997, 1998a,b). Milner's hypothesis (1995, 1997, 1998a,b; Milner & Goodale, 1995, 2006) was based on the findings that, in monkeys, the superior temporal cortex receives afferent inputs from both the inferior temporal areas as well as from the inferior parietal lobe and intraparietal sulcus, thus representing a site for multimodal sensory convergence (Baizer, Ungerleider & Desimone, 1991; Bruce Desimone & Gross, 1981; Felleman & Van Essen, 1991; Jones & Powell, 1970; Morel & Bullier, 1990; Rozzi *et al.*, 2006; Seltzer & Pandya, 1994;). Moreover, it has also been show that cells in the superior temporal gyrus integrate information about form, motion (Oram & Perret, 1996) and spatial position of objects (Baker *et al.*, 2000). These findings have lead to the idea that the rostral parts of the superior temporal cortex (like the ones damaged in my neglect patients) might act as an interface between the dorsal and the ventral visual streams (Karnath, 2001; Milner & Goodale, 1995; 2006).

Initially, it was suggested that the areas damaged in DF were responsible for the computations involved in memory-guided actions (e.g., Goodale, Jakobosn & Keillor, 1994). My findings would agree with this, as I also found that lesions in the middle occipital gyrus were highly (and solely) associated with high terminal errors in delayed reaching (see Figure 15 and Table 15). However, I have additionally shown that areas in the superior temporal lobe may also play a role in this form of action-control. Therefore, I would hypothesize that both the LOC (damaged in DF) and the superior temporal cortex (mostly damaged in my neglect patients) are responsible for

the encoding and/or retrieval of the long-term representations of spatial locations. Although the specific role of these areas remains unknown, one hypothesis would be that these areas are involved in the encoding and/or retrieval of this information and forwarding to parietal areas for the action execution. This might explain why although optic ataxia improves with a delay, the performance of such patients remains suboptimal when compared to that of healthy controls (e.g., Himmelbach & Karnath, 2005). Admittedly these suggestions are very hypothetical, but they may provide a theoretical basis for future experimental manipulations.

In a very controversial article, Glover (2004) has strongly argued that the functions of the inferior and superior parietal lobe dissociate for action planning (target selection and selection of an appropriate motor program) and control (action monitoring and adjustment) respectively. In a reply to this paper, Goodale and Milner (2004) state that like Glover (2004) they have always argued that both the ventral stream and the inferior parietal lobe play a role in action planning, but that there is an additional distinction to be made between motor planning and motor programming that Glover (2004) neglected. In particular, Goodale and Milner (2004) propose that the dorsal visual stream is involved in both the motor programming (pre-specification of motor parameters) and on-line control, but that the ventral visual stream in conjunction with the inferior parietal lobule plays a role in action planning. In line with this, Carey, Harvey and Milner (1996) have shown that DF will often make errors in selecting the correct part of a knife (e.g., will grasp a knife by its serrated edge), despite grasping it with perfect skill. With the present data I was not able to dissociate planning from programming mechanisms, but I would agree that the inferior parietal lobe certainly plays a role in planning

mechanisms, as lesions in this area were most strongly associated with increase reaction time to contralesional targets.

Moreover, the existence of several sub-streams within the dorsal stream has also been proposed. More specifically, Rossetti *et al.* (2006) argue that a dorsal-dorsal pathway, including the dorsal part of the parietal and pre-motor cortices, is involved in the fast on-line visuomotor computations for targets in the 'here and now', with optic ataxia as a typical disturbance. In addition, they suggest that another stream, which they call ventro-dorsal, including ventral areas of the parietal lobe and pre-motor and pre-frontal areas, is involved in complex planning and programming relying on high representational levels and with hemispatial neglect as a core disorder. Moreover, they suggest the existence of a third ventral-prefrontal pathway (bypassing parietal areas) that mediates delayed actions, with visual form agnosia as core pathology.

The present findings disagree with Rossetti *et al.* (2006)'s view, in that here I found that patients with neglect are also impaired in delayed reaching. Moreover, Karnath *et al.* (2004), along with the present findings, show that the maximum lesion overlap in these patients is not in the inferior parietal lobe, but in the superior temporal cortex. On the other hand, I have also reviewed evidence from both neuropsychology and neuroimaging that suggests that the 'vision for action' system includes the precuneus and the inferior parietal lobe (Milner & Goodale, 1995, 2006). In fact, my data suggests that patients with lesions to the precuneus area and to the inferior parietal lobe present slower latencies to start a movement. Although, futures studies are needed, I would argue in line with Milner and Goodale (1995, 2006) that the parietal lobe is mainly involved in the computations necessary

for both programming and on-line control of 'here and now' actions, whereas a third hybrid stream (perhaps from the LOC and/or inferior temporal cortex to the superior temporal areas) mediates the computations involved in delayed actions. Nonetheless, recent imaging studies (e.g., Himmelbach *et al.,* 2009) have indicated that areas in the parietal lobe are activated for delayed action execution. Therefore, whether this third stream bypasses the parietal lobe deserves consideration in future work.

In a similar vein, Fogassi and Luppino (2005) suggest that while the superior parietal lobe plays a role in the visual guidance of action, the inferior parietal lobe plays a role in high-level visuomotor representations that contribute, in the right-hemisphere, to the perception of spatial relationships. Moreover Rizzolatti and Matelli (2003) also suggest a functional dissociation within the PPC. They argue for the existence of a dorsal-dorsal stream, similar to the on-line system proposed by Milner and Goodale (1995, 2006), but they suggest that the inferior parietal lobe is part of a ventral-dorsal stream, which plays a role in both perception and action. They argue that while right inferior parietal lobe lesions cause neglect and this area plays a role in both perception and action, the left inferior parietal lobe is important for action recognition, grasping and object manipulation, with lesions here leading to limb apraxia. Returning to my findings in the delay experiment, it could be that the proposed hybrid stream includes both the temporal and inferior parietal lobules (around the temporo-parietal junction). However, the observation that patients with apraxia are able to perform delayed reaching would suggest that the left inferior parietal lobe may not be involved on tasks that test ventral-dorsal streams interaction (Ietswaart *et al.*, 2001). In line with this, I also found that damage to the right inferior parietal lobe was less

involved with the deficits in delayed reaching when compared to lesions in the superior temporal cortex (see Table 15).

In sum, I would suggest that my findings are in line with the proposal that neglect is more associated with ventral, rather than dorsal visual stream damage (Milner & Goodale, 1995, 2006). Nevertheless, the proposal that there is a third visual stream ending in the temporal-parietal junction, mediating both perception and action, is still in its infancy and needs further investigation.

Methodological issues

The lesion analysis technique used here represents a significant advance in brain lesion mapping, yet it also presents inherent limitations that I would like to outline. The relatively small sample size included in the present thesis could lead to a risk of over-interpreting anatomical findings. Indeed, a larger sample like the one of Karnath *et al.* (2004), which included 140 patients collected over 7 years, would have been ideal. Yet, this was obviously impossible to achieve in a PhD time limit. Nonetheless, the consistent finding across the different comparisons points to relatively reliable results.

Moreover, the anatomical MRI and CT scans used in the present study were primarily done for clinical purposes. Mixing CT and MRI scans is not the best approach, as CT images are limited in their spatial resolution. What I would have liked to have done is to only include patients who had undergone high-resolution imaging, but this would have markedly reduced the sample size. Moreover, in ideal conditions the imaging should have been done within days of the experiment. In addition, the lesion analysis could potentially be biased towards posterior damage as most patients with

neglect presented concomitant visual field deficits whereas most of the RH-patients had no visual field deficits. Further studies are needed to confirm the present results by comparing a group of neglect patients with a non-neglect group with similar occurrence of hemianopia.

In addition, a major challenge in any anatomical study of hemispatial neglect is that the lesions vary in extent and location between individuals, which reduces the power of the analysis. One approach to overcome this caveat is to only include patients with restricted lesions, but this leads to a reduction on the number of patients and biases the conclusions towards identifying small brain systems. Here, I have dealt with this issue by using an unselected sample, in terms of lesion location, and also by including patients without neglect.

Furthermore, MRI or CT scans might not necessarily show the full functional extent of a lesion, in that areas that appear intact may not be functioning 'normally' due to the effect of white matter disconnection, diaschisis or limited perfusion. Indeed, white matter damage was repeatedly implicated with the motor deficits reported here. In a recent study, Karnath, Rorden and Ticini (in press) argued that damage to gray matter structures is a stronger predictor of neglect than white matter lesions. Future experiments using diffusion tensor tractography will be necessary to clarify the possible role of fiber tract lesions in reaching deficits.

An important caveat is related to the current definitions of hemispatial neglect as there are several subtypes of neglect (for a taxonomy consult Vallar, 1998) and this has been ignored by researchers in the field. In particular, it is important to clarify that throughout this thesis the patients were diagnosed with neglect by applying paper and pencil tests in

peripersonal space (i.e., cancellation, drawing and line bisection) without assessing neglect of far space or personal neglect. Thus it could be argued that the neglect patients included here were unimpaired in immediate on-line reaching as they presented only with a particular subtype of the condition, namely peripersonal neglect. In future experiments, it would be relevant to apply tasks that assess personal and extrapersonal neglect in addition to the ones used in the present experiments. For example, personal neglect could be assessed with the 'Fluff test' (i.e., patients are asked to remove post-its placed in their body parts) and extrapersonal neglect could be diagnosed with a room description task (i.e., patients are asked to describe objects in far distances). This would clarify if patients who present personal and/or extrapersonal neglect are also not specifically impaired in reaching. Indeed, Committeri *et al.* (2007) observed that patients with personal neglect had lesions that maximally overlapped in the inferior parietal lobe, one of the regions that was also involved in the reaching deficits reported here. On the other hand, patients with peripersonal neglect had lesions in the STG, which is in line with the present findings. To further enhance the knowledge on this puzzling and severe syndrome researchers need to define more clearly what type of patients are included in their studies.

Alternative interpretations and future directions

An alternative interpretation for the present findings is that the neglect patients were unimpaired in immediate reaching because they were using their right-hand to perform the movement. It could be that reaching with the right-hand depends mainly on the contralateral hemisphere, which is spared in my patients. Indeed, I could have asked patients to reach with their left

hand, but many of my patients also presented hemiparesis. In addition, I could have also tested patients with left-hemisphere lesions, but again neglect is less common in such cases. In a similar vein, it has been suggested that whilst the right hemisphere plays a role in determining the spatial position of a target, the left hemisphere is involved in selecting the appropriate motor program and in monitoring the movement (Fisk & Goodale, 1988). However, the present data would disagree with this simplistic view, as patients with right-hemisphere lesions were shown to be impaired in open loop reaching and presented increases in reaction and movement times.

One question that I have been repeatedly asked is why neglect patients can reach towards leftward targets, but still 'bump' into objects located on their left whilst walking? Indeed, one of the neglect patients included here (FH) was perfectly able to reach to a leftward target, but when she was walking towards the exit she bumped her head against the left side of the doorway. One possibility is that the immediate reaching task taps into different mechanisms than 'real-world' obstacle avoidance. Indeed, walking around a crowed room or even through a door is a much harder and demanding task than reaching to a single flash of light in a box. Thus, I would predict that if several distracters were presented amongst a target, this neglect patient (and possibly others to) would have difficulty to perform the task.

Furthermore, lesions in the inferior parietal lobe were consistently associated with all the motor deficits reported here. Nonetheless, future experiments should try to investigate alternative reasons and ask if this is indeed a motor and/or an attention-related impairment. Rizzolatti *et al.*

(1987) put forward the 'premotor' theory of attention, which postulates that covert shifts of attention and eye movements share common neural circuits and that these attentional shifts represent eye movements that are planned, but not executed. In other words, the act of shifting one's attention between locations may just represent the intention to act. In addition, Masud Husain and his research group (e.g., Husain & Nachev, 2007; Nachev & Husain, 2006; Singh-Curry & Husain, 2009) defend a view that the right inferior parietal lobule does not fit the dorsal-ventral dichotomy and propose that this area is important in maintaining attention in the current task goals as well as encoding salient events in the environment. They reviewed evidence that suggests that this area is a crucial node in a fronto-parietal system involved in many non-motor and non-spatial functions, like sustained attention, detecting salient or novel events, phasic alerting and switching between task-sets. Therefore, the consistent involvement of the inferior parietal lobe in the abnormalities found here could also result from the role of this area in such tasks. However, very recently, Striemer *et al.* (2009) showed that although both attentional and reaching deficits were present in a patient with optic ataxia CF (who suffered bilateral damage in the superior parietal lobe and intraparietal sulcus), these deficits did not follow the same pattern. Striemer *et al.* (2009) suggested that their observation that only the reaching errors were modulated with target eccentricity (but not the time to detect a target in the ataxic field) indicate that attention and visuomotor control depend on independent neural mechanisms.

Chapter 2 indicates that there is a difference between on-line and off-line control of actions in neglect patients, but this finding requires further confirmation. One prospect would be to ask neglect patients to point to the

horizontal mirror position of a presented target (i.e., anti-pointing, Carey, Hargreaves & Goodale, 1996). Indeed, it has been shown that patient DF (Goodale, Jakobson & Keillor, 1994) is impaired when asked to pantomime a grasp to a location beside an object. If the hypothesis that solely off-line actions are affected by neglect is true, than neglect patients would be expected to be inaccurate when anti-pointing, but not when pointing directly at the target. Moreover if this proves to be the case, it would show that the impairments found here for delayed reaching are not simply due to lack of visual information about target location during movement, as for the anti-pointing task the target remains visible throughout the reach. Also, future experiments should test if optic ataxic patients improve with this paradigm, similarly to when a delay is interposed between stimulus and response.

Also, the specific role of the dorsal and ventral stream areas for delayed actions remains largely unknown. For example, does the dorsal stream activity for delayed actions, found in neuroimaging studies, reflect the storage of information and/or the planning of the movement based on the ventral stream input? The two visual streams model provides no specific prediction for the participation of ventral structures during the different phases of delayed movements (encoding, retention, execution). It would be very useful to overlap the areas damaged in DF and MC with the areas found here for the pathological overshoot errors in delayed pointing. Similarly, the study of the brain activation patterns of MC, DF and of neglect patients, when performing delayed actions should provide more clues towards understanding the neural basis of such movements. Moreover, imaging neglect patients would allow testing if their dorsal visual stream is activated in these patients for immediate actions. Finally another avenue

would be to deliver TMS pulses over parietal, temporal and the LOC regions at different phases of the delayed action (encoding, retention and execution). This would clarify the particular role of these areas in the healthy brain.

Finally, one important question to ask is if I could use the spared reaching abilities in neglect patients to improve their awareness of the contralesional side of space? This will be fully addressed in Part II of this thesis, where I report the immediate and long-term effects of visuomotor feedback training in patients with hemispatial neglect.

Part II: Rehabilitating hemispatial neglect

Introduction

In the UK someone has a stroke every five minutes (The Stroke Association) and hemispatial neglect affects up to 70% of stroke patients (e.g., Bowen, McKenna & Tallis, 1999; Stone *et al.*, 1993). Moreover the presence of hemispatial neglect is the single best predictor of poor functional recovery from stroke in everyday life (Buxbaum *et al.*, 2004; Gillen, Tennen & McKee, 2005; Katz *et al.*, 1999) and it induces a considerable burden on the patients and their families (Barrett *et al.*, 2006). For example, neglect patients fail to navigate correctly, bump into objects on the left side of space and as a result often injure themselves. Moreover neglect also causes a substantial burden to the NHS. The Stroke Association estimates that the direct cost of stroke to the NHS is £2.8 billion and to the wider economy is £1.8 billion. In addition, there are about 70,000 stroke survivors in Scotland, many of whom require long term support from their unpaid carers (The Stroke Association Scotland Office). These numbers are alarming and consequently, in the last century, via systematic application of cognitive neuroscience, investigators have tried to create rehabilitation methods to improve the recovery of patients suffering from hemispatial neglect. A brief review of the most studied techniques to date is presented below.

Different methods to treat neglect: a brief review

One of the most commonly used interventions to ameliorate neglect symptoms is visual scanning training (e.g. Lawson, 1962). This method is

based on the findings that neglect patients fail to explore the left hemispace and are abnormally oriented toward the right hemispace. Its objective is to facilitate neglect recovery by left sided cueing techniques, such as a red line located on the left side of a page. Improvements after scanning training have been found in reading and writing, cancellation tasks and activities of daily living (e.g., Antonnucci *et al.*, 1995; Piccardi *et al.*, 2006; Pizzamiglio *et al.*, 1992). In addition, Pizzamiglio *et al.* (1992) reported that the improvements obtained after visual scanning training remained at least five months after the end of the training, although no control group was included in this study.

An alternative approach is trunk rotation therapy (e.g., Karnath, Schenkel & Fischer, 1991), in which patients are simply trained to rotate their torsos to the contralesional side in relation to their head position. Karnath, Schenkel and Fischer (1991) showed that when the patients' head, trunk and visual fields were aligned with the middle of a projection screen they presented longer saccadic reaction times in the left visual field than in the right visual field. However, increased saccadic reaction time to left stimuli could be compensated for by rotating the patient's trunk leftwards (while the head and eyes were centred with the middle of the projection display). Wiart *et al.* (1997) conducted a randomized control trial to test a training procedure that combined scanning training with trunk rotation and found significant improvements in neglect assessment measures and activities of daily function which were maintained one month after treatment.

Vibration of the neck muscles, obtained by transcutaneous electrical stimulation, has also been shown to transiently improve visual detection and exploration of the left side of space, cancellation and visual straight ahead judgement (e.g., Karnath, 1994; Karnath, Christ & Hartje, 1993; Schindler *et*

al., 2002; Schindler & Kerkhoff, 2004). In addition, Schindler *et al.* (2002) conducted a crossover study, comparing the improvements after visual scanning training with the effects of combining visual scanning training with neck muscle vibration. They found that the combined treatment had relatively long-lasting (2 months) effects in visual straight ahead pointing, reading, cancellation, tactile exploration and self care, when compared to visual scanning training alone. It has been suggested that both neck muscle vibration and trunk rotation may improve neglect by manipulating the position of the egocentric frame of reference (e.g., Karnath, Schenkel & Fischer, 1991). Though there are some experimental data to support these methods, many authors have argued that trunk rotation and, specially, visual scanning training require patients to be aware of their difficulty in order to compensate actively for their rightward orientation bias, which a lot of them find difficult in everyday life (e.g., Harvey *et al.*, 2003). Furthermore in a systematic review by Luauté *et al.* (2006a), it was concluded that the long-term benefits of these approaches remain unclear as their effects, when applied in isolation, are usually transitory.

Other rehabilitation studies have investigated the impact of sensory stimulation techniques on neglect symptoms, such as caloric and optokinetic stimulations. Caloric stimulation is based on the observations that if cold water is placed into the left external ear canal the vestibular-ocular reflex induces a slow phase of nystagmus toward the stimulated ear (Rubens, 1985). Immediate positive effects after vestibular stimulation have been observed in cancellation tasks, personal neglect and anosognosia (e.g., Cappa *et al.*, 1987; Rode *et al.*, 1998; Rubens, 1985; Vallar *et al.*, 1990). However, the effects of this form of treatment are usually transitory lasting no

more than 10-15 minutes (Rode *et al.*, 1998) and the technique is somewhat unpleasant (Rorsman, Magnusson & Johansson, 1999). Additionally, Pierce and Buxbaum (2002) argued that since most studies involve acute patients the potential benefits of this treatment in chronic neglect remains to be investigated. Optokinetic stimulation involves the presentation of a leftward moving background on a computer screen, which originates a slow eye movement to the left creating the illusion that stimuli are being displaced rightwards. This type of stimulation has been shown to immediately improve line bisection, visual straight ahead pointing, size estimation and reading (e.g., Bisiach *et al.*, 1996; Karnath, 1996; Kerkhoff *et al.*, 1999, 2006; Pizzamiglio *et al.*, 1990; Vallar *et al.*, 1993). In addition, Kerkhoff *et al.* (2006) have reported that after 2-week post-training positive effects remained on line bisection, cancellation and reading. In addition, these authors reported that the treatment was more effective than visual scanning training. Although this rehabilitation approach is less unpleasant and simpler than caloric stimulation its effects remain controversial. In particular, Pizzamiglio *et al.* (2004) found no immediate or long-term improvements on BIT tests in a randomized control trial where optokinetic stimulation and visual scanning training were combined.

Another technique put forward to treat neglect is limb activation training (LAT). LAT consists in asking patients to make (even small) movements with the contralesional limb towards the contralesional side of space. It is based on the idea that using the contralesional limb improves perception of the affected side by activating the premotor circuits of the lesioned hemisphere. LAT has been found to produce improvements on classical neglect measures (e.g., BIT and line bisection), left sided motor

function, daily life activities and to reduce hospital stay (e.g., Karla *et al.*, 1997; Samuel *et al.*, 2000; Robertson & North, 1992, 1993, 1994; Robertson, Hogg, & McMillan, 1998; Robertson, North & Geggie, 1992; Robertson *et al.*, 2002). In addition, the effects of LAT on left sided motor function have been found to last even after 2 years post-training (Robertson *et al.*, 2002). Brunila *et al.* (2002) examined the effect of combining LAT with visual scanning training and found improvements in reading, letter cancellation and in copying a complex figure, which were well maintained 3 weeks post-training. Nonetheless, Luauté *et al.* (2006a) argued that the short or long-lasting functional impact of LAT remains to be shown in a randomized control study as neither Robertson *et al.* (2002), nor Karla *et al.* (1997) found improvements in functional measures, like the Barthel Index, the Catherine Bergego Scale or the behavioural BIT tests.

Another approach shown to improve neglect symptoms is sustained attention training. This technique aims to facilitate spatial awareness via the modulation of non-lateralised deficits in sustained attention/arousal (Robertson *et al.*, 1997). Usually it consists in training patients (self-endogenously) to 'switch up' their sustained attention system by learning and, further, using verbal self-instructions. Improvements using this technique in 8 chronic neglect patients have been found on attention measures and cancellation tasks, which were maintained for 2 weeks (Robertson *et al.*, 1995). In addition, Robertson *et al.* (1998) found that an auditory sound before a visual stimulus improved awareness of the left side of space in 8 neglect patients. However Thimm *et al.* (2006) reported that although alertness training improved neglect symptoms, the benefits disappeared after four weeks post-training.

Many recent studies have also used prism lenses to treat neglect, following the work of Rossetti *et al.* (1998). Prism treatments usually require the patients to wear prisms that induce a rightward optical shift of 10-15° and point to visual targets. This procedure requires a short adaptation period in that the reaching errors are initially shifted rightwards, but pointing repetition leads to compensatory leftward corrections. In addition, prism removal leads to 'after-effects' in that the errors become biased towards the left side of the target. One possibility is that prism adaptation alleviates neglect by recalibrating the sensory-motor information in the left hemispace, through the visual and/or the proprioceptive mismatch the prisms induce (e.g., Chokron *et al.*, 2007). Effects of this treatment have been found in classical neglect measures (e.g., cancellation), straight ahead pointing, visual exploration towards the left side of space, contralesional somatosensory perception, reading, wheel-chair driving, postural control and mental representation (e.g., Angeli, Benassi & Ladavas, 2004; Farné *et al.*, 2002; Frassinetti *et al.*, 2002; Jacquin-Courtois *et al.*, 2008; McIntosh, Rossetti & Milner, 2001; Pisella *et al.*, 2002; Rode, Rossetti & Boisson, 2001; Rossetti *et al.*, 1998; Sarri *et al.*, 2008; Saevarsson *et al.*, 2009; Serino *et al.*, 2006; Tilikete *et al.*, 2001; Vallar *et al.*, 2006). More recently, in a control trial study with 13 patients Frassinetti *et al.* (2002) reported that the benefits of prism adaptation lasted for 5 weeks. Although this technique has recently been identified as a promising intervention for neglect (e.g., Chokron *et al.*, 2007) and some authors have even suggested that it may be the new cure for neglect (Mattingley, 2002), it is important to note that not all patients improve after wearing prisms or adapt to the prisms (see for example Frassinneti *et al.*, 2002; Rosseaux *et al.*, 2006; Sarri *et al.*, 2008). Furthermore, the long-

term improvements in daily life activities (e.g., wheel-chair driving or functional scales) remain to be verified in a randomized control trial.

Despite many attempts to improve the symptoms of patients suffering from hemispatial neglect the long-term potential of these treatments remains unclear and their efficacy controversial with effects usually transitory (for reviews see Bowen & Wenman, 2002; Chokron *et al.*, 2007; Luauté *et al.*, 2006a; Pierce & Buxbaum, 2002; Robertson & Manly, 2002; Robertson & Halligan, 1999). Bowen, Licoln and Dewey (2002) concluded that the positive effect of rehabilitation in neglect patients remains unproven. Several reasons are behind the failure of studies to show positive rehabilitation effects in neglect. For example, many studies have only assessed treatment effects with paper-and-pencil or computerized tasks not assessing the functional effects of treatment. This is surprising since rehabilitation is '*the provision of planned experience to foster brain changes leading to improved life functioning*' (Robertson, 1999, pp.385). Additionally, researchers have used many different assessment protocols, outcome measures and have included small sample sizes, which make cross-study comparisons and statistical meta-analysis difficult (Bowen, Lincoln & Dewey, 2005). Furthermore, at present there is no consensus regarding the best outcome measure in either clinical practise or research and as pointed out by Bowen, Lincoln and Dewey (2005) there is a clear need for developing new functional outcome measures. Nonetheless, some techniques have produced, at least, short-term improvements in neglect symptoms and this is encouraging for future attempts. In addition, the cost of not treating brain damaged patients has a great impact in terms of dependency and lowered

quality of life, so the investigation of neglect rehabilitation effectiveness is a matter of urgency (Robertson, 2002).

The present study: investigating the effects of visuomotor feedback training

In the present study the immediate and long-term effects of visuomotor feedback training in patients with hemispatial neglect were investigated. This intervention has its roots in a seminal paper by Robertson, Nico and Hood (1995). These authors performed two experiments to evaluate if neglect might be adjustable by changing the purpose of the reaching response to objects. In a first experiment, 10 neglect patients were asked either to point to the centre of a rod with a pencil and, in another condition, to reach for the rod with a pincer grip and pick it up so that it would be balanced (see Figure 16 in the Methods section). They found that the rightward deviation was significantly reduced in 9 patients when they reached towards metal rods so as to pick them up in the centre, compared to when they were asked to point to their centres. In the second experiment, 13 neglect patients were asked to point to the centre of a rectangular box with a swivelled lid and then to place a coin at the centre of this lid, in a position sufficiently central to prevent the lid tilting and the coin falling into the box. The authors observed that 10 patients showed smaller rightward deviations when placing the coin than when just pointing to the centre. They argued that their results indicate that a small change in the purpose of an action has a significant effect on neglect.

In a subsequent study Robertson, Nico and Hood (1997) asked neglect patients to point to the centre of a rod (pointing condition) or to grip the centre of a rod without lifting it (control condition) and in another

condition to repeatedly grip and pick up the rod at its centre until they were satisfied that they had found the centre (training). They found that patient's grips were more central in the condition where they were allowed to pick it up, when compared to when they only grasped the rod without lifting it. They also examined the short-term effects of visuomotor feedback of the unbalanced rod in 16 patients with neglect on star cancellation and on the line bisection task of the BIT, as well as on the bisection of large lines and the rod pointing condition. Interestingly, significant positive effects were found on the line bisection task and on the cancellation task of the BIT, up to 20 minutes post-training. This was not the case for the control condition. Surprisingly, no effect was found on the rod pointing or on the bisection of the large lines, which are perhaps more intervention-specific tasks. Nonetheless, considering that the brief training condition consisted of only nine trials it was encouraging that significant effects were found even twenty minutes following the intervention.

Harvey *et al.* (2003) then examined the extent to which a more intensive version of this visuomotor feedback training could produce immediate and more enduring improvements in a randomized control trial with 14 chronic neglect patients. The intervention group was asked to reach, lift and balance rods at their centre whilst patients in the control group reached and lifted the right-hand side of the rod. Patients underwent a 3-day experimenter-administered practise of rod lifting and then the immediate effects were measured with a line bisection task, the landmark test (i.e., the patient is asked to judge which end of the line is closer to a central landmark) and the real object test (i.e., reach and grasp the centre of three household objects). After this experimenter-led intervention patients

continued the rod practise in a self-administered manner for a further 2-week period (home-based intervention). Effects were measured before and after the home-based treatment and again after one month follow-up with a large test battery including the BIT, the Balloons test, the elevator and lottery sub-tests of the test of everyday attention, the 'Barthel Functional measure of activities of daily living' and the Catherine Bergego Scale. They found significant improvements on the landmark task after the 3-day intervention in the group that received visuomotor feedback training, but not in the control group. Moreover, the intervention group also improved significantly on the BIT conventional sub-tests between the end of the training and the 1-month follow-up.

Robertson, Nico and Hood (1995, 1997) suggested that the perceived mismatch between the two sensory systems (phenomenological visual representation and sense of unbalance and sight of the rod tipping) might increase the patient's awareness of their neglect. In other words, the perception-action conflict might act as a cue to scan leftwards by reducing anosognosia and thus improving performance in paper and pencil tests. However, Harvey *et al.* (2003) did not find any improvements with the Catherine Bergego Scale, which assesses anosognosia in everyday life, suggesting that this might not be the case.

Moreover, Robertson, Nico and Hood (1995, 1997) alternatively postulated that by intending to act on an object neglect may be reduced. This assumes that motor manipulative responses (pick up the rod at the centre) may have access to unique streams of information not available for non-motoric judgements (pointing to the perceived centre of a rod). Robertson, Nico and Hood (1995, 1997) postulated that the prehensile

movements towards objects involved in the training allow 'leakage' of information about their spatial extent, via an unaffected stream of information available for motor-manipulative responses through some type of 'dorsal-to-ventral recalibration' (Robertson, 1999; Milner & Harvey, 2006). In other words, by drawing the patients' attention to the mismatch within the task it might be possible to 'bootstrap' the patients' perceptual ability onto better visuomotor performance through the intention to act and subsequent feedback of this action (Harvey *et al.*, 2003).

Therefore visuomotor feedback training has theoretical relevance to this thesis as it applies the predictions of Milner and Goodale (1995, 2006)'s model to neglect rehabilitation. As previously mentioned, according to this model it is hypothesized that the dorsal visual stream is relatively functional in these patients and that consequently their visuomotor behaviour may be unaffected by the condition. In line with this view, in the previous chapters I have confirmed that neglect patients are not specifically impaired in target-directed reaching towards leftward targets (with or without visual feedback) and other studies have also found the same pattern in grasping objects on the left side of space (e.g., Harvey *et al.*, 2002).

Thus, the current experiment aims to assess the immediate and long-term extent to which visuomotor feedback training, initially performed by Robertson and colleagues (1995, 1997) and extended by Harvey and colleagues (2003) may improve the performance of classic neglect measures, but also more ecological tasks.

As in Harvey *et al.* (2003)'s study, the intervention group was asked to reach, lift and balance rods at the centre, 'readjusting until satisfied with the judged central grip', whilst the patients in the control group reached and

lifted the right-hand side of the rod only. The intervention group therefore received proprioceptive, as well as visual feedback, on how well they grasped the centre of the rod; however both groups received a comparable amount of motor experience of reaching and lifting rods. Participants, having mastered the exercise for two days with the experimenter present (experimenter-led intervention), embarked on a home-based intervention of 2 weeks, in which they repeated the training independently (home-based intervention). The number of intervention trials and sessions in the present study is slightly different from that of Harvey *et al.* (2003). In particular in each of the two experimenter-led sessions, participants performed only 54 rod-lifting trials. This was done to assess if a shorter number of sessions would produce similar improvements to what Harvey *et al.* (2003) found with three sessions of 72 rod-lifting trials each. The home-based intervention was identical to the one performed by Harvey *et al.* (2003).

Moreover, as the long-term impact of any rehabilitation attempt is crucial, the potential effects of visuomotor training feedback were evaluated at 4-months follow-up, in contrast to the one-month post-training period examined in Harvey *et al.* (2003)'s study. In addition, as in Harvey *et al.* (2003)'s study, the effects of the programme were measured with the BIT conventional sub-tests and the line bisection, landmark and balloons tests. However, here I also examined the effects of the training in different outcome measures from the ones used by Harvey *et al.* (2003), in an attempt to assess improvements in a more ecological valid manner.

The impact of any treatment in the daily functioning of patients is a crucial factor to determine its relevance. Harvey *et al.* (2003) did not find any effects of visuomotor feedback training on the 'Barthel functional evaluation

index of activities of daily living' and indeed Bowen and Wenman (2002) suggested that this measure is insensitive to rehabilitation outcome. Moreover the most commonly used scales (e.g., Barthel Index) focus on the physical consequences of the stroke, not assessing other dimensions of health-related quality of life, such as social role function. Therefore, the present study applied the recently developed Stroke Impact Scale. This Scale is a stroke-specific measure of recovery designed for repeated administrations to track change over time for both clinical and research settings. Importantly, this scale has been shown to be valid, reliable and sensitive to change and assesses several domains of daily life functioning (Duncan *et al.*, 1999a; 2002; 2003).

Many patients suffering from neglect may also show a horizontal displacement of the sagittal midline to the ipsilesional side (Karnath, 1996). This alteration of the egocentric reference can be tested by requiring the subject to point straight ahead in the dark and several investigators have found the performance of neglect patients to improve on this measure after prism adaptation (e.g. Pisella *et al.*, 2002; Rode, Rossetti & Boisson, 2001; Sarri *et al.*, 2008). Therefore, a straight ahead pointing task was also applied in the present study.

Moreover, many neglect patients may present neglect of extrapersonal space (i.e., space beyond reaching). There are no current standardised measures of neglect of far space (Robertson & Halligan, 1999), but in previous rehabilitation studies, this symptom has been evaluated using a room description task. Frassinetti *et al.* (2002), designed a room description task to evaluate the effects of prism adaptation in far space and observed a reduction of left omissions and, more impressively, that this

improvement was maintained after 5 weeks post-training. Based on the fact that this task has been shown to be sensitive to the training outcomes it was also implemented in the present study.

Method

Participants

The initial aim of this study was to recruit 16 neglect patients (eight in the control and eight in the intervention group). Patients were randomly allocated to either group, but with an attempt to match for neglect severity, as assessed with the BIT conventional sub-tests and the Balloons test. However, the sample size ended up uneven between the intervention group (N=8) and the control group (N=5) because two patients that were initially allocated to the control group did not complete the training (one patient died and the other one refused to continue for medical reasons).

The neglect inclusion criteria were the same as in Part I. After the neuropsychological assessment, the neglect patients were allocated to the intervention group (mean age 64.0, SD 8.9) or to the control group (mean age 65.2, SD 7.8). Patients were told that the study investigated the potential of a relatively new rehabilitation technique that may help them to notice things around better, especially on their left side. On average, patients participated in the study four months after stroke onset and there were no differences between the groups in terms of onset times. The groups also did not significantly differ in terms of age, cognitive abilities (as assessed with the sub-test of the WAIS-R) and neglect severity (i.e., BIT conventional sub-test scores, the Balloons lateralized index and the mean line bisection error).

The patients' demographic and clinical data are presented in Table 16. Although, lesion overlap analysis was not carried out in the present study, the location of the damage is reported in Table 16.

Note that some patients tested in the presented study were also tested in the experiments of Part I and this is highlighted in Table 16. Patients DS, AM and JK only started the rehabilitation training after Chapter 1 and 2's experiments were carried out. However, due to stroke severity and mobility issues patients AB, FH, JH and MJ performed the behavioural experiments of Part I after taking part in the present rehabilitation study (and they still presented neglect see Table 1 and 11).

Table 16 - Demographic and clinical data of the neglect patients. Patient's initials are in bold and italic when they also participated in the experiments of Part I.

Group	Patient	Gender	Age	Scan	Etiology	Lesion location	TO	VFD	EXT	BIT	Line bisection	Balloons
Intervention	***AB***	F	70	MRI	Infarct	R. Temporo-occipital	1	Yes	(-)	104	28	30
	AK	F	67	CT	Infarct	R. posterior Fronto-insula-parietal	1	No	No	121	16	43
	DS	F	64	MRI	Infarct	R. Fronto-temporo-occipital	3	Yes	(-)	91	82	50
	FH	F	80	MRI	Haemorrage	R. Temporo-parietal	5	Yes	(-)	72	86	0
	JH	F	55	MRI	Infarct	R. Fronto-temporo-parietal	10	Yes	Yes	132	14	50
	JMA	F	52	MRI	Infarct	Bilateral occipital (L. predominant)	3	Yes	(-)	112	-67	33
	MJ	M	59	CT	Infarct	R. Frontal-temporo-parietal-occipital	2	Yes	(-)	73	63	0
	MMU	F	65	CT	Infarct	R. MCA, basal ganglia, L. frontal	4	Yes	Yes	64	35	0
							Intervention group means			***96***	***32***	***25***
Control	***AM***	M	63	CT	Infarct	R. Fronto-temporal-parietal-insular	5	Yes	Yes	130	11	50
	AMC	M	76	CT	Infarct	R. parietal	3	Yes	Yes	79	24	0
	JK	F	69	CT	Infarct	R. Fronto-temporal	3	No	No	141	15	44
	JR	M	63	CT	Infarct	R. Fronto-insular-occipito-basal ganglia	5	Yes	(-)	14	83	0
	PI	M	55	MRI	Infacrt	R. Fronto-temporo-parietal	2	Yes	(-)	83	50	11
							Control group means			***89***	***36***	***21***

R = Right hemisphere; L. = Left hemisphere; TO = time since injury onset until baseline assessment (months); VFD = visual field defect; EXT = extinction; BIT = Behavioural Inattention Test conventional sub-tests score (cut-off = 129); Line bisection represents the average error (in mm) obtained with 20 lines (200mm length), no sign is equivalent to a rightward error and a negative sign is equivalent to a leftward error (cut-off = 6mm, Halligan, Manning & Marshall, 1990); Balloons represents the lateralized index score in sub-test B (patient is impaired when this index is lower than 45%); (-) unable to diagnose extinction.

Training stimuli

Three wooden rods (1.1cm diameter, 0.63g in weight) of 50, 75 and 100cm in length were used. Each rod was presented horizontally on a test mat in front of the patient, with the middle of the mat in line with the patient's body midline. Additionally, to reduce the possibility that patients reached for rods according to a fixed external reference in the background environment, rods were presented to the left and right of the body midline with a deviation of 10cm. The test mat (160cm x 30 cm) indicated the correct rod positions for the spatial location of each of them (central, right and left).

Procedure

After the neuropsychological assessment (see patients section), the patients were randomly allocated to either the intervention or control group. If the time interval between neuropsychological assessment and baseline was longer than eight weeks, the BIT conventional sub-tests, the line bisection task and the Balloons test were re-administered in a second session. However, if this was not the case only the remaining outcome measures were applied. That is, the landmark task, the room description task, the straight ahead pointing task and the Stroke Impact Scale (see outcome measures section for a description of these measures).

Following the 'evaluation' baseline sessions, the rehabilitation rod lifting exercise was introduced and administered by the experimenter in two consecutive sessions of approximately 30 minutes each. Participants were shown where to place the rehabilitation mat in relation to themselves and were told where each rod should be placed in relation to the rod size and labelling on the mat in a practise trial. For the intervention group, patients

had to reach for the rod with a pincer grip (using the forefinger and the thumb) and try to lift it up in its centre so that it would be balanced; if they felt that it was not balanced then they could repeat the trial until satisfied (see Figure 16). For the control group patients were instructed to reach for the rod on its right-hand side with a pincer grip (using the forefinger and the thumb) and to lift it up from the mat on that side. Once the trial was completed, patients positioned the rod to its original position (top of the mat). In addition, both groups were instructed that whilst lifting a rod off the mat they should not move it away from the starting position (indicated on the mat). Patients used their ipsilesional hand and the order of the rod-lift trials was randomized across sessions and patients.

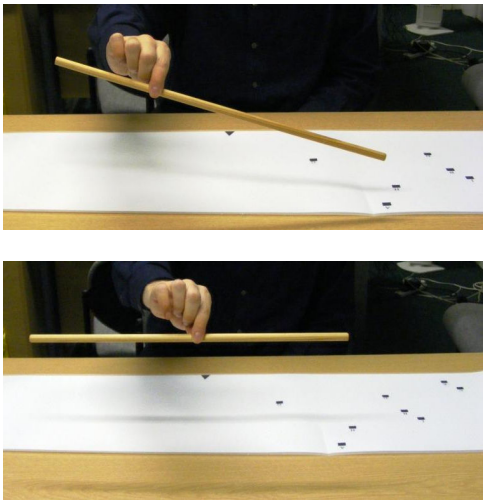

Figure 16. Dramatization of the behaviour of a neglect patient during visuomotor feedback training. In the top picture the rod is unbalanced as the subject grasped the rod to far rightwards from its centre. In the bottom picture the rod is balanced as subject correctly grasped it at its centre.

In each experimenter-led session, lifts of each rod and at each location were repeated six times creating 54-rod lifts. In the last experimenter-led session the following tests were administered: BIT

conventional sub-tests, line bisection and landmark tasks and the Balloons test.

After this two-day intervention, the patient repeated the training independently at their homes. During this home-based intervention the exercise consisted of 72-rod lifts (eight times per rod and location) for each of the 10 sessions, carried out over a period of two weeks. To control correct execution in the home-based intervention, participants were given a record sheet containing the order of trials (for each of the 10 sessions) and were required to mark each trial they performed. Furthermore, the experimenter monitored performance via regular phone contact to the patients and their families.

At the end of the home-based intervention, to evaluate the therapeutic effectiveness of the rehabilitation programme all participants were re-assessed with the complete battery of outcome measures, which included the BIT conventional sub-tests, the line bisection and landmark tasks, the Balloons test, the Stroke Impact Scale, the straight ahead pointing task and the room description task. Finally, after 4 months post-training all outcome measures were again applied to assess long-term effects. Below the experimental sequence is summarized:

Baseline

Step 1. Neuropsychological assessment and allocation of subjects

Step 2. Outcome measures: BIT conventional sub-tests, line bisection, Balloons test, landmark task, room description task, straight ahead pointing, Stroke Impact Scale

Experimenter-led intervention

Step 3. Intervention or Unspecified training (according to allocation) with the experimenter present (54-rod lifts)

Step 4. Intervention or Unspecified training (according to allocation) with the experimenter present (54-rod lifts)

Step 5. Outcome measures: BIT conventional sub-tests, line bisection, Balloons test, landmark task

Home-based intervention

Step 6. Both control and intervention group repeated the training independently for 10 days over a two-week period (72-rod lifts per session).

Step 7. Outcome measures: BIT conventional sub-tests, line bisection, Balloons test, landmark task, room description task, straight ahead pointing, Stroke Impact Scale

Follow-up

Step 8. Four months after the intervention patients were re-assessed with all the outcome measures: BIT conventional sub-tests, line bisection, Balloons test, landmark task, room description task, straight ahead pointing, Stroke Impact Scale

Outcome measures

To reduce learning effects the order of the administration of the measures was counterbalanced across sessions (baseline, experimenter-led, home-based, follow-up) and participants. As previously mentioned, in addition to the measures used to assess neglect (BIT conventional sub-tests, line bisection and Balloons) additional tasks were applied and these are described below.

Landmark task

This measure was adapted from Harvey, Milner and Roberts (1995). Patients were presented with 10 horizontal black lines (20cm x 1mm) that were already centrally transacted by a vertical mark (6mm x 1mm), the landmark. Four lines had landmarks of 1 and 2mm to the left and right of the true centre and the other six were positioned in the true centre. Lines were presented on individual sheets of A4 paper and subjects were asked to point, with their ipsilesional limb, to the end of the line closer to the landmark. Different orders of presentation were applied between sessions and participants. The percentage of centred lines reported as being shorter on the contralesional side was computed.

Room description

For the room description task (adapted from Frassinetti *et al.*, 2002), 14 objects were positioned in the patient's living room and along his/her midline (seven on the left and seven on the right). The patients sat in the centre of the room with their back to one of the walls and were blindfolded until the start of the trial. A table was placed in the centre of the room in front of the patient with eight objects, four on the left and four on the right (glue tube, stapler, pencils and booklets). Additionally, along the left and the right side of the room, three objects were positioned on each side (A3 posters, calendar and carton boxes). The position of the objects was randomized across assessments and patients. Patients were asked to name the new items seen in front of them in the room for a period of 2 minutes and the experimenter took a note of the number of objects reported on each side.

Straight ahead pointing

In the straight ahead pointing task (adapted from Rode, Rossetti & Boisson, 2001), patients were blindfolded and sat in front of a horizontal wooden board (87cm length and 54cm height). Patients were required to point straight ahead from a resting position while their head was kept aligned with the body's sagittal axis by the experimenter. They were instructed about the movement itself in that it should be fast, in one go, with the forearm extended when hitting the board (located app. 40cm from the patient). Ten pointing trials were performed, to obtain a reliable average value. After every trial the experimenter registered the horizontal displacement of the pointing movement by marking its endpoint on a sheet of paper that covered the board. The sheet was attached to the board and contained a line that indicated the centre of the board (invisible to the participant as he/she was blindfolded), which was aligned with the patient's body midline and thus represented the objective end-point of the body midline. The mean absolute displacement from the centre (in degrees) was later computed.

Stroke Impact Scale

The UK English version of the Stroke Impact Scale (version 3.0; Duncan *et al.*, 1999a,b,c; 2002, 2003) contains 59 items and assesses the following eight domains: strength of the contralesional limbs; contralesional hand function; mobility; emotion; communication; memory and thinking; social participation; activities of daily living/instrumental activities of daily living (ADL/IADL). The individual is asked to rate each domain on a scale from one to five. In addition, the scale contains a question to assess the individual's global perception of stroke percentage recovery, which ranges from 0 (no recovery) to 100 (full recovery). The scoring of the scale was conducted

through a database (in Microsoft Access) provided on-line by the Kansas University Medical Centre (http://www2.kumc.edu/coa/SIS/SIS_pg2.htm).

Whenever possible, the Stroke Impact Scale (Proxy version) was rated by a family member who lived with the patient. However, the experimenter applied the scale to three patients (i.e., JH, MJ and FH), as there was no carer available.

Results

The effects of visuomotor feedback training were analysed with a 2 X 4 mixed analysis of variance with group (intervention versus control) as a between factor and phase (baseline, experimenter-led, home-based and follow-up) as a within factor separately for the outcome measures (the BIT, line bisection, Balloons test and landmark test). The deviation in degrees on the straight ahead pointing task, the number of contralesional objects omitted on the room description task and the normalized scores obtained for each domain of the Stroke Impact Scale were analysed with 2 x 3 ANOVAs. Group was analysed as a between factor and phase (baseline, home-based and follow-up) as within effect. Pairwise comparisons were performed with the Bonferroni adjustment ($p < .05$). Results are reported for each measure separately.

Behavioural Inattention Test

In Table 17, the descriptive statistics for this measure are presented per group and phase. The analysis of variance on the total score of the BIT conventional sub-tests revealed no main effect of group. However, there was

a main effect of phase [$F_{(3,33)}$ = 8.09, p < .001], in that overall participants improved on this measure with time. Pairwise comparisons revealed that the BIT scores were significantly lower at baseline, when compared to the experimenter-led (mean difference = -18.7, p < .01), home-based (mean difference = -22.6, p < .01) and follow-up sessions (mean difference = -21.4, p < .05). There was no significant difference between the experimenter-led, home-based and follow-up scores.

Table 17 – Means and standard errors (in parenthesis) of the BIT conventional sub-tests total score per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	96.1 (8.9)	89.4 (22.5)
Exp-led	127.0 (3.4)	96.0 (22.6)
Home-based	135.6 (2.6)	95.0 (22.4)
Follow-up	126 (9.6)	102.4 (24.8)

Most importantly, the interaction between group and phase [$F_{(3,33)}$ = 3.71, p < .05] was also significant. Pairwise comparisons revealed that the intervention group improved significantly with the training, whilst the control group showed no amelioration between assessments (see Figure 17). In particular, the intervention group presented higher scores after the experimenter-led and home-based training sessions when compared to the baseline score (p < .01 and p < .01). In addition, the BIT scores of the intervention group increased significantly after the home-based session when compared to the experimenter-led session (p < .05). In fact at home-based assessment, the intervention group had significantly higher scores

than the control group (p < .05). No differences between the groups were obtained for the baseline, experimenter-led and follow-up sessions. Importantly, after 4 months post-training, the BIT score remained significantly higher than at baseline in the intervention group only (p < .05). In the intervention group, the score at follow-up did not significantly differ from the one obtained at the experimenter-led and home-based assessments.

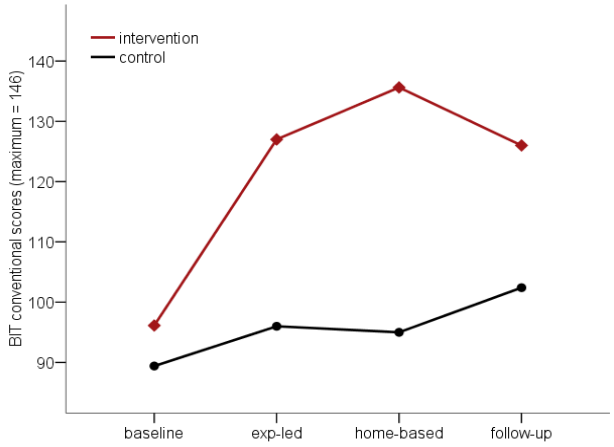

Figure 17. BIT conventional sub-tests total score (maximum = 146) per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

Examination of the individual scores of the intervention group revealed that all patients markedly improved on the BIT after two rod-lifting sessions and continued improving after the 10 home-based sessions (see Table 18). At follow-up only two patients (FH and MM), out of the eight studied in the intervention group, decreased their performance on the task. Curiously these were the most severe neglect patients at baseline (as determined by the BIT overall score and by the BIT sub-tests of star cancellation and figure and shape copying scores).

Table 18. Individual scores of the neglect patients on the BIT conventional sub-tests (maximum = 146) per group and phase.

Group	Patient	Baseline	Experimenter-led	Home-based	Follow-up
	AB	104	123	131	129
	AK	121	136	142	145
	DS	91	130	131	143
	FH	72	123	129	103
	JH	132	135	138	139
	JMA	112	138	146	142
	MJ	73	122	142	139
Intervention	MMU	64	109	126	68
	AM	130	133	122	134
	AMC	79	88	89	134
	JK	141	143	144	143
	JR	14	15	13	10
Control	PI	83	101	107	91

To investigate this further an analysis of variance was carried out for each sub-test separately. Namely a 2 x 4 mixed ANOVA was run on each contralesional score of the cancellation tasks (line, letter and star) and on the scores obtained in the line bisection, copying and drawing sub-tests. This revealed that, although both groups improved over time for all sub-tests (for simplicity this is not reported here), only for the star cancellation sub-test did the patients of the intervention group improve significantly between phases when compared to the control group (see Table 19). That is only for this sub-test, the interaction between phase and group was significant [$F_{(3,33)} = 3.71$, $p < .05$]. Post-hoc tests revealed that, only in the intervention group, the number of stars cancelled on the contralesional side of space increased from baseline, to experimenter-led ($p < .01$), home-based ($p < .01$) and follow-up assessments ($p < .05$). The scores of the intervention group did not

differ significantly between the experimenter-led, home-based and follow-up assessments. Moreover, the intervention group cancelled significantly more stars after the experimenter-led and home-based sessions when compared to the control group ($p < .05$ and $p < .01$, respectively; see Figure 18). No significant differences were observed between the two groups at baseline or at follow-up.

Table 19 – Means and standard errors (in parenthesis) of the number of stars cancelled on the contralesional side of space (maximum = 27) per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	11.1 (3.7)	11.8 (4.7)
Exp-led	23.4 (1.0)	12.0 (5.4)
Home-based	25.1 (1.1)	10.6 (4.7)
Follow-up	21.9 (3.3)	17.9 (3.9)

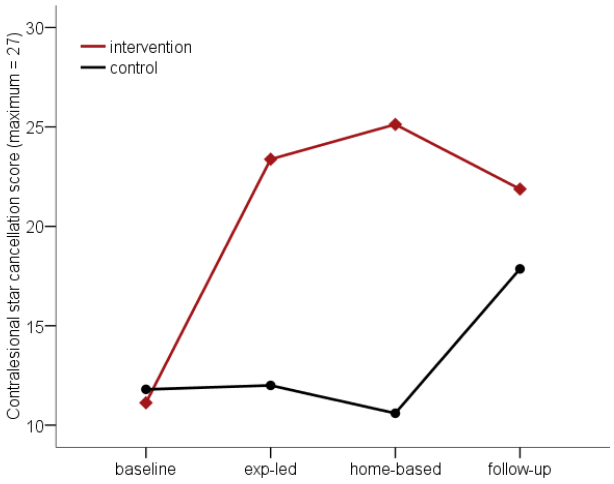

Figure 18. Number of stars cancelled on the contralesional side of space per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

Again the examination of the individual scores of the intervention group revealed that all the patients markedly improved on star cancellation after the experimenter-led and home-based sessions (see Table 20). At follow-up only two patients (FH and MM), out of the eight included in the intervention group, markedly decreased their performance on the task when compared to the home-based assessment.

Table 20. Individual contralesional star cancellation scores (maximum = 27) of the neglect patients per group and phase.

Group	Patient	Baseline	Experimenter-led	Home-based	Follow-up
	AB	17	23	27	27
	AK	17	24	26	27
	DS	0	23	25	26
	FH	0	26	26	17
	JH	22	22	27	27
	JMA	26	27	27	26
	MJ	2	18	25	25
Intervention	MMU	5	24	18	0
	AM	19	23	14	23
	AMC	7	4	6	22
	JK	26	27	27	27
	JR	0	0	0	7
Control	PI	7	6	6	10

Line bisection

As one of the patients presented right neglect (JM), only the absolute errors from the true centre (i.e., regardless of sign) were analysed. In Table 21 the mean and standard errors are presented for the line bisection absolute error. A 2 x 4 Anova showed that there was a main effect of phase [$F_{(3,33)} = 6.04$, $p < .01$], but pairwise comparisons did not reveal any significant effects. In

addition, no other effects were significant. This is surprising, as from Table 21 it seems that the intervention patients' mean errors decreased from baseline to the other phases and at an individual level all the intervention patients improved after the two exp-led sessions in their line bisection performance. However, there was a trend towards a significant interaction between phase and group (p = .08). In particular, post-hoc comparisons showed that in the intervention group the bisection errors were smaller after the training sessions (experimenter-led and home-based) when compared to the baseline performance on this task (mean difference = -34mm, p < .01; mean difference = -32.2mm, p < .05, respectively). No significant differences between phases were obtained for the control group.

Table 21 – Means and standard errors (in parenthesis) of the absolute line bisection errors (in mm) per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	48.8 (10.3)	36.3 (13.4)
Exp-led	15.0 (7.3)	34.0 (16.1)
Home-based	16.6 (8.7)	22.0 (13.5)
Follow-up	19.7 (9.0)	26.2 (13.5)

Balloons test

No main effects and no interaction between group and phase were observed for the lateralized index score (see Table 22 for descriptive statistics). Further ANOVAs were carried out on the number of items cancelled on the sub-test A and B of this test and this also did not reveal any significant differences between the groups nor significant interactions between group

and phase. As not all the patients were impaired at baseline a further ANOVA was carried out including only the patients with a marked lateralized deficit, but the main effects or the interaction between phase and group were also not significant.

Table 22 – Means and standard errors (in parenthesis) of the lateralized index score of the Balloons Test per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	25.8 (7.9)	21.0 (10.8)
Exp-led	38.6 (8.5)	23.4 (10.6)
Home-based	44.1 (5.5)	33.1 (9.7)
Follow-up	30.5 (7.1)	29.7 (10.1)

Landmark task

No main effects and no interaction between group and phase were observed for the proportion of centred lines judged as shorter on the contralesional side of space (see Table 23 for descriptive statistics).

Table 23 – Means and standard errors (in parenthesis) of the proportion of centred lines judged as shorter in the contralesional side of space per group before the intervention (baseline), after experimenter-led intervention (exp-led; 2 sessions), after home-based training (10 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	83.3 (11.3)	76.7 (19.4)
Exp-led	75.0 (14.8)	66.7 (19.0)
Home-based	77.1 (15.1)	60.0 (19.4)
Follow-up	85.4 (12.4)	62.1 (17.0)

Straight ahead pointing

No main effects and no interaction between group and phase were observed for absolute error in straight ahead pointing (see Table 24 for descriptive statistics).

Table 24 – Means and standard errors (in parenthesis) of the absolute error (in degrees) for the straight ahead pointing task per group before the intervention (baseline), after home-based training (total 12 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	13.2 (5.0)	18.7 (3.4)
Home-based	8.9 (2.3)	11.0 (2.5)
Follow-up	14.2 (2.5)	11.0 (4.9)

Room Description Task

No main effects and no interaction between group and phase were observed for the number of items reported on the contralesional side of space. However, as can be seen from the Table 25, at baseline patients in the intervention group only missed one object on the contralesional side of space, indicating that they were unimpaired at the task.

Table 25 – Means and standard errors (in parenthesis) of the number of objects omitted in the contralesional side of space (maximum = 7) per group before the intervention (baseline), after home-based training (total 12 sessions) and after 4-months post-training (follow-up).

	Group	
Phase	Intervention	Control
Baseline	1.3 (0.6)	3.0 (1.3)
Home-based	1.0 (0.6)	2.8 (1.3)
Follow-up	0.9 (0.6)	2.0 (1.3)

Stroke Impact Scale

No main effects and no interaction between group and phase were observed for the following domains of the scale: strength of contralesional limbs, contralesional hand function, memory and thinking, communication, emotion and social participation (see Table 26 for descriptive statistics for each of the Scale domains).

There was a main effect of phase for the stroke recovery domain [$F_{(2,22)}$ = 5.61, p < .05] but pairwise comparisons were not significant. Moreover, the interaction between phase and group was significant for the mobility domain [$F_{(2,22)}$ = 4.22, p < .05]. As can be seen on Table 26 it seems that the intervention group's scores increased at follow-up in respect to the baseline score however, pairwise comparisons were not significant. A 2 x 2 Anova was run with group as between factor and phase as within (baseline, follow-up) for the mobility domains, but the effect of group or interaction between the factors was not significant.

Table 26 – Means and standard errors (in parenthesis) for the normalized score of the Stroke Impact Scale per domain and per group before the intervention (baseline), after home-based training (total 12 sessions) and after 4-months post-training (follow-up).

Domain and phase	Group	
Strenght of contralesional limbs	Intervention	Control
Baseline	53.1 (14.1)	34.6 (11.2)
Home-based	43.0 (13.0)	31.3 (5.9)
Follow-up	46.3 (13.9)	23.8 (5.0)
Contralesional hand function	Intervention	Control
Baseline	41.2 (14.0)	6.0 (3.7)
Home-based	33.8 (16.1)	14.0 (8.7)
Follow-up	44.4 (16.1)	8.3 (8.3)
Memory	Intervention	Control
Baseline	73.2 (7.5)	47.1 (15.1)
Home-based	69.1 (7.4)	67.8 (10.8
Follow-up	74.3 (6.4)	55.7 (12.1)
Communication	Intervention	Control
Baseline	89.3 (4.4)	78.6 (7.4)
Home-based	84.7 (6.1)	82.1 (6.6)
Follow-up	87.2 (5.3)	86.6 (9.0)
Emotion	Intervention	Control
Baseline	61.5 (4.6)	54.9 (9.9)
Home-based	63.5 (5.5)	55.0 (11.9)
Follow-up	59.8 (4.0)	51.6 (10.6)
Social participation	Intervention	Control
Baseline	56.4 (12.5)	30.2 (10.1)
Home-based	52.4 (12.9)	49.7 (10.7)
Follow-up	44.8 (11.6)	39.0 (17.5)
Stroke recovery	Intervention	Control
Baseline	45.0 (11.6)	28.0 (3.7)
Home-based	51.3 (10.2)	48.0 (10.2)
Follow-up	60.0 (9.3)	43.0 (13.0)
Mobility	Intervention	Control
Baseline	51.7 (11.2)	35.5 (9.9)
Home-based	49.6 (12.2)	43.9 (11.8)
Follow-up	60.8 (13.2)	31.1 (7.8)
ADL/IADL	Intervention	Control
Baseline	50.6 (10.9)	35.7 (6.7)
Home-based	50.9 (10.7)	46.0 (8.7)
Follow-up	58.8 (10.5)	38.2 (9.1)

In addition, for the ADL/IADL domain there was a significant interaction between group and phase [$F_{(2,20)}$ = 4.73, p < .05]. Pairwise comparisons revealed that whilst the control group did not differ between baseline, home-based and follow-up assessments, the intervention group scores were significantly higher at follow-up than before the training (mean difference = +8.1, p < .01). No significant differences were obtained between baseline and home-based scores in the intervention group (mean difference = +0.3). Also, the two groups did not differ at any point in time. These observations suggest that the patients who underwent visuomotor feedback training were markedly more independent in activities of daily living at 4 months post-training, whilst the control group remained at a similar level between assessments (see Figure 19).

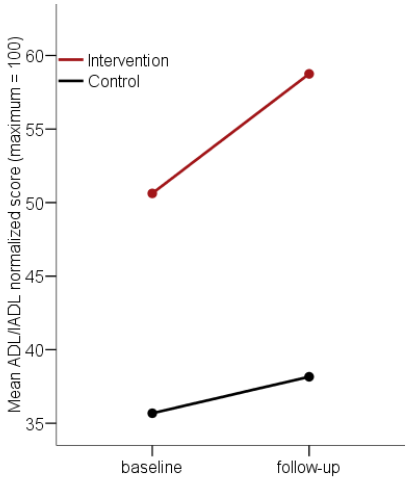

Figure 19. Normalized score obtained on the ADL/IADL domain of the Stroke Impact Scale per group before the intervention (baseline) and after 4-months post-training (follow-up).

In terms of individual scores on the ADL/IADL domain it was observed that all the 8 patients in the intervention group improved at follow-up (see Table 27).

To investigate this further a Pearson correlation analysis was ran on the percentage of improvement between the baseline and follow-up assessments on the ADL/IADL domain and the percentage of improvement in the star cancellation and BIT tests, but this was not significant.

Table 27. Individual normalized scores of the neglect patients for the ADL/IADL domain of the Stroke Impact Scale per group and phase.

Group	Patient	Baseline	Home-based	Follow-up
	AB	90	93	95
	AK	40	30	50
	DS	95	100	100
	FH	68	60	80
	JH	28	38	38
	JMA	28	33	33
	MJ	48	35	55
Intervention	MMU	10	20	20
	AM	31	55	28
	AMC	33	47	33
	JK	53	53	55
	JR	15	13	13
Control	PI	48	63	63

Discussion

The aim of the present study was to examine the effects of visuomotor feedback training in neglect patients when compared to a control group who received unspecified training only. In addition, long-lasting effects were

examined four months post-training, which constitutes a longer time period than the one examined in previous studies (Harvey *et al.*, 2003; Robertson, Nico & Hood, 1997). Furthermore, an attempt was made to examine the effects in a more ecological manner by including tasks such as the room description, straight ahead pointing and the Stroke Impact Scale.

Immediate effects of visuomotor feedback training

Significant improvements in the patients of the intervention group were found on the overall score of the conventional sub-tests of the BIT after only 2-days of visuomotor feedback training and these improvements markedly increased after the 10 home-based sessions (see Figure 17). In fact after these 10 training sessions, the intervention group had markedly improved on the BIT when compared to the control group and to the baseline and experimenter-led assessment sessions. A separate analysis on each sub-test of this battery revealed that the patients cancelled more items on the left side of space after the 2-day training and improved even more after the 10 home-based sessions (see Figure 18).

The improvements found here for the BIT diverge from the ones obtained by Harvey *et al.* (2003), who failed to find any short-term effects on the BIT and its sub-tests. Nonetheless the present results agree with the study by Robertson, Nico and Hood (1997) who also found immediate improvements on star cancellation that lasted for 20 minutes after the training. One possibility is that the patients tested in Harvey *et al.* (2003)'s trial were significantly[1] more chronic (mean of 12 months post-stroke) than

[1]A one-way Anova revealed significant differences between Harvey *et al.* (2003)'s intervention patients' TO and the ones included in the present study [$F_{(1, 14)} = 11.90$, $p < .01$].

the ones tested here (mean of 4 months post-stroke). On the other hand, the intervention patients tested here were significantly[2] more impaired on the BIT (mean = 96.1) when compared to the patients included in Harvey *et al.* (2003)'s study (mean BIT = 124). Perhaps this increase in severity at baseline left more 'room' for improvements.

In terms of the line bisection errors, similarly to Harvey *et al.* (2003)'s observations, no significant improvements were observed in line bisection in the main ANOVA. This result is surprising since this task may be considered as the most similar to the training procedure. Nonetheless a trend was observed, in that patient's ipsilesional deviations from the true centre of the line were smaller after the 2-day intervention, albeit this was not observed after the home-based training or at the follow-up assessment. In line with the present observations, Robertson, Nico and Hood (1997) also found a similar pattern of results as their significant effects were observed on the measures that were considered less training-specific. Regarding the Balloons performance no immediate effects were found for this measure either, replicating Harvey *et al.*'s (2003) observation.

Harvey *et al.* (2003) found significant effects after the 3-day experimenter-led sessions on the landmark test, in that the patients in the intervention group made fewer leftward judgements than the control group. In the present study I did not find any improvements on this task. However, Harvey *et al.* (2003)'s effect was somewhat small, in that patients made one less leftward response after the 3-day training. In addition, the authors did not assess if these improvements remained after the home-based intervention. On the other hand, in the present study, participants were

[2]A one-way Anova revealed significant differences between Harvey *et al.* (2003)'s intervention patients' BIT scores and the ones included in the present study [$F_{(1, 14)} = 6.64$, $p < .05$].

asked to point to the side of line that was closer to the landmark (motor version), whereas in Harvey *et al.* (2003)'s study it seems that they were asked to judge this verbally (perceptual version). It remains an open question if these different task instructions played a role in the null finding in the present study. Alternatively, the number of training sessions could also account for these discrepant results as in the present study less training was provided in the experimenter-led sessions than in Harvey *et al.* (2003)'s study.

Another possible explanation of the null training effects on landmark performance could be that the training might have produced no effect on the perceptual distortion present in my neglect patients. In line with this view, Harvey and Milner (1997) observed that after one year post-stroke two neglect patients showed smaller errors in the line bisection task, but were still impaired in the landmark task, when compared to their performance at two months post-stroke. Based on these findings, Harvey and Milner (1997) suggested that the landmark task could be a more sensitive measure for identifying 'real' recovery of perceptual deficits.

In addition, in line with previous findings (e.g. Pisella *et al.*, 2002; Rode, Rossetti & Boisson, 2001), at baseline all neglect patients presented a significant ipsilesional shift in straight ahead pointing. However, no improvements were found on the task between baseline and home-based assessments. This result contrasts with the consistent findings that prism adaptation ameliorates the rightward deviation in open-loop subjective straight ahead pointing (e.g., Sarri *et al.*, 2008). It is likely that, prism adaptation has much stronger effects on this measure than visuomotor feedback training. Indeed it has been repeatedly shown that 10 degree

prisms cause a strong 'after-effect', in that the patients straight ahead judgements are shifted about 8 to 9 degrees leftwards (see Pisella *et al.*, 2002; Sarri *et al.*, 2008). Yet, the improvement on this measure after prism adaptation is not consistent across patients. For example, Pisella *et al.* (2002) found that whilst in one of the two patients studied (PE) the straight ahead judgement was close to normal four hours, and two and four days post-training, the other patient (SA, who showed the most severe deviation of 14.9 degrees) was still at the same level, as at baseline, in all post-training assessments. In addition, they observed that patient PE did not improve in line bisection whilst patient SA did. Pisella *et al.* (2002) argued that line bisection and straight ahead pointing might depend on separate neural mechanisms. Moreover, it has been shown that straight ahead pointing abnormalities may not be exclusive to neglect patients and may not always correlate with other neglect tests (e.g. Bartolomeu & Chockron, 1999; Chokron & Bartolomeu, 1997; Farne, Ponti & Ladavas, 1998). This is not surprising given that neglect is now considered a multi-component syndrome.

To investigate whether the subjective straight ahead task taps into different neural mechanisms from the usual neglect measures a further correlation analysis was performed between the straight ahead pointing error and the scores obtained in the neglect diagnostic measures. This revealed that, at baseline, the bisection errors significantly correlated with the BIT overall scores[3] and with the balloons lateralized index score[4] whilst the errors in the straight ahead pointing task did not correlate with the scores obtained in any of these neglect measures. Alternatively, it could be argued

[3] ($N = 13$, $r = -0.68$, $p < .05$)
[4] ($N = 13$, $r = -0.82$, $p < .01$)

that the severe ipsilesional biases in the straight ahead judgement were unaffected by visuomotor feedback training. Indeed, my patients were as impaired in the present study as patient SA in Pisella *et al.* (2002)'s study and seemed to be more impaired than the patients included in Sarri *et al.* (2008)'s study. In particular, the mean error in Sarri *et al.* (2008)'s patients was 9°, whilst in the present study neglect patients presented an average shift of 15.3°.

It would have been interesting to test the straight ahead pointing performance of the patients immediately after each experimenter-led session. However, due to patient tiredness this was not possible and thus this measure was only repeated after the home-based training (total 12 sessions). Nonetheless, it is interesting to note that whilst there was a trend for improvement in line bisection, no such effect was observed for straight ahead pointing, perhaps agreeing with the view that these two tasks depend on separate neural mechanisms.

I also did not find any immediate effects of visuomotor feedback training in the room description task. However, it is worth noting that (by coincidence) most intervention patients were at ceiling at baseline already. Thus future experiments with patients who present extrapersonal neglect are needed. In addition, although I hoped to find a generalization of the effects to daily life activities (as measured by the Stroke Impact Scale) immediately after the training this was not observed. Nonetheless, long-terms improvements were observed in this measure and these will be discussed below.

Long-lasting effects of visuomotor feedback training

The long-term maintenance of treatment effects is obviously a crucial component of any rehabilitation technique and it is well known that this is very difficult to obtain in patients with neglect. However, the present study provides very promising results in several ways in this respect.

First, the immediate improvements on the BIT, and on one of its cancellation sub-tests, were maintained in the intervention group at follow-up assessment. Importantly, the control group did not improve on these scores between any of the sessions. These findings are remarkable since the follow-up assessment was carried out four months post-training, which, as far as I know, is the longest period of time investigated in any neglect rehabilitation randomized control trial reported to date. The present findings extend the observations of Harvey *et al.* (2003), who observed improvements on the BIT in the intervention group at one-month follow-up.

Second, and perhaps more important, is the observation that 4 months post-training, the intervention group markedly ameliorated their score on the ADL/IADL domain of the Stroke Impact Scale, whilst the control group remained at the same level as at baseline (see Figure 19). The ADL/IADL domain of the scale assesses important aspects of the patient's daily routine including eating, dressing, personal hygiene, household tasks, shopping, social activities, recreation, family role and the ability to control their own life as well as to help others. Thus, the present observations show that patients who underwent visuomotor feedback training were more functional and independent at follow-up, when compared to their baseline performance. The fact that the effect appeared at 4-months post-training, and not immediately after the 12 training sessions, could be related to the

so-called sleeper effect. As argued in Harvey *et al.* (2003), such an effect has been observed in the rehabilitation literature and may reflect the late consolidation of learning after training.

In line with this view, one possibility would be that the daily life improvements of the patients were not so noticeable immediately after therapy when compared to the improvements found in paper and pencil measures. One could hypothesize that visuomotor feedback training had an immediate impact on the patients' ability to look and find items on the left side of the world that gradually gave them more independence in their daily lives. This would explain why immediately after the training no improvements were found on the scale. However, it has to be noted that no significant correlations were found between the improvements on the neglect measures (BIT overall score and star cancellation) and the improvements on this functional domain, perhaps due to the small sample size (see Stroke Impact Scale section of the Results).

Moreover, the observation that visuomotor feedback training ameliorated the daily life of neglect patients has implications not only for the significance of this technique, but also shows that the relatively new Stroke Impact Scale seems to be sensitive to cognitive rehabilitation effects in neglect patients. McDowd *et al.* (2003) found that poorer attentional performance in stroke patients was associated with an increased negative impact of stroke on daily functioning as assessed with the Stroke Impact Scale. These findings and the present results suggest this scale might be sensitive to the impact of neglect in daily life functioning and to rehabilitation outcome. In fact, to the best of my knowledge, no previous randomized control study has reported such long-lasting improvements in a functional

rating scale in neglect rehabilitation studies. It will be interesting to see if future studies can replicate the present findings with a larger sample of patients, even when using other rehabilitation approaches. Future studies could also assess the long-lasting effects of this rehabilitation at different time points (e.g., one month, four months and one year).

In addition, a future avenue would be to assess the impact of visuomotor feedback training in other ecological tests, such as wheel-chair driving, postural control, walking through doorways. Based on the present findings of a trend for an improvement in the mobility domain I would predict that, with larger sample size, improvements could be observed here too. In addition, as significant improvements were found in cancellation tasks it would be interesting to test if these could also be observed in oculomotor behaviour (e.g., increase of number of saccades, faster saccadic reaction time and higher saccadic amplitude in the contralesional side of space). In fact, my initial plan was to assess the immediate effects of the training using an eye-tracking visual search task adapted from the Balloons test. However, unfortunately this was not achieved because most patients were constrained to their homes and some others could not be calibrated in the eye-tracker.

The findings obtained in the present study are very encouraging for future attempts, however there are serious caveats regarding the allocation and randomization procedure that need to be addressed in future studies, in which an attempt should be made to respect the guidelines of the Consolidated Standards of Reporting Trials (CONSORT; Begg *et al.*, 1996). First, the present study was carried out by a single experimenter, who assessed the patients, assigned them to a treatment group, delivered the treatment and assessed its outcome. Ideally a team of 'blind' researchers

should have been involved in these different stages to prevent a bias in estimating the effects of the treatment. More specifically, and according to the CONSORT, those administering the treatment and those assessing the outcomes should be blinded to group assignment. In addition, the randomization procedure was also not in line with the recommendations of the CONSORT group. In particular, although the patients were randomly allocated to each treatment group an attempt was made to match the groups in terms of neglect severity by the single experimenter. A more appropriate method would have been to have another researcher randomly allocate the patients through the minimization procedure (e.g., Altman & Bland, 2005). This randomization method ensures that excellent balance between groups is obtained for several prognostic factors even for small samples and is best performed with a free and automated software tool (Evans, Royston & Day, 2004). In fact, unfortunately most studies of neglect treatment do not respect the CONSORT guidelines. Therefore, if researchers *seriously* wish to apply cognitive neuroscience findings to aid neglect symptoms they should use more rigorous patient allocation methods and blinding designs. These methods will allow a more accurate and transparent description of the different treatment effects.

As mentioned in the Introduction, one of the mechanisms proposed to explain the improvement of visuomotor feedback training is a 'dorsal to ventral' recalibration (Milner & Harvey, 2006; Harvey *et al.*, 2003; Robertson, Nico and Hood, 1995, 1997; Robertson, 1999). In particular, these authors have suggested that spared dorsal stream areas in neglect patients allow them to use visual and proprioceptive feedback to bootstrap their perceptual experience. Indeed, I have shown in Chapter 1 that patients with neglect

(and some of them took part of this rehabilitation trial) use visual feedback efficiently in the guidance of their actions. Thus, in the future it will be interesting to perform lesion analysis to understand which neglect patients benefit from this type of therapy, for example by subtracting the lesions of patients who improved by those who did not, or by using statistical analysis to test which damaged voxels are associated with reduced improvement in a particular task. The number of patients in the present study was relatively small as it was not possible to recruit more patients due to time constraints. In addition, for this same reason it was also not possible to select the patients in terms of unilateral right-hemisphere lesions. Thus it was not possible to conduct a meaningful lesion analysis here.

Interestingly, two patients in the intervention group (FH and MM) did not show the maintenance of improvements at follow-up. Although the number of trials needed to achieve the rod balancing was not formally recorded I recall that these patients needed a high number of lifts for each rod. These patients were also the most severe neglect patients included here (see Table 16), so perhaps a higher number of training trials would be necessary for improvement maintenance. Future attempts using visuomotor feedback training should measure adaptation to training, similarly to what is done in prism adaptation studies. This could be done, by recording the number of trials needed to achieve rod balancing for each rod size and location.

Another possibility is that these patients did not benefit from the training at long-term, due to their lesion location. This hypothesis could also explain the discrepant findings between the present study and Harvey *et al.* (2003)'s findings. Indeed these authors postulated that if a patient has

damage to dorsal stream areas then they might not benefit from the intervention. In Chapter 1, I have shown that reaching impairments in open loop conditions are not specific to neglect patients but may occur if the patient has additional lesions to the lentiform nucleus or parietal-frontal areas. Therefore, based on these findings I would hypothesize that the ability to use sensory feedback efficiently depends on such areas and if patients have damage there they should find the rod balancing procedure very difficult and benefit less from the technique. As proposed by Harvey *et al.* (2003), it would have been useful to compare conditions in which the patient was asked to point to the centre of the rod (perception) and gripped the rod at its middle (action). This would have provided some indication if the patients' vision for action' system was relatively more spared than their 'vision for perception' stream. Indeed, it is fair to assume that if patients had dorsal visual stream damage they would not be able to correctly reach and grasp for the rods and/or to use sensory feedback to realize that the rod is unbalanced.

Previously, Robertson, Nico and Hood (1997) found that participant's grips were more central in a condition where they were allowed to pick the rod up, when compared to when they only grasped the rod without lifting it. Edwards and Humphreys (1999) reported a single-case study of a neglect patient (MP) who improved in rod bisection when grasping (when compared to pointing) only under visual feedback conditions. When both vision of the hand and target were unavailable both pointing and grasping responses produced the same amount of rightward bias. The authors suggested that the improvement of grasping under visual feedback could be due to on-line visuomotor adjustment, which resulted in consequent improved performance

in their patient. In other words, they suggest that the vision of the rod tipping to the left side was responsible for the improvements caused by visuomotor feedback training, whereas the sense of unbalance did not seem to play a strong role in this. The application of this paradigm with a larger group of patients should reveal more of the mechanisms involved in this type of training. Moreover, one could place magnets on the rod to manipulate the sense of its weight. This would test if the improvements in grasping the centre of a rod depend on the sense of unbalanced weight to the left. In addition, this could be further exploited by including a condition in which the presence of visual feedback is manipulated.

Furthermore, it would be interesting to test if visuomotor feedback training produces immediate effects on the performance of neglect patients in delayed reaching in a similar way as it ameliorates star cancellation and even line bisection (Robertson, Nico & Hood, 1997). Indeed, in Chapter 2, I have shown that these patients, just like DF, are specifically impaired in these off-line tasks and their errors correlate with their performance on the BIT and line bisection test. Future experiments should therefore test these patients before and after the intervention in delayed leftward reaching. If the training ameliorates the performance of patients in this task, this will provide further evidence that it improves processes supposedly carried out by the ventral visual stream through possible spared mechanisms in the dorsal visual stream.

In a similar vein, it has been suggested that visuomotor feedback training and prism adaptation make use of the same sensorimotor processes (Harvey *et al.*, 2003). In particular, prism lenses cause a mismatch between the proprioceptive sense of arm location and the visual experience of this.

Similarly, during visuomotor feedback training there is a mismatch between the initial perception of the rod's length and the unbalanced rod when it is lifted. In other words, the patient is initially misguided by his perception of the rod (shorter to the contralesional side) and reaches to far ipsilaterally from the centre, but then by lifting the rod realizes that he/she was incorrect. Similarly to what happens during prism adaptation the patients correct their reaches until successful performance is achieved.

In Sarri *et al.* (2008)'s study a preliminary lesion subtraction analysis was conducted to identify the lesioned voxels in patients that did not show improvement on a cancellation task after prism adaptation. Interestingly, the authors observed that patients who did not benefit from prisms had lesions located in the right intraparietal region and the inferior parietal lobe and middle frontal gyrus white matter. This result fits well with the PET study of Luauté *et al.* (2006b), that reported that the PPC was implicated in the beneficial effects of prism adaptation in neglect patients and that the patients who did not improve suffered lesions in the right infero-posterior parietal lobe.

Furthermore, an fMRI study with healthy subjects found that reaching whilst wearing prisms significantly activated the PPC when compared to reaches without the prisms (Clower *et al.*, 1996) and this has been recently extended by an event-related fMRI study by Luauté *et al.* (2009). The later authors observed that during the earliest phase of prism exposure, the anterior intraparietal sulcus was primarily implicated in error detection, whereas parieto-occipital sulcus was implicated in error correction. Luauté *et al.* (2009) observed that cerebellum activity progressively increased during prism exposure and argued that the observed time course indicates that the

cerebellum might promote neural changes in superior temporal cortex, which was selectively activated during the later phase of prism exposure and could mediate the effects of prism adaptation on cognitive spatial representations. Thus it would be interesting to compare the effects of visuomotor feedback training and prism adaptation in the same set of patients. Another possible avenue would be to conduct an fMRI study to determine the neural basis for the effects of visuomotor feedback training in both healthy participants and patients.

Conclusion

Taken altogether, the present findings show that visuomotor feedback training improves neglect symptoms and crucially that these improvements are long lasting, as they were present 4-months post-training. Importantly, I have shown that the training also seems to bring benefits to the patient's daily lives, which were present at follow-up. Notably, the control group did not improve with more unspecified training in any of the measures used. There is no doubt that a blinded randomized control trial with a larger sample of patients will be needed to confirm the present results and that future experiments are also needed to understand the neural mechanisms behind such improvements. Nonetheless, these findings are very encouraging, as based on the report that most neglect recovery occurs in the first three weeks (Stone *et al.*, 1992), the patients included here can be classified as chronic (4-months post-stroke). Moreover, in contrast with other neglect therapies (e.g., prism adaptation), visuomotor feedback training is simple, non-evasive, cost-effective, can be conducted solely by the patients with almost no supervision, and does not require long periods of training.

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