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Cognitive and anatomical correlates of neglect for peripersonal and extrapersonal space

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by

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ABSTRACT

Spatial neglect is a neurological disorder where patients typically fail to orient or respond to events on their left side. Moreover, recent studies suggest that the severity of neglect may depend specifically on whether stimuli are presented within or beyond arm's reach. However, the evidence for such a general functional dissociation between near and far space processing in the brain remains conflicting: The majority of research has been focussed on line bisection errors which reflect only one small aspect of neglect behaviour. In addition, some behavioural findings suggest a functional dissociation only if a motor response is required. Finally, to date, the critical areas involved in distance related space processing have not been identified.

Thus, it remains not only unclear whether neglect in near and far space is a task- and response independent phenomenon but also which damaged brain areas impair distance related space processing. In order to answer these questions the present study compared line bisection and visual search performance and its anatomical correlates in near and far space by using a combined single case- and group study approach.

The results showed that neglect restricted to near or far space can vary not only depending on the type of task but also on the type of response required. Visual search tasks were particularly sensitive in detecting the dissociation between those two space sectors. Anatomically, neglect for near space was mainly associated with occipito-parietal lesions and medio-temporal structures, including the posterior cingulate. Neglect for far space was found to result from focal damage of medial, ventro- temporal structures and the prefrontal cortex. In conclusion, neglect for near and far space does not seem to result from a general impairment in distance related processing but from a combination of factors related to specific task demands as well as the location and extent of the brain damage.

Declaration

This dissertation, entitled "Cognitive and anatomical correlates of neglect for peripersonal and extrapersonal space" is the result of my own scientific investigation. All verbatim quotes have been clearly distinguished and their sources clearly acknowledged. No part of this dissertation has been submitted for any other qualification.

Lina Aimola

December 2008

To my family

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CHAPTER 1

General introduction

1.1 Unilateral neglect: definition and clinical symptoms

Of all the neuropsychological disorders that follow right hemisphere damage, none has been as widely studied as unilateral spatial neglect. Most of its striking features have captured the interest of many clinicians and researchers for more than sixty years and yet its multicomponential nature is still a matter of debate.

The essence of the neglect syndrome is classically summarized by Heilman (1980) as: "[...] the failure to report, respond, explore or orient to stimuli predominantly located on the contralesional hemispace that cannot be attributed to sensory or motor deficits [...]". The wide phenomenology of neglect described over the years led to an expansion of Heilman's original definition by characterising the syndrome as a deficit of spatial cognition which can compromise awareness, attention, perception, action/intention and the physical representation of the self and the surrounding world. Clinical studies found that right hemisphere lesions result in more frequent, severe and long lasting contralesional neglect than left hemisphere damage (De Renzi, 1970; Gainotti, 1972; Denes et al., 1982; Weintraub and Mesulam, 1987).

Many manifestations of the deficit can be clearly detected by simply observing a patient's everyday interactions. Especially in the acute phase, neglect patients show a pathological "magnetic attraction" towards their ipsilesional side which is characterized by a marked deviation of the head, eyes and trunk towards the ipsilesional field (Halligan and Marshall, 1993). More generally, their spontaneous behaviour reveals a substantial lack of awareness for events and items located on the contralesional side of space. They commonly collide with objects or ignore people on the affected side unless these are explicitly pointed out. Patients might fail to eat from one side of the plate and dress or groom only one side of the body. In the most severe forms of neglect, patients might even fail to recognise their contralesional extremities as their own. While walking about, sometimes they can easily get disoriented as they may show an extreme tendency to turn towards the ipsilesional side of space. In social situations some may fail to establish eye contact and appear to stare at one point in space away from the interlocutor. They may also assume an inappropriate distance with others and face social isolation. In some cases the disorder may manifest itself in a psychiatric form. Mesulam (1981), for example, reported the case of a patient with left neglect and delirium tremens who used to shout at phenomena occurring apparently only on his right but not on his left. Many of these patients manifest problems with the spatial aspects of basic skills such as copying, drawing, reading and writing (Halligan and Marshall, 1993). For example, they can draw only one side of an object or miss letters at the beginning or at the end of words or half of the entire page of a newspaper. Taken together, all these difficulties can compromise dramatically the quality of the patients' life and that of their relatives. Although the acute signs of neglect may remit spontaneously over the first few weeks after brain injury, in a substantial number of cases the condition can persist for several months or even years after stroke (Halligan et al., 1991; Halligan and Cockburn, 1993).

1.2 Assessment of neglect

A wide range of diagnostic tools is used in clinical practice to evaluate different types of neglect symptoms. Each task engages different visuospatial abilities which have to be assessed thoroughly for a comprehensive diagnosis of the patients' deficits. The importance of using multiple diagnostic tests is based on the fact that the severity of the disorder often varies depending on the type of task used. Some of the most traditional bedsides tests are copying and drawing from memory, line bisection, cancellation and reading/ writing.

1.2.1 Copying and drawing from memory

Copying and constructional tasks represent some of the simplest but yet highly informative ways of investigating the variety of the neglect phenomenon. In a clinical setting when asked to copy or draw a scene or a single object, patients with left neglect tend to confine their drawings to the right side of the page and typically omit more details on the left side as compared to the right side of the object. In contrast, when asked to draw from memory, patients are no longer constrained by the sensory features of the stimulus configuration and must depend on previously acquired information (Halligan and Marshall, 1993a). As in copying, drawing from memory often results in an adequate representation of one side of the figure with the other side omitted or largely distorted despite the fact that the figure might have a well-known symmetrical configuration such as a clock face (Halligan and Marshall, 1993a). In this test, patients with left neglect might confine all or most of the 12 numbers on the right side of the clock or fill in only the numbers on the right. Another interesting type of deficit which can be revealed by both copying and drawing tasks is object-centred neglect. This pattern is observable when patients report only half of the details of objects regardless of its position with respect to their body midline (Figure 1.1).

Figure 1.1 Examples of neglect in copying (A) and drawing from memory (B).

Halligan and Marshall (1997) also described the effect of neglect on the work of the English artist TG who was able to reach and draw on the left contralesional side of the page despite omitting salient features of objects and figures contained in it (Halligan and Marshall 2001)(See Figure 1.2). Despite their asymmetric performance, patients can appear satisfied with the final product and some authors have named this behaviour as "pathological completion" (Halligan and Marshall, 1994). This term refers to a positive symptom[1] where patients with neglect mentally "fill-in" the missing information of the drawing, probably on the basis of the correspondence between their current perceptual experience and semantic knowledge (Halligan and Marshall, 2001). The work of several professional artists has been significantly affected by their visual neglect following right hemisphere damage and the analysis of their drawings provided useful insights into the symptomatology of neglect (Cantagallo and Della Sala, 1998) (Figure 1.3). For example the case of the famous film director FF described by Cantagallo and Della Sala (1998) demonstrated that impaired performance on visuospatial tasks can be accompanied by complete awareness of such deficit and preserved mental representation of space.

Figure 1.2 Drawing made by artist TG after his stroke (Halligan and Marshall, 1997).

[1] Classic neurology typically differentiates between negative and positive symptoms: the formers represent the direct consequence of the lesion while positive symptoms derive from the release of centres connected with the damaged brain part. In the case of neglect, a negative symptom can be the characteristic lack of awareness for information coming from the neglected field whereas positive symptoms can manifest themselves in the shift of processing capacity toward the ipsilesional side (Rizzolatti and Berti, 1993).

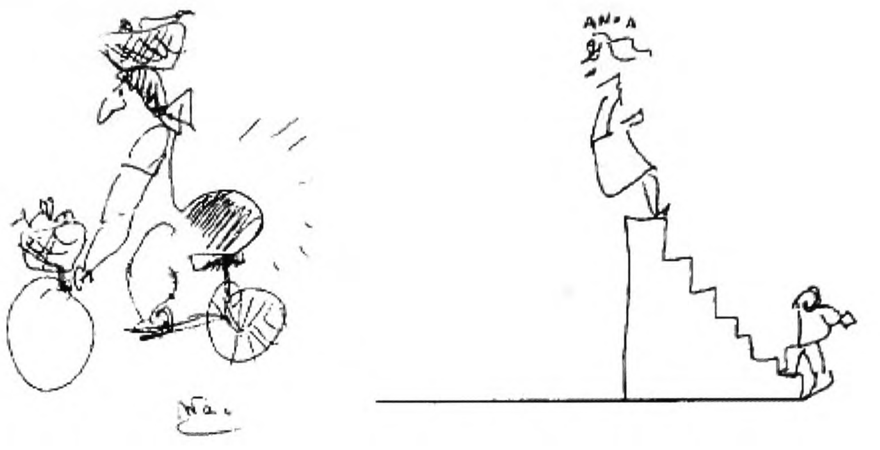

Figure 1.3 Drawing of patient FF from Cantagallo and Della Sala (1998).

1.2.2 Line bisection

In the classic line bisection paradigm patients are asked to mark with a pencil the midpoint of a 20 cm horizontal line presented on a white sheet of paper with its centre aligned with their body midline. Typically, patients with left neglect bisect the line toward the right of the true centre with varying degree of error (Figure 1.4). Healthy individuals on the other hand, tend to place their bisection mark slightly to the left of the true centre of the line, a phenomenon known as *pseudoneglect* (Bowers and Heilman, 1980).

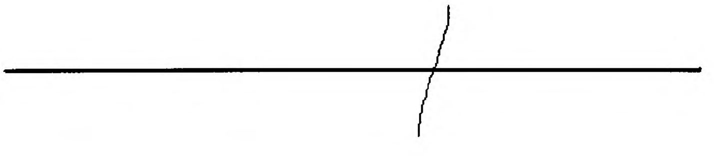

Figure 1.4 Typical rightward bisection error in neglect.

In general, when performing a line bisection task one has to direct attention to both ends of the line, estimate and half the line's length, maintain these segments in working memory and compare them to determine whether or not they are equal (Mennemeier et al., 1997). Patients with neglect appear unable to compute these visuospatial operations but the exact significance of an impaired performance on this apparently simple task is still poorly understood (McIntosh, 2006). Important factors which may contribute to elucidate this issue are the variations in bisection performance depending on the stimulus properties such as line length, spatial position of the stimulus with respect to the body midline and line orientation. Early studies documented, for example, a linear relationship between line length and absolute bisection error whose amplitude increased systematically with longer lines (Riddoch and Humphreys, 1983; Bisiach et al., 1983; Butter et al., 1988; Nichelli et al., 1989; Halligan and Marshall, 1988; 1989b; Marshall and Halligan, 1989b; 1990). The reverse pattern was observed for very short lines with which some neglect patients can show a "cross-over" effect by making leftward errors (Halligan and Marshall 1988; 1989c; Harvey et al., 1995b; Marshall and Halligan, 1989b; Tegnér and Levander, 1991b). In addition to line length, varying the horizontal position of the stimulus with respect to the viewer can also modulate the magnitude of the bisection error. Compared to centrally presented lines, left neglect can be reduced by placing the stimulus in the right hemifield or increased when presented in the left hemifield (Heilman and Valenstein, 1979; Schenkenberg et al. 1980; Nichelli et al., 1989). The latter manipulation can give rise to a phenomenon analogous to the cross-over effect in which some patients make leftward errors for lines presented in the right hemispace while erring rightward for lines of the same length located on the left with respect to the body midline (McIntosh, 2006). Variations of the bisection performance as a function of line orientation was described by Burnett-Stuart et al. (1991) who showed that rightward bisection errors can be more prominent when the lines are presented horizontally compared to other clockwise orientations.

1.2.2.1 Explaining line bisection behaviour in neglect

Several hypotheses have been put forward to explain the mechanisms underlying the bisection errors observed amongst patients with neglect. Bisiach et al. (1983) suggested that neglect patients fail to see the end part of the leftward portion of the line but correctly bisect the portion which they do see. This explanation, however, can not account for the fact that many patients continue to make rightward, albeit somewhat smaller, errors even after their attention has been drawn to the left endpoint of the line prior to bisection (Heilman and Valenstein, 1979; Harvey et al., 1995a; Ishiai et al., 1995; Nichelli et al., 1989; Riddoch and Humphreys, 1983). Subsequently, Bisiach (1998b) proposed that, although patients are able to see the whole extent of the line, they may perceive its left portion as progressively "relaxed" and the right half as progressively "compressed" relative to its objective length. Consistent with this interpretation, when required to double the length of a given line, patients with neglect tend to show a leftward over-extension and a rightward under-extension (Bisiach et al. 1994, 1998b; Chokron et al., 1997; Doricchi et al., 2002; Savazzi et al. 2004). Neglect patients can also show a bias in judging the leftward portion of a pre-bisected line (Bisiach et al. 1998b; Harvey et al., 1995a; Milner et al., 1993) or lateralized shapes (Irving-Bell et al., 1999; Kerkhoff, 2000; Milner and Harvey, 1995; Milner et al., 1998) as being smaller than the right portion. Generally, the hypothesis of the compression of the leftward portion of the line proposed by Bisiach (1998b) would predict a rightward bisection error at all line lengths which progressively decreases with decreasing length (Bisiach et al. 1998b). Consequently, this model can not fully explain the occurrence of the cross-over effect for short lines.

Chatterjee and colleagues (1995) tried to explain bisection errors in neglect patients by referring to deficiencies of both excitatory and inhibitory attentional mechanisms. According to the authors' view, patients with neglect bisect long lines ipsilesionally because of defective excitatory representation of the most contralesional portion of the line in the damaged right hemisphere. Conversely, short lines can reveal failure of the inhibitory mechanisms in the same hemisphere leading to confabulatory over-extension of the left end of the line and paradoxical leftward error. It is not clear, however, whether this assumption can be extended to account for cross-over effects associated with lines presented in the right hemispace (McIntosh et al., 2005).

Halligan and Marshall (1989b, 1990) outlined a psychophysical explanation for line bisection performance in neglect in their “scantrack” model. In their view, the line bisection task requires the subject to compare the two halves of the line and transect it such that the two lengths are perceived as subjectively equal. The sector of the line where neglect patients can place their subjective midpoint without noticing that the objective length of the two segments is different seems abnormally enlarged compared to normal subjects. The authors named this sector “the zone of indifference”. Patients with left neglect have a strong tendency to orient attention initially rightward (Kinsbourne, 1993) and when performing line bisection tasks they may initiate a few eye-movements rightward from their first fixation and rarely look leftward before bisecting (Ishiai et al., 1989, 1992, 1995, 2001; Kim et al., 1997). This pattern led Halligan and Marshall to assume that patients might approach the indifference zone from the right thereby producing their typical rightward displacement errors. The cross-over effect on the other hand, would take place by entering to the indifference zone with a left-to-right scanning path for short lines as they provide “less stimulus to pull attention rightward” so that the neglect subject would therefore be free to attend to the line’s objective midpoint (Halligan and Marshall, 1989b). In addition, the authors specified that small lines may elicit a more normal pattern of left-to-right attentional scanning in neglect patients as they can be perceived foveally in a single fixation even in the presence of hemianopia. According to this logic, one could hypothesize that if the presentation of lines within the right hemispace would increase the likelihood of a left-to-right scan path, then the scantrack model could potentially account for cross over bisections in right hemisphace (McIntosh, 2006).

Recent findings by Ishiai et al. (2006) cast some doubts on some aspects of Halligan and Marshal’s interpretation of bisection behaviour. Ishiai and co-workers investigated extensively the pattern of exploratory eye movements in neglect patients during bisection tasks and provided valuable contributions in the interpretation of bisection behaviour in neglect. Firstly, the authors emphasised that patients’ bisection responses should be evaluated not just by considering the entire line length but also with respect to its attended segments which was not explicitly contemplated within Halligan and Marshall’s framework (Ishiai et al., 2006). Secondly, they demonstrated that although the direction of approach toward the zone of indifference can influence the bisection error on the attended segment of the line, a left-to-right scanning approach to the subjective midpoint predominated amongst their group of neglect patients. More importantly, patients who mainly approached the subjective midpoint from the right, bisected the attended segment significantly leftwards in concomitance of the leftmost fixation. These oculomotor patterns and further findings supporting the ability of neglect patients in understanding the concept of length comparison[2] , led Ishiai and co-workers to put forward the idea that line bisection is not a task which investigates the ability of comparing the right and the left extent of a line (Ishiai et al., 1989, 1994a, 1994b, 1998). The patients appear instead to respond exclusively with respect to the right endpoint of the line regardless of how far leftward they explored it. This assumption was used by Kinsbourne (1993) in support of his qualitative account on line bisection behaviour. The author suggested that neglect patients are unable to sustain simultaneous awareness of both ends of the line in order to judge its length. Therefore, a rightward or leftward error could result depending on how far left patients move their attention before placing the transection mark: "[...] more likely patients fixate as far leftward as the severity of their rightward attentional bias permits and optimistically make their mark at that point" (Kinsbourne, 1993). Accordingly, patients may only respond at some distance to the left of the right endpoint whose representation is held over the lack of awareness for the left end to which they can not refer. An experimental evaluation of Kinsbourne's hypothesis on line bisection behaviour was carried out by McIntosh et al. (2005) who manipulated independently the location of the left and right end of the lines to be bisected by their group of neglect patients. McIntosh et al. quantified for each patient the influence of the two endpoints as weightings which predicted the patient's dynamic pattern of bisection behaviour, according to the changes in the horizontal position of the stimulus' endpoints (McIntosh et al., 2005). The authors demonstrated that the left endpoint of the line had no significant influence upon the location of the bisection mark while the right endpoint had an extreme impact (McIntosh et al., 2006). The authors interpreted this effect as a form of "representational extinction" which affects the patient's awareness of the bisection stimulus (McIntosh et al., 2005). In other words, the two endpoints seem to compete for attention but the right end systematically wins over the left end because of the patient's limited attentional resources and strong rightward attentional bias. Their data replicated also the classical

[2] The findings refer to Ishiai et al.'s studies in which neglect patients recognised the inadequacy of their bisection errors whilst they were forced to fixate the left endpoint of the line (1989) or when judging pre-transected lines (1998). In another study neglect patients performed well on a line extension task which required extending a line leftward to double its length (1994a, 1994b).

effects obtained by varying line length and spatial position of the stimulus, with bisection errors becoming more rightward for longer lines and for lines at more leftward location with respect to the body's midline. The cross-over effect for shorter lines was also reported. McIntosh and co-workers therefore suggested that their findings allow for the possibility of modelling neglect bisection behaviour without assuming that responses arise from the patient's "best" comparison between left and right extent of the line. Secondly, the cross-over effect would not require any special explanation because similarly to rightward errors, it may be generated when the left endpoint is not represented in awareness (McIntosh, 2006). The endpoint-weighting model stands out more as an accurate quantitative re-description of the bisection performance in neglect patients rather than a comprehensive explanation of the phenomenon. Nevertheless, it promotes a new perspective which tries to explore beyond the mere direction of the error on bisection behaviour no longer considered as an error relative to the true midpoint but as a location in peripersonal space upon which the two line's endpoints have independent influences.

1.2.3 Cancellation and visual search tasks

Cancellation tasks are part of the classic bedside diagnostic tools which, in comparison to other tests such as copying and drawing from memory, can provide a more quantitative measurement of neglect deficits. In this type of task, patients have to explore and cross out specific targets (i.e. letters, stars, bells) which are randomly distributed amongst several distractors on an A4 sheet. Generally, patients with neglect perform their search inefficiently without any obvious systematic strategy and usually omit targets located on the contralesional (left) side of the display (Figure 1.5). In addition, they may show a tendency to revisit previously detected ipsilesional items. The severity of patients' visual exploration impairments can become more evident, for example, by increasing the number of distractors, when the stimuli are presented in an unstructured array or when there is a high similarity between the targets and the distractors (Weintraub and Mesulam, 1988; Eglin et al., 1991; Grabowecky et al., 1993; Aglioti et al., 1997; Hildebrandt et al., 1999). Given the characteristic failure of neglect patients in reacting and orienting ipsilesionally, Ferber and Karnath (2001) considered cancellation tasks particularly sensitive in detecting exploration impairments which, in their view, would represent the core deficits of the syndrome. The distinctive asymmetrical search performance shown by patients with neglect together with its variability depending on the above mentioned characteristics of search arrays, has been primarily attributed to the presence of attention deficits such as an ipsilateral attentional bias (Kinsbourne, 1987) or an ipsilateral disengagement deficit of attention (Posner et al., 1987) which will be described in section 1.5. More recent evidence suggests, however, that some aspects of visual search in neglect may also be related to deficient spatial working memory abilities (Husain et al., 2001; Wojciulik et al., 2001; Malhotra et al., 2004; 2005), compulsive motor perseveration (Na et al, 1999; Rusconi et al., 2002) and oculomotor deficits (Ishiai et al., 1987; Rizzo and Hurtig, 1992; Karnath et al., 1994).

Typically, while performing a cancellation task, neglect patients tend to show a linear right-to-left decrement of target detection and the neglect magnitude may change depending on the relative amount of stimuli on both sides of the display (Halligan et al., 1992b; Marhsall and Halligan, 1989a; Small et al., 1994). For example, neglect can be more severe when there are more stimuli on the ipsilateral than in the contralateral hemifield. However, when there are no ipsilateral distractors, patients can be as accuate in the contralateral side as in the ipsilateral side of space. In addition, the overall size of the visual scene represents another critical factor that can potentially modulate neglect (Eglin et al., 1994). In particular, neglect can be more severe by increasing the overall horizontal extent of the display (Stark and Coslett, 1991; Eglin et al., 1994). The effect of the size of the search area on spontaneous exploration behaviour in neglect was documented by the findings of Behrmann et al. (1997) and Karnath et al. (1998). Both studies investigated neglect patients' eye movement pattern during visual search in an array of randomly distributed letters. However, while Behrmann et al. (1997) used a small search area with a horizontal extent of ± 22.5° to the right and left of the body's mid-sagittal plane, Karnath et al. (1998) presented a larger stimulus array of ± 140° that surrounded the patient. The former study found a steep gradient in the patients' eye movement pattern with increased number of fixations from the left to the right of the search field. In contrast, Karnath et al. (1998) showed that the fixations during patients' spontaneous visual search were symmetrically distributed around an exploration centre which was deviated ipsilesionally. In a subsequent study, Karnath and Niemeier (2002) explained the above discrepancy between the two findings by directly comparing the search behaviour of neglect patients while they explored the whole surrounding space or only a specific portion of it. The authors observed the same bell-shaped exploration pattern shifted toward the right when patients were instructed to search the full extent of the search field and a left-right asymmetric gradient when they had to explore a smaller well-defined sector of the visual display. Accordingly, Karnath and Niemeier (2002) suggested that search behaviour in neglect patients can be modulated by the horizontal extent of the visual display.

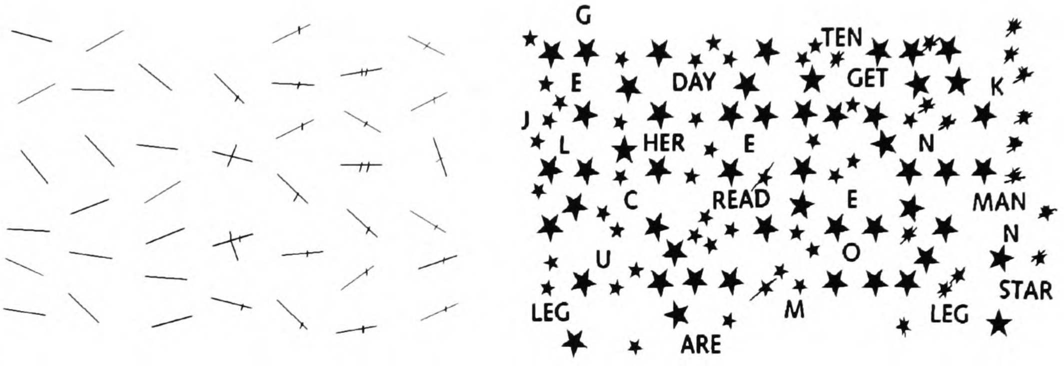

Figure 1.5 Example of neglect performance of the same patient in two different cancellation tasks.

1.2.3.1 The role of saccades in lateralised visual search

As eye movement patterns reflect the distribution of overt attention across the visual space (Findlay and Walker, 1999; Liversedge and Findlay, 2000), the study of saccadic scan paths in neglect patients also contributed to elucidate the mechanisms behind their pathological search performance during cancellation tasks. Eye movements recordings during visual exploration of scenes have shown that these patients, in comparison to normal subjects and right brain damaged patients without neglect, spontaneously tend to orient their initial eye fixations towards the (right) ipsilesional half of a display and rarely return back to the midline or cross into the contralesional hemi-field (Sprenger et al., 2002).

In addition, hypometric amplitude of contralesional exploratory saccades and prolonged mean durations of single fixations on the contralesional side have also been reported (Chédru et al., 1973; Ishiai et al., 1987; Walker et al., 1996; Zihl and Hebel, 1997;

Heide and Kömpf, 1998). More recently, studies reporting non-directional and not lateralized deficits of exploratory saccades in neglect patients demonstrated, however, that an abnormal primary oculomotor pattern can not on its own account for their impaired asymmetric search performance in cancellation tasks (Behrmann et al., 1997; Barton et al., 1998; Niemeier and Karnath, 2000; Husain et al., 2001). As Behrmann et al. (2001) observed that the kinematic of saccades in their group of neglect patients was normal, the authors suggested that hypometric contralesional saccades in neglect is due to impaired motor planning rather than execution.

Lesion location represents another factor which could also influence pathological saccadic search behaviour in neglect depending on the type of visual search required. Frontal Eye Field (FEF) damage compromises mainly the voluntary exploration of space and the implementation of systematic search strategies (top-down intentional serial search). In contrast, parieto-temporal injuries affect prevalently the reflexive orienting of attention (bottom-up stimulus driven search) resulting in hypometric targeting saccades (Sprenger et al. 2002).

1.2.3.2 Revisiting targets during visual search

Another factor that could affect the visual exploration pattern in neglect is spatial working memory (SWM) impairment (Sprenger et al., 2002). The behavioural manifestation of this deficit in cancellation tasks is not directly associated to contralesional omissions (negative symptom) but appears to be more specifically related to repetitive search behaviour (positive symptom) towards previously detected targets (Husain et al., 2001; Wojciulik et al., 2001; Malhotra et al., 2004; 2005; Olk and Harvey, 2006). This tendency can arise from their inability to retain and update targets' locations across saccadic eye movements during active spatial exploration. Husain et al. (2001) demonstrated that the re-fixation rate of targets correlated not only with the severity of neglect but also with the working memory load of the visual search task. Further neuropsychological studies showed that, although SWM deficits alone cannot justify a poor visual exploration performance in patients with neglect, when occurring together with an ipsilateral attentional bias they can exacerbate neglect behaviour in cancellation tasks (Mahotra et al. 2004; 2005; Pisella et al. 2004).

Not all neglect patients present SWM deficiencies, however, it would be expected to occur in those whose damage involves the critical areas supporting SWM abilities (De Renzi et al., 1977; Owen et al., 1990; Walker et al., 1998). In particular, Mahotra et al. (2005) reported that poor SWM performance in their group of neglect patients was associated with lesions of the white matter underneath both the right temporo-parietal junction and the supramarginal gyrus together with the insula[3]. These anatomical findings are in line with previous neuropsychological studies that have shown an association between similar brain areas and SWM deficits in neglect patients (Husain et al., 2001; Wojciulik et al., 2001; Pisella et al., 2004).

Apart from a deficient SWM, it has been suggested that the tendency of patients with neglect to re-fixate and re-mark previously detected targets could also reflect compulsive motor perseverations (Na et al., 1999; Rusconi et al., 2002). Although generally, patients with severe neglect resulting from large brain lesions may be more likely to show perseverations, studies on perseverative behaviour during target cancellation in neglect reported most frequently frontal and basal ganglia damage (Na et al., 1999; Rusconi et al., 2002). In general, the compulsive tendency to revisit previously detected targets can be considered one expression of the wide range of uncontrolled motor activity towards the ipsilesional right side of space after right brain damage (Yamadori et al., 1986; Bogousslavsky et al., 1988; Mori et al., 1985). Not many studies have investigated in detail the association between neglect and perseverative behaviour, yet they all concur on the fact that the combined effect of productive motor perseverations with defective contralesional exploration abilities and awareness deficits exacerbates the search performance of patients with neglect.
Thus, taken together, visual search and cancellation paradigms in particular allow the observation of some of the typical manifestations of neglect which can be exacerbated when occurring in concomitance of the above independent deficits.

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[3] In the first experiment of Malhotra et al.'s study (2005) neglect patients carried out a vertical version of the Corsi block test were they had to manually replicate a sequence of spatial locations. With this version of the task, the region of maximum overlap in the neglect group with worst SWM performance was located in the right temporo-parietal junction. In a second experiment the authors used another version of the same task which provided a "purer" measure of vertical SWM as it did not require memory for sequence and manual responding. In this condition the two major regions of maximum overlap in the neglect group with SWM impairment were located in the right supramarginal gyrus and insula (Malhotra et al., 2005).

1.2.4 Reading and writing

Reading and writing tasks are also widely used in the clinical assessment of neglect. Right brain damaged patients with left neglect may tend to omit the left part of a word or lines of text and this tendency can be observed in reading (neglect dyslexia) as well as in writing (neglect dysgraphia). Neglect patients with left hemisphere damage who showed the reverse pattern of errors, involving the right portion of words, have also been described (Hillis and Caramazza, 1989, Warrington, 1991; Warrington and Zangwill, 1957). In some cases, reading deficits can be the only obvious form of detectable spatial disorder (Baxter and Warrington, 1983; Costello and Warrington, 1987) and, together with letter omissions, most of the reading errors involve the addition or substitution of letters to form alternative words. Examples of simple deletion of initial letters could be reading "chamber" as "amber" or "fable" as "able" whereas reading "lass" as "glass" or "yellow" as "pillow" are clear demonstrations of addition and substitution errors from the target word.

In the domain of reading deficits in neglect, a general differentiation can be drawn between *spatial* and *positional neglect dyslexia.* In the former, the reading error depends on the spatial conventional left-to-right location of the letters in words, whereas in the latter the errors occur always at one end of the words irrespectively of their orientation. These two patterns can be dissociated by presenting patients with upside-down or mirror- reverse words or also with rotated passages of text (Ellis et al. 1987; Caramazza and Hillis, 1990). For example, patients with spatial dyslexia and left neglect would make errors to the left-most letters with ordinary words in conventional format but if the words are presented vertically their errors would not be concentrated in any particular part of the stimulus. In contrast, patients with positional left neglect dyslexia, would still omit or modify the left part of words even when they are vertically oriented. According to Caramazza and Hillis (1990), the type of representation impaired in this latter case is a "stimulus-centred letter shape map" based on left-right and not first-last coding.

As with reading, writing can also be impaired and in addition to the typical part-word omissions or substitutions (neglect dysgraphia), patients might tend to confine most of the text into the ipsilesional half of the page (Ellis et al. 1987; Hecaen and Marie, 1974). Omissions in writing have been interpreted by Ellis et al. (1987) as an inability of using visual and kinaesthetic feedbacks to monitor and control the complex sequence of movements required in handwriting (Ellis et al., 1993).

1.3 Multicomponent aspects of neglect

Clinical and experimental findings show that neglect can fractionate into a large number of conceptually distinct and clinically dissociable components in relation, for example, to the motor or perceptual demands of a particular task (perceptual vs. pre-motor neglect), sensory modality (visual, auditory or tactile neglect), spatial reference frames (egocentric vs. object-centred neglect) or spatial distance (personal, peripersonal or extrapersonal neglect) (Halligan, 1995).

1.3.1 Perceptual and pre-motor neglect

The distinction between perceptual (input-related) and motor (output-related) deficits in neglect is one of the dichotomies most extensively investigated in the syndrome. In this context, perceptual deficits generally refer to the inability to fully construct a complete internal map of the external space which results instead biased towards ipsilesional over contralesional inputs. Motor deficits on the other hand, indicate failure in programming or implementing motor acts (i.e. saccades, reaching) upon that space. For example, a typical manifestation of perceptual neglect would be the incapacity of detecting contralateral visual or somatosensory stimuli in the absence of any primary sensory deficits. This phenomenon is also known as "hemi-inattention" (Heilman et al., 1985). Pre-motor neglect instead refers to those conditions where the patient shows reluctance to perform motor activities with either limb in or towards the contralateral half of external space in the absence of any primary motor deficits (Vallar, 1993). This deficit is also defined as "hemispatial" or "directional hypokinesia" and it can be associated to bradykinesia or directional hypometria. The former, refers to slowness in the execution of movements towards the side of space opposite to the lesion, while the latter indicates the inability to move an effector contralaterally with sufficient amplitude. The pre-motor component of neglect must be distinguished from "motor neglect" which refers to the unwillingness to move the contralesional limbs spontaneously towards either halves of space without any primary motor deficit (Vallar, 1993). When patients' attention is drawn to their affected limb (i.e. by a verbal command), however, they are able to perform normal movements effortlessly. Motor neglect represents, thus, a space-independent impairment which can also occur in the absence of spatial neglect (de la Sayette et al., 1989; Laplane and Degos, 1983; Valenstein and Heilman, 1981; Barbieri and De Renzi, 1989).

Several studies investigated whether defective hemispatial attention or motor-intention abilities are primarily responsible for spatial neglect. Some authors tried to dissociate those two components by decoupling the direction of the movement of the hand from the visual control of the display (Vallar, 2001). For instance, Bisiach et al. (1990) devised a bisection paradigm (the Pulley Device) by using a loop of string stretched horizontally around two pulleys. The patients were asked to place an arrow midway between the two pulleys. In the congruent condition, patients held the arrow on the upper string to move it normally, whereas in the incongruent condition they displaced the lower string laterally which moved the arrow in the opposite direction. Under this condition, if neglect was caused by a motor intentional deficit, the bisection error in the congruent and incongruent conditions should have moved in opposite directions (Bisiach et al., 1990). Six out of 13 patients demonstrated a significant reduction of neglect in the incongruent condition suggesting that they had a significant motor intentional deficit. In the majority of Bisiach et al.'s (1990) patients, both the perceptual and the pre-motor deficits was considered as determinant for left neglect with an overall prevalence of the perceptual factor. A similar logic was applied to a cancellation task in Tegnér and Levander's study (1991a) where the authors tried to decouple the direction of hand movements from the patient's visual control by using a mirror. In the normal, congruent condition, patients showed typical left-sided omissions while their performance varied considerably when they performed the same task in the incongruent condition looking at a mirror-reversed display (i.e. left sided targets were seen on the right side). Ten out of 18 patients deleted stimuli on their "visual right" in the incongruent condition (which was left in the congruent condition) showing a deficit linked more to the perceptual field rather than to a motor bias. Compatible with a pattern of pre-motor neglect, four patients consistently marked lines on their right in both congruent and incongruent conditions. The remaining patients cancelled lines in the centre of the display, a pattern of performance that was interpreted as indicating a combination of both deficits.

Na et al. (1998) investigated the same issue both with line bisection and cancellation tasks. In their study, neglect patients observed their own performance on a video monitor which again displayed the task either normally (congruent condition) or right-left reversed (incongruent). Using this apparatus Na et al. (1998) found that six out of 10 patients showed the same type of neglect in both tasks. However, three patients demonstrated pre-motor neglect in the line bisection task (rightward error in both congruent and incongruent condition) and perceptual neglect for the cancellation task (left omissions in the congruent condition and right omissions for the incongruent condition). The last patient showed pre-motor neglect in the line bisection but could not be classified for the cancellation task (Na et al., 1998).

A further attempt to decouple these two components in neglect comes from Milner et al. (1993) with an alternative paradigm named the Landmark task. In this task, participants are usually asked to judge which end of pre-bisected lines is shorter or longer giving a verbal or a manual response (i.e. pointing). Choosing consistently the contralesional segment as shorter (or the ipsilesional segment as longer) would reflect a perceptual-attentional bias while consistent choices of the ipsilesional segment during each type of judgment (shorter and longer) would indicate the presence of a motor-intentional (pointing) or verbal response bias. Bisiach et al. (1998a) devised a modified version of the Landmark task that allowed a separate calculation of pre-motor and perceptual biases together with a score range for normal performance. As well as for the previous paradigms, the use of the Landmark task corroborated the hypothesis that motor-intention and attention deficits can appear separately but often they tend to co-exist even in the same patient (Milner et al., 1992; 1993; Bisiach et al., 1998a; Harvey et al. 1995a). The possibility that perceptual and pre-motor deficits in neglect could be related to damage to separate neuroanatomical substrates was also considered. Mesulam (1981; 1999) suggested that anterior damage can cause a pre-motor deficit in neglect while posterior lesions may be more associated with the perceptual aspects of neglect. This dichotomy is partially supported in the literature which nevertheless demonstrates contradicting findings (Bisiach et al., 1990; Coslett et al., 1990; Tegnér and Levander, 1991a; Butter et al., 1988; Làdavas et al., 1993; Bisiach et al., 1995; Nico, 1996; Harvey et al., 1995; Bisiach et al., 1998a; Mattingley et al., 1998). For example, patients with frontal lesions may be particularly vulnerable with tasks requiring incompatible motor responses and this alone would lead to an apparent pre-motor deficit (Hussain et al., 1998; 2000). By comparing some of the most representative line bisection techniques[4] used to differentiate pre-motor and perceptual neglect, Harvey at al. (2002) demonstrated substantial inconsistencies in the way they tend to classify neglect patients. However, according to the authors, Bisiach's (1998a) version of the Landmark task seems to be the most accurate research tool in that respect (Harvey et al., 2004). Ultimately, Harvey et al. (2004) suggested that it might not be productive to dichotomise the patients but rather consider motor-intentional and attentional deficits along a continuum in which the different types of task can tap into with different degrees according to their intrinsic demands.

1.3.2 Multisensorial neglect

Although neglect is predominantly assessed in the visual domain, it can compromise multiple sensory modalities, such as acoustic or tactile. Several studies reported clinical cases of modality-specific neglect in which the deficit is present in one modality but not in another (De Renzi, 1989; Bisiach et al. 2004).

1.3.2.1 Olfactory neglect

Bellas et al. (1988) investigated neglect in the olfactory system which could be of particular interest given that unlike other sensory modalities the nerves carrying information about olfactory stimuli project predominantly to the ipsilateral hemisphere. When presenting two different smells simultaneously, one to each nostril, the authors found that patients with left neglect caused by right hemisphere damage showed extinction for the stimulus presented to the left nostril. This outcome further confirms that patients' impairment originates at high levels of sensory analysis (Young, 1994).

[4] The tasks used were the Overhead Task (Nico, 1996), the Pulley Device (Bisiach et al., 1990) and the Landmark task (Milner et al., 1992).

1.3.2.2 Auditory neglect

While very little research has been done in the area of neglect for the olfactory modality, many more studies have investigated neglect related to the auditory system. In the auditory domain, patients with neglect can show pathological performance in a variety of auditory tasks especially for those requiring identification and localization of contralesional sounds.

For example, during an identification task with dichotic sound presentation, neglect patients may show the so called "dichotic extinction". This phenomenon represents the auditory homologue of visual extinction (see paragraph 1.4.3) for which, under conditions of double aural stimulation, patients ignore the contralateral sound. Moreover, for tasks requiring overt single sound localization, patients may make systematic directional errors including "alloacusis" (allochiria for sounds) by shifting the perceived location of sounds from the contralesional to the ipsilesional hemispace. Although these types of error have been shown to correlate with the severity of visual neglect (Pavani et al., 2004), they can also dissociate from it (Bisiach et al., 1984; Soroker et al., 1997). Clarke and Bellmann (2004) put forward the idea that sound identification and localization errors in neglect may reflect the disruption of specific attentional processes. As for visual extinction, dichotic extinction may be due to a different allocation of attentional resources between the two hemispaces after the two stimuli have been spatially segregated from each other pre-attentively (Sussman et al., 1999; Yabe et al., 2001; Clarke and Bellmann, 2004). In contrast, neglect for contralesional sound localization appears to be more related to the presence of an ipsilateral spatial bias or a distorted representation of space (Clarke and Bellmann, 2004). These interpretations are supported by novel experimental approaches adopted in recent sounds identification studies in neglect patients. They all concur in considering their contralesional auditory deficits as related to higher-level spatial processing problems rather than to mere left ear-suppressions (Pavani et al., 2004). Interestingly, some studies observed also that neglect patients reported their head/body midline to be aligned with sounds that were instead displaced to the ipsilesional side of space (Vallar et al., 1995; Kerkhoff et al., 1999). This pattern is compatible with several non-auditory studies which demonstrated that neglect patients can present indeed an altered perception of their subjective head/body midline with respect to the external visual space (see paragraph 1.5.3.2). Cases of double dissociations between errors of sound localization and dichotic extinction showed how these two functionally distinct auditory symptoms in neglect can originate from damage to separate anatomical structures (Bellmann et al., 2001): Basal ganglia lesions seem to cause contralesional omissions in condition of double stimulation while systematic contralateral errors on sounds localization appear associated to fronto-temporal-parietal damage.

1.3.2.2 Tactile neglect

De Renzi et al. (1970) first investigated the tactile exploration of space in neglect patients. In their experiment, subjects were asked to move their forefinger along the alley of a maze hidden behind a curtain and search for marbles placed at the end of one of four lateral arms. Failure to find the marbles in the contralateral hemispace within a time limit of 90 seconds was considered as evidence of tactile neglect. As the authors observed a strong association between visual and tactile search deficits, they concluded that neglect can be thought as a supramodal disorder of spatial representation (De Renzi et al., 1970). This interpretation has not always received unanimous support as some studies failed to demonstrate any concomitant impairment in the tactile domain in patients with visual neglect (Fuji et al., 1991; Hjaltason et al., 1993; Villardita, 1987).

Other authors (Chedru, 1976; Gentilini et al., 1989) have suggested that unilateral deficits in manual exploration of a search space may be induced by vision as visual inputs from the ipsilesional side of space could contribute in shifting attention towards it thereby increasing contralesional neglect (Chokron et al., 2002). Accordingly, it may be conceivable that asking a neglect patient to perform a tactile exploration tasks while blindfolded would reveal a less marked search imbalance between the two halves of space than when the same task is carried out with the aid of vision (Chedru, 1976; Gentilini et al., 1989; Chokron et al., 2002). However, Karnath and Perenin (1998) sustained that in neglect patients the whole frame of exploratory behaviour is shifted ipsilesionally, regardless of the modality of exploration used (Karnath and Perenin, 1998; Karnath, 1996). Clearly, the above inconsistencies amongst studies of tactile neglect could be due to the different tasks and methodological options adopted to asses tactile neglect. By taking into consideration the limitations of previous approaches, Schindler et al. (2006) compared the visual and tactile exploration patterns of a group of right hemisphere damaged patients with and without neglect within the same workspace. The authors found that amongst patients with neglect, the pattern of search distribution was skewed ipsilesionally for both modalities. A significant correlation between the degree of tactile and visual shift in exploration activity was also observed. Based on their results, Schindler et al. (2006) concluded that deficient search behaviour in patients with neglect can be due to defective coordinate transformation processes from unimodal to multimodal spatial reference frames leading to a supramodal ipsilesional orientation bias. This latter hypothesis, which conceives the surrounding space as a multimodal entity, has been extensively influenced and refined by the study of visuospatial neglect across several modalities (Kerkhoff, 1999; Ladavas et al. 2000; Farné, Dematte and Ladavas, 2003). Anatomically, tactile neglect may arise from damage to those brain structures that are crucial for multisensory integration and contribute to a stable, multimodal representation of external space (Anderson et al., 1997).

1.3.3 Space representation and neglect

1.3.3.1 Egocentric and allocentric reference systems

The study of neglect heavily contributed to elucidate the mechanisms involved in the cognitive reconstruction of the surrounding space which is subjectively experienced as a stable, coherent and multisensory unit. To navigate successfully in the environment it is important for example to know the position of one's own body in relation to a relevant object which, in turn, has its intrinsic position with respect to other objects. To extract this information the brain uses two main reference frames or coordinate systems with an origin and axes. One system of coordinates is called "egocentric" as it defines spatial positions with respect to the observer's body sagittal plane (Farah and Buxbaum, 1996). Retina-, head- or trunk-centred reference frames are part of such egocentric system. For example, visual stimuli are initially encoded in retinal frames of reference whose origin is at the observer's fovea and whose axes denote the displacement of the stimulus from the fixation point (Farah and Buxbaum, 1996). Head-centred frames can be instead used for sounds localization while trunk- arm- and hand-centred coordinates are mainly involved in planning reaching and grasping movements (Farah and Buxbaum, 1996).

Egocentric frames of reference can be rather variable and constantly updated as the representation of stimulus location changes whenever the viewer changes positions.

The other coordinate system is called “allocentric” and codes one event in space with respect to another extrapersonal event independently of the viewer’s position. When allocentric coordinates are centred on the intrinsic canonical axis of a specific object they are called “object-centred” (Farah and Buxbaum, 1996). Compared to the egocentric coordinate system, allocentric reference frames are characterised by location and orientation invariance. Namely, the localization of the constituent parts of an object is the same irrespective of its location or orientation because when the object moves the frames of reference move with it (Farah and Buxbaum, 1996).

Clinical studies reported how each of the two principal reference systems can be selectively affected in neglect patients (Halligan and Marshall, 1993a; Umilta’, 2000; Halligan et al., 2003) and the respective behavioural consequences can be especially observed with tasks such as drawing, copying and reading (see also section 1.2.1 and 1.2.4). During drawing or copying tasks, patients can either omit items on the contralesional side of a picture relative to their body midline or, alternatively, they can neglect the contralesional side of an object in the picture regardless of its position relative to the viewer. Similarly, in a reading task, they can omit the contralesional part of a word (neglect dyslexia) or of one entire page (Costello and Warrington, 1987; Karnath and Huber, 1992). Object and space based neglect symptoms are not mutually exclusive as they can be found in combination in the same patient. Accordingly, it has been suggested that neglect is associated with a disturbed representation of space at a level where egocentric and object-centred coordinates systems are integrated (Niemeier and Karnath, 2002a).

Egocentric and allocentric coordinate systems can define the spatial location of extrapersonal events with respect to all the three spatial dimensions: horizontal (left/right), vertical (up/down) and radial (near/far). The presence of neglect in right brain damaged patients is generally investigated along the horizontal axis but asymmetrical performance has also been described along the vertical (up/down) and the radial dimension of space (near/far). In addition, cases of neglect for the back space have also been reported.

Vertical or "altitudinal" neglect has been shown for visual, tactile or auditory bisection paradigms (Rapcsak et al., 1988; Butter et al., 1989), reading and visual search (Nichelli et al., 1993) and for covert orienting of attention tasks (Làdavas et al., 1994). The common finding amongst these studies is that the lower left part of space is either omitted or responded to with a slower reaction time (Pitzalis et al., 1997). For example, in cancellation tasks patients with vertical neglect tend to omit in most cases the lower left quadrant of the array (Morris et al., 1986; Halligan and Marshall, 1989d; Mark and Heilman, 1988; but see Robertson and North, 1993), while with bisection task they generally tend to mark the vertical line below (Shelton et al., 1990; Ergun-Marterer et al., 2001) or sometimes above (Rapcsak et al., 1988) the true midpoint.

1.3.3.2 Neglect for near and far space

Cases of double dissociation in neglect along the radial axes (near/far) contributed to support the idea that different space sectors, within and beyond reaching distance, are differently represented in the human brain. Halligan and Marshall (1991a) described the case of a neglect patient who showed impaired performance in line bisection only when the task was carried out within near space but not in far space. The opposite behavioural pattern was reported by Vuileumier et al. (1998) whose patient showed contralateral neglect for far but not for near space while performing visuospatial tasks such as cancellation, reading, bisection and square completion. There are also cases of double dissociations with neglect for the body surface (personal neglect) in which patients fail to explore the contralateral part of their bodies despite no sign of the disorder within their proximal reaching space (Bisiach et al., 1986; Guariglia and Antonucci, 1992). Damage of the occipito-parietal and temporal areas seems to be responsible for neglect in near space, while selective impairments restricted to far space appear associated with occipital and ventro-temporal lesions (Halligan and Marshal, 1991a; Vuilleumier et al., 1999; Berti and Frassinetti, 2000; Bjoertomt et al., 2002). Personal space seems to be coded by the same neuronal population coding near space (Rizzolatti and Berti, 2002).

1.3.3.3 Neglect for the back space

Impairments of the representation of the back space instead have been investigated by Vallar et al. (1995) who observed that their neglect patients mislocalized auditory stimuli delivered in back space. The authors linked this pattern of result to an ipsilesional shift of attention resources which was, however, less pronounced than that observed in front space. More recently, Viaud-Delmon et al. (2007) described the cases of two patients who, in a mental imagery task, were asked to describe verbally and draw from memory the maps of known locations. They showed severe left representational neglect when asked to describe or draw places as imagined in front of them, but not when they imagined the same places to be located behind them. The authors hypothesized that back space imagery would not share the same neuronal pathway as front space representation as in the rear space egocentric reference frames could not be used (Viaud-Delmon et al., 2007).

All the above observations in neglect suggest that the surrounding space is coded by multiple functionally distinct but interacting reference systems.

1.4 Associated deficits

Commonly, in addition to its constellation of symptoms, the neglect syndrome may be accompanied by additional disorders which can occur independently of neglect and are interesting in their own individual phenomenology such as primary sensory and motor deficits (i.e. hemiplegia, hemianesthesia, hemianopia), allochiria, alloaesthesia, anosognosia, somatoparaphrenia and extinction.

1.4.1 Primary sensory and motor deficits

Even if neglect per se cannot be due to primary motor and sensory impairments, yet these deficiencies may accompany the range of associated deficits, increasing the patiens' level of disability. The additional symptoms can affect the motor (hemiplegia), somatosensory (hemianesthesia) or visual (hemianopia) systems preventing the perception of elementary contralesional inputs or the execution of motor actions with the contralesional limb(s). Hemiplegia refers to partial or total paralysis of one side of the body due to damage of the primary motor cortex while hemianesthesia defines the loss of sensation, typically tactile or pain, on one side of the body following somatosensory cortex injury. In contrast, visual field loss or hemianopia occurs instead after damage of primary visual pathways and/or occipital cortex.

Disentangling the behavioural effects of these elementary sensory and motor deficits from neglect-related impairments is not always straightforward. However, the use of neurophysiological techniques such as sensory or visually evoked potentials may provide reliable information on the integrity of the peripheral sensory pathways (Vallar et al., 1991; Spinelli et al., 1994; De Keyser et al., 1990). For example, normal sensory and visually evoked potentials for contralateral stimuli in patients with neglect would suggest that their deficits most likely involve higher levels of spatial awareness processes. In addition, some patients with neglect for contralesional tactile stimuli may be able to detect them when asked to place their (stimulated) left arm for example closer to the ipsilesional (right) side of their trunk (Smania and Aglioti, 1995; Aglioti et al., 1999). Hemianestetic patients instead would be unable to report contralesional tactile stimuli independently of their limbs' position relative to the body midline. In the motor domain, patients with motor neglect can overcome their reluctance to use their contralateral limb if they are verbally instructed to pay attention to it, while hemiparetic patients in these circumstances are unlikely to fully regain the use of their contralesional limbs.

1.4.2 Hemianopia

In the clinical setting, neglect is primarily assessed in the visual modality which, in the first instance, can provide some of the most evident signs of the syndrome. However, visual field deficits are frequently present in patients with neglect and although fundamentally different, the discrimination of these two disorders in one individual can sometimes generate a diagnostic dilemma (Kerkhoff, 2001). The combined presence of neglect and homonymous left hemianopia in particular would obviously complicate the interpretation of a patient's impairments as it is difficult to discriminate how much is due to the presence of neglect only. There are, however, several fundamental differences which can lead towards a correct differential diagnosis between the two disorders.

Firstly, at an anatomical level left or right hemianopia are equally likely to occur after damage of the visual pathways and/or striate cortex which affects the elaboration of visual information from either hemifield. Neglect on the other hand, can be present even in absence of any occipital damage and is predominantly observed after right hemisphere lesions. In comparison to an elementary visual field loss, the type of impairment causing neglect occurs at a higher level of representation of the surrounding space and of one's own body. Hemianopic patients are instead fully aware of both hemifields and body parts and in daily life they often tend to compensate for their visual field deficit by moving their eyes and head towards the affected side. This strategy would hardly be adopted by a patient with neglect for whom the contralateral side of space simply does not exist.

Secondly, a visual field assessment with dynamic perimetry would reveal a sharp clear-cut between the boundary of the intact and the blind region of the visual field in hemianopic patients reflecting their damage in the primary visual cortex (Driver and Vuilleumier, 2001; Kerkhoff 2001). This is very different from the spatial nature of the loss in conscious perception which characterizes the neglect syndrome. In fact, a kinetic perimetric assessment of patients with neglect would show that the border between neglected and non-neglected hemifield is highly variable. In this case, the ability to detect visual stimuli tends to decline gradually for items located further towards the affected side of space (Kinsbourne, 1987; Làdavas et al., 1990; Smania et al., 1998; Driver and Vuilleumier, 2001; Kerkhoff, 2001).

Thirdly, under conditions of central fixation, hemianopic patient would not be able to detect a single light presented in their blind visual field while maintaining central fixation (but see Cowey et al., 1998). In contrast, many patients neglect patients without visual field loss may be able to detect such a light on the affected side when presented on its own but they could miss when another light appears simultaneously on the ipsilesional side (Bender and Teuber, 1946; Critchley, 1953; Wortis, Bender and Teuber, 1948). This phenomenon, which occurs during double simultaneous stimulation, is known as extinction since the ipsilateral event is said to "extinguish" the contralateral one from awareness (see paragraph 1.4.3).

A further difference between neglect and a primary visual field defect is that the visuospatial disorder affecting neglect patients can be modulated by body posture. In hemianopic patients a blind visual hemifield remains blind regardless of the current position of the eye in the orbit or of the head relative to the trunk (Driver and Vuilleumier, 2001). In the case of neglect patients instead, these extraretinal factors have been shown to modulate the detection of visual stimuli. For example, if the patient neglects a contralateral visual stimulus while looking straight ahead, he/she may be able to detect it when directing gaze only or both gaze and head ipsilesionally (Kooistra and Heilman, 1989; Vuilleumier et al., 1999). Passively rotating the trunk towards the affected side of space while maintaining straight ahead eye- and head position, can also increase patients' ability to detect contralesional stimuli which would be otherwise neglected (Karnath et al., 1991). In contrast, none of these effects can be observed in patients with hemianopia (Driver and Vuilleumier, 2001).

1.4.3 Extinction

Another common deficit which may be associated with neglect is known as extinction. Patients with this condition can detect single stimuli in both ipsilesional and contralesional space but they "extinguish" contralesional stimuli when presented simultaneously with ipsilesional stimuli. The phenomenon can be observed within the visual, auditory and tactile domain and even between two events in separate sensory modalities. This latter pattern is known as cross-modal extinction and occurs when, for example, a patient fails to detect a tactile stimulus delivered to the left hand in the presence of a concurrent contralesional visual stimulus and vice versa (Mattingley et al., 1997). Originally considered as a mild form of neglect, extinction is now increasingly recognised as a distinct disorder which can also be observed independently of neglect (Pavlovskaya et al. 2007). The reason of this distinction is based on the evidence that extinction is equally common after damage to either sides of the brain (Milner, 1997) whereas neglect is more common following right hemisphere damage (Driver and Mattingley, 1998; Karnath, Ferber and Himmelbach, 2001). In addition, extinction and neglect appear to have dissociable neuronal substrates: according to Karnath et al. (2003) extinction seems to arise more frequently than neglect alone following damage to the temporal-parietal junction (TPJ), while neglect without extinction is more associated with damage in the superior temporal gyrus (STG) and planum temporale. The TPJ is indeed prevalently related to stimulus detection and not to the active and spontaneous exploration of targets arrays, which seems instead to engage more the STG and planum temporale (Corbetta et al., 2000).

While extinction characterises only partially the variegate phenomenology of neglect, it condenses a critical general principle which can be applied to many aspects of the syndrome (Driver and Vuilleumier, 2001). This refers to the observations that patients' spatial deficit appears most apparent in those situations when multiple stimuli compete for attention. That is, information coming from the ipsilesional side of space dominates and prevails over that from the contralesional side which consequently falls outside the patient's perceptual awareness. The competitive advantage of ipsilesional stimuli can, however, be reduced under conditions in which the patient is instructed to expect a stimulus from the contralesional side or to ignore any concurrent ipsilesional event (Mattingley, 2001). Similarly, patients can improve considerably when they try to deploy their attention exclusively towards a single hemifield (contralateral or ipsilateral) compared with those conditions in which they must divide their attention between hemifields (Smania et al., 1998; Mattingley et al., 2000). In addition, the number of extinguished tactile stimuli can be significantly reduced by crossing the patient's arms so that they occupy a single hemispace or opposite hemispaces (Smania and Aglioti 1995; Aglioti et al., 1999). Even when the arms remain uncrossed, the severity of tactile extinction can be also reduced simply by bringing the hands close together within a single hemispace (Mattingley, 2002). The time synchrony under which the stimuli are delivered can also be crucial in triggering extinction. Contralesional extinction appears indeed maximal under conditions of simultaneous presentation of the concurrent stimuli and minimal the more the contralesional event precedes the ipsilesional one (di Pellegrino et al., 1997; Guerrini et al., 2003). A motor analogue of perceptual extinction can be observed when actions initiated by the left hand are disrupted by the simultaneous preparation and execution of movements with the right hand (Mattingley, 2002). For example, while performing a bimanual tapping task the contralateral hand may be unable to continue the sequence until the ipsilateral hand stops (Mattingley et al., 1998). In a study of the effects of limb activation on visual extinction, Mattingley et al. (1998) demonstrated that the detection of contralesional targets increased considerably by using the affected hand to initiate each trial. This finding indicates that activity within the motor system can influence perceptual selectivity in patients with neglect and extinction.

Functional brain imaging and transcranial magnetic stimulation (TMS) have provided important contributes to the investigation of the neuronal substrate of extinction as well as valuable insights into the mechanisms which could cause it. In a positron-emission tomography (PET) study Fink et al. (2000) showed that for unilateral letter arrays presentations, brain activity was maximal in early visual areas of the contralateral occipital cortex. For bilateral array presentation instead, neural activity in the same visual areas was significantly reduced compared to that of unilateral arrays. These authors suggested that this pattern of results indicated some degree of neuronal suppression arising from interhemispheric rivalry (Mattingley, 2002). Pascual-Leone et al. (1994) showed that repetitive TMS pulses over the left/right parietal cortex can induce visual extinction in healthy individuals while similar stimulation of the occipital cortex yielded the same number of misses for both unilateral and bilateral trials presentation. Similarly, single-pulse TMS over the left/right parietal cortex can also generate extinction in the tactile modality (Oliveri et al., 1999). Interestingly, Oliveri et al. (2000) showed that TMS stimulation over the unaffected left hemisphere reduced the severity of contralateral tactile extinction in right-brain damaged patients especially after parietal cortex inhibition. The authors argued that the temporary disruption of the activity of the intact hemisphere may have restored the competitive balance which has been altered by brain damage. This outcome reinforces the idea that extinction results from an interhemispheric competitive bias which favours the stimuli (ipsilesional) elaborated by the intact hemisphere (left) (Mattingley, 2002). Taken together, the above evidence suggests that extinction can be considered as a pathological space-specific deficiency in distributing attentional resources simultaneously to multiple targets (Driver and Vuilleumier, 2001).

1.4.4 Allochiria

Allochiria consists in the displacement of a sensation or external stimulus to the corresponding other half of the body or space in the homologous location (Marcel et al., 2004). The terms allochiria and alloaesthesia are often used indiscriminately but the two phenomena are substantially different and for diagnostic specificity should be considered as separate. Alloaesthesia denotes mislocation of a sensation or external stimuli to a remote position along the same body part or side of space. The essential difference appears to be thus whether "migration" occurs to the opposite side of the body or space (allochiria) or if it is reported somewhere else along the same half of the body or hemispace (alloaesthesia). Allochiria can take place in various sensory modalities but principally in somatosensation (Bisiach and Berti, 1995; Kawamura et al., 1987; Meador et al., 1991). Migration of stimuli can be reported in more than one modality in the same patient but can also be modality-specific or more prominent in one modality, depending on the appropriateness of the testing materials (Marcel et al., 2006).

Kawamura et al. (1987) showed that allochiria can be related to spinal cord lesions and hypertensive cerebral haemorrhage. These authors hypothesized that when crossed sensory fibres are severely damaged on one side, sensory inputs could be consequently conducted through the uncrossed fibres on the opposite side giving rise to misplacements of stimuli location (Kawamura et al., 1987). The disorder appears highly associated with parietal lobe damage and visuospatial neglect (Bisiach and Berti, 1995) as indeed spatial migration of perceptual experience can be a frequent characteristic of the syndrome. A typical example of such phenomenon is the ipsilesional crowding of contralesional stimuli during drawing tasks (i.e. all the twelve numbers placed to the right half of a clock face). Halligan et al. (1992a) described an example of co-occurrence of allochiria and neglect in which the patient transferred to the right side of a symmetric object items that were located on its left side. The same patient did not show allochiria while copying asymmetric drawings. Given the association between allochiria and spatial attention, Marcel et al. (2004) hypothesized that allochiria may reflect poor spatial selection abilities especially in keeping the stimuli in an ignored location separate from those in an attended location. Accordingly, since in patients with neglect the representation of the spatial source on the affected side is impaired, migration (allochiria) takes place because stimuli can not be linked to a stable spatial representation of their objective location (Marcel et al., 2004).

1.4.5 Anosognosia and somatoparaphrenia

In most cases, patients with neglect can be either completely unaware of their deficits, especially in the acute stage, or show some awareness at a later stage of their illness when they may generally acknowledge that they can miss items on the affected side but yet continue to do so while carrying out a task (Driver, 2001). This denial of symptoms is defined as anosognosia and may have an enormous impact on the process of recovery. Lack of insight into one's own pathological state can lead the patient to blame others or the situation for their errors and as a result they do not tend to modify their behaviour or to recognise the need for therapeutic intervention. This deficit is prevalently associated with right hemisphere damage which generally can lead to alterations of emotional and attitudinal processes implicated in self-concern and self-attribution of perceptual experiences (Marcell et al., 2004).

Anosognosia can take several forms. Some patients for example deny explicitly that they are paralysed or when questioned about their impairments some can become selectively mute or dysarthric or answer in an irrelevant fashion (Weinstein, 1994). Others can also make jokes about their disabilities in a ludic manner. While in most cases, both anosognosia and neglect are present, they may be dissociable for example in those patients showing severe verbal denial but mild neglect or marked neglect and no verbal denial (Weinstein and Friedland, 1977; Weinstein and Kahn, 1955). Anosognosia can also dissociate between various deficits. For example a patient may deny paresis of one limb but admit problems with reading or taking care of one side of his/her body (personal neglect) (Adair et al., 1995). Measures of anosognosia have been found to correlate more strongly with signs of spatial neglect in daily life than when the disorder is assessed with conventional batteries (Azouvi et al., 1996). In the context of a rehabilitation program, unawareness of symptoms represents the first obstacle clinicians usually have to deal with for any successful remission of the patient's range of deficits. It is important to be aware of the mental state of the patient and clinicians should recognise that denial has positive-adaptive as well as negative-maladaptive aspects which need to be taken into consideration (Weinstein, 1994). In contrast to the initial lack of concern for their condition, patients might experience episodes of depression and anxiety when they become progressively aware of their neglect during the course of clinical improvement (Weinstein, 1994). Vuilleumier (2000) put forward the idea that anosognosia might involve lack of affective drive to respond to uncertainties about currently bodily states or current cognitive capabilities. Consequently when present, this deficit can certainly aggravate the characteristic cognitive profile of patients with neglect.

Lesion analyses of anosognosic patients have demonstrated that unawareness of hemiplegia appears related to lesions of the white matter, basal ganglia, pre-motor cortex (Berti et al., 2005) and the insular region (Karnath et al., 2005a) while chronic unawareness for hemianopia is often associated with right parietal damage (Koehler et al., 1986). Although anosognosia for hemianaesthesia seems also related to insular and basal ganglia (putamen) damage, the involvement of the temporal areas appears to be more frequent (Spinazzola et al., 2008). It might be possible that the lack of insight for other types of symptoms might be due to different lesion sites and this would support the hypothesis about the presence of a distributed cerebral network for awareness and consciousness (McGlynn and Schacter, 1997). Thus, discrete self-monitoring processes, when selectively compromised by specific brain damage, may cause selective disorders of awareness (Spinazzola et al., 2008).

To date, a full variety of symptoms of abnormal awareness has been described which range from lack of concern or apparent forgetfulness through minimization, rationalization to delusional conceptualizations about one's body parts. This last phenomenon is also known as somatoparaphrenia which represents one type of monothematic delusion where the person denies ownership of a limb or an entire side of the body. Patients may have the delusion that their affected limbs do not exist or they may claim that they belong to somebody else and can refer to them as they were either inanimate or animate objects (Weinstein, 1994). Misidentifcations such as the belief that the patient has one or more extra limbs or phantom limbs can also occur (Weinstein, 1954). This disorder arises typically within the context of schizophrenia or dementia but it can result also from focal dysfunctions such as traumatic brain lesions. Contrary to conventional delusions, this condition does not present the persecutory or grandiose content typical of most idiopathic psychotic disorders since it concerns only deficits confined to one side of the body and tends to co-occur with unilateral neglect. Somatoparaphrenic manifestations do not indicate that patients with neglect are somehow mentally deteriorated. There is, however, a strong association with mood changes, environmental disorientation and reduplicative phenomena following right hemisphere damage (Levine et al., 1991; Weinstein and Kahn, 1955).

1.5 Theories of neglect

Several theories have been developed to account for the various behavioural manifestations of the neglect syndrome. These can be broadly grouped into three major approaches which consider neglect as a deficit of *spatial attention*, *sustained attention* or as a disturbed *internal representation of space*.

1.5.1 Spatial attention models

Some of the most influential attentional hypotheses refer to different types of impaired mechanisms: *spatial unawareness* or *inattention deficit*, *right hemisphere dominance for spatial attention* (Heilman and Valenstein, 1979; Bowers et al., 1980), *ipsilesional spatial attentional bias* (Kinsbourne, 1970; Anderson, 1996) or *disengagement deficit* (Posner, 1984).

1.5.1.1 Inattention

The spatial unawareness or inattention hypothesis states that patients with neglect fail to act and explore the contralesional space because they are unaware of the stimuli located in it or, because those stimuli appear less salient compared to the ones located ipsilesionally. According to this idea, neglect patients would omit contralesional targets in a cancellation task because they are unaware of them or bisect only the portion of the line which they are aware of. This hypothesis is supported by several observations documenting how the severity of neglect can be reduced by instructing the patients to attend a contralesional stimulus (i.e. cue) and increased by asking them to attend an ipsilesional stimulus (Riddoch and Humphreys, 1983; Butter et al., 1990; Butter and Kirsch, 1995).

1.5.1.2 Right hemisphere dominance for spatial attention

Several attentional models are based on the assumption that the right hemisphere is dominant for spatial attention and they all try to explain the phenomenology of neglect in a slightly different fashion. Heilman and Van Den Abell's model (1980), for example, states that the left hemisphere deploys attentional resources mainly within the right hemi-space and shifts the attentional focus mostly in a rightward direction while the right hemisphere coordinates the distribution of attention within both hemi-spaces and shifts the attentional focus in both directions. In the normal state, attention can be shifted to any motivationally relevant direction but there might also be a slight bias favouring the left hemi-space given that the right hemisphere, which devotes more resources to spatial attention, is more likely to be engaged in attentional tasks. This model is supported by event-related potentials (ERP) and PET studies showing electroencephalogram desynchronisations and metabolic activation of the left hemisphere only after right-sided sensory stimulation (i.e. visual or tactile), while the right hemisphere showed these changes after stimulation from either side (Desmedt, 1977; Heilman and Van Den Abell 1980; Reivich et al., 1983; Pardo et al., 1991). Similarly, functional imaging studies showed greater activation of the right hemisphere during attentional shift to both hemi-spaces (Nobre et al., 1997; Gitelman et al., 1999) and increased cortical activation of the left hemisphere only when attention was shifted within the right hemi-space (Corbetta et al., 1993). This evidence is in line with Heilman and Van Den Abell's model (1980) as lesions of the left hemisphere generally do not result in contralesional neglect as severe, frequent and long-lasting as when the damage involves the right hemisphere (De Renzi et al., 1970; Gainotti et al., 1972; Oxbury et al., 1974; Denes et al., 1982; Weintraub and Mesulam, 1987). Indeed, the left hemisphere would confine and shift the attentional focus within the contralesional hemi-space while the right hemisphere's faculty of controlling the distribution of attention in both hemi-spaces would instead compensate for the deficit. This inter-hemispheric difference in allocating spatial attention would explain the higher incidence and severity of neglect after right hemisphere damage.

More explicit assumptions about the strength and spatial attention mecchanisms of the two hemispheres were made by Anderson (1996) in his mathematical model of neglect. The model assumes a weaker and more contralaterally (around 10°-20° eccentricity towards the right side) shifted salience function of the healthy left hemisphere and a relatively stronger salience function generated by the right hemisphere extending over both hemi-fields (Anderson, 1996). Similarly to Heilman's model, a disruption of the stronger right hemisphere salience function would lead to left neglect, while damage to the left hemisphere would be compensated by the bilaterally operating right hemisphere attentional system (Kerkhoff, 2001).

1.5.1.3 Orienting vector model

Kinsbourne's (1970) orienting vector model agrees with Heilman's notion regarding the presence of an ipsilesional attentional bias as the core mechanism behind the neglect syndrome. However, the crucial difference is that in Kinsbourne's model this attentional bias is not due to the hypoactivity of the right hemisphere but to the hyperactivity of the intact left hemisphere. This hypothesis is based on the assumption that each hemisphere generates an attentional vector towards the opposite hemi-space balancing their respective attentive processes. Thus when one hemisphere is injured, the other becomes disinhibited leading to an attentional bias towards the ipsilesional hemi-space (ipsilesional hyperattention). Kinsbourne explained the greater severity of neglect following right hemisphere damage by considering the attentional vector of the left hemisphere slightly stronger that that of the right in the intact brain. Consequently, the suppression of the weaker leftward attentional vector after right hemisphere injury, would lead to stronger attentional bias toward the right hemi-space compared to the leftward attentional bias resulting instead from left hemisphere damage. Therefore, following Kinsbourne (1977; 1987), the typical search pattern of a neglect patient would resemble a gradient-like distribution of spatial attention with a continuously increased likelihood of stimulus detection from the left side (minimum) to the right side (maximum) along the horizontal axis.

Consistent with the orienting vector model, Làdavas et al. (1990) demonstrated that right brain damaged (RBD) neglect patients were faster in detecting targets in the right hemispace compared to RBD patients without neglect. In this case, according to Kinsbourne's model, neglect patients' attention for the right hemi-field was enhanced with respect to RBD controls as a reflection of increased disinhibition of the left hemisphere. However, subsequent findings seemed not completely compatible with this model as the right hemisphere which should have a weaker attentional vector appears instead dominant for spatial attention mechanisms. Several reaction times (RT) studies, for example, found that RBD neglect patients were slower than normal controls in detecting both contralesional and ipsilesional targets – a pattern that correlated also with the severity of neglect (Bartolomeo and Chokron, 2002). That neglect does not result from a hyperactive left hemisphere is also supported by functional brain imaging studies of diaschisis in neglect which demonstrated a widespread hypometabolism in both the lesioned and the intact hemisphere (Fiorelli et al., 1991; Pantano et al., 1992; Perani et al., 1993). In addition, recovery from neglect seemed to correlate with restoration of normal metabolism not only in the unaffected regions of the right hemisphere but also in the left hemisphere (Pantano et al., 1992; Perani et al., 1993).

1.5.1.4 Disengagement of attention deficit

A further attentional model was formulated by Posner et al. (1980) who considered neglect as a deficit of disengagement of attention from stimuli located on the ipsilateral side of space. These authors studied the spatial attention impairments of patients with parietal lesions with a target detection paradigm named "Covert Orienting of Visuo-spatial Attention Task" (COVAT). In this task subjects are presented with three horizontally arranged boxes and they are asked to respond when the target (asterisk) appears to one of the two lateral boxes while maintaining eye fixation on the central box. The target is preceded by a cue indicating in which box (left or right) the target will appear. Cues can be either central (an arrow presented in the central box) or peripheral (brief brightening of one peripheral box). Valid cues correctly predicts the box in which the target will occur while invalid cues indicate the wrong box[5]. In healthy subjects valid cues typically reduce reaction times while invalid cues increase them. This suggests that the cue prompts an attentional orienting towards the cued location which speeds up the processing of targets appearing in that region and slows down responses to targets appearing in other locations (Bartolomeo and Chokron, 2002).

[5] In this paradigm, when the large majority of the cues are valid, the cues are said to be *informative* of target presentation. Alternatively, they can be *uninformative* when the target can appear with equal probability in the cued and uncued location. With short stimulus-onset asynchronyes (~300) between the cue and the target, non informative cues would attract attention automatically or exogenously. Informative cues instead would prompt an endogenous attentional shift based on the strategic predictability of target presentation.

Posner et al. (1984) found that the performance of patients with parietal lobe lesions was particulary affected by the trials with invalid cues. In those conditions, patients' attention was indeed shifted towards the ipsilesional right visual field (i.e. right) yielding a dramatic increase (cost) of reaction times for contralesional targets. This was the case for voluntary as well as reflexive attentional shift. Although this RT pattern was present in both RBD and LBD patients, it was considerably larger in those with RBD. In addition, the observed RT cost-effect for invalidly cued targets, correlated significantly with the extent of the lesion in the superior parietal cortex (Posner et al., 1984). Accordingly, the authors suggested that patients with neglect following right parietal damage can have a deficit in "disengaging" the attentional focus from a current ipsilesional to a relative contralesional event. In order to test the disengagement hypothesis, Mark et al. (1988) compared the visual exploration of patients with neglect in a traditional cancellation task by asking them to either mark each target with a pen or to erase each detected target. The authors hypothesised that when the targets were erased, patients would not have difficulties in disengaging their attention from them leading to a reduced attentional bias. In the marking condition, a part from making contralateral omission, the patients also tended to return systematically towards the ipsilesional half of the page to cancel the same targets again. Conversely, their overall search performance improved during the erasing condition in which presumably the salience of ipsilesional stimuli was reduced.

A problem of disengagement from ipsilesional stimuli could explain some aspects of neglect such as failure in directing attention and explore the contralateral hemi-space in visual search tasks. However, it is worth noticing that the group of right parietal damaged patients in Posner et al.'s study showed little or no clinical signs of neglect (Bartolomeo and Chokron, 2002). Thus, it was not possible to find any direct evidence for a relationship between the observed RT pattern and clinical neglect. However, Morrow and Ratcliff (1988) conferred more consistence to Posner's interpretation of the neglect syndrome by demonstrating an association between the impaired RT pattern for invalid contralesional targets with a measure of clinical neglect (e.g. cancellation, bisection, copy). In addition, a recent meta-analysis of 27 studies which used the Posner paradigm with brain damaged patients indicated that the disengagement deficit appears larger in patients with right hemisphere damage and especially with neglect, than in those showing no neglect and left hemispheric lesions (Losier and Klein, 2001). One limitation of the disengagement model is the assumption that neglect patients must first engage their attention ipsilesionally in order to show a deficit in shifting their attention contralesionally. It has been shown, however, that even without any external visual input which could potentially engage attention, the exploratory behaviour of patients with neglect appears biased towards the ipsilesional side of space (Karnath and Fetter; 1995; Karnath et al., 1996).

1.5.2 Impaired sustained attention

The approach which considers neglect resulting from failure of non spatially-lateralized attentional functions arises from Heilman et al.'s observations (1978; 1979) of low levels of arousal and sustained attention in neglect patients. Robertson et al. (1997) found that an auditory sustained attention task significantly discriminated between right hemisphere damaged patients with and without neglect. The task required patients to maintain an internal count of a string of tones which were separated by intervals of approximately three seconds. Moreover the authors observed a strong correlation between the severity of neglect as assessed with standard clinical tasks (i.e. star cancellation, line bisection, figure copying) and the degree of impairment on the sustained attention task. A further study carried out by Robertson and co-workers (1998) demonstrated how lateralized deficits in neglect patients can be modulated by manipulating the level of tonic alertness. Their patients showed a pathological delay in detecting visual stimuli presented on the left visual field compared to the ones on the right visual field. However, the patients' delayed responses to events on the left were significantly reduced when periodic unpredictable warning sounds were played centrally or even on the right of the stimuli display. The authors concluded that the alerting tones increased the patients' level of alertness via bottom-up stimulation which allowed them to overcome their rightward bias and increase their ability to detect stimuli from the left (Robertson et al., 1998). This result indicates that a tonic deficit in sustained attention can exacerbate the lateralised deficit shown by neglect patients. Other studies have shown that chronic spatial neglect can be related to a persistent impairment in sustained attention (Samuelson et al., 1998; Hjaltason et al., 1996; Maguire and Ogden, 2002), while patients who recover from neglect can show improved sustained attention performance (Samuelson et al., 1998). Further evidence for a non-lateralized deficit of attention in neglect patients is provided by several studies which found impaired performance in both hemifields with different paradigms such as L/R target detection or multiple objects tracking task (Chatterjee et al. 1992; Duncan et al., 1999; Battelli et al., 2001). Valuable contributions in this respect also come from studies on the “attentional blink” phenomenon. This effect refers to impairment in identifying a second target (probe) because of the processing of a previous target (prime) in a rapid serial visual presentation task. Hence the attentional blink protocol allows one measuring the temporal dynamic capacity of visual selective attention which is “the time taken by the visual system to identify a visual stimulus before it is free to detect the subsequent one” (Husain and Rorden, 2003). Usually, healthy individuals fail to report the probe if it occurs within 400 ms after the prime whereas patients with neglect in comparison can show a more severe and protracted attentional blink effect (Husain et al., 1997b; 2003). Using this protocol, Husain et al. (1997b) found that neglect patients can be indeed dramatically impaired in visual-processing abilities even when attention does not have to be shifted across space. Importantly, in Husain et al.’s study the level of deficit demonstrated on this non-spatially lateralized task correlated with the severity of neglect. However, Shapiro et al. (2002) demonstrated that this impairment can also take place amongst patients with IPL and STG damage but without neglect. Taken together, these findings suggest that although non-lateralized deficits of sustained attention can not be considered as the direct cause of neglect, when combined with spatially lateralized impairments the gravity of the syndrome can intensify (Husain and Rorden, 2003). In addition, under these circumstances, the process of recovery could potentially become much slower.

1.5.3 Space representation models

1.5.3.1 Distorted topographical representation of space

The representational model of neglect formulated by Bisiach and Luzzatti (1978; 1981) assumes that space is topologically represented in the brain and in neglect patients this representation appears distorted. Their hypothesis was based on the observation that when their neglect patients were asked to describe from memory the dome square in Milan from one perspective, they were unable to recall left-sided details. However, when they were subsequently asked to describe the details of the same square from the opposite perspective, they failed to recall the left-sided features which had been described previously from the other perspective (as in that occasion they were located on their right hand site). Bisiach et al. (1981) attributed this deficit to a disruption of the mental representation of left space in the right hemisphere. Thus, the omission of left-sided details while recalling the details of a familiar place was not due to abolition of the information but to an inability to activate the part of the representation that fell to the left of the mental image (Bisiach et al., 1981). Given their results, the authors speculated that there are at least two basic mental representations that are needed to perform a spatial task: one representation of the target and one of the environment. Since neglect patients are able to detect ipsilateral stimuli, their failure to detect contralesional stimuli cannot be due to a loss of the representation of the target. Rather, if knowledge of the contralesional space is destroyed, attention might not be fully directed to it as there is no longer knowledge of that space (Heilman, Watson and Velenstein, 2002). The same principle can be applied to deficits of motor exploration in neglect: if knowledge of the contralesional space is lost, one may fail to act in or towards that portion of space (Heilman, Watson and Velenstein, 2002). In this way, both attentional and intentional deficits in neglect patients may be explained by a representational deficit. However, since not all patients with neglect show impaired mental imagery and some patients with imagery deficit may not necessarily have neglect (Guariglia et al., 1993), a representational deficit cannot therefore account for all types of spatial neglect (Heilman et al. 2002). In a subsequent revision of his model Bisiach et al. (1994; 1996) argued that the representation of the contralateral space in neglect patients is not lost but somehow distorted with compression of the ipsilesional side and extension of the contralesional one.

This conceptualization of space anysometry was put forward to account for some behavioural patterns of neglect patients observed during tasks where they had to reproduce line segments or distances (Bisiach et al., 1994; 1996; Milner and Harvey, 1995). When required to double the length of a given horizontal line or a distance between two dots with a pen, some patients may tend to overextend contralesionally and underextend ipsilesionally (Savazzi et al. 2004). According to Bisiach et al.'s (1994; 1996) anisometry hypothesis, neglect patients reproduce the contralesional half of a line as longer than the ipsilesional one as they underestimate the horizontal extent of stimuli located contralesionally due to an over extension or "abnormal relaxation" of the affected space. Conversely, they overestimate the ipsilesional half of a line as a result of an "abnormal compression" of the attended space. Some authors suggested that the above phenomena are mainly due to the presence of visual field deficits such as hemianopia which would prevent the full examination of stimuli's horizontal extent but not a distorted spatial representation (Doricchi and Angelelli, 1999; Ferber and Karnath, 2001). Namely, the lack of retinal inputs from the contralateral hemifield, would induce hypermetric compensatory scanning patterns towards the blind hemifield leading consequently to size overextension. However, in support of Bisiach et al.'s framework, Harvey et al. (2001; 2002; 2003) demonstrated that space distortion is not necessarily related to hemianopia or biased oculomotor behaviour in neglect patients. In later studies Bisiach et al. (1998b; 1999) observed that when asked to extend horizontal segments, relative[6] contralesional overextension seems to be the prevalent pattern amongst neglect patients, although relative contralesional underextension can also occur in some cases. The authors suggest that, even if less frequent, this latter tendency may be linked to a "higher degree of contralesional overrelaxation of the medium for space representation" present amongst those patients with more severe neglect (Bisiach et al., 1998b; 1999). However, their model does not fully explain why a relative contralateral overextension on a line extension task reverses to a relative contralateral underextension depending on the severity of neglect.

Halligan and Marshall (1991a) and Milner (1987) also argued in favour of a "compression" of the perceived visual surroundings in neglect, but their interpretation of the nature of space distortion in neglect is the opposite to that described in Bisiach's model: Halligan and Marshall considered that the compression of the subjective visual space is uniform along the horizontal axis and "pushed in" from the *contralesional* side, whereas Milner claimed that the compression progressively increases from right to left. Karnath and Ferber (1999) on the other hand, by asking neglect patients to adjust ten red LEDs equidistantly along a semicircle positioned in front of them, found no evidence for a distortion of subjective space representation, neither in terms of uniform compression of the visual array nor of a combined extension on the contralateral and

[6] Bisiach et al. (1999) specified that the term "relative" "is added in order to underline the fact that the left over- or underextension is independent of the absolute errors made by the patients on the line extention task. Relative left over- or under extension, may be found when patients overextend line segments both left- and rightward, as well as when they underextend them in both of these directions".

compression on the ipsilesional side of space. However, it is important to stress that Karnath and Ferber (1999) investigated space representation as distance between objects rather than of single objects in space like in Bisiach et al.'s studies (1994; 1996). Therefore it might be possible that in neglect patients, disturbances in encoding the spatial relations between objects with respect to the body might occur independently from deficits in processing single objects or their constituent parts (Milner et al., 1993; Milner and Harvey, 1995; Karnath and Ferber, 1999). There is indeed evidence supporting separate neuronal substrates for these two different space-related processes (Andersen et al., 1993; Olson and Gettner; 1995).

1.5.3.2 Ipsilesional shift of egocentric reference frames

An alternative model within the framework that considers neglect deficits as the result of an altered representation of space was conceptualized by Karnath et al. (1994; 1995; 1997). This model conceives that in neglect patients, the transformation that converts peripheral sensory inputs coordinates (i.e. from the retina or muscle spindles) into a supramodal body-centred reference system is working with a systematic error resulting in a horizontal shift of the spatial reference frame to the ipsilesional side of space (Karnath, 1994).

Karnath et al's hypothesis is supported by several studies that demonstrated a reduction of neglect symptoms by manipulating those peripheral sensory inputs essential for an egocentric representation of the external space (Karnath, 1994). Rotation of the trunk towards the contralateral side of space, vibration of the contralateral posterior neck muscles (Karnath et al., 1993), vestibular (Cappa et al., 1987) or optokinetic stimulation (Pizzamiglio et al., 1990) can indeed generate a transient shift of the ipsilesional displacement of the subjective body sagittal plane of neglect patients towards the contralesional side of space. Accordingly, an ipsilesional deviation of the egocentric reference system would skew the whole field of exploration away from the affected side causing the typical asymmetric visual exploration deficits in patients with neglect. To explore the visual search pattern across both hemifields, Karnath and Fetter (1995) and Karnath et al. (1996) recorded the eye movements of neglect patients up to ±50° during spontaneous visual exploration for which they were asked to search for a (non-existent) light spot located somewhere in a darkened room. In line with their deviation model, the patients' frequency pattern of fixations resulted to be symmetrically bell-shaped with the centre of the distribution shifted at +15° degree towards the ipsilateral side of space. This outcome undermines the assumption of the gradient model of Kinsbourne (1977; 1987) which conceives instead a continuous increase of exploratory activity along the horizontal axis from left to right. The divergent results on frequency distribution pattern of visual exploration observed in neglect patients may be explained by the different size of the search arrays used in different studies (i.e. computer screen versus the whole visual field (See also section 1.2.3).

In a subsequent study, Karnath et al. (1997) observed that their idea of the ipsilesional deviation of egocentric space representation could not be applied to goal-directed arm movements. Their group of neglect patients did not show a direction-specific deviation of trajectory towards the ipsilateral side of space while pointing to targets within their proximal space (Karnath et al., 1997a). The authors argued that this result may imply different neuronal representations for spontaneous exploratory and goal-directed behaviour. The former could be subserved by inferior parietal areas as important site for egocentric space representation whereas the latter may be more associated with superior parietal cortex involved in visuomotor processes and reaching behaviour (Karnath, 1997b). However, it is important to stress that not all manifestations of neglect can be related to a pathological shift of the body midline as some studies demonstrated no deviation of the perceived sagittale in straight ahead pointing tasks (Hasselbach and Buttler, 1997; Farnè et al., 1998). Some authors suggested that the inconsistencies among the studies that investigated the presence of a displacement of the egocentric reference system in neglect may be due to the additional presence of visual field deficits or damage of parietal areas (Niemeier and Karnath, 2002b). Indeed, on the one hand hemianopia seems to generate a contralesional displacement of the midline which would compensate the ipsilesional shift of the egocentric reference system associated with neglect. On the other hand, given the crucial involvement of the parietal lobe in computing the perceived body orientation in the horizontal dimension, neglect patients with extensive parietal damage may be more likely to show an ipsilesional shift of the egocentric midline compared to those whose lesion is restricted to temporal or frontal areas.

Overall, given the compound and dissociable symptomatology in neglect patients, it seems very unlikely that any of the above models can provide a comprehensive explanation of the mechanisms underlying the syndrome. Although the main distinction can be drawn between models attributing neglect to impaired attentional processes and those postulating a distorted spatial representation, they are not mutually exclusive. For instance, it is conceivable that a distortion of spatial reference systems can interact with a biased allocation of attentional resources in space. In addition, the co-occurrence of a generalised sustained attention impairment could contribute to exacerbate the symptomatic picture of patients with neglect. Therefore, a more fruitful approach would perhaps be to try to integrate the valuable contribution of each model in explaining the multicomponential nature of neglect.

1.6 Anatomy of neglect

Lesion analysis and neuroimaging techniques are progressively providing a more accurate definition of the neuroanatomic substrates underlying the neglect syndrome.
The most frequent causes of neglect in humans are infarctions in the territory of the right, less often the left, middle cerebral artery (MCA) (Vallar, 1993). The resulting lesions may encompass one or several brain areas which appear to be the crucial sites that when damaged cause the syndrome: the inferior parietal cortex (Vallar and Perani, 1986), the temporal parietal junction (Vallar and Perani, 1986; Mort et al., 2003), the superior temporal gyrus (Karnath et al., 2001, 2004), the inferior and medial frontal gyrus (Husain and Kennard, 1996; Mort et al., 2003). In addition to cortical damage, lesions of subcortical structures, involving the right basal ganglia or thalamus are also known to produce neglect (Damasio et al., 1990; Karnath, 2002; Watson and Heilman, 1979; Watson et al. 1981).

1.6.1 Parietal cortex

The right inferior parietal cortex (i.e. angular gyrus) has traditionally been considered the crucial lesion site which would commonly generate the disorder (Paterson and Zangwill, 1944; Vallar and Perani, 1986). A number of, neurophysiological and neuroimaging studies demonstrated that this area receives converging inputs from the visual, auditory and tactile modalities but also proprioceptive and vestibular signals about the position of the limbs, head and eye (Driver and Vuilleumier, 2001). It is assumed that these polysensory inputs concur to construct a stable representation of the visual environment for directing attention processes (Andersen et al., 1997; Macaluso et al., 2005). In addition, converging evidence over the years demonstrated how this brain area plays a critical role in shifting and reorienting the focus of attention in space from one position to another (Corbetta and Shulman, 2002). Damage of the inferior parietal lobe (IPL) may thus explain the presence of an ipsilesional attentional bias in neglect patients which results in a deficit of attentional shift ("disengagement") towards the affected side of space.

The IPL is also involved in the operations of monitoring intentions with the outcome of goal-directed actions. In this way it would act as an interface between intentions and actions, by modulating for example exploratory activities (i.e. eyes and hands) in the surrounding space according to internal behavioural goals (Danckert and Ferber, 2005). Accordingly, Karnath and Niemeier (2002; 2003) demonstrated that patients with neglect following IPL damage can indeed show a task-dependent deficit in their exploratory motor behaviour. In addition, lesion of the angular gyrus can impair a dynamic internal representation of one's body (Blanke et al., 2002; Tong, 2000), deficit not uncommon in patients with neglect (Danckert and Ferber, 2005). In a lesion overlap study with right brain damaged patients, Mort et al. (2003) demonstrated that the core brain region that when damaged causes neglect is the angular gyrus resulting in profound deficits of visuospatial awareness.

1.6.2 Temporal Parietal Junction

It has been demonstrated that damage of the right temporal parietal junction (TPJ) may lead to a more severe and persisting pattern of visuospatial deficits in neglect patients due to a non spatial generalized sustained attention impairment (Samuelsson et al., 1998; Robertson et al., 1997; Hjaltason et al., 1996; Maguire and Ogden, 2002). Some of the effects generated by right TPJ damage have been observed using Posner type paradigms where valid and invalid cues would predict the location of the incoming target (See session 1.1.5.1.4). Neglect patients with TPJ damage but spared SPL, appeared unable or very slow in detecting unattended targets after an invalid exogenous cue but were still able to use the probabilistic value of an endogenous valid cue to predict the position of a target (Friedrich et al. 1998). Neuroimaging studies demonstrated activation of the right TPJ during overt reorienting of exogenous attention toward targets at an uncued location or covert shifting of attention across visual fields (Corbetta et al., 2000; 2002; Yantis et al., 2002). These results suggest a specific involvement of this region in the deployment of reflexive attention towards those stimuli which are behaviourally relevant irrespectively of their position in the surrounding space (Danckert and Ferber, 2005). In other words, the right TPJ would play the role of a "salience detector" in the mechanisms of exogenous stimulus-driven orienting of attention which can be impaired in neglect patients.

1.6.3 Temporal cortex

While the IPC and the TPJ subserve more specific functions related to shifting the attentional focus and detection of salient stimuli in the environment, the superior temporal cortex (STC) represents one of the anatomic areas largely involved in the multimodal representation of space as a coherent whole.

A critical role of the STC in neglect has only recently been suggested by Karnath et al. (2001), following the findings of an anatomical group study who aimed at isolating the anatomical region involved in the core deficit of spatial neglect (i.e. impaired visual exploration). In disagreement with previous studies, the right STC appeared to be the centre of lesion overlap for spatial neglect and this provocative new finding led to conspicuous debate on the criteria of patients selection (i.e. neglect patients with hemianopia were not included in the sample). However, in a later study Karnath et al. (2004) replicated the same anatomical outcome in a larger and unselected sample of 140 right hemisphere damaged patients. The latter result contributed to challenge even further the issue on the definition of the "critical" neuronal substrates of neglect.

It has been suggested that the STC is involved in the analysis of objects properties as well as their location in space (Karnath, 2001). According to this idea, the STC encodes space through both object-centred and egocentric reference frames. Neglect patients with STC damage would, therefore, show failure in processing both object - and space - related information (Karnath, 2001). However this hypothesis was not entirely confirmed by two recent group studies which revealed distinct areas of dysfunctional tissue associated with viewer-centred (egocentric) versus stimulus-centred (object-centred) neglect within 48 hours from stroke onset (Hillis, Newhart, Heidler, Barker et al., 2005; Hillis, Newhart, Heidler, Marsh et al., 2005). Viewer-centred neglect was related to hypoperfusion of the right angular gyrus, right supramarginal gyrus and right visual association cortex, while only the presence of stimulus/object centred neglect was associated with hypoperfusion of the right superior temporal gyrus.

1.6.4 Frontal cortex

Cases of neglect following frontal lobe damage only have also been reported (Husain and Kennard, 1996; Mort et al., 2003) but are fairly rare in comparison to damage to other brain regions such as the parietal and temporal cortex. The pattern of recovery of neglect patients with frontal injury is quicker than those with more posterior damage but the reasons behind this pattern are still unclear (Rorden, 2003). The frontal areas which when damaged appear to cause neglect are the inferior (IFG) and medial frontal gyrus (MFG) (Husain and Kennard, 1996; Mort et al., 2003) encompassing part of the homologue of the Broca's area (Husain and Kennard, 1997).

Previous reports stressed the presence of directional motor impairments in neglect patients with frontal lesions (Meador et al., 1988; Bisiach et al., 1990; Coslett et al., 1990). However, this assumption was undermined when it became clear that slowed initiation of contralesional movements (hypokinesia) can also occur following parietal damage only (Heilman et al., 1985; Mattingley et al., 1992). A number of studies demonstrated that neglect patients with frontal damage perform poorly on high density cancellation tasks with a relatively preserved performance in line bisection tasks (Binder et al., 1992; Husain and Kennard, 1997; Maeshima et al., 1995) while patients with parietal injury can be impaired on both tasks (Binder et al., 1992). These observations can be explained by the pivotal role played by the right inferior frontal lobe in target selection and information filtering (i.e. irrelevant distractors). Thus, high sensitivity to distractors load in visual search tasks could represent one feature of those cases of frontal neglect (Husain and Kennard, 1997). However, given that also parieto-temporal lesions can lead to impaired search performance, a neglect deficit following frontal lobe alone does not seem to resemble or exacerbate any distinctive symptomatology or functional difference in comparison.

1.6.5 Subcortical structures

At a subcortical level, Karnath et al. (2002; 2005) demonstrated that damage to the pulvinar and some basal ganglia structures, such as the putamen and caudate nucleus, can also be associated with spatial neglect. These findings are in line with numerous neurophysiological and neuroimaging studies supporting in particular the role played by the pulvinar in selective attention (Petersen et al., 1985; Corbetta 1991), visual scanning (Ungerleider and Christensen, 1979) and engagement of the attentional focus (Posner, 1990). Given the neuronal connections of the STG with the putamen, caudate and pulvinar, Karnath and colleagues suggested that those structures could represent a cortico-subcortical network subserving spatial awareness in humans which can result in spatial neglect when damaged (Karnath et al., 2002). According to Karnath et al. (2002; 2005), focal damage to those subcortical structures could also cause critical metabolic cortical dysfunctions via diaschisis which could be sufficient to generate neglect.

1.6.6 Neuronal networks

The alternative perspective which tries to emphasise more a network approach rather than the traditional localization approach could be more promising in elucidating the neuronal correlates of neglect.

Mesulam (1981; 1999) formulated one of the first anatomical models which introduced the concept of spatial attention as a distributed function mediated by a network of cortical areas whose damage causes spatial neglect. The cortical epicentres of this network are the posterior parietal cortex (IPS), frontal cortex (FEF, premotor and prefrontal areas), anterior cingulate (AC) with numerous interconnections with the ascending reticular activating system (ARAS), thalamus, striatum and superior colliculus. Each node of the network provides "a different but interactive and complementary type of neuronal encoding so that behaviourally relevant targets in the environment can be represented mentally and become the target of further action and exploration" (Mesulam, 1988). The posterior parietal component represents a critical gateway which links distributed channels of spatially relevant information with each other and with multiple channels of motor output (i.e. orienting, reaching, grasping, scanning and exploring). The frontal component converts the strategies for attentional shifting and the trajectory-based templates provided by the parietal cortex into specific motor acts (i.e. sequence of eye movements) useful to navigate efficiently in the surrounding space. The limbic component in the cingulate cortex assigns motivational relevance to the extrapersonal events and sustains the level of effort needed for the execution of attentional tasks (Mesulam, 1988). According to this model, lesions involving network epicentres are likely to cause multimodal neglect, while lesions that disconnect the network from other areas of the brain could cause modality-specific neglect.

Another influential anatomical model which conceived spatial neglect as the result of damage of a specific network within a multicomponent attentional system was introducted by Posner and colleagues (Posner and Petersen, 1990; Posner and Rothbart, 1991). The brain areas involved are the same as those mentioned in the Mesulam model but they are organized into three interconnected networks: anterior, posterior and vigilance network. The anterior network (frontal cortex - cingulate cortex) is responsible for target detection, the posterior network (posterior parietal cortex - pulvinar - superior culliculus) for orienting attention to new locations and the vigilance network (noradrenergic locus ceruleus system) for maintaining an efficient alerting state. The mechanism of orienting can be subdivided into three different operations: disengaging attention from its current focus, moving attention to a new position and re-engaging attention at the new location. At a neuronal level, the posterior parietal cortex disengages the attentional focus from the current stimulus, the superior colliculus shifts the attentional focus to the spatial position where the new stimulus is located and the pulvinar re-engages the attentional focus on it. According to Posner, spatial neglect results from damage of the posterior network of the attention system and, as mentioned previously, it is principally characterized by a "disengagement" deficit from the ipsilesional to the contralesional side of space (Posner and Petersen, 1990).

More recently, following new developments in neuroimaging techniques and ERP, a novel anatomical model of attention formulated by Corbetta and colleagues provided an alternative framework to explain the phenomenology of spatial neglect and visual orienting (Corbetta et al., 2000; 2002; He et al., 2007). This model is based on two attentional networks: dorsal and ventral. The former is bilateral and interconnects the inferior parietal sulcus (IPS) with the frontal eye fields (FEF) while the latter, is strongly right lateralised and links the temporal parietal junction (TPJ) to the inferior frontal gyrus (IFG). The dorsal network is recruited during voluntary endogenous orienting of attention towards lateralized stimuli, target detection/recognition and response selection. In contrast, the ventral network is active during the operations of stimulus-driven exogenous reorienting toward unattended visual targets independently of their spatial location. In particular, the TPJ component of this network plays a critical role in alerting mechanisms by detecting the saliency of novel stimuli in the environment. These two systems work in concert to assure an effective interaction with external events: while the signals from the dorsal components are related to a voluntary processing of the target (endogenous orienting) the ventral system provides an alerting signal to indicate that the anticipated event has occurred. However, when the targets appears to an unexpected location, the alerting signal from the ventral system "informs" the dorsal system (via exogenous orienting) that something worth localizing has occurred (Corbetta et al., 2002). Accordingly, damage to different components of these two networks can compromise specific attentional mechanisms leading to some of the peculiar symptoms observed in the neglect syndrome. Neglect patients with damage to the dorsal network (SPL/IPS), are unable to select endogenously stimulus location and shift the attentional focus in space. Moreover, the characteristic sensory-motor bias in orienting and responding more promptly towards their ipsilesional side, is more related to functional/anatomical dysfunctions of the dorsal system. On the other hand, damage of the ventral network (TPJ-IGF), can lead to vigilance impairments noticeable especially during the acute stage. In addition, a dysfunction of the non spatial alerting mechanisms may generate a decrease of "alerting input" and functionally inactivate the ipsilateral dorsal network (Corbetta et al., 2005). This dysfunction in turn may cause a reduction of contralateral voluntary (endogenous) orienting of attention. In light of these observations, Corbetta et al. suggest that spatial neglect can reflect the conjunction of structural and functional damage to the ventral and dorsal attentional networks (Corbetta et al., 2000; 2002; He et al., 2007). This framework would explain both spatially lateralized (i.e. ipsilesional attentional bias) and non-lateralized (low alertness, impaired visuospatial working memory) deficits in neglect patients (He et al., 2007).

Another interesting contribution which conceives neglect as the result of large-scale networks damage comes from Bartolomeo and collaborators (2007). These authors reviewed a large body of findings supporting the major role played by intra and inter-hemispheric disconnection in the neglect syndrome. On this ground, these authors formulated a fronto-parietal disconnection hypothesis which considers two long-range pathways linking the parietal and the frontal lobes whose dysfunction could generate neglect. These two pathways represent two different branches of the superior longitudinal fasciculus (SLF): the SLF II originates in the angular gyrus and occipito-parietal area and projects to the dorsolateral prefrontal cortex, while SLF III connects the supramarginal gyrus with the ventral premotor area 6 (Brodmann), area 44, frontal operculum and area 46 (Schmahmann and Pandya, 2006). The inactivation of the right SLF II causes rightward deviation in line bisection (Thiebaut de Schotten et al., 2005) whereas lesions of the right SLF III also correlate with left omissions on visual search tasks (Doricchi and Tomaiuolo, 2003). The authors suggested that the idea of considering neglect as a disconnecting syndrome could be strengthen in the future if further studies demonstrate a strong relationship between selective lesions of these two pathways and particular patterns of functional deactivation in the cortex and behavioural dissociations in neglect symptoms (Bartolomeo et al., 2007).

In summary, the approach that conceives neglect not just related to damage of one single critical brain area but rather as a dysfunctional interaction between large-scale networks, appears to provide a more comprehensive picture of the neuroanatomy that when damaged causes its wide and heterogeneous symptomatology.

CHAPTER 2

The contribution of the neglect syndrome in the study of near and far space attention in the brain

2.1 Peripersonal and extrapersonal space coding: behavioural characteristics and neuroantomy

In the field of spatial cognition, the study of the neglect syndrome has contributed not just to unveil the presence of several reference frames through which the brain defines different positions in space, but has also provided evidence in support of the idea that different space sectors may be processed by discrete neuronal substrates. This hypothesis is based on copious neurophysiological findings from animal research which showed how different brain systems mediate the perceptual-motor interaction within *peripersonal* or near space (the region immediately surrounding the body) and *extrapersonal* or far space (the region beyond one's arm reaching) (Previc, 1998; 1990; Halligan et al., 2003; Karnath, 2002).

Neurophysiological findings in monkeys suggest that the behavioural distinction between peripersonal and extrapersonal space has its neuronal counterparts in specific parietal and frontal regions which appear to code selectively for the space within and beyond reaching distance (Colby et al., 1993; 1996; Latto and Cowey, 1971; Leinonen et al., 1979; Duhamel et al., 1997).

In a comprehensive review of neurophysiological studies, Rizzolati and Berti (2002) described two different circuits that seem particularly involved in the encoding of peripersonal and extrapersonal space. The first network is the *oculomotor circuit* formed by the lateral intraparietal area (LIP) and the frontal eye fields (FEF). The second is the *reaching circuit* (or somatomotor circuit), comprising the ventral intraparietal area (VIP) and the premotor area F4. In the former, the neurons respond to visual stimuli regardless of the distance of the stimuli from the viewer and their motor properties are exclusively related to eye movements (Andersen, 1997; Snyder et al., 1997; Colby and

Goldberg, 1999). In the latter network, most neurons are bimodal, responding to both tactile and visual stimuli. They respond predominantly to three-dimensional visual objects and their motor activity is related to the movement of body parts. Most importantly, they are only active if visual stimuli are presented within the animal's reaching distance (Gentilucci et al., 1983; 1988; Graziano and Gross, 1993; 1994). Interestingly, the two circuits seem to code space in different ways. The receptive fields of the oculomotor circuit are coded in *retinal coordinates*. In contrast, the reaching circuit codes space in *egocentric coordinates* at a single neuron level, and their receptive fields remain anchored to the body parts to which they are related regardless of eye or limb position (Gentilucci et al., 1983; 1988; Graziano Gross, 1993; 1994; Fogassi et al., 1996). In addition to oculomotor deficits, damage to the LIP-FEF circuit produces an ipsilesional attentional bias as well as unawareness for contralesional stimuli in monkeys. In this case, the deficit appears particularly severe in far extrapersonal space. In contrast, lesion of the VIP-F4 circuit results in inattention for stimuli presented contralaterally to brain damage, which is especially severe when stimuli are presented near the monkey's body and face (peripersonal space). One neurophysiological study in monkeys carried out by Rizzolatti et al. (1983) investigated the presence of hemi inattention deficits restricted to peripersonal and extrapersonal space. Unilateral ablation of the frontal eye field (area 8) resulted in neglect for visual objects located in contralesional far space. In contrast, unilateral ablation of frontal area 6 (which receives direct projections from area 7b, rostrally to the inferior parietal lobules) generated an attentional bias for visual and tactile stimuli limited to contralesional near space.

Several models on how 3-D space can be partitioned from a behavioural and neuropsychological point of view have been proposed. One of the most comprehensive is the model put forward by Previc (1998) who described how peripersonal (near) and extrapersonal (far) space may be associated with specific sensory-perceptual and motor processes. The author also suggested that each of these space sectors are characterized by a predominant system of coordinates to decode the spatial location of the surrounding objects in relation to the observer (egocentric) or to the relative position between the objects themselves (allocentric).

Peripersonal or near space is the space where the operations of reaching, grasping and objects manipulation take place. The sensory inputs prevalently used within near space are visual, somatosensory-proprioceptive and vestibular. The type of visual information that dominates peripersonal space subserves global form analysis, depth computation and perception of motion which is conveyed by the magnocellular pathway of the dorsal high visual stream. It has been demonstrated that these perceptual mechanisms are indeed biased towards the lower visual field (Christman, 1993; Raymond, 1994; Regan et al., 1986; Rubin et al., 1996; Yo and Wilson, 1992). In contrast, there is little need for local colour and fine shape analysis within peripersonal space as the behaviourally relevant objects brought into near space have already been recognised (Previc, 1990). In addition, for the operations of reaching and grasping typically carried out within peripersonal space, information about the colour of the to-be-grasped object for instance is less relevant than its global form and orientation.

Somatosensory and proprioceptive inputs regarding the position of the eyes, arms, hands and other musculoskeletal components in space are also fundamental sensory information needed in near space. For instance, animals deprived of somatosensory and proprioceptive inputs can show deficient reaching performance even when vision information is available (Cohen, 1961). Similarly, vestibular signals on the position of the head in space are critically integrated with the smooth oculomotor operations (i.e. vergence, pursuit) that are more frequently carried out in peripersonal space (Previc, 1990; Magnusson et al., 1986; Steinman et al., 1990).

The major motor operations implemented in near space regard the control and coordination of hand and arm movements required during reaching and grasping together with the programming and execution of the oculomotor response which assists in such processes. Head movements are also important in the integration of manual control and gaze mechanisms as evident in the close coupling between head and hand movements during manual tasks (Smeets et al., 1996) and the higher pointing accuracy when the head is free to move compared to when it is not (Jeannerod and Biguer, 1987; Marteniuk, 1978).

The coordinate system prevalently used within peripersonal space is body-centred or egocentric (Gaffron, 1958; Marteniuk, 1978; Previc, 1990). To be accurate, actions such as grasping must be finely tuned to the absolute, not relative, size of an object and to its location with respect to the observer (Goodale et al., 2005). Egocentric frames of reference appear, therefore, more functional for the behavioural goals associated to grasping and object manipulation which are mainly implemented within peripersonal space. This idea is reinforced by the multisensory nature of the egocentric system which is shaped through the integration of multiple sensory inputs (i.e. visual, tactile).

In contrast, the operations that are carried out especially in extrapersonal far space regard searching for and recognising objects or any relevant visual targets in the environment (Previc, 1998). Extrapersonal space is also the space where most of the visually mediated social interactions involving face perception take place (Previc, 1998). The complexity of stimulus perception and recognition processes that occur in far space requires also access to previous knowledge of the surroundings through visual memory mechanisms (Previc, 1998). In addition, distal space is also related to more specific episodic and topographical memory processes useful to help orientation and navigation in the extrapersonal visual environment (Gaffron, 1958; Barrash et al., 1996).

The predominant sensory modality in extrapersonal space is vision. The type of visual information used in far space is mostly provided by the parvocellular pathway of the ventral stream which subserves the mechanisms of colour processing, high-resolution contour analysis and feature integration. The particular emphasis on the visual system for distal space processing relies on the fact that other senses, such as the olfactory and auditory, do not posses sufficient spatial resolution to contribute effectively to the operations of object recognition (Perrot et al., 1990). Proprioceptive, vestibular and tactile information is also of little use for extrapersonal space operations.

The motor processes implemented in far space appear mainly restricted to saccadic eye movements (Previc, 1998). The shorter latency of saccades to upper-field compared to lower-field located targets and the greater likelihood of making an upward initial saccade during visual search represent important indicators of the predominance of saccadic oculomotor scanning towards extrapersonal space (Brandt, 1940; Chedru et al., 1973; Hall, 1985; Previc, 1996; Zelinsky, 1996). This upper field bias which characterises extrapersonal space has been demonstrated not only for visual objects search but also for visual objects memory, colour persistence, facial recognition, categorical encoding and perception of ambiguous shapes (Brandt, 1940; Previc and Blume, 1993; Previc, 1996; Cherry and Parks, 1989; Takala, 1951; Heider and Groner, 1997; Hines et al., 1987; Drain and Reuter-Lorenz, 1996; Niebauer and Christman, 1998). Previc suggested that, to avoid oculomotor and attentional imbalances, the upper-field bias observed for far space may serve to compensate the lower-field bias which characterises near space (Previc, 1998).

Although the operations carried out within far space involve visual search, local objects and scene recognition, Previc (1998) claimed that the major coordinate system used within extrapersonal space is not allocentric but prevalently egocentric, especially in relation to the retinal position of a visual stimulus with respect to the fovea (retinotopic). The author justified his claim given the key role played by foveation in distal space encoding (Previc, 1998).

In contrast, Goodale and Haffenden (2005) suggested that allocentric coding may be more functional compared to the body-centred coordinate system for the operations of fine object recognition which are carried out primarily in extrapersonal space. The identification of a particular item in the environment is indeed independent of its size, orientation and position with respect to the viewer and preserves instead the relations between an object's parts and its surrounding (Goodale et al., 2005). Taken together, it seems thus that extrapersonal space representation may rely on both egocentric and allocentric reference systems.

In the light of the specific operations carried out within near and far space, it has been suggested that the anatomical substrates supporting the representation of these two space sectors may broadly be represented by the dorsal and ventral high visual pathways (Previc, 1990) (see also Figure 2.1). According to Previc (1990), the dorsal-ventral dichotomy for near and far space coding is consistent with the specialization of the dorsal stream for manual visuomotor coordination since these operations are more typically performed within peripersonal space. Conversely, the specialization of the ventral stream for colour processing, complex feature integration and object recognition can be associated to the greater importance of these processes in distal space as these types of fine local analysis have little relevance during reaching operations. While this functional specialisation is by no means absolute because motion, form perception and objects recognition can be, after all, carried out in both near and far space, specific perceptual and motor operations may be, however, of greater relevance within one sector of space compared to the other. In addition, the dorsal and the ventral pathways differ more in their processing strategies which are more functional for different regions of the visual space than in the particular types of information they deal with (Previc, 1990).

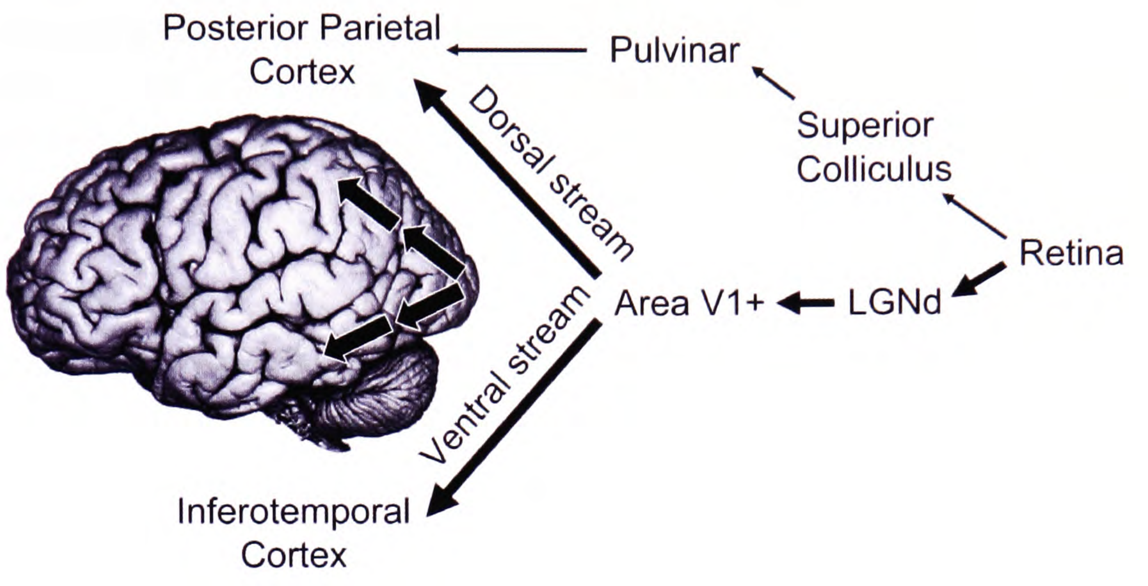


Figure 2.1 The major routes of visual input into the dorsal and ventral streams from Goodale, (2008).

Previc's predictions on the dorsal and ventral stream dichotomy for proximal and distal space coding and Rizzolatti et al.'s (1983a) neurophysiological findings in primates, led some authors to investigate the possibility that distinct neuronal networks may be responsible for near and far space attention also in the human brain.

To date, only two neuroimaging studies have investigated a potential differentiation of the cortical areas relevant for coding near and far space in humans. Both studies were carried out by Weiss et al. (2000; 2003) using line bisection paradigms with healthy participants. For the comparison of near versus far space, the visual stimuli were displayed either on a monitor screen within or beyond reaching distance. Both investigations revealed that, overall, line bisection performance in peripersonal space elicited neural activity in the left dorsal occipito-parietal cortex and premotor cortex while far space attention was associated with the ventral occipital cortex bilaterally and the right medial temporal regions. A transcranical magnetic stimulation (TMS) study by Bjoertomt et al. (2002) provided further evidence for a functional segregation of visuospatial processing between near and far space. In this experiment, healthy subjects performed a forced-choice paradigm where they had to indicate whether the left or right part of pre-transected lines appeared longer. Stimulation of the right posterior parietal cortex or the ventral occipital lobe selectively induced a significant rightward shift of the perceived midpoint for lines presented in near versus far space respectively. Taken together, the pattern of results provided by both Weiss et al. (2000; 2003) and Bjoertomt et al. 's (2002) studies provided some preliminary evidence for the dorsal-ventral stream dichotomy proposed by Previc (1990) for near and far space representations which appear to be neuronally segregated also in the human brain.

To date, only a small number of clinical studies investigated the presence of dissociations between neglect for near and far space. In broad terms, the patients who showed neglect deficits only in far space presented damage in the right occipito-temporal regions and left thalamus (Vuilleumier et al., 1999; Shelton et al., 1990; Barrett et al., 2000) while those clinical cases with neglect for near space only, had fairly large lesions involving right occipital, parietal and temporal areas (Halligan and Marshall, 1991a; Mennemeier et al., 1992; Berti and Frassinetti, 2000). These anatomic patterns appear rather ambiguous as there seems to be some brain regions equally involved in both types of neglect. Unfortunately, the authors did not provide an accurate anatomic analysis which would have allowed a distinction to be made on whether specific areas within a distinct brain region may cause neglect for near or far space when damaged. As such, it remains still difficult to derive specific anatomo-clinical associations between regional brain damage and symptoms restricted to near and far space. The prediction of a specific role played by the dorsal and ventral visual streams for near and far space representation appears, thus, not fully supported by the above clinical findings.

In addition, there are inconsistencies between the anatomical patterns observed in the clinical cases and the results of the neuroimaging studies which have investigated near and far space attention. In particular, although the PET studies of Weiss et al (2000; 2003) demonstrated that performing a line bisection task elicits neuronal activity in different areas depending on space distance, the activation patterns observed were bilateral or left lateralised which is in contrast with the predominant involvement of the right hemisphere in the manifestation of neglect symptoms.

Taken together, the above evidence suggests that the frequency of space related dissociations in neglect patients remains largely unknown and the clinical studies available to date have not provided a sufficiently accurate definitions of those brain structures which, when damaged, result in neglect restricted to near or far space. In this context, a more comprehensive integration between neuroimaging and neuropsychological findings still needs to be done in order to understand better the mechanisms and the neuronal substrates that when damaged cause neglect within and beyond reaching distance.

2.2 Peripersonal and extrapersonal neglect: lesion studies and methodological issues

The first case of dissociation between neglect for near but not for far space was documented in a single case study by Halligan and Marshall (1991a). The patient, after a stroke in the territory of the right middle cerebral artery, showed marked rightward errors on a line bisection task when carried out in near space. The bisection error was, however, completely absent or attenuated when the task was performed in far space (Halligan and Marshall, 1991a). The same dissociation was reported one year later by Mennemeier et al. (1992) who described a patient with occipital-parietal and posterior temporal damage whose neglect was worse in near compared to far space. The peripersonal deficit of this patient was multimodal as her neglect was present during both a visual and tactile line bisection task. Berti and Frassinetti (2000) also reported the case of a patient whose neglect was more pronounced in near compared to far space based on his performance on a line bisection task.

To date, three single cases of neglect restricted to far space only have been described. The patient of Vuilleumier et al. (1999) sustained damage in the right occipito-temporal cortex. She was assessed on several tasks both in peripersonal and extrapersonal space (cancellation, line bisection, circle counting, word reading and square completion) and in all tasks, a marked left neglect for far but not for near space was observed (Vuilleumier et al., 1999). In addition, Barrett et al. (2000) reported the case of a patient with a left anterior thalamic infarction who showed a contralesional bisection error for far space but not for near space on a line bisection task. In the same vein, Shelton et al. (1990) described a patient with bilateral brain damage to occipito-temporal regions whose rightward line bisection errors were larger in far compared to near space.

Space related dissociations in patients with neglect have also been investigated in some group studies. Cowey et al. (1994), for example, showed a significantly bigger rightward misplacement on a line bisection task in far space compared to near space in five patients with neglect. The same type of task was used by these authors in a subsequent study in which they replicated their earlier results in a larger group of neglect patients (Cowey et al., 1999). More recently, Neppi-Modona et al., (2007) explored the frequency of space related deficits in near and far space also with a line bisection task in 28 right brain damaged patients. No effect of distance was observed, neither for the patients with neglect, classified with a preliminary screening procedure, nor for those with no sign of the syndrome. Within the patient group, however, some individual cases of neglect restricted to either space sectors were observed. This result in particular stresses the necessity of studying near and far space dissociations with both a group and a single-case study approach.

Interestingly, one dominant pattern that emerges from the above clinical studies is that the majority of cases where assessed with a line bisection paradigm to investigate the presence of neglect restricted to specific space sectors. Although line bisection represents an important diagnostic tool it is by no means sufficient to explore the symptomatic spectrum of neglect as some patients may show the disorder, for instance, only in visual exploration tasks. This behavioural pattern suggests that line bisection and cancellation tasks involve distinct visuospatial operations: the former requires the subject to focus attention on the horizontal extent of one single specific object (the line), while the latter entails the subject to scan randomly structured multiple object arrays (i.e. digits, letters or symbols). It has not only been shown that neglect-related performances in these tasks correlate poorly but also that both paradigms engage different brain structures (Marshall et al., 1992c; Feber and Karnath, 2001; Binder et al., 1992; McGlinchey-Berroth et al., 1996; Rorden et al., 2006). Tasks like line bisection or perceptual size judgment seem to involve mainly posterior brain regions (occipito-parietal), while visual exploration abilities appear more associated to the contribution of anterior areas (temporal, insular, frontal) (Binder et al., 1992; Rorden, et al., 2006).
Together with the single case study of Vuilleumier et al. (1999), Butler et al. (2004) initiated a first exploration on the incidence of visual search impairments across different spatial distances in patients with neglect. The authors carried out an experiment where right hemisphere damaged patients, with and without neglect, were

asked to perform a cancellation task in near and far space. Both groups demonstrated poorer performance in far compared to near space but only the neglect patients showed a progressive decrease of target detection from the right toward the left visual field (Butler et al., 2004).

As Butler at al. (2004) did not include a line bisection paradigm in their study, it was not possible to verify whether the different cognitive mechanisms engaged by the two neglect tasks are more or less vulnerable to space distance in a direct head to head comparison between the two tests.

One attempt in this direction was made by Keller et al. (2005) who investigated both line bisection and visual exploration performance in near and far space in a group of right brain damaged patients. Their results for line bisection demonstrated that neglect severity increased significantly with distance. However, no significant dissociation between peripersonal and extrapersonal space was observed in the cancellation task. The results of Keller et al.'s (2005) study would imply that distance can alter line length estimation and focal attention for one single object but not visual exploration abilities in detecting multiple targets in a display. Further investigations are needed to verify this hypothesis which is based, after all, only on one study. Most importantly, as Keller et al.'s patients used a stick to carry out the tasks in far space, it is possible that the lack of a distance effect in the cancellation task may have been due to a dynamic remapping of far space into the agent's near space as described for other cases of spatial neglect (Berti and Frassinetti, 2000).

Taken together, as the vast majority of the clinical studies that investigated distance related deficits in neglect patients used line bisection paradigms, it remains to be clarified whether visuo-spatial processes associated with cancellation tasks are equally vulnerable to space distance effects compared to line length estimation. In other words, it is still unclear whether neglect restricted to near or far space represents a task independent phenomenon or whether it is directly related to the specific demands of the task.

The issue related to the type of task is not the only one which requires further investigations in the field of distance related deficits in neglect. Another important aspect to consider is the distinction between the so called "motor" tasks that require a directional motor response (i.e. manual line bisection tasks) and "perceptual" tasks that require a perceptual judgment of the stimuli or a verbal response (i.e. Landmark-V task). Bearing in mind that there is not such a thing as a purely perceptual or motor task in psychology (Milner and Goodale, 2008), the fundamental difference between motor and perceptual tasks here is related to the presence or absence of a *directional* manual response to perform the task chosen (i.e. bisection or cancellation) to assess space related deficits in neglect.

One of the first group studies which has investigated the presence of neglect for near and far space was carried out by Pizzamiglio et al. (1989). The authors used the Wundt-Jastrow area illusion test, a perceptual judgment task which, in contrast to manual line bisection, did not require a directional movement towards the stimulus. Instead their right hemisphere damaged patients were asked to provide a verbal response on which of two fans of the same shape was longer. In this experiment, the performance in near and far space was highly positively correlated, leaving the authors unable to demonstrate the presence of dissociable distance related deficits. As the clinical studies that followed appeared more successful in demonstrating distance related dissociations by using manual tasks (i.e. line bisection), the suggestion that near and far space representation may rely on output-related mechanisms was made (Halligan and Marshal, 1991a; Pizzamiglio et al., 1989; Mennemeier et al., 1992; Shelton et al., 1990; Vuilleumier et al., 1998; Cowey et al., 1994; 1999). In other words, the representation of peripersonal and extrapersonal space may be dependent on the preparation and execution of specific motor acts implemented upon those space sectors which in turn could influence the perception (and attention) of sensory stimuli (Rizzolatti, 1983b; Rizzolatti and Camanda, 1987).

However, more recently, behavioural findings suggest that distance based deficits in neglect patients may occur even in absence of a directional manual response (Pitzalis et al. 2001; Butler et al., 2004). Pizalis et al. (2001), for example, directly compared the performance of neglect patients with both a manual and verbal line bisection paradigm in near and far space. The group analysis revealed no significant effect of distance but by examining individual performances in each version of the task (motor vs verbal), some patients showed more severe neglect in far compared to near space. Although less frequent, the opposite behavioural pattern was also observed. Accordingly, the authors concluded that their results undermine the hypothesis that the involvement of a motor component in the response plays a critical role in the manifestation of distance related bisection errors in neglect (Pizalis et al. (2001). Also in the verbal visual search task used in the group study of Butler et al. (2004) no directional manual response was required. The target detection gradient shown by their neglect patients was significantly worse in far than in near space.

In contrast to previous findings, these latter results suggest that the presence of a directional motor response when performing a task may not be as crucial to detect distance related behavioural dissociations as previously thought. This idea is also supported by the evidence of a PET study carried out by Weiss et al. (2003) who compared the performance of healthy participants on a line bisection task in near and far space. In one condition (manual bisection) subjects were asked to point at the centre of the line with a laser pointer, whereas in another (bisection judgment) they had to press specific response keys indicating whether the presented line was correctly bisected or not. While the authors found different activation patterns for near and far space attention (see section 2.1), neuronal activity was not modulated by the presence/absence of a directional motor response.

Findings on the effects of tool use in the representation of peripersonal and extrapersonal space have increased the debate on whether to consider distance related dissociations in neglect patients as independent of the motor demand of the task. Berti and Frassinetti (2000), for example, demonstrated how the boundaries between near and far space can be modulated by the use of a tool. Their patient showed neglect in near space when he had to reach or point to the centre of a horizontal line. When he performed the same task in far space with a laser pen, his performance was less severe than that observed in near space. If he had to use a stick in far space his neglect became, however, as severe as in near space. Based on this evidence, the authors suggested that in their patient neglect became also evident beyond arm's reach distance because, through the use of a tool, far space had been remapped as near space. Thus, the stick, by acting as an extension of the subject's arm, expanded the boundaries of peripersonal space to include all the space between the patient's body and the stimulus (Berti and Frassinetti, 2000). Berti and Frassinetti's findings are complemented by those of Ackroyd et al. (2002) who reported the case of a patient who performed a visual target detection task with a pencil and a ruler in near and far space. The patient's more severe neglect in far space compared to near space was alleviated when he had to point to visual targets with a ruler but not with a shorter instrument (a pencil). In this case the ruler may have extended the more preserved representation of near space into far space resulting in a better detection performance. These findings support the idea that acting in a particular spatial domain can affect the activation of the neuronal representation of different space sectors in the brain. In other words, the activation of near and far space representations, and consequently, the awareness for stimuli presented in these specific sectors of space, may not only depend on perceptual computations (i.e. depth) but also on the type of action performed within proximal and distal space (Berti et al., 2001).

Overall, the inconsistent findings observed for visuospatial tasks involving a verbal or directional motor response in near and far space is partially due to the relative lack of studies that considered removing a direct contact between the individual and the stimuli compared to those which have investigated space related disorders with manual tasks. Most importantly, except for the study of Pitzalis et al (2001) there are no investigations that have directly compared, along different space distances, the performance of the same group of patients for the same test with and without a directional motor response. This approach should provide a better understanding of the specific role played by output-related processes in encoding different space sectors. In this way, it might be possible to verify whether the type of response is crucial in modulating the manifestation of neglect deficits restricted to near or far space.

2.3 Aims of the study

Taken together, the above clinical findings show that the role played by the cognitive mechanisms engaged by different tasks (i.e. bisection vs. cancellation) and the type of response (perceptual vs. motor) has not been sufficiently investigated to draw any firm conclusions regarding their specific contribution to distance related neglect phenomena. Consequently the first aim of the present study was to investigate whether behavioural dissociations between neglect for near and far space occur independently of task demands or if they can be modulated by the type of cognitive mechanisms elicited by the task used. In addition, the potential effect of the presence/absence of a directional motor response in the manifestation of neglect deficits in the same task within and beyond reaching distance was evaluated.

At the anatomical level, neurophysiological, neuroimaging and TMS studies support an association between the dorsal and ventral visual streams with near and far space representation respectively. This hypothesis, however, does not fully reconcile with the lesion patterns found in the clinical cases of neglect restricted to either near or far space described to date. As second aim, therefore, the present study focussed on a direct evaluation of those brain areas damaged in those neglect patients with space related deficits to verify whether damage in the territories of the dorsal and ventral streams is crucial for the occurrence of near and far space neglect.

In the first experimental chapter (chapter 3), two newly devised tasks were used to assess the presence of neglect deficits in near and far space in right hemisphere damaged patients. Prior to the experimental study with neurological patients, a preliminary investigation was carried out with young healthy participants and three right brain damaged patients to set the appropriate level of task difficulty and suitability for subsequent use. The results of this initial pilot work provided useful suggestions on how to simplify response requirements for the patients. In addition, some of the behavioural indexes of performance were also refined to allow a more accurate evaluation of the patients' deficits. In a subsequent experiment, the modified versions of the tasks were trialed in a large group of neurologically intact subjects to define the "boundaries" of normal performance for both tasks in near and far space. This normative sample was used to select age and education matched control subjects whose performance was compared against that of a case series of right hemisphere damaged patients. The behavioural deficits shown by these patients were also discussed in the light of their specific brain damage.

The second experimental chapter (chapter 4) focussed on exploring the incidence of neglect deficits in near and far space in a large unselected group of right brain damaged individuals. The patients were evaluated based specifically on their performance in cancellation and line bisection tasks in both space sectors. Within this large group, the cases showing a clear dissociation between near and far space neglect were considered for a preliminary anatomical investigation to clarify the neuronal underpinnings of space related deficits in neglect.

Finally, in the third experimental chapter (chapter 5), a group of unselected right hemisphere damaged patients were assessed in near and far space again with cancellation and line bisection tasks. In addition, they also underwent a structural 3D MRI scanning. By using a VBM (Voxel-based morphometry) correlational approach it was possible to investigate which brain areas, when damaged, provided the greater contribution to impaired performance in each space sector separately for each individual task. In this way, the anatomical substrates of distance related deficits in neglect were explored. Moreover, the specific brain structures that were uniquely involved in visual search and line bisection abilities within near and far space were investigated. Together, the anatomical findings in the single case series and in the group studies provided some clarification on whether the dorsal and ventral visual pathways have a discrete association with near and far space representation at a neuronal level.

The last chapter (chapter 6) includes a general discussion in which the methodological and anatomical issues addressed in the individual chapters have been brought together in the attempt to reconcile the findings of this dissertation with that of previous studies. In addition, the specific contributions of the present research to advance the body of knowledge already available in the field of space related deficits in neglect has been discussed.

CHAPTER 3

Visuo-spatial attention in near and far space: tasks' piloting and a case series study

3.1 Introduction

One interesting pattern that emerges from the studies on space related dissociations in neglect patients refers to the prevalent tendency to explore these deficits with a line bisection task. While this versatile test has been widely used for clinical and experimental purposes to assess spatial neglect, it cannot provide on its own a complete picture of the patient's visuospatial impairment. Other classical diagnostic tools to evaluate neglect are cancellation tasks which engage completely different cognitive mechanisms compared to line bisection. Both tests provide distinct information about the patients' visuospatial deficits and it is not uncommon to observe behavioural dissociations between the two tasks (Halligan and Marshall, 1992c; Marshall and Halligan, 1995; Ferro and Kertesz, 1984; Ferber and Karnath, 2001).

To date, only two studies combined line bisection and cancellation tasks for the assessment of neglect deficits in near and far space Keller et al. (2005) demonstrated a distance effect in neglect patients only with line bisection while Vuilleumier et al.'s patient (1999) showed neglect restricted to far space in both tasks. This evidence is not sufficient, however, to clarify the role played by the type of task in the manifestation of neglect restricted to specific sectors of space.
In addition, the presence/absence of a directional motor response to perform the task represents another factor which seems to play a role in the manifestations of space related dissociations in neglect patients. Most of the clinical studies that used a motor task appeared successful in detecting neglect deficits restricted to either near or far

space (Halligan and Marshal, 1991a; Mennemeier et al., 1992; Shelton et al., 1990; Vuilleumier et al., 1998; Cowey, 1994; 1999). However, more recent studies, seem to support the possibility that distance related neglect may also occur without a direct motor interaction between the agent and the stimulus (Pitzalis et al., 2001; Butler et al., 2004). The latter evidence is, nevertheless, too limited to clarify whether the presence of a directional manual response represents a crucial factor in detecting neglect deficits restricted to near or far space. Therefore, the issue on whether radial (near far) asymmetries in neglect patients are independent of the presence/absence of a ballistic motor response still needs to be verified.

The first experiment of the present study was designed to examine the effectiveness and the demands of two newly devised experimental tasks engaging the same visuospatial abilities as cancellation and line bisection tasks. These tasks were used to investigate distance related deficits in neglect patients in near and far space. The first experimental paradigm represents a modified and computerised version of a visual exploration task usually used in the clinical setting named the Balloon test (Edgworth et al., 1998). The clinical version of the test (Balloon-test version B) requires crossing out 10 circle targets distributed among 90 'balloon' distractors (circles of the same diameter with an adjoining vertical line) on a spreadsheet within three minutes. The computerised version of this task designed for the present study requires instead the detection of one single target (the balloon without the string) amongst multiple distractors (balloons) with no time limit. The second task, named the Landmark task, is a perceptual line bisection paradigm which was designed and adapted from Milner et al. (1992). The task involves focussing attention to a single pre-bisected horizontal line and comparing the relative length of the two line segments.

A preliminary pilot investigation (study one) was carried out to evaluate any potential flaws of the new paradigms which would eventually be used with neurological patients. For this purpose, in the first instance, a sample of undergraduate students took part in experiment one to evaluate firstly how neurologically healthy subjects might cope with the demands of the tasks and secondly the appropriate level of difficulty. For this first pilot study, also three right brain damaged patients without neglect carried out the tasks.

Their performance provided useful suggestions on the modifications which needed to be implemented on the paradigms in order to make them more suitable for patients' assessment. In addition, the possibility that a deficient performance on these tasks may be due to factors related to brain damage in general but not to the presence of neglect could be ruled out.

In study two, a larger group of healthy participants performed the modified versions of the two tasks to collect baseline data which could be used to compare patients' performance on. For both experiments, performances of healthy subject in near and far viewing distance were expected to be consistent.

Finally, three neglect patients were assessed with these new versions of the Balloon and Landmark task to contrast their performance in near and far space with and without a directional motor response (i.e. perceptual vs. motor condition). The perceptual and motor conditions were adopted to verify whether the presence or absence of a directional motor response represented a critical factor in detecting behavioural dissociations between near and far space in neglect.

3.2 Study one: Pilot study of the experimental tasks in healthy participants and right brain damaged patients without neglect

3.2.1 Experiment one

3.2.1.1 Materials and Methods

3.2.1.1.1 Subjects

3.2.1.1.1.1 Healthy participants

Twenty-two (12 female and 10 male) right-handed undergraduate students (Mean age = 20 years, SD = 3 years) with normal or corrected to normal vision took part in the experiment. Subjects were all naive regarding the purpose of the study and all gave written consent to participate. Before the experiment, they filled in a questionnaire regarding their general health condition and medical history. None of them suffered from any psychiatric or neurological disorder or was taking any kind of medication at the time of testing.

3.2.1.1.1.2 Patients

DG is a 60 years old male patient (education 13 years) with subcortical right brain damage of the corona radiata. After the stroke in 1998, he showed abnormalities of mental processing, executive functions and emotional tone. He suffered some motor impairments similar to those observed in patients with cerebellar degeneration but no sign of cognitive decline was reported (MMSE 28/30). The patient showed not sign of neglect which was assessed with a battery of standard clinical tests (line bisection, star cancellation, Bells test, drawing form memory and scene copying; see section 3.4.1.2. for the full description of the tasks).

BC is a 55 years old male patient (education 8 years) who sustained right parieto-fronto-temporal damage following an ischemic event occurred in 2006. The patient showed hemiplegia and hemianestesia of the left hemisoma but no sign of hemispatial neglect was found at the time of testing. The assessment for visual neglect included the same tests used for patient DG. His MMSE performance was within the normal range (29/30).

MS is a 51 years old female (education 10 years) who had right hemisphere infarct in the middle cerebral artery territory in 2001. At the time of testing the patient was alert and oriented in space and time but very fatigable with frequent fluctuations of her emotional tone. She showed no sign of cognitive decline (MMSE 28/30). Also MS's performance on the neglect standard battery did not reveal any sign of impairment.

3.2.1.1.2 Experimental paradigm:

The Balloon task

For the visual search task, called the Balloon task, 36 white stimuli (2° x 1° of visual angle) were presented against a black background (Figure 3.1). The array consisted of one single target (the balloon without the string) presented amongst 35 distractors (balloons). In each trial, the target together with the distractors appeared randomly at one of the 36 possible positions of the display in a six by six matrix. Eighteen stimuli were thus presented within each hemi-field (left and right). At the beginning of each trial, four white dots (0.5° x 0.5°) located at the corners of an imaginary square (4° x 4°) converged over 400 ms into a single dot at the centre of the display. This procedure was used to enhance central fixation. The stimulus array was presented after 500 ms and remained on screen until response. The inter-trial interval was 2000 ms. For each spatial condition (near and far), 45 trials were delivered overall, including nine catch trials in which no target was present. Subjects were instructed to detect the target and respond as accurately and as quickly as possible with their right hand by pressing one of three response keys on a computer keyboard. For targets presented in the left/right hemi-field they had to press the number "1/2" key respectively and the "0" key for a target absent response. Total number of correct response and response times were recorded for further analysis.

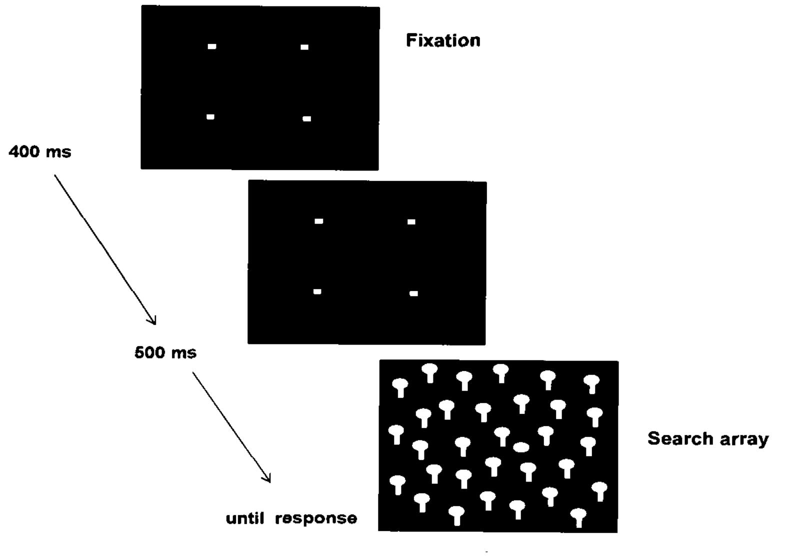


Figure 3.1 Fixation presentation for 400 ms where four dots converge to a single central dot which is followed by the search array after 500 ms.

3.2.1.1.3 Procedure

Subjects performed the Balloon task in near and far space. In both space conditions, the stimuli were presented at eye level with the centre of the display aligned with the subject's sagittal plane. The paradigm was designed and run using E-Prime software with a Philips laptop connected to a Toshiba projector located behind each participant for the presentation of the stimuli. The distances between the subject's head and the display were 57 cm for the near space condition and 114 cm for the far space condition. The visual angle of the display was kept constant (60.31° x 40.21°) across both spatial conditions. Participants carried out the tasks in complete darkness in order to minimize the influence of any visual cues in the environment. Space conditions were counterbalanced between subjects who carried out 10 practice trials before the experiment.

3.2.1.2 Results

In this task the data of two subjects were excluded from the analysis as their average accuracy score was two standard deviations below the group average. The group average for the response times was calculated as the mean of each subject's median response time and the number of correct target detections transformed into mean percentage values. Accuracy and response times were analysed separately.

3.2.1.2.1 Healthy participants

A 2x2 repeated measures ANOVA with distance (near/far) and target field (left/right) as within-subject factors was carried out. For accuracy, the main effect of distance was significant [$F(1, 19)= 5.24, p < .05$] indicating that overall subjects were slightly more accurate in far space compared to near space (Mean near = 90.1%, SD = 1.13; Mean far = 92.67%, SD = 1.37). The main effect of target field was not significant [$F(1,19) = .075, p=.79$], nor was the interaction between target field and distance [$F(1,19) = .021, p =. 886$]. The latter result indicates that there was no distance related visual field advantage for target detection (See also Figure 3.2).

The same analysis for the response times yielded neither a significant main effect for distance [$F(1, 19) = 1.36, p = .25$] nor for target field [$F(1,19) = .035, p = .853$]. There was no significant distance x target field interaction [$F(1,19) = .423, p = .523$]. Thus as shown in Figure 3.3, subjects were equally fast in detecting targets irrespective of spatial distance (Mean near = 1400 ms, SD = 71.14; Mean far = 1459 ms, SD = 63.43) and target field (Mean left = 1421 ms, SD = 85.77; Mean right = 1437 ms, SD = 65.05).

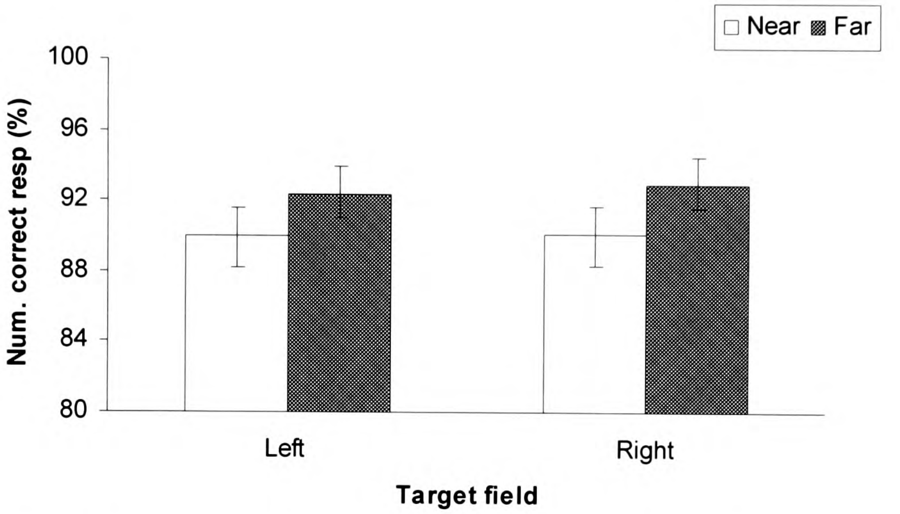


Figure 3.2 Mean visual search accuracy and SE as a function of distance (Near, Far) and target field (Left, Right) of the healthy participants.

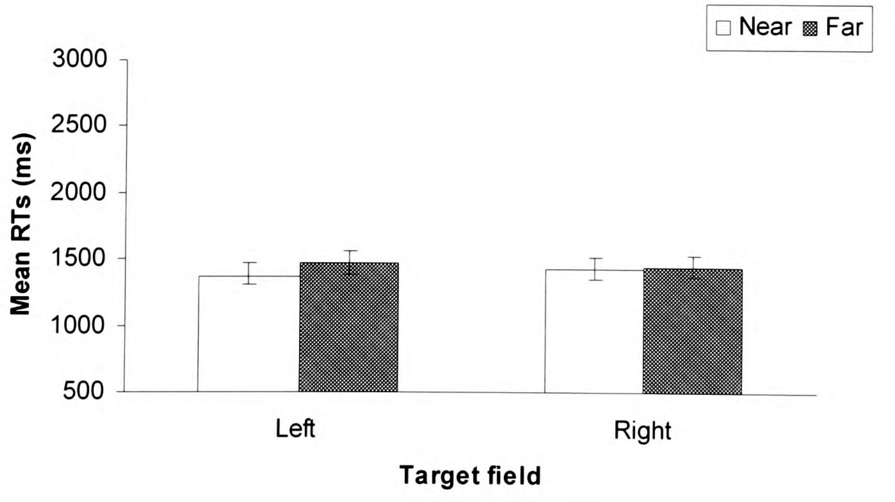


Figure 3.3 Mean response times and SE as a function of distance (Near, Far) and target field (Left, Right) of the healthy participants.

3.2.1.2.2 Patients

As illustrated in Figure 3.4, the patients showed an overall average accuracy of 88% correctly detected targets (SD = 5.43) in near and of 86% (SD = 7.40) in far space. In both spatial conditions they were equally accurate in both visual fields. Table 3.1 shows the search accuracy level reached by each patient.

Table 3.1 Individual accuracy (%) scores of each patient across visual field (Left, Right) and spatial distance (Near, Far) in the Balloon task.

Patient	Near		Far	
	Left	Right	Left	Right
DG	94	89	83	94
BC	83	94	78	89
MS	83	83	94	78
Mean (SD)	86.67 (6.35)	88.67 (5.51)	85.00 (8.19)	87.00 (8.19)

The patients were overall slightly faster in detecting targets in near (Mean = 7.44 sec, SD = 3.24) than in far space (Mean = 8.93 sec, SD = 2.17). In both spatial conditions they were faster in the left compared to the right visual field (See Table 3.2 for individual response times). These results are shown in Figure 3.5.

Table 3.2 Individual response times (sec.) for each patient across visual field (Left, Right) and spatial distance (Near, Far) in the Balloon task.

Patient	Near		Far	
	Left	Right	Left	Right
DG	9.09	6.58	6.19	11.53
BC	7.76	12.76	6.60	9.48
MS	4.10	4.36	8.29	6.10
Mean (SD)	6.69 (2.58)	7.90 (4.35)	7.03 (1.11)	9.04 (2.74)

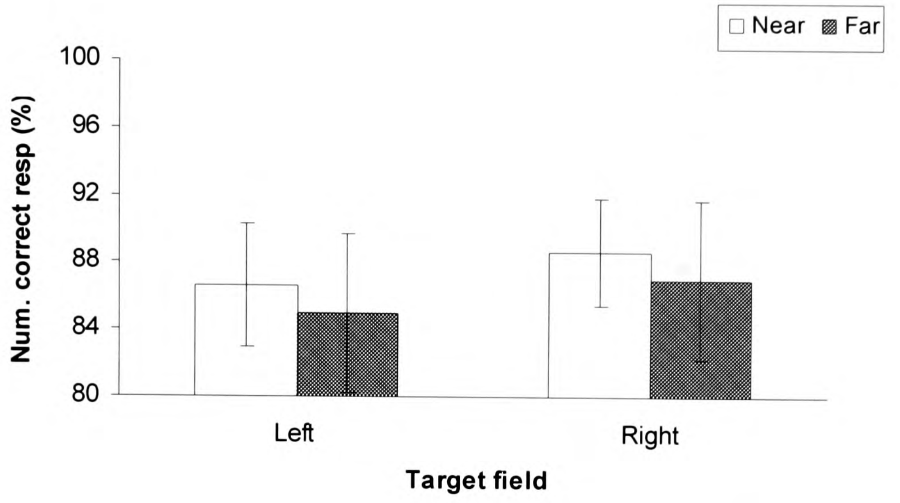


Figure 3.4 Mean visual search accuracy and SE as a function of distance (Near, Far) and target field (Left, Right) for the three right brain damaged patients.

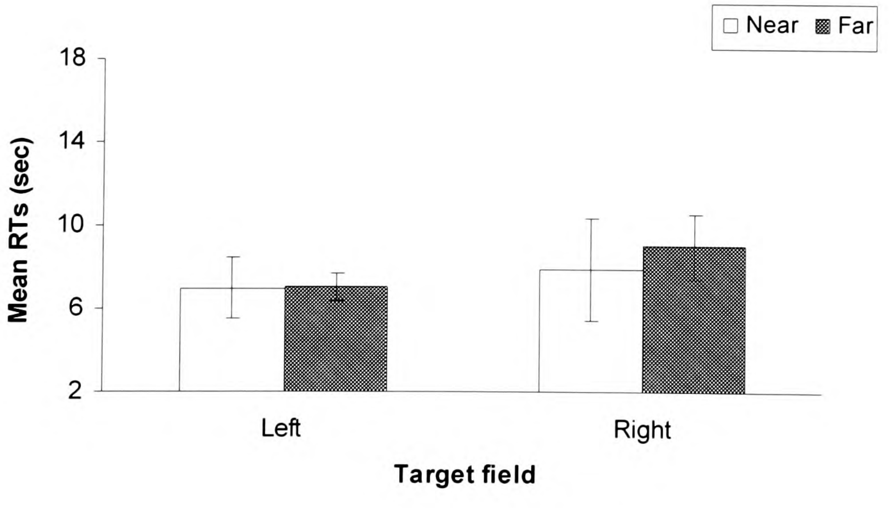


Figure 3.5 Mean response times and SE as a function of distance (Near, Far) and target field (Left, Right) for the three right brain damaged patients.

3.2.2 Experiment two

3.2.2.1 Experimental paradigm

The Landmark task

The Landmark task was adapted from Milner et al. (1992). During this task subjects were presented with white horizontal lines (20° x 1° of visual angle) against a black background. All lines were pre-bisected with the bisection mark placed at the objective centre of the line or 1 to 5 mm (in 1mm steps) to the left or right of the true centre. Subjects were asked to judge the relative length of each of the two line segments. In one session, they were asked to judge which end of the line was shorter while in another session they had to decide which end was longer. In addition, each session (shorter or longer) was subdivided into three different blocks corresponding to three specific horizontal sectors within the display: left, centre and right. For each of these three sectors, twenty trials were presented: ten centrally bisected lines, five with a leftward misplacement from the objective centre (from 1 to 5 mm) and five with a rightward misplacement. Thus for each "shorter" or "longer" session, 60 trials were presented overall. Variation of the horizontal location of the stimuli was introduced to verify whether the classical increase of pseudoneglect magnitude for left presented lines (McCourt and Jewell, 1999) could be replicated across space distances. The task was carried out in near and in far space resulting in a total of 120 trials for each distance condition. Spatial conditions (near and far), type of judgment (shorter and longer) and stimulus position in the display (left, centre, and right) were counterbalanced among subjects. Stimuli were presented one at a time and stayed on screen until subjects made their response. No central fixation point was presented between the trials and following each response, the next stimulus appeared after a one second delay. Subjects had to make a forced-choice judgement by pressing one of two different response keys on the number pad with their right hand. If they considered the left segment as shorter (or longer) than the right one, they had to press the number "1" key on the keyboard; if they thought that the right segment of the line was shorter (or longer), then they had to press the number "2" key. Subjects were instructed to respond as quickly and as accurately as possible.

The two different types of judgment ("shorter" or "longer") for the same stimuli in two separate sessions served to control for any response bias which can sometimes influence the performance in the Landmark task (Bisiach et al., 1998a). This phenomenon refers to the tendency of some subjects to make consistent left or right key presses irrespective of whether they perceive the left or right segment of the line to be longer. By judging centrally bisected lines, subjects' responses reflect a genuine perceptual judgment when they make an equal number of left and right key presses. For example, if subjects perceive the bisection mark to the left of the objective centre, they should indicate that the left side is shorter, or that the right side is longer in a consistent way in both sessions. On the other hand, if subjects show a tendency to make left key presses regardless of the type of judgment they are asked to make, this would reveal a left response bias. The same principle can be applied to neglect patients. According to Bisiach and colleagues (Bisiach, 1998), a patient with predominantly perceptual neglect (Input-Related Neglect, IRN) should tend to judge the left part of the line as shorter (or the right as the longer). In contrast, a patient with a rightward response bias (Output-Related Neglect, ORN), should be more inclined to choose the rightmost line portion, regardless of whether he/she is asked to indicate the longer or the shorter segment. IRN can be defined as a pathological shift of the *point of subjective equality* (PSE) (i.e., the position of the transection that would produce two subjectively equal segments) towards one side (Milner et al., 1992). ORN, instead, can be conceived as a trend to "ignore" the perceptual experience of the line making instead a "default" response towards one side (typically the ipsilesional one). In this case left neglect patients respond "right" not as a reflection of their visual experience, but because dominated by a rightward ORN.

3.2.2.2 Procedure

The experimental procedure adopted for experiment two was the same as for experiment one in terms of spatial distance (Near and Far), apparatus, visual angle and room setting (see section 3.2.1.1.3 of this chapter for details). Spatial conditions (Near and Far) were again counterbalanced among subjects who carried out 10 practice trials prior the experimental session.

3.2.2.3 Results

Two indexes were calculated for each participant: IRN (Input-Related Neglect) as a measure of the perceptual bias (PB) and the ORN (Output-Related Neglect) as a measure of the response bias (RB). The formula for each of these indexes is as follows:

$$\text{IRN index: } PB = (LS + RL)/2$$

$$\text{ORN index: } RB = (RS + RL)/2$$

PB represents the "perceptual bias", RB is the "response bias" and LS (left shorter), RL (right longer) and RS (right shorter) are the percentage of "left" responses in the shorter condition, of "right" responses in the longer condition and of "right" responses in the shorter condition respectively.

Three subjects were excluded from the analysis as their RB index was 2 standard deviations above the group average. Only the responses for the centrally bisected lines were analysed, as left and right bisected lines were used as fillers. An IRN index of >50% indicates a right perceptual bias while an IRN index of <50% implies a left perceptual bias or pseudoneglect. Accordingly, an IRN equal to 50 would indicate an unbiased perceptual judgment. The same principle can be applied to the ORN index: a high score is related to a right response bias and vice versa. Similarly, an ORN of 50 would imply the absence of a response bias.

3.2.2.3.1 Healthy participants

Two separate 2x3 repeated measures ANOVAs were carried out for response and perceptual bias respectively with distance (near, far) and stimulus position (left, centre and right) as the two within-subjects factors. Significant results were followed-up by dependent t-tests which were Bonferroni-corrected for multiple comparisons.

Response bias. There were no significant main effects [distance: $F(1,18) = 2.28$, $p > .05$], [stimulus position: $F(2,36) = .18$, $p > .05$]. There was a distance x stimulus position interaction which reached significance [$F(2, 36) = 3.35$, $p < .05$]. This interaction revealed a difference in responses bias in near and far viewing space which was greater for centrally presented lines: Indeed, in the near condition, there was a slight tendency for subjects to make more "right" key presses (Mean = 53.9, SD = 12.6) whereas in the far condition, this bias was reversed with subjects tending to make more "left" responses (Mean = 47.1, SD = 10.7). However, this difference did not reach statistical significance once Bonferroni correction [$p = .02$] was applied [$t(18) = 2.56$, $p > .02$]. Non significant were also the comparisons of mean response bias recorded for either the left [$t(18) = -1.00$, $p > .02$] or the right presented lines [$t(18) = 1.01$, $p > .02$] across near and far space. These results suggest that on the whole, subjects did not make "default" responses towards one particular side ("left" or "right"). These results are illustrated in Figure 3.6.

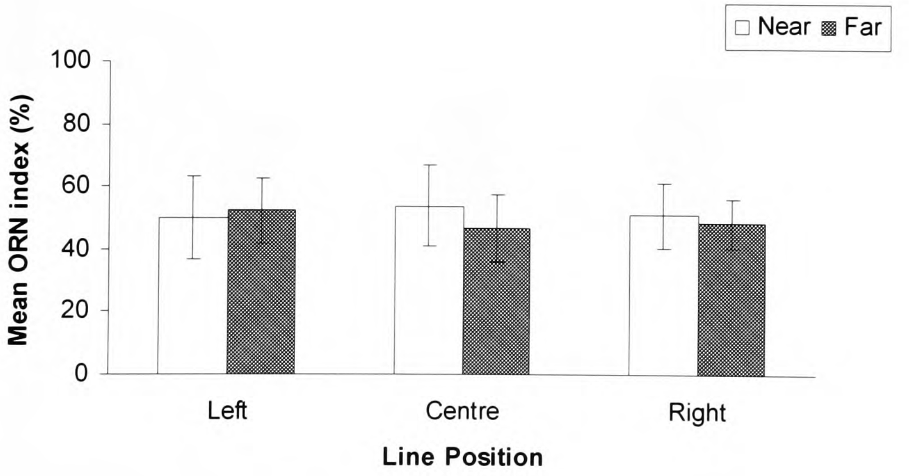


Figure 3.6 Response bias (ORN index) and SE as a function of distance (Near, Far) and stimulus position (Left, Centre, Right) for healthy participants.

Perceptual bias. There was only a significant main effect for stimulus position [$F(2,36) = 6.27$, $p < .005$] but not for distance [$F(1,18) = .51$, $p > .05$]. There was no significant interaction between distance and stimulus position [$F(2,36) = .97$, $p > .05$]. Overall, for lines in the left position, the left segment was perceived to be longer and the right segment shorter [Mean left = 38.22, SD = 3.09]. Interestingly, the magnitude of this leftward perceptual bias was reduced for lines in the central [Mean = 44.14, SD = 2.21] and right [Mean = 48.88, SD = 2.20] position. Post-hoc analyses [$p = .02$] revealed a significant difference in the amount of the leftward bias for left and right stimulus positions [$t(37) = -3.62$, $p = .001$], but not between centre and left position [$t(37) = -2.35$, $p = .024$] or centre and right positions [$t(37) = -2.14$, $p = .039$]. The results are illustrated in Figure 3.7.

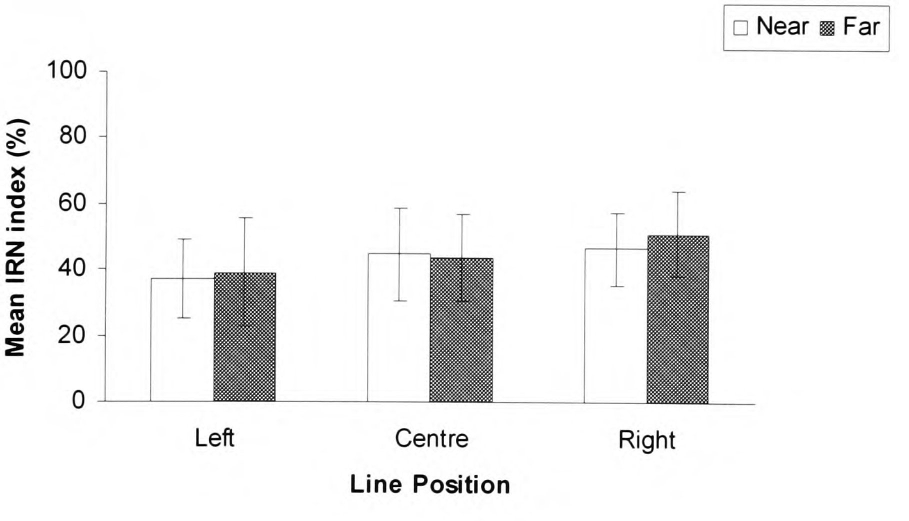


Figure 3.7 Perceptual bias (IRN index) and SE as a function of distance (Near, Far) and stimulus position (Left, Centre, Right) for healthy participants.

3.2.2.3.2 Patients

Response bias: In near space, patients showed a slight tendency to make right key presses regardless of the stimulus position. As shown in Figure 3.8, this tendency was again present in far space but only for centrally and right presented lines. In contrast, they tended to make left key presses for the lines presented in the left visual field. See table 3.3 for individual scores.

Table 3.3 Individual response bias scores for each patient across line position (Left, Centre, Right) and spatial distance (Near, Far).

Patient	Near			Far		
	Left line	Central line	Right line	Left line	Central line	Right line
DG	67	52	45	52	58	58
BC	45	57	55	42	50	65
MS	60	68	67	50	55	54
Mean (SD)	57.33 (11.24)	59.00 (8.19)	55.67(11.02)	48.00 (5.29)	54.33 (4.04)	59.00(5.57)

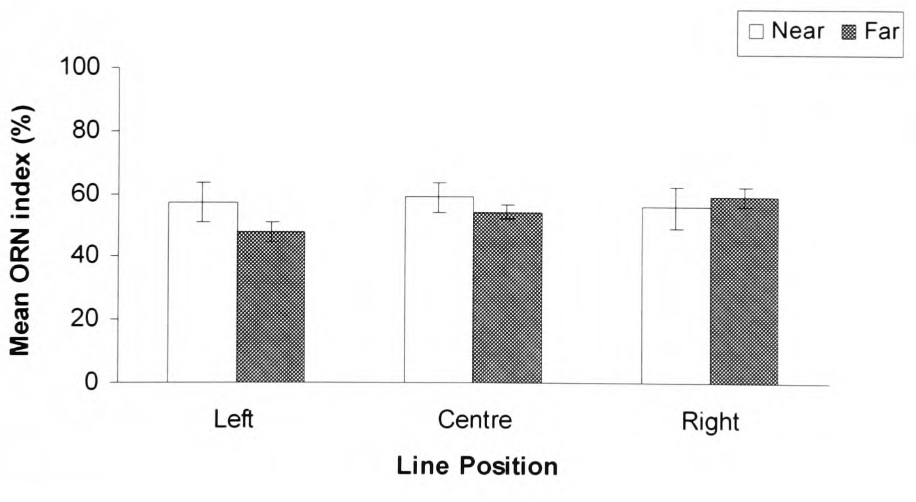


Figure 3.8 Response bias (ORN index) as a function of distance and stimulus position in the right hemisphere damaged patients.

Perceptual bias: In near space, the patients showed a leftward perceptual bias for the lines presented centrally and in the left visual field. A rightward perceptual bias was instead observed for the stimuli in the right visual field. The patients showed the same pattern in the far space condition. These results are shown in Figure 3.9 while individual scores are reported in Table 3.4.

Table 3.4 Individual Perceptual bias scores for each patient across line position (Left, Centre, Right) and spatial distance (Near, Far).

Patient	Near			Far		
	Left	Central	Right	Left	Central	Right
DG	42	52	65	48	52	58
BC	45	47	55	40	45	65
MS	35	45	52	50	48	68
Mean (SD)	40.67 (5.13)	48.00 (3.61)	57.33 (6.81)	46.00 (5.29)	48.33 (3.51)	63.67(5.13)

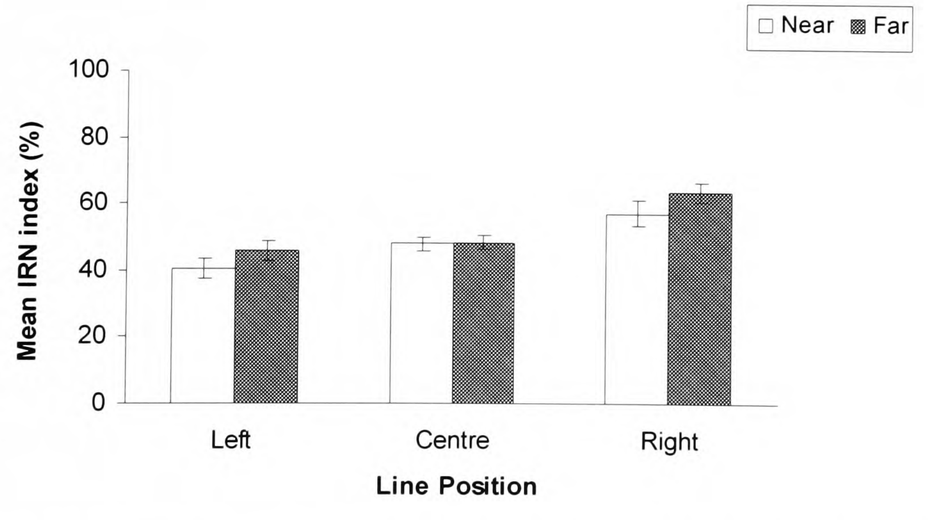


Figure 3.9 Perceptual bias (IRN index) as a function of distance (Near, Far) and stimulus position (Left, Centre, Right) in the right hemisphere damaged patients.

3.2.2.4 Discussion of study one

The results of this preliminary pilot investigation on healthy participants and right hemisphere damaged patients without neglect indicated that some minor modifications were needed in order to make the new paradigms more suitable for patients' assessment. The adjustments involved a simplification of the response recording and redefinition of some behavioural indexes of performance. Most importantly, the possibility that impaired performance in the new tasks may simply be due to brain damage per se was excluded.

In the Balloon task healthy subjects demonstrated to be equally accurate in both visual fields regardless of the space distance they performed the task. Overall, there was a significant advantage of target detection in far space compared to near space. This pattern could not be explained in terms of differences in the response times as the subjects were equally fast in both distance conditions. Although the age gap between the patients and the healthy participants did not allow for a direct statistical comparison, it was evident that the patient group's accuracy was lower but clearly well above chance level. In addition, the patients' accuracy was not modulated by spatial distance. The same pattern was found for the patients' response times: although clearly slower in detecting the target, there was no difference in response times between near and far space.

Taken together, the results suggest that although the patients found the search task harder, they were still performing within adequate accuracy given their neurological condition (88% near space, 86% far space). In addition, none of the three patients did show any lateralised or distance related deficit. This latter result, however, must be taken with caution given the small number of patients tested resulting in higher variability.

The evaluation of the performance of the healthy participants and that of the patients on the Balloon task led to some considerations regarding the task's suitability. The fact that normal participants did not show any difficulty in performing the Balloon task, suggested that the task parameters chosen (i.e. type of stimuli, number of trials) were effective for its purpose. In addition, although the level of accuracy reached by the patients was, as expected, below that of healthy participants, it was not too low to justify any adjustment on the level of search difficulty which was indeed considered suitable for assessing visual search abilities in neurological individuals. The only modification applied to this paradigm was a simplification of the response recording keys which appeared to be taxing for the patients while performing the task. They found indeed demanding to retain into memory several response keys linked to different types of response (i.e. "1" left target, "2" right target and "0" target absent). This difficulty could lead to an incorrect response recording which may enhance the likelihood of false negative or positive responses and increase decision times. All these factors could cause misinterpretations of the patients' performance.

Of the three studies (Vuilleumier et al., 1999; Keller et al., 2005; Butler et al. 2004) that have investigated the effect of distance on visual exploration abilities, only Butler et al. (2004) reported the performance of a group of ten neurologically healthy controls and of ten right brain damaged patients without neglect. Both groups showed a significantly lower probability of detecting targets in extrapersonal (far) space compared to peripersonal (near) space which is the opposite pattern shown by experiment one. With regard to the performance of healthy subjects in the present study and in Buttler et al.'s (2004), one possible explanation for this discrepancy could be found in the different age range between the two groups. Butler et al.'s (2004) control participants had a mean age range of 58 years as they were selected to match their right hemisphere damaged patients whereas in study one a group of young undergraduate students (mean age 20 years) were recruited for a preliminary evaluation of how healthy subjects would deal with the demands of the new paradigms. While the specific role played by age on visual exploration abilities across different space distances may be difficult to pinpoint, this considerable age discrepancy makes any kind of performance comparison between the two studies fairly questionable.

Whether age differences can modulate visual search abilities across near and far space could be studied by comparing the visual exploration performances of young and elderly healthy subjects in both distance conditions with the same task. This possibility was tested in study two where a large group of young and elderly adults performed the Balloon task in near and far space. Although the group of patients in experiment one was more comparable with that of Butler et al.'s (2004) in terms of age range, it is not possible to put forward any interpretation on the results discrepancies between the two studies given the smaller number of patients recruited for the present pilot study.

In the Landmark task, apart from a slight tendency to show a left response bias in far space and a right response bias in near space for centrally presented lines, healthy subjects made, overall, a genuine perceptual judgement of the stimuli. The patients instead showed a slight rightward response bias in both near and far space. In both groups, the perceptual bias in comparing the two line segments was not affected by viewing distance.

The tendency in healthy subjects to bisect lines slightly towards the left is also known as *pseudoneglect* and represents a phenomenon consistently observed in the normal population especially when bisection is carried out manually in near space (Jewell and McCourt, 2000).

Two studies investigated more directly the effect of distance on line bisection performance in the normal population using a procedure which, as well as the Landmark task of the present study, did not require a directional motor response (McCourt and Garlinghouse, 2000; Varnava et al., 2002). They found leftward errors in near space and significantly reduced leftward or even rightward errors in far space (McCourt and Garlinghouse, 2000; Varnava et al., 2002). These findings are inconsistent with the lack of a distance effect shown in experiment two. This discrepancy might be due to some methodological differences amongst the studies. McCourt and Garlinghouse (2000), for example, used a tachistoscopic forced-choice technique (FCT) which produces a much larger effect size (-1.2mm or -1.3mm) when measuring the magnitude of pseudoneglect compared to traditional manual methods of adjustment (MOA) techniques (-0.3mm or -0.4mm) (Jewell and McCourt, 2000). In Varnava et al. (2002) study instead, subjects were asked to bisect lines on a computer screen by moving a cursor towards what they thought was the line midpoint with the starting position of the cursor at the left or right end of the line. The implications of the methodological differences between the above studies and the present pilot will be examined in more details in the discussion section of the next study.

The overall rightward perceptual bias shown by the patients in the Landmark task did not change substantially from near to far space. Only Pitzalis et al. (2001) reported the performance of a group of right hemisphere damaged patients without neglect in a Landmark task which, similarly to the one used in experiment two, did not require a directional motor response across near and far space. In line with the behavioural pattern shown by the three patients in study one, Pitzalis et al. (2001) observed a consistent performance between near and far space for their group of right brain damaged patients.

A further variable that was included in the present investigation for the Landmark task was the stimulus position in the visual field (left, centre and right). Overall healthy participants showed a leftward perceptual bias as they tended to perceive the left segment of the line as longer than the right one. However, irrespectively of viewing distance, subjects' perceptual experience of the stimulus changed as a function of its horizontal position. Their leftward bias was more pronounced for the lines positioned in the left visual field and decreased progressively toward the centre and right visual fields. The same pattern was observed for the patients except for a rightward bias for the lines presented in the right visual field.

Several studies support the above effect of stimulus position for near space both for manual line bisection (Reuter-Lorenz et al., 1990; Luh, 1995; McCourt and Jewell, 1999) as well as perceptual line judgment tasks (Milner et al., 1992). The increase of the pseudoneglect magnitude showed by the healthy participants for stimuli presented in the left compared to the right hemifield is interpretable within the activation-orientation theory (Kinsbourne, 1970; 1993). This hypothesis suggests that lateralized placement of stimuli increases activity in the contralateral hemispheres to the extent that, for example, presentation of stimuli in the left visual hemispace would increase the activation of the right hemisphere inducing a leftward shifting of the attentional resources along with a greater leftward bisection error. The present study found this pattern also in far space. According to activation-orientation theory, the smaller leftward bias observed for the patients may be related to a reduced activity of the damaged right hemisphere.

Despite a slight response bias, both healthy participants and the patients did not show any difficulty in performing the Landmark task. However, following informal feedback from Toraldo and co-workers on the results of this preliminary pilot study, some parameters of the task were modified to allow for improved assessment of the perceptual bias.

According to their paper (Toraldo et al., 2004), the authors suggested that the RB and PB indexes may have a practical utility in clinical contexts as they provide a fast and simple differential diagnosis between perceptual and motor components in neglect (IRN and ORN) but they appear less useful for deriving scientific conclusions due to their reciprocal influence. For instance, a patient who responds rightwards in all trials (in both the "longer" and the "shorter" condition) would obtain a PB of 50 which is the equivalent of no IRN while the exact estimation of the patient's perception of the lines would be instead still unknown. Even for less extreme cases of response bias, the artificial truncation does not allow the PB index to reach extreme values. For example "if RB = 75 it is impossible to obtain a PB score higher than 75 or lower than 25" therefore the absolute degree of IRN is generally underestimated (Toraldo et al., 2004). To overcome the above problem of dependence between the range of variations which occurs for PB and RB, Toraldo et al. (2004) suggested two alternative mathematically independent indexes. Their measure for IRN is the PSE (*point of subjective equality*) between two sections of a bisected line while M represents their index for ORN. The PSE provides an estimation of the point where the two segments are subjectively identical considering the probability p of the subjective midpoint (SM) falling to the left or to the right of a given landmark position. M instead is a linear transformation of the RB index and indicates the probability that a response will be made in the direction opposite to the subject's SM. The mathematical independence of these two indexes means that every possible value of PSE can combine with every possible value of M and vice versa without an artificial reduction of their respective range (as for PB and RB). Furthermore, the availability of confidence intervals for both indexes provides a measure of the uncertainty of the observed estimates to minimise the possibility of false positive errors (i.e. incorrect diagnosis). Neurological patients can show generally high uncertainty when performing line bisection tasks and this tendency can make the PSE and M indexes unstable. When there is complete guessing, the average estimate of PSE would be "0" (no bias) irrespective of the real PSE whereas in presence of partial guessing, the PSE estimate would still be on average correct (Toraldo et al., 2004). The M index instead, could be even more unstable than PSE as it can be influenced by both complete and partial guessing generating an overestimation or underestimation of the presence of a motor bias deficit in the patient. In addition, to detect guessing behaviour, Toraldo et al. (2004) introduced the index SD which corresponds to the shallowness of the cumulative normal curve. If a patient shows a SD value higher than 34.94 (99% of the area under the Gaussian curve), he/she should be considered as having guessed in at least some trials. This information should then be taken into account in the interpretation of the performance.

Given the above considerations, the version of the Landmark task used for the pilot study was readapted so that the new PSE and M indexes could be calculated accordingly. To this purpose, the main modifications that needed to be implemented concerned the locations of the transection marks and number of trials (See section 3.3.1.2.2 for details).

3.3. Study two: Definition of a baseline of normal performance for the Balloon and the Landmark tasks in near and far space

After implementing the necessary modifications described in the discussion of the pilot study, the new experimental tasks were considered suitable for the assessment of distance related visuospatial deficits in neglect patients. At this stage, for both tasks, a baseline of normal performance needed to be defined to compare the patients' performance on. To this purpose, a large group of neurologically healthy adults was recruited so that for each neglect patient tested a suitable group of age and education matched controls could be selected amongst a fairly wide range of individuals. In addition, the performance of the young members of the present group of adults was compared to that of the older members to explore potential age effects on visuospatial abilities across near and far space.

3.3.1 Materials and methods

3.3.1.1 Subjects

Forty right handed healthy adults (age range = 26 – 74 years, SD = 17.8; education range = 27 – 7 years, SD = 4.93) took part in the experiment. Twenty subjects represented the group of younger adults (Mean age = 30.2 years, SD = 3.36; Mean education = 19.45 years, SD = 3.66) while the remaining 20 represented the group of the elderly adults (Mean age = 64.3 years, SD = 6.42; Mean education = 14.75 years, SD = 4.41). All participants provided written information on their general health conditions before the experiment. None of them was under any kind of medication at the time of testing or reported history of neurological or psychiatric disorder. All participants provided informed consent and were appropriately debriefed after they completed all the tasks.

3.3.1.2 Experimental paradigms

3.3.1.2.1 The Balloon task

The task was the same as in study one (section 3.2.1.1.2). The only difference compared with study one was a modification of the response keys. Subjects were asked to press response key "1" when they detected the target (balloon without the string). Again, for "target absent" responses they were required to press the key "0". For the purpose of statistical analysis, the total number of correct responses for each hemi-field was then calculated a posteriori by the experimenter. Response times were also recorded.

3.3.1.2.2 The Landmark task

The same pre-bisected white lines (20° x 1° of visual angle) were presented against a black background. In each trial the line was transected on one of nine landmark positions (-60, -30, -15, -5, 0, 5, 15, 30, 60 mm). Participants were asked to make a judgment about the length of the two line segments. As in study one, participants were tested in two sessions: in one session they were asked to judge which end of the line was shorter while in another they had to decide which end was longer. Each session (shorter or longer) was subdivided in three different blocks corresponding to the three specific positions within the display: left, centre and right. Six stimuli per Landmark transection were presented with 54 trials for each horizontal position. For each session (shorter or longer) 162 trials in total were administrated. Consequently, in each spatial condition (near or far) 324 trials were presented overall.

Spatial conditions (near and far), type of judgment (shorter and longer) and horizontal stimulus position in the display (left, centre, and right) were counterbalanced. All stimuli were presented randomly one at the time and stayed on screen until the response was made. No central fixation point was presented between the trials and, following each response, the next stimulus appeared after a 1 second delay. As in experiment one, for each forced-choice judgment subjects had to press with their right hand the same response key on the number pad: number "1" for left segment shorter (or longer) and number "2" for right segment shorter (or longer).

3.3.1.3 Procedure

The procedure was the same as in study one (section 3.2.1.1.3)

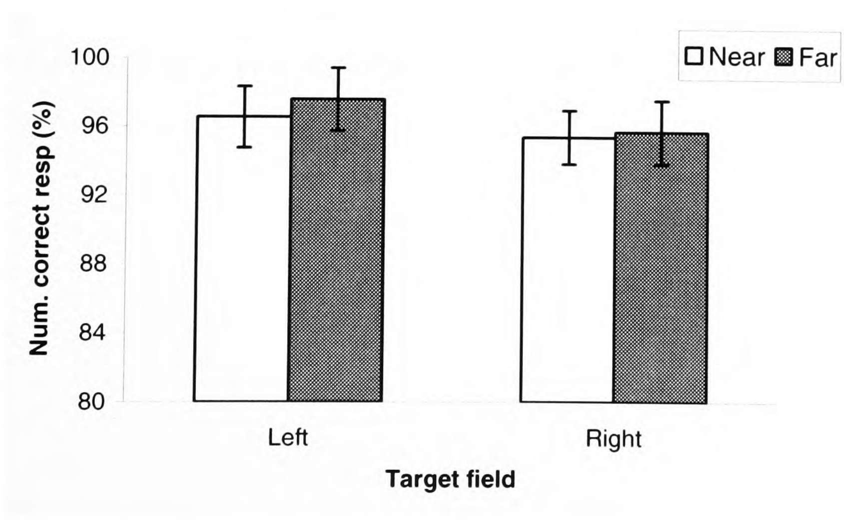
3.3.2 Results

3.3.2.1 The Balloon task

Two separate 2 x 2 x 2 repeated measures ANOVAs with distance (Near/Far) and target field (Left/Right) as within-subject factors and with group (Young/Elderly) as between-subjects factor were carried out for accuracy and reaction times respectively.

The accuracy analysis revealed no significant main effect of distance [$F(1, 38 = .17, p > .05$] or target field [$F(1, 38) = .002, p > .05$]. A significant main effect of group [$F(1, 38) = 37.34, p < .01$] indicated that the young adults reached a higher level of accuracy [Mean = 96.3%, SD = 3.45] than that the elderly participants [Mean = 85.2%, SD = 5.29]. None of the interactions were significant [$F(1, 38) \leq 1.45, p > .05$]. The accuracy scores of both age groups are shown in Figure 3.10.

A



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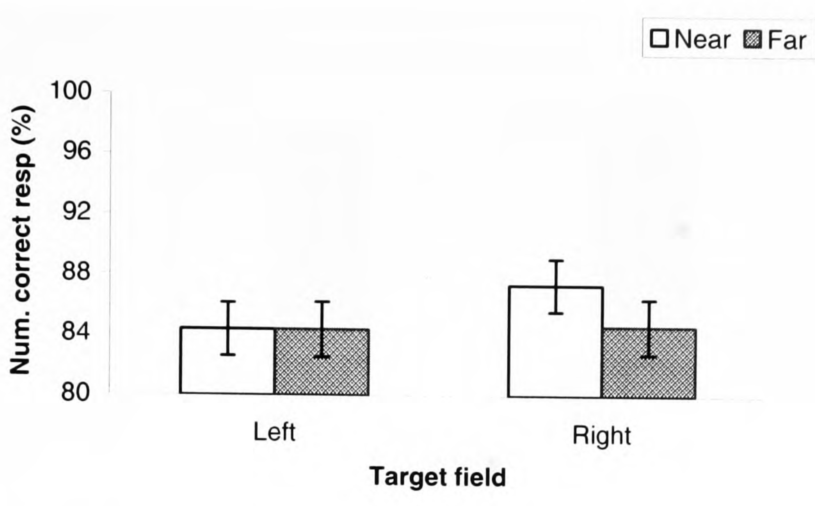
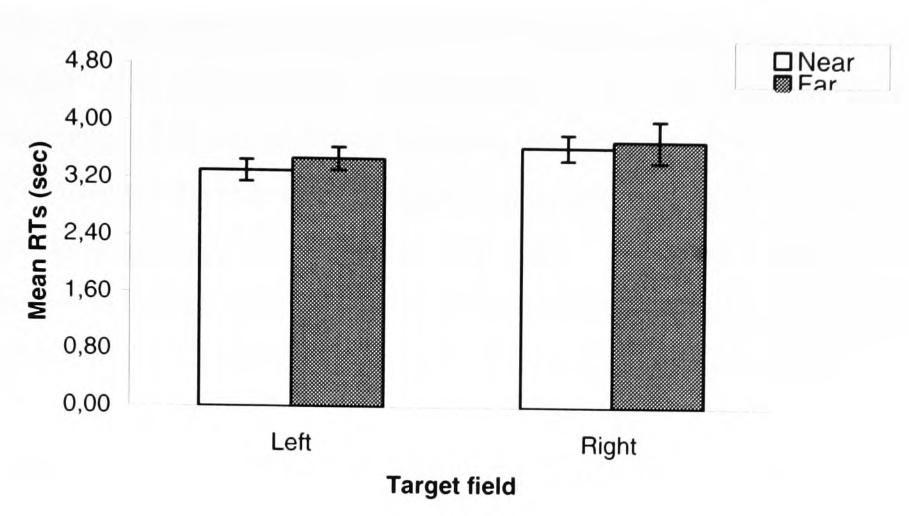


Figure 3.10 Mean visual search accuracy and SE as a function of distance (Near, Far) and target field (Left, Right) for (A) the young and (B) the elderly participants.

The ANOVA of the response times showed a significant main effect of target field [$F(1,38) = 6.24$, $p < .05$] indicating that subjects were overall faster in detecting targets in the left [Mean = 3.47 sec, SD = 0.95] than in the right visual field [Mean = 3.75 sec, SD = 0.16]. The main effects of distance did not reach significance [$F(1, 38) = .182$, $p > .05$] as all subjects demonstrated the same response speed in near [Mean = 3.59 sec, SD = .98] and in far space [Mean = 3.63 sec, SD = .15]. Regardless of space distance, the members of both groups [Mean young = 3.55 sec, SD = .16; Mean elderly = 3.67 sec, SD = .16] were equally fast in detecting the target stimuli [$F(1,38) = .30$, $p > .05$]. None of the interactions were significant [$F(1,38) \leq 1.78$, $p > .05$]. These results are shown in Figure 3.11.

A



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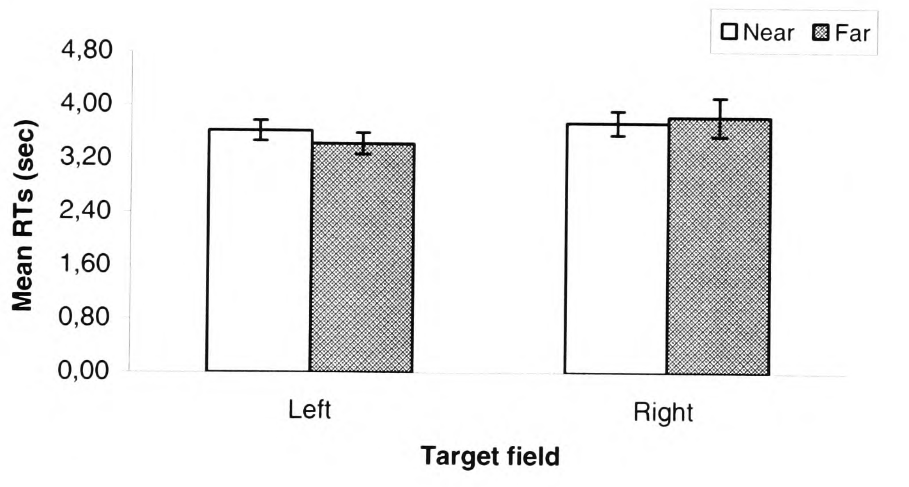


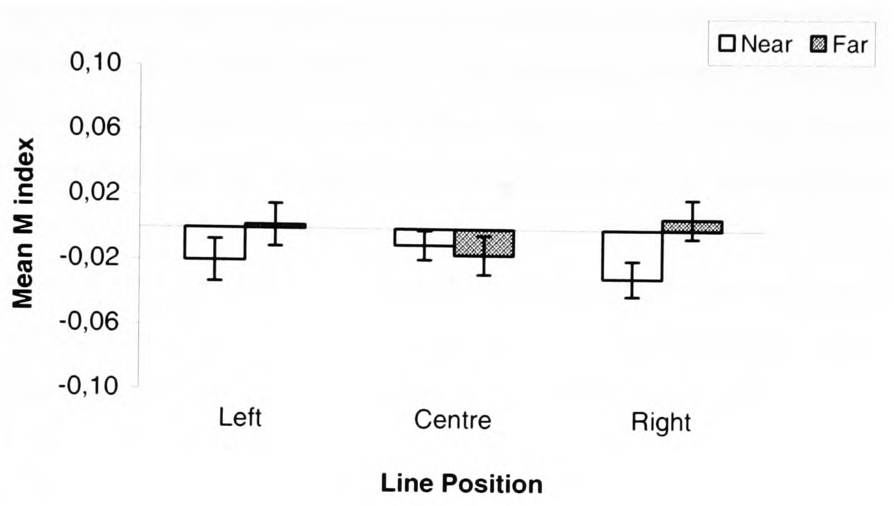
Figure 3.11 Mean response times (sec) and SE as a function of distance (Near, Far) and target field (Left, Right) for (A) the young and (B) the elderly participants.

3.3.2.2 Landmark task

An electronic worksheet for the automatic computation of the PSE and M indexes was used (www.masson.it/cortex/database/PC_Toraldo_40_3.htm). The number of "left shorter" and "right longer" responses for each landmark transection location was considered. For the statistical analysis, two separate 2 x 3 x 2 repeated measures ANOVAs for the response (M index) and perceptual bias (PSE index) were carried out, with distance (near, far) and stimulus position (left, centre and right) as within-subjects factors and group (young/elderly) as between-subjects factor. Significant results were followed-up by Bonferroni-corrected t-test for multiple comparisons.

Response bias. There were no significant main effects [distance: $F(1,38) = 0.21$, $p > .05$], [stimulus position: $F(2, 76) = 1.13$, $p > .05$], [group: $F(1,38) = 1.36$, $p > .05$]. Only the 3-way interaction of distance x stimulus position x group was significant [$F(2, 76) = 3.88$, $p < .05$]. This result was followed up by two separate repeated measures ANOVAs for each age group respectively with distance (near, far) and stimulus position (left, centre and right) as within-subjects factors. For the elderly group no significant main effects [distance: $F(1, 19) = 1.52$, $p > .05$; stimulus position: $F(2, 38) = .866$, $p > .05$] or interaction [$F(2, 38) = .55$, $p > .05$] was observed. The analysis for the young group showed that the main effect of stimulus position [$F(2, 38) = 4.16$, $p < .05$] and the distance x stimulus position interaction were significant [$F(2, 38) = 4.07$, $p < .05$]. The main effect of distance did not reach significance [$F(1, 19) = .44$, $p > .05$]. The significant main effect of stimulus position indicated that young subject demonstrated a different response bias depending on the location of the line on the display. Post-hoc comparison [$p = .02$] revealed that regardless of spatial distance, subjects showed a rightward response bias for stimuli presented on the left visual field which was significantly different from the leftward response bias obtained for centrally presented stimuli [$t(39) = 2.73$, $p < .01$]. No difference was observed between the response bias for the lines presented centrally and on the right visual field [$t(39) = -.38$, $p > .02$] and between the left and the right visual field [$t(39) = 1.81$, $p > .02$]. The interaction indicated that the young subjects' response bias changed significantly across near and far space depending on the horizontal position of the stimuli. Post hoc analysis [$p = .02$] revealed no significant change in the young subjects' response bias between near and far space neither for targets presented on the left [$t(19) = 1.14$, $p > .05$] centrally [$t(19) = .31$, $p > .05$] or on the right [$t(19) = -2.01$, $p > .05$]. Overall, these results showed that the response bias of both groups was not affected by space distance and they only differed in the directions of their response bias for the lines presented in the left visual field for which the elderly tended to make left key presses and the younger right key presses. In absolute terms, this difference was not substantial as the response bias of both groups was very close to zero (no bias). These results are illustrated in Figure 3.12.

A



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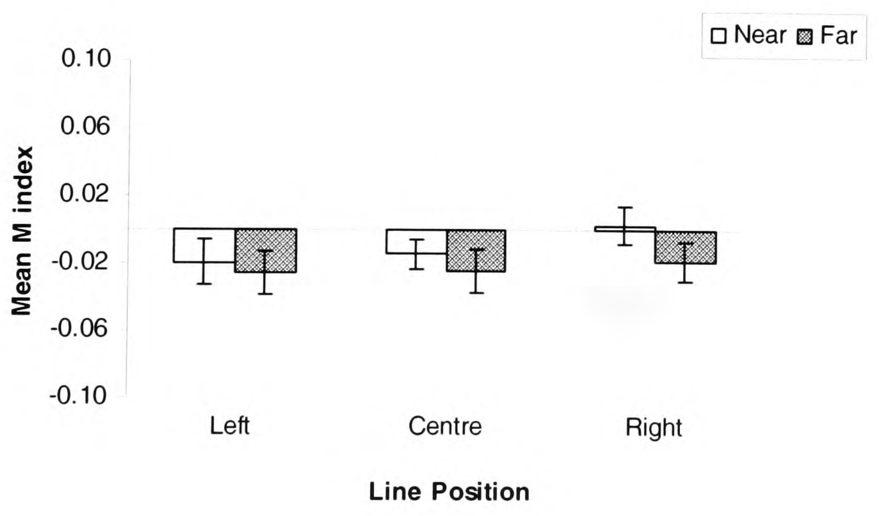
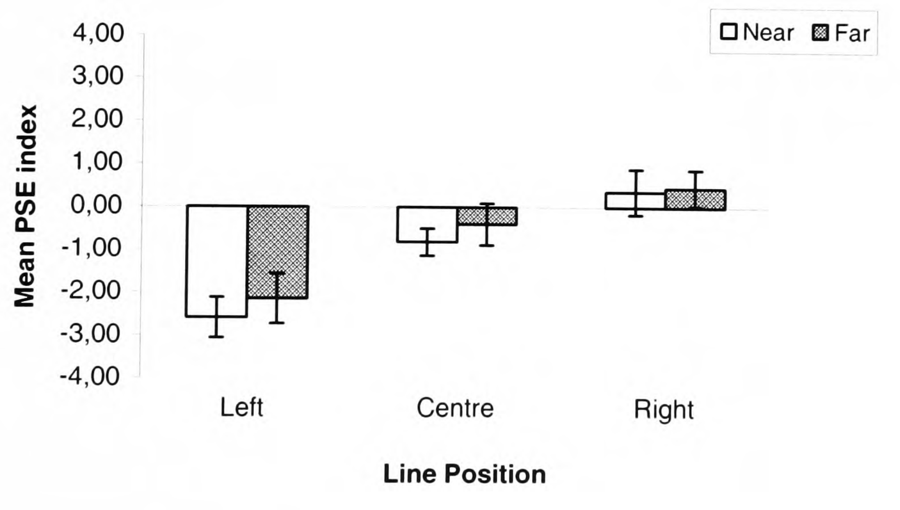


Figure 3.12 Response bias (M index) and SE as a function of distance (Near, Far) and stimulus position (Left, Right) for (A) the young and (B) the elderly participants.

Perceptual bias. The ANOVA yielded a significant main effect of stimulus position [$F(2,76) = 25.14$, $p < .01$] with no main effect of distance [$F(1,38) = 0.48$, $p > .05$]. A significant main effect of group [$F(1,38) = 4.92$, $p < .05$] indicated that, regardless of stimulus position and space distance, the young participant showed a leftward perceptual bias [Mean = -.86, SD = .42] while the elderly subjects demonstrated a rightward perceptual bias [Mean = .14, SD = .32]. None of the interactions were significant [$F(2,76) \leq 2.66$, $p > .05$]. Also in this case, the left segment was perceived as longer and the right segment as shorter especially for left presented lines [Mean left = -1.50, SD = .31] when compared to lines presented centrally [Mean centre = -.30, SD = .26] and in the right visual field [Mean right = .73, SD = .30]. Post-hoc analysis [p = .02] revealed that the amount of leftward perceptual bias was significantly larger in the condition of left compared to central stimulus position [$t(79) = -4.91$, $p < .001$]. The rightward perceptual bias observed for right presented lines was significantly different form the leftward perceptual bias associated with the conditions of left [$t(79) = -7.38$, $p < .001$] and central [$t(79) = -3.64$, $p < .001$] stimulus position.

A



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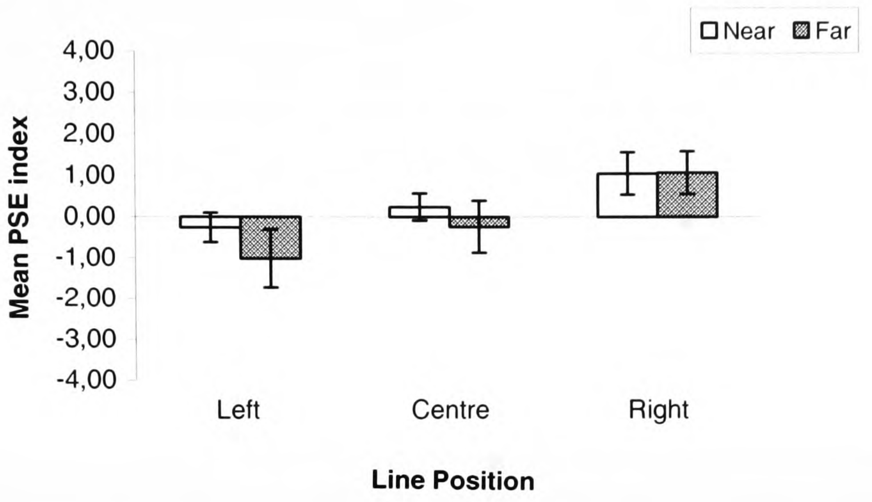


Figure 3.13 Perceptual bias (PSE index) and SE as a function of distance (Near, Far) and stimulus position (Left, Centre, Right) for (A) the young and (B) elderly participants.

3.3.3 Discussion of study two

By testing a large group of healthy adults, study two allowed the setting of a baseline against which the performance of patients with neglect could be compared when using the final versions of the Balloon- and Landmark tasks. In addition, a direct comparison between young and elderly participants demonstrated that although age can affect the accuracy level in a visual search task or the perceptual and motor bias during line length estimation, it did not modulate the performance across near and far space.

For the Balloon task, viewing distance did not affect the visual search abilities of both groups as all subjects were equally accurate in near and far space. In addition, spatial distance did not affect the subjects' overall search accuracy or their performance within visual fields. In addition, subjects demonstrated to be overall faster in detecting targets in the left compared to the right visual field regardless of spatial distance and age.
Once again, these results are not consistent with that of Butler et al. (2004) who observed a significantly higher target detection rate in near space compared to far space

in their group of elderly controls. This time, Butler et al.'s (2004) participants are more comparable with the elderly group who took part in study two. Consequently, as the age issue in this case is no longer relevant in justifying the inconsistencies between both studies, it would be worth examining some methodological differences. For instance, Butler et al. (2004) asked subjects to read out aloud all the targets (letters and numbers) printed on a white sheet which was presented in front of them in near space and projected to the wall in the far space condition. Participants had to detect 48 targets in total, presented along 49 randomly distributed distractors with a time limit of two minutes. In the present study instead, stimuli were projected onto the wall in front of the subjects in the same fashion in both near and far space to make the two conditions more comparable. By darkening the experimental room, the effect of external cues was also minimised and subjects could only see the white stimuli against a black background whose edges were undistinguishable from the rest of the wall. In this way, by making the stimulus presentation equal between the two space conditions, the effect of different search strategies in near and far space associated possibly to the presence of reference cues (i.e. sheet edges, day light in the room) was minimised.

The fact that Butler et al.'s (2004) subjects had to detect multiple targets, while in the present study the stimulus display contained only one target, makes the two tasks different also in terms of level of difficulty, which might have engaged the subjects' attentional resources to a different degree. The Balloon task is a typical search task which requires one to look for "the absence of a differentiating feature" (the line intersecting the circle) (Treisman and Gelade, 1980) which engages participants in a serial-like search in the same way that conjoining two features does (Behrmann et al. 2004). For this reason, it is possible that this kind of task generates a pattern of search efficiency resembling more a classical conjunction search task (slow and prone to errors) than a feature search task (fast and highly accurate) (Duncan and Humphreys, 1989). In contrast, Butler et al.'s (2004) task seems to fulfil more the characteristics of the latter category of search tasks due for instance to a higher discriminability between targets and distractors which is known to elicit greater search efficiency compared to when the target/distractor difference is low (i.e. Balloon task) (Duncan and Humphreys, 1989).

Another aspect which may have increased the search demands in the Balloon task was the lower target to distractor ratio compared to Butler et al.'s paradigm. The different patterns of efficiency prompted by the two tasks appear thus related to their different level of difficulty which contributes to explain why two comparable groups of elderly healthy subjects yielded contrasting results on their visual search abilities. This argument is supported by the different overall accuracy level reached in the two studies regardless of space distance [Butler et al.'s Mean = 97%; study two Mean = 85%].

Another important difference which may explain the discrepant results between Butler et al.'s (2004) and the present study is the distance which was used as extrapersonal space. In the present study, stimuli in far space were projected at 114 cm away from the subject's body midline whereas for the same condition Butler et al. (2004) presented their displays at a 250 cm distance. In a comprehensive review on space representation Previc (1998) defined several space sectors within and beyond reaching distance from the body. A distance of 114 cm extends toward what Previc described as "focal extrapersonal" space within which the major operations that take place include colour processing, high-resolution contour analysis, feature integration for search and recognition of objects and faces. A distance of 250 cm away from the body instead extends toward what Previc (1998) defined as "ambient extrapersonal" space in which the operations of orientating and navigation in relation to objects and topographically defined sites occur. Accordingly, it might be possible that the two studies assessed search abilities within functionally different extrapersonal space sectors. Why visual search performance should be more vulnerable within ambient extrapersonal space than focal extrapersonal space is not clearly explicable.

With respect to the effect of age on visual search abilities, the young group was overall significantly more accurate than the elderly group irrespectively of the sector of space in which they performed the task. Despite this general accuracy advantage of the young over the elderly participants, the exploration skills of each group were not affected by spatial distance. The younger subjects of study one, however, performed significantly better in far space compared to near space in the Balloon task. This latter finding could be interpreted in light of the pivotal role played by the right hemisphere in allocating visuospatial attention resources which, in accordance with Heilman et al.'s (1995) theory, seems particularly biased towards distal space[7]. There is some evidence showing that the right hemisphere is predisposed to more rapid aging than the left hemisphere (Goldstein and Shelly, 1981; Meudell and Greenhalgh, 1987; Robinson and Kertzman, 1990) and this aging asymmetry led some authors to hypothesized the presence of uneven changes in the brain mechanisms of spatial attention across the two hemispheres (Jewell and McCourt, 2000). This idea has already been tested with line bisection tasks for which young participants tend to err towards the left of the true centre (pseudoneglect) while older adults tend to show a rightward bias. If this tendency is related to an age-related decrease in the ability of the right hemisphere to allocate attentional resources then the poorer performance in far space observed for the elderly participants of study two compared to the younger subjects of study one could be in part justified. If ageing affects to some degree the efficiency of certain cognitive abilities and reduces their asymmetric segregation between the two hemispheres, then their respective attentional biases for specific space sectors as hypothesized by Heilman et al. (1995) (LH-near space; RH-far space) might be both reduced. This pattern could lead consequently to an equivalent performance in near and far space as observed in study two for older adults.

In the Landmark task, again subjects' performance was not modulated by spatial distance. This result is in contrast with that of two other studies that investigated the effect of distance with "perceptual" line bisection paradigms in healthy subjects. McCourt and Garlinghouse (2000) observed a greater leftward bias in near space compared to far space. The authors interpreted this result as a consequence of the use of a tachistoscopic forced-choice (FCT) methodology which, as mentioned in study one, seems to produce a larger effect size in detecting pseudoneglect when compared to manual method-of-adjustment procedures (Jewell and McCourt, 2000). By requiring from subjects a simple button press response, the influence of gross directional manual responses in the bisection performance was ruled out in both McCourt and Garlinghouse's (2000) and the present study. The FCT methodology can, however, minimise the effect of systematic errors related to scanning eye movements by

[7] Heilman et al.'s (1995) theory on the hemispheric asymmetry for near and far space attention hypothesises that each hemispheres is "attentionally tuned" towards a specific spatial sector: the right hemisphere has a propensity to direct attentional resources mainly away from the subject's body (extrapersonal far space) while the left hemisphere's visual cognitive activities would instead take place especially within the space closer to the viewer (peripersonal near space).

restricting the stimulus exposure to 150 ms which is too short to initiate saccadic eye movements (Carpenter RHS, 1988). No time limit instead was set for the exploration of the stimulus in the present study. The influence of uncontrolled random scanning patterns might have increased the variability of the perceptual bias within the group as subjects tend to err toward the side from which oculomotor scanning starts (Jewell and McCourt, 2000). This factor might explain why McCourt and Garlinghouse (2000) detected a larger leftward bias (pseudoneglect) compared to the present study and a distance effect between near and far space. The authors did not explain, however, why pseudoneglect should be more pronounced in near than in far space. One possibility is that this latter pattern may be related to left-to-right scanning effects associated to reading and writing learned habits of the western populations. Since these daily operations are carried out prevalently in near space, a leftward bias in proximal space may be stronger than in distal space.

The absence of a directional manual response in the present study might have reduced even further the magnitude of an already small leftward bisection error in both distance conditions. However, although with a smaller effect size compared to a FCT methodology, the fact that pseudoneglect has been consistently detected in the normal population by many studies even without restricting viewing conditions (Jewell and McCourt, 2000), makes the present version of the Landmark task still a valuable tool for the measurement of perceptual asymmetries in line bisection judgments. Most importantly, as the Landmark task was ultimately devised for a population of brain damaged patients, it was not ideal to limit the stimulus presentation to a very short period of time as this would have increased the task difficulty and reduced the likelihood of obtaining a genuine perceptual judgment of the stimuli in favour of guessing behaviour.

As mentioned earlier, also Varvara et al. (2002) investigated line bisection performance across near and far space in a group of healthy participants and, in contrast to the findings of study two, observed a significant effect of distance with opposite bisection errors in near (leftward) and far (rightward) space. It is worth mentioning that the technique of response used by Varvara et al (2002) was rather different than that of the present study. In both studies, stimuli were presented in a computer screen while Varvara et al's (2002) subjects had to bisect the line manually by moving a cursor along the whole extent of the stimulus, the participants of study two had to press the button relative to the direction of their perceptual judgment (left or right) of a pre-bisected line. The motor requirements between the tasks used in the two studies are clearly different as Varnava et al.'s (2002) technique seemed to require a type of target-directed movement which more closely resembles a directional manual movement compared to a simple button press. Accordingly, the presence of a leftward bias for near space and a rightward bias for far space might have been induced in Varnava et al.'s (2002) study by this minor but perhaps crucial motor involvement of the upper limb in the bisection performance of their subjects. In addition, the presence of a cursor might have contributed to elicit asymmetrical performance between space distances. A left start of the cursor, which prompted a left-to-right scanning strategy, was indeed consistent with a left-to-right shift in bias as distance increased (Varnava et al., 2002). This effect was not consistent, however, in the condition of right start of the cursor. The subjects of the present study instead, had no restriction on the directions of their eye movements. Overall, the different degree of motor involvement of the upper limb to perform the task and the presence of a cursor for the monitoring of the scanning direction might have been critical in yielding a distance effect that was instead absent in study two.

With respect to the effect of age on line bisection performance across space distances, study two demonstrated that the perceptual bias of young adults did not differ compared to that of the elderly between near and far space. This result suggests that, as with visual exploration, distance related line length judgment abilities are not affected by age. However, regardless of spatial distance, the overall perceptual bias showed by the elderly differed significantly from that of the young participants. The point of subjective equality of the elderly was indeed shifted towards the right whereas that of the young subjects was shifted towards the left. These findings are in line with other studies that observed the tendency of elderly adults to make rightward bisection errors while young subjects tend to err toward the left of the true centre (Jewell and McCourt, 2000). As mentioned previously, this pattern seems associated with the age-related decrease in the ability of the right hemisphere to allocate spatial attention (Goldstein and Shelly, 1981; Meudell and Greenhalgh, 1987; Robinson and Kertzman, 1990).

A further variable taken into consideration was the horizontal position of the stimulus on the display. Overall, the magnitude of the pseudoneglect was again larger for left presented lines and gradually switched to a rightward bias for the ones located on the right visual field regardless of spatial distance. This pattern seems very consistent across the normal population for line bisection performed in near space and is consistent with Kinsbourne's activation-orientation theory (1970; 1993). This approach states that left hemispatial stimulation increases left-biased attention by arousing the right hemisphere and vice versa for the inputs coming from the right visual field. Study two replicated the above effect of stimulus position which was consistent not only for near but also for far space.

At this stage of the present study, the baselines results for the Balloon and the Landmark tasks were set so that the performance of right brain damaged patients could be evaluated across near and far space. In the next section, a case series of three patients with neglect (SV, MF and JA) was described. Patients' visuospatial deficits were assessed in proximal and distal space and their performance was evaluated depending on the type of task used, type of response and space sector affected. In addition, a close examination of the site of their lesion contributed to interpret the nature of their impairment. Although this was possible for MF and JA, patient SV's assessment could not be completed due to her clinical condition and high fatigability. Thus, only in this case, it was not possible to evaluate the effect of a directional motor response on her visual search and bisection behaviour.

3.4 Visuospatial neglect in near and far space: A case series

3.4.1 Methods and procedure

3.4.1.1 Subjects

3.4.1.1.1 Patient SV

SV is a 70 years old female patient (education = 8 years) who was referred to the Nuovo Ospedale Civile Sant'Agostino Estense in Modena on July 2006 following an ischemic event. Damage was reported in the territory of the right posterior cerebral artery in correspondence of the occipito-parietal area and posterior arm of the internal capsule. The right thalamus was also damaged. The patient was oriented and able to answer questions or execute simple commands. Neurological examination revealed spontaneous deviation of the head and gaze towards the ipsilesional (right) side of space, left hemiplegia of upper and lower limbs, left hemianestesia, left hemianopia, tactile extinction, anosognosia and left neglect.

3.4.1.1.2 Controls

Ten female control subjects matched for age (Mean = 68, SD = 6.35) and years of education (Mean = 9.2 SD = 4.57) were selected from the database of healthy controls. They all provided written consent to take part in the study. None of the controls had a history of psychiatric or neurological disorder, alcoholism or epilepsy and were under any kind of medication at the time of testing.

3.4.1.2 Neuropsychological tasks and assessment of neglect

The battery used to assess spatial neglect included the following tests (See Appendix, page 1): Bells test (Gauthier et al., 1989), Star cancellation (Halligan et al., 1989a), line bisection, drawing from memory (clock face) and scene copying (Gainotti et al., 1972). The same assessment was carried out in far space. For this purpose, all the above tests (except for the drawing and copying tasks) were administered with an overhead projector positioned behind the patient at a distance of 320 cm from the wall. In this condition, SV was asked to respond by using a laser pointer. In near space the patient carried out the task with a pencil at a distance of 40 cm form the stimuli presented on an A4 spreadsheet. The visual angle of the stimulus projection was kept constant across the two conditions (43° x 31°) The patient's performance on the neglect screening tests is summarised in Table 3.5.

The Bells test

In the Bells test (Gauthier et al., 1989) subjects were asked to detect 35 targets (black ink silhouette of bells), presented on A4 paper sheet amongst 280 distractors (i.e. objects, animals, tools). All the stimuli were arranged in a pseudo-random array. The targets were equally distributed in seven columns (three on each half of the sheet and one in the middle). In the near space condition patients had to cross the targets with a pen whereas in far space they had to point to all the targets they could find with the laser pointer. The cut-off value for left neglect was more than six left-sided omissions (Azouvi et al., 2006). In case of right sided omissions, only the cases presenting at least two omissions more on the left than on the right were considered to fulfil the criterion for left neglect.

Star cancellation

The star cancellation test consists of an A4 page printed with 56 small stars, 52 large stars, 13 letters, and 10 short words (Halligan et al., 1989a). The goal of this test was to have the patient locate and cross out all of the small stars with no time limit. According to the Behavioural Inattention Test (BIT) scoring criteria, a cut-off of three target omissions was considered. In the presence of right side omissions, only the cases with at least two omissions more on the left than on the right were considered as a criterion for left neglect.

Line bisection

In the line bisection task (BIT version), patients were asked to mark with a pencil the centre of three horizontal lines (20 cm x 0.1 cm) placed respectively on the right, centre and left of an A4 sheet. Deviation from the true centre was measured in mm with positive/negative values indicating rightward/leftward deviations. These values were averaged across the three lines. The cut-off for left-sided neglect was set at ±6.5 mm of deviation from the true midpoint or 13% of the line length (Azouvi et al., 2006). Each score was converted in degrees of visual angle so that the performance in near and far space could be compared with homogeneous measurements. The cut-off value converted in degree of visual angle was ±0.93° for near space and ±0.11° for far space.

Scene copying and drawing from memory

In the copying task the patient was asked to copy on a horizontal A4 sheet a scene including (from the left to the right) a tree, a fence, a house with a left sided chimney, and a second tree (Gainotti et al., 1972). In the spontaneous drawing part, she was asked to draw three symmetrical objects: a house, a flower and a clock-face. In the clock drawing task, the patient was required to place the 12 hours in a circle drawn previously by the experimenter. The scoring procedure considered omissions, accuracy and layout of the drawing according to the following criteria: 3 = incomplete and misplaced to the right, 2 = incomplete on the left but correctly positioned, 1 = complete but misplaced on the right, 0 = complete and correctly placed. Any score above "0" was considered to indicate neglect. The final score for the drawing from memory part was obtained by averaging the scores across the three drawings.

Table 3.5 SV's results for the clinical assessment of neglect in near and far space.

	Space	
Tests	Near	Far
Bells test	2/34§ (0L/2R)	19/34 (8L/11R)
Star cancellation	8/54 (0L/8R)	43/54 (21L/22R)
Line bisection	+19.35°	+1.69°
Drawing from memory	3‡	N.A.
Scene Copying	3	N.A.

§ Overall number of correctly reported items; L: correct left; R: correct Right

° Deviation in degree of visual angle

‡ "3": incomplete and misplaced to the right

N.A. Not administered

The clinical tests for visuospatial neglect showed a severe impairment on both cancellation tasks. In addition, SV showed a large rightward misplacement of the bisection mark together with clear signs of neglect observable on the drawings. Some of the items were indeed either incomplete on the left hand side or misplaced toward the right half of the sheet. SV's performance in far space was, however, less impaired than in near space. For both cancellation tasks, SV was able to detect some contralateral targets in far space while no item on the left hand side of the sheet was found when she carried out the tasks in near space. The patient's bisection error was also more severe in near compared to far space.

3.4.1.3 Experimental tasks

The new versions of the Balloon and the Landmark tasks were administered in near and far space respectively. Tasks properties are described at pages 72 and 91 for the Balloon task and 78 and 91 for the Landmark task. The procedure was the same as described in section 3.2.1.1.3 (page 74). For the Landmark task, the stimuli were presented only on the centre of the screen. Accordingly, there were 54 trials for each session (shorter or longer). Thus, 108 lines were presented for each spatial condition (near or far).

Data analysis

Two programs, SINGLIMS and RSDT devised by Crawford et al. were used to verify whether the patient's performance on the Balloon and the Landmark task was significantly different from that of the matched controls (Crawford and Howell, 1998; Crawford and Garthwaite, 2002). The program Singlims is a computerized adaptation of the modified t-test formula by Sokal and Rohlf (1995) and it verifies whether a patient's score in one test is significantly lower than that of controls (Crawford and Howell, 1998). Likewise, RSDT (Revised Standardized Difference Test) represents the computerised adaptation of the Payne and Jones' formula (1957) and compares the difference between a patient's performance on two or more tasks with the distribution of differences observed in controls. Thus, the former test was used in order to evaluate whether SV's performance was significantly below that of the controls in each space condition. The latter method was used to verify whether her change in performance from far to near space differed significantly from that of the controls. For the Landmark task, the normal ranges for PSE and M indexes were derived from the mean ±2 SD of the 10 normal controls. Following Toraldo et al. (2004), the cut-off for the SD index was set at the controls' mean +1.5 SD.

3.4.2 Results

3.4.2.1 Balloon task

In each spatial condition (near and far), participants' overall accuracy was calculated by collapsing the mean accuracy data across left and right visual field. SV's overall accuracy [Near: Mean = 47%; Far: Mean = 48%] was significantly poorer than that of the control group [Near: Mean = 83%, SD =13.37; Far: Mean = 81%, SD = 12.93] in both near [$t(9) = -2.56, p < .05$] and far space [$t(9) = -2.408, p < .05$].

To verify whether the pattern of target detection ability in SV between the left and the right visual field was abnormal, the difference in accuracy between the right and the left visual field recorded for the patient was compared with that of the control group for each space condition separately. The difference in accuracy between the two visual fields observed in SV was significantly larger than that of the control group in both near [$t(9) = 14.83, p < 0.001$] and far space [$t(9) = 7.265, p < 0.001$]. In both spatial distances the patient was indeed fairly more accurate on the right than on the left visual field. The descriptive data are shown in Table 3.6.

Table 3.6 Balloon task: mean (SD) percentage of correctly detected targets by SV and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far).

	Near			Far		
	Left	Right	$_{R-L}$ Diff	Left	Right	$_{R-L}$ Diff
SV	0	94	94	6	89	83
NC	80.80 (14.29)	84.90 (12.8)	4.10 (5.78)	80.60 (15.62)	80.70 (10.45)	0.10 (10.88)

Using the same difference data, another set of analysis was carried out to verify whether any change in performance between the two space distances seen in the patient was significantly different from that observed in the control group. SV was more accurate on the right than on the left visual field and this asymmetric performance was significantly more prononounced in near than in far space [$t(9) = 5.93, p < 0.001$]. These results are shown in Figure 3.14.

No analysis was carried out for the response times as in the near space condition the patient did not respond correctly to any of the targets presented in the left visual field. The descriptive data are shown in Table 3.7

Table 3.7 Balloon task: mean (SD) response times (sec) for correctly detected targets by SV and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far).

	Near			Far		
	Left	Right	R-L Diff	Left	Right	R-L Diff
SV	-	8	-	15	8	-7
NC	3.57 (0.75)	4.01 (1.15)	0.44 (0.88)	3.43 (1.11)	4.18 (2.29)	0.74 (1.47)

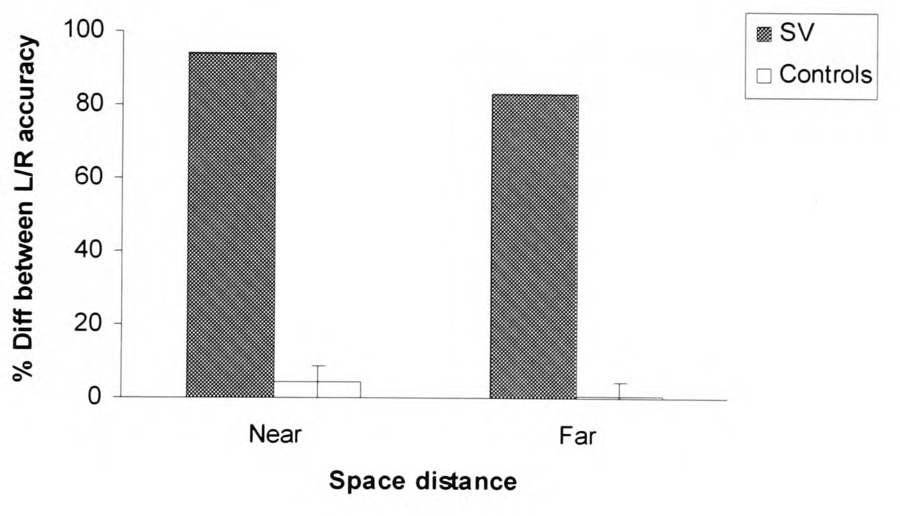


Figure 3.14 Difference in accuracy between the left and right visual field in near and far space for SV and the control group. Positive/negative values indicate a rightward/leftward bias in accuracy.

3.4.2.2 The Landmark task

For the Landmark task, the patient's PSE fell outside the range of the control group in both distance conditions (see Table 3.8 and 3.9). The amplitude of her rightward perceptual bias was, however, considerably larger in near than in far space. In addition, SV showed a rightward M index in far space which fell outside the normal range in the far but not in the near space condition. As the patient's SD indexes (Near: 5.12; Far: 7.68) was substantially higher than the cut-offs for perceptual uncertainty (Near: ≤1.48; Far: ≤1.96), her rightward M index was considered as the result of a partial guessing behaviour and not of a genuine ipsilateral motor bias. However, even in the presence of partial guessing, the patient's PSE estimation can still be considered reliable (Toraldo et al., 2004).

Table 3.8 Landmark results in near space for patient SV following Toraldo et al.'s (2004) procedure.

	Near				
	PSE	CI (PSE)	SD	M	(CI) M
SV	75	[63.53 86.47]*	5.12	0.13	[0.04 0.21]
NC	0.02 (1.37)	[2.76 -2.76]	≤ 1.48	-0.01 (0.03)	[0.05 -0.06]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

Table 3.9 Landmark results in far space for patient SV following Toraldo et al.'s (2004) procedure.

	Far				
	PSE	CI(PSE)	SD	M	(CI) M
SV	37.50	[12.54 62.46]*	7.68	0.72	[0.61 0.83]*
NC	-0.66 (2.13)	[3.61 -4.93]	≤ 1.96	0.05 (-0.12)	[-0.02 -0.17]

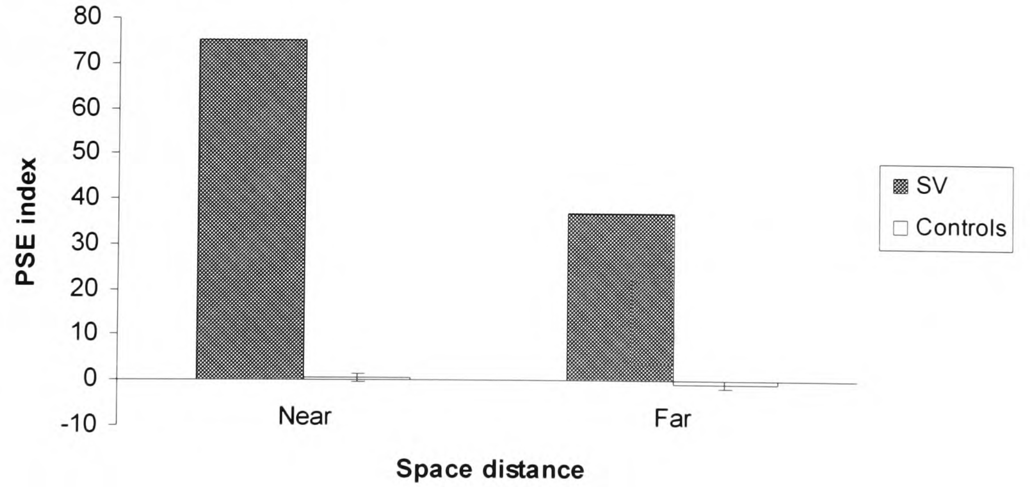
PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

In addition to the confidence interval diagnostic criterion recommended by Toraldo and co-workers (2004), further statistical analyses were carried out.

The rightward perceptual bias shown by SV was significantly larger than that of the controls in both near [$t(9) = 52.18, p < .001$] and far space [$t(9) = 16.85, p < .001$]. The patient's rightward bias was, however, significantly larger in near than in far space compared to the controls [$t(9) = 18.20, p < .001$]. These results are summarized in Figure 3.15 (A).

The M index for SV, indicating a tendency of "right" responses, was significantly higher that that of the controls in the near [$t(9) = 4.49, p < .01$] and far space [$t(9) = 17.87, p < .001$] conditions. Across the two space distances, her motor bias was significantly higher in far than in near space compared to the controls [$t(9) = 7.06, p < .001$] (Tables 3.8 and 3.9). These results are shown in Figure 3.15 (B).

A



B

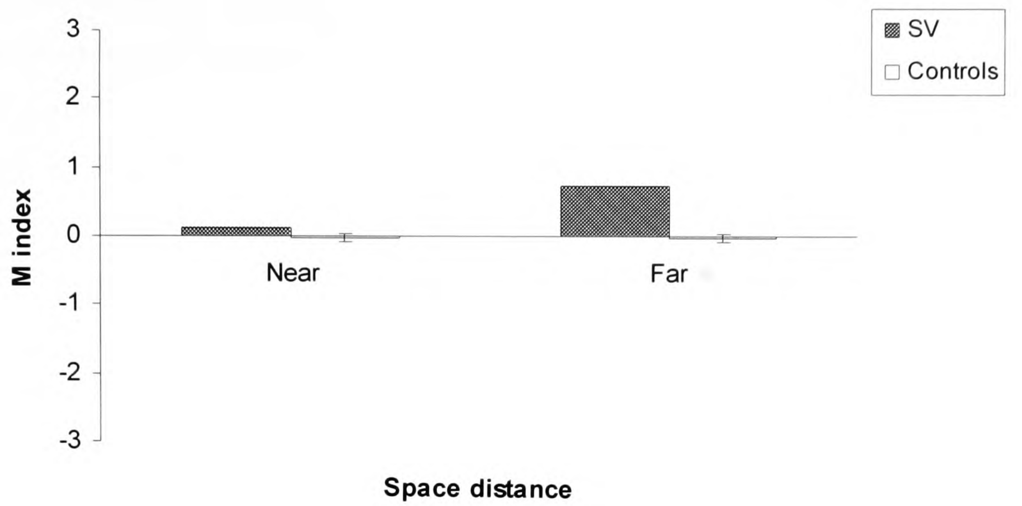


Figure 3.15 Landmark performance as a function of spatial distance (Near, Far) for SV and the control group. Positive/negative values indicate a rightward/leftward (A) perceptual bias and (B) response bias.

In summary, SV demonstrated impairments in both near and far space and in both experimental tasks. In the Balloon task, she showed an asymmetrical search pattern being more accurate in the right than the left visual field. This search asymmetry was, however, significantly more prominent in near than in far space. In the Landmark task, the patient's rightward PSE index fell clearly outside the normal range defined by the control group. This rightward perceptual bias was again more pronounced in near compared to far space. SV had also an abnormal rightward response bias index (M) which appeared larger in far than in near space.

3.4.2.3 VBM analysis

A morphometric analysis of SV's MRI scan was carried out to identify more specifically the brain areas of grey matter loss as a result of the ischemic stroke. This procedure allows the detection of damage that is not visible with the naked eye during ordinary inspection of the brain scans.

A three dimensional T1-weighted MRI image of the patient was acquired on a 3 tesla Philips Achieva MRI scanner. The voxel size was 1 x 1 x 1, field of view 256 mm with a matrix size of 256 x 256 x 124. Voxel Based Morphometry (VBM) was carried out using SPM5 (Welcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm).

To correct for global differences in brain shape, the MRI image of the patient was normalized to standard stereotactic space and segmented to extract grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF). In order to preserve volumetric information, modulation of voxel values by the Jacobian determinants was performed on the segmented GM and WM images. The modulated GM and WM images were then smoothed with an 8 mm FWHM Gaussian Kernel. A subtraction analysis between the Montreal Neurological Institute (MNI) grey matter template (provided in the SPM5 package) and the patient's 3D MRI image was carried out. The MNI template was obtained from 151 subjects and smoothed using an 8mm FWHM Gaussian. As shown in Figure 3.16, the brain areas showing grey matter loss in SV included the right occipital areas in correspondence of the lingual gyrus, cuneus and fusiform gyrus, in addition to the posterior cingulate, insula, parahippocampal gyrus, thalamus and left cerebellum (See also Table 3.10). Only grey matter was considered in the analysis.

Table 3.10 Brain areas of grey matter loss in patient SV

Brain Areas	L/R	Talairach coordinates X Y Z
Lingual Gyrus BA 18	R	2, -81, 6
Cuneus BA 17	R	3, -80, 12
BA 18	R	2, -77, 9
Posterior Cingulate BA 30	R	5, -68, 13
BA 23	R	6, -66, 12
Fusiform Gyrus BA 19	R	25, -58, -10
Insula	R	42, -5, 2
Parahippocampal gyrus BA 37	R	26, -42, -8
Thalamus (Dorsomedial nucleus)	R	2, -15, 4
Cerebellum	L	-40, -58, -19

R: right L: left

Figure 3.16 Areas of grey matter loss in patient SV. The images are presented in neurological convention (R/R, L/L).

3.4.3 Discussion

Following an ischemic stroke, patient SV sustained damage of the right extrastriate cortex, posterior cingulate area, insula and thalamus. Lower grey matter density in the left cerebellum was also detected. The clinical assessment of neglect revealed impairment on both cancellation and line bisection tasks which appeared more severe in near than in far space. In the Balloon task, SV's search performance was impaired in both distance conditions. Her asymmetric visual search pattern in favour of the right visual field was, however, significantly more pronounced in near than in far space. In the same vein, the patient's results in the Landmark task showed a rightward perceptual bias which induced her to underestimate the length of the left line segment – a tendency that was considerably larger in near compared to far space. SV's rightward response bias instead was greater in far than in near space. This latter tendency may be related to the partial guessing behaviour of the patient (SD > 1.96) which can make the estimation of the M index unstable across several testing sessions. Despite partial guessing, the estimation of the PSE index remains, however, still reliable (Toraldo et al., 2004).

The fact that SV showed more severe neglect in near space than in far space supports the idea that distinct mechanisms are involved in the allocation of attention across different sectors of space and that they can be selectively compromised by specific neuronal damage. Patient SV showed also left homonymus hemianopia but the fact that her performance changed significantly across space distances suggested that SV's deficits may be more associated to an attentional impairment rather than to her visual field loss.

In the present study, both visual exploration and line bisection tasks were used to investigate whether impairment of different visuospatial skills is consistent across space distance. As with the patient described by Vuilleumier et al. (1998), SV is the second case reported showing space related neglect in both line bisection and visual exploration. The visuospatial deficits of Vuilleumier et al.'s (1998) patient were confined to far space while SV showed more severe neglect in near space. These cases contribute to support the hypothesis that neglect restricted to a specific sector of space can occur independently of the type of task used.

The involvement of a directional motor response has often been considered crucial for showing dissociations in neglect patients between near and far space (Pizzamiglio et al., 1989; Vuilleumier et al., 1999). This idea has recently been questioned by some behavioural and neuroimaging studies. Pitzalis et al (2001) and Butler et al. (2004) for example demonstrated that near and far space neglect can be observed even when the task does not require a ballistic movement of the upper limb toward the stimuli. In addition, Weiss et al. (2003) showed different neuronal activations for a line bisection task carried out in near and far space which was not modulated, however, by the presence/absence of a motor response. In the present study, the patient was asked to indicate her answer with a simple button press in both experimental tasks. The fact that SV showed a dissociation between near and far space under a condition where the involvement of a directional motor response was minimised undermines the hypothesis that overt motor tasks are more successful in detecting distance related deficits in neglect. Accordingly, the surrounding space may not only be coded in terms of motor programs (i.e. grasping, oculomotion) but it is also shaped through sensory information (i.e. visual, proprioceptive inputs). Given the patients' clinical conditions, unfortunately it was not possible to verify whether SV's space specific impairment would have been modulated if she had carried out the tasks with a directional motor response.

Patient SV sustained damage to the right extrastriate cortex, posterior cingulate, insula, thalamus and left cerebellum. Neglect patients with posterior brain damage (i.e. occipital and parietal) have been shown to be more impaired in line bisection than in visual exploration tasks which involve more anterior brain structures (i.e. insula, superior temporal- and frontal cortex). SV presented a posterior occipital-cingulate lesion and a more anterior insula damage which could probably explain her impairment in both the Landmark and the Balloon task. An investigation of the respective functions and neuronal interconnections of these regions may help to explain why her neglect deficits were more severe in near than in far space.

The brain areas shaping the dorsal and the ventral visual stream have been associated with near and far space representation (Previc, 1990; Weiss, 2000; 2003; Bjoertomt et al., 2002). Neurophysiological and neuroimaging studies seem to support this dichotomy but the outcomes of the clinical studies with neglect patients provide a less neat picture of the neuronal substrate involved in the attentional processes for the two space sectors. Amongst the studies that investigated space related dissociations in neglect, only three patients have been reported whose deficit were worse in near than in far space (Halligan and Marshall 1991; Mennemeier et al., 1992; Berti and Frassinetti, 2000). Three other single cases and several group studies have shown the opposite pattern (Vuilleumier et al. 1999; Shelton et al., 1990; Barrett et al., 2000; Cowey et al., 1994; 1999; Keller et al., 2005; Butler et al., 2004). The brain areas damaged in those patients with far space neglect generally involve occipito-temporal regions whereas near space neglect has been described in concomitance of extensive brain lesions which included both parietal and temporal areas (Halligan and Marshall 1991; Mennemeier et al., 1992; Berti and Frassinetti 2000).

As to the role of the occipital cortex, a neuroimaging study on multisensory representation of peripersonal space in normal subjects showed that the visual areas of the right calcarine sulcus and the posterior collateral sulcus showed preference for visual stimuli in near over far space regardless of proprioceptive information referring to hand position (Makin et al., 2007). Consequently, the authors hypothesised that these areas of the occipital cortex may code peripersonal space based specifically on visual information of the surrounding stimuli, while other areas such as the anterior intra parietal sulcus can show preference for near stimuli when both visually and proprioceptive inputs (hand position) are available. In another study, Quinlan and Culham (2007) demonstrated that the activity of the occipital areas can be modulated by different viewing distances by keeping the visual angle constant. The authors observed a preference for near versus far stimuli vergence with diffuse activation through large parts of the primary visual cortex (i.e. V3A) whose intensity peaked in the parieto-occipital sulcus. Quinlan and Culham's finding (2007) suggests that the occipital cortex may contribute to the representation of peripersonal space by providing the dorsal pathway with depth-related information useful for the operations of reaching and grasping. Further support to the idea that primary visual areas (i.e. V1, V2 and V4) are prevalently involved in near space encoding is provided by several neurophysiological studies (Trotter et al., 1992; Gonzalez and Perez, 1998; Dobbins et al., 1998; Rosenbluth and Allman, 2002). Dobbins et al. (1998), for instance, observed that among the cells that had a significant response modulation with viewing distance in early visual areas of monkeys, those showing greater response by increasing proximity of the stimuli (nearness cells) were the most representative compared to far-space tuned neurons (farness cells).

Although not very common, neglect has also been observed following cingulate cortex damage (Watson et al. 1973; Heilman et al., 1983) which represents one of the transmodal nodes in the neuronal network model for spatial attention proposed by Mesulam (1990). The author suggested that damage to this area can impair the ability to shift anticipatory attention towards expected events of motivational relevance (Mesulam, 1981). The functional component that was damaged in patient SV is the posterior region of the cingulate cortex (PC) which is specifically involved in visuospatial mechanisms. Posterior cingulate neurons are recruited during the monitoring of eye movements towards behaviourally salient stimuli in connection with the fronto-parietal network (FEF-SPC) of visuospatial orienting (Vogt et al., 1992). Several neuroimaging studies, for instance, showed that the posterior cingulate gyrus promotes the speed of visual target detection especially when attentional shifts are induced by anticipatory cues (Kim et al., 1999; Hopfinger et al., 2000; Mesulam et al., 2001; Mohanty et al., 2008). This pattern led the authors to suggest a possible role of the posterior cingulate as neuronal interface between motivation and spatial attention in detecting external events. It is worth highlighting that the dorsal and the ventral visual pathways are associated with the respective dorsal (dPC) and the ventral (vPC) subdivisions of the PC. The dPC includes areas 23d, d23a/b/c and 31, while the vPC includes areas v23a/b. The Brodmann's areas of the posterior cingulate area damaged in SV correspond to BA23 and the retrosplenial area BA30. From the morphometric analysis carried out on SV's MRI scan, it was not possible to discriminate clearly which subdivision of area 23 was damaged. However, her major impairment in near space would be more compatible with a dPC damage which receives inputs from the dorsal visual stream through its rich connection with the superior parietal cortex. Neuroimaging studies demonstrated the involvement of dPC during visual feedbacks in relation to moving hands during tasks of reaching, pointing and grasping (Grafton et al., 1996; Inoue et al., 1998). Overall, the involvement of PC in the operations of visual spatial orientation towards salient stimuli and monitoring of hand movements could lead to consider this area as relevant for the neuronal representation of near space. The retrosplenial area, also damaged in SV, has direct connections with dPC. This area participates in memory-associated visuospatial functions such as topographical orientation through its connections with the hippocampus. As SV was not assessed for her topographical memory it is not possible to evaluate the possible impact of her retrosplenial and parahippocampal injury. This latter brain structure, also damaged in SV, has been specifically associated with neglect deficits following posterior cerebral artery stroke (Mort et al., 2003).

Several neuroimaging studies have shown the involvement of the insula in visuospatial attention (Gitelman et al., 1999; Kim et al., 1999; Nobre et al., 2000) and in the mechanisms of stimulus-driven spatial orienting (Hahn et al., 2006). In addition, in light of its connections with limbic and sensorimotor cortices, the insula integrates internal affective states with external multisensorial stimulation. Consistent with its role as a polisensory area, cases of multimodal left neglect have been observed following injury of the right insula (Berthier et al., 1987; Manes et al., 1999). More recently, Karnath et al. (2001, 2004, 2006) suggested that the right insula, together with the superior temporal cortex (STC) and temporal parietal junction (TPJ), represent the crucial cortical sites responsible for neglect. According to these authors, the multimodal neurons of these structures would integrate different sensory inputs - vestibular, auditory, neck proprioceptive, visual, olfactory - to create a high order representation of the body's position and its surrounding space which is clearly disrupted in the neglect syndrome. Within this framework, the severe visuospatial impairments shown by SV can be related to the disruption of an essential component of this neuronal system responsible for a stable reconstruction of egocentric spatial reference frames. The patients with neglect after right insula damage reported so far have only been assessed within their peripersonal space; it is, therefore, still unknown whether damage to the insular cortex would generate a visuospatial impairment in extrapersonal space. This area has tight interconnections with the superior temporal cortex which is believed to receive convergent inputs from both the dorsal and the ventral stream (Morel and Bullier, 1990; Baizer et al., 1991). Accordingly, the insula could indirectly contribute to the multimodal representation of both peripersonal and extrapersonal space. However, the involvement of this area in oculomotor control and in the functional mechanisms of motor coordination of the upper limb through its direct and reciprocal interconnections with the inferior parietal cortex (dorsal stream) may lead to assign to the insular cortex a greater role in near space coding.

The morphometric analysis revealed also damage of the right thalamus and left cerebellum. Several studies reported impaired body schema, anosognosia for hemiplegia and neglect in patients with right thalamus damage (Kumral et al., 1995; Motomura et al., 1986; Waxman et al., 1986; Vallar and Perani, 1986; von Giesen et al., 1994; Watson and Heilman, 1979; Karnath et al., 2002). Neurophysiological and neuroimaging studies support the role of this subcortical structure in many attentional processes such as information filtering, attentional shift and alertness (LaBerge and Buchsbaum, 1990; Robinson, 1993; Ungerleider and Christensen, 1979; Gitelman et al., 1999; Rafal and Posner, 1987; Sturm et al., 2006), but it seems that only lesions of certain thalamic nuclei can result in neglect (Park et al., 2006). For example, a study by Karnath et al. (2002) provided further support to the special role played by the pulvinar in attentional processes by identifying it, as well as the ventral and the dorsal lateral nuclei, as one of the sites of common lesion overlap in a group of neglect patients with subcortical damage. The thalamic area damaged in SV was circumscribed to the mediodorsal nucleus which, although not typically associated with the occurrence of neglect, can decrease arousal levels, generate fluctuation of attention and impairments of volitional horizontal gaze when damaged (Schmahmann, 2003; Kumral et al., 1995; Schmahmann and Pandya, 2008). These deficits can potentially increase the severity of neglect symptoms. A PET study by Weiss et al. (2000) demonstrated the involvement of the left thalamus in line bisection judgment when performed in near but not in far space. This result is not in line with the laterality of SV's right thalamic damage. In addition, a single case study demonstrated that left thalamus infarct can result in neglect restricted to far space only (Barret, et al., 2000). These inconsistencies do not allow a clear definition of the precise role played by the thalamus in the representation of peripersonal and extrapersonal space.

SV also had damage in the posterior lobule of the left cerebellum (Crus I and II). This structure has usually been associated with operations of voluntary motor control but clinical and neuroimaging evidence suggests that the cerebellum is also involved in higher order cognitive functions (Schmahmann and Pandya, 2008). Functional neuroimaging data, for example, showed activations of the left cerebellum in visuospatial tasks such as line bisection judgment (Fink at al., 2000b; 2002). It has been demonstrated that motor and attention performance activate distinct cerebellar regions (Allen, 2000). Motor tasks activate most commonly the right anterior cerebellum area (anterior quadrangular lobule, central lobule and anterior vermis) while the most common site of cerebellar activation during attention tasks is the left superior posterior area (the posterior part of the quadrangular lobule and superior part of the semilunar lobule) which is also damaged in patient SV. As each cerebellar hemisphere projects to the contralateral supratentorial regions by crossed cerebello-cerebral anatomical connections (Baillieux et al., 2008), the left cerebellar damage of SV is consistent with her left neglect deficits. It has been shown indeed that patients with right-sided cerebellar lesions tend to be more impaired in their verbal abilities while those with left-sided cerebellar lesions have more difficulties with visuospatial tasks (Kalashnikova et al., 2005; Hokkanen et al., 2001). SV's visuospatial impairments were more pronounced in near than in far space and the possible contribution of the cerebellum in the representation of proximal space may be related to its rich interconnections with the dorsal stream through the pontine nuclei. The abundant projections from the dorsal extrastriate and parietal areas to the cerebellum shape an important network for the sensory guidance of skilled bi-manual coordination movements which is essential in near space. In contrast, the cerebellum receives very few or no projections from the brain areas part of the ventral stream (Glickstein, 2000) as it may be more involved in visuospatial abilities implemented in proximal space than distal space.

Taken together, SV's left neglect affected her visual search- and line length estimation abilities but her impairment was more severe in near than in far space. Damage of anterior structures such as the insula is consistent with her lateralised performance in the Balloon task while lesions of the posterior extrastriate visual cortex and left cerebellum may account for her rightward perceptual bias in the Landmark task. The patient's greater impairment in near compared to far space could be due to the destruction of essential neuronal inputs from the posterior cingulate and cerebellum to the parietal cortex (dorsal stream) impairing visuospatial orienting and actions within reaching space. Most importantly, given the crucial contributions of the insula in the representation of one's body position in space, damage of this structure may have compromised the reconstruction of egocentric reference frames that are fundamental for near space coding. Accordingly, in this particular case, a more severe neglect in near than in far space resulted not only from a dysfunction of the dorsal stream but also from damage of other brain sturctures which are not strictly part of this pahway spacialised for near space coding.

The patients whose deficits will be described in the next section were studied to explore the extent to which the presence/absence of a directional ballistic movement can modulate the degree of their space specific deficits. In addition, their different patterns of performance will also be discussed in relation to the location of their brain damage.

3.4.4 The cases of MF

3.4.4.1 Methods

3.4.4.1.1 Subjects

3.4.4.1.1.1 Patient MF

MF is a 31-year old right handed male who, following a traumatic brain injury in 2004, sustained damage in the right orbitofrontal and ventro-medial temporal areas. After his accident MF developed post-traumatic amnesia, twitching of the left upper and lower limbs and the left side of his face, mild constructional apraxia and substantial concentration difficulties. No visual field deficits (i.e. hemianopia) were present. His family noticed a mild change in his personality after the accident and described him as more irritable, inclined to lose his temper easily and absentminded during his daily activities. MF is the manager of a local bar and ecological observations reported by the patient himself are of interest and alerted the experimenter to further investigations. He reported that his customers often complained about him serving and taking orders more readily from the clients on one side of the bar (on his right) while directed his attention to those standing on his left only when they alerted him verbally. He was not particularly troubled by his problems and he spontaneously commented: "I don't know what they have to complain about, they all get served eventually if they shout!". During his everyday activities he also reported that he frequently run into doors or pieces of furniture. He was however, unconcerned about these problems and despite his relatives and friends' complaints, MF appeared largely unaware of his difficulties. Three years after his accident MF was referred for a comprehensive neuropsychological examination. The results of his assessment are shown in Table 3.11.

3.4.4.1.1.2 Controls

In all tasks, MF's performance was compared with that of 12 healthy male controls matched for age and education (Mean age = 30.5, SD = 2.11; Mean education = 21.4, SD = 2.71). All the participants gave their informed, written consent to take part in the study and had no history of psychiatric disorder, brain damage, epilepsy or drug addiction. None of the control subjects were under any medications when testing took place.

3.4.4.1.2 Neuropsychological assessment and neglect tests

For MF a standard neuropsychological battery revealed a selective attentional deficit. No impairment of his linguistic and memory abilities was found (Table 3.11).

Table 3.11 MF's results in the neuropsychological battery

Tests	MF	Reference sample§
Mini Mental State Examination (MMSE)	29/30	29.25 (0.62)
Confrontational naming	19/20	19/58 (0.79)
Verbal Paired Associated	14/24	19.00 (3.36)
Rey's Complex Figure Test		
- Copying	30/36*	35.18 (1.40)
- Delay (10 min.)	9.5/36	19.86 (5.45)
Semantic Fluency	55	61.33 (15.77)
Phonemic Fluency	35	47.42 (12.12)
Digit Span Forward	8	6.83 (1.11)
Digit Span Backward	6	5.42 (1.31)
Raven's Progressive Matrices	33/36	34.00 (2.04)
Stroop Task		
- Error Intreference Effect	0	0.00 (0.00)
- Time Iterferation Effect	21.5*	10.06 (4.64)
Digit Cancellation		
- Correct Responses	53*	58.08 (1.98)
- False Allarms	0	0.00 (0.00)
- Omissions	7*	2.00 (2.00)
- Execution time (sec)		
- Matrix 1	15	21.90 (7.37)
- Matrix 2	29	29.77 (7.18)
- Matrix 3	38	38.22 (7.88)
Visuoconstructive Apraxia Test	13/14	13.75 (0.45)
Ideomotor Apraxia Test - Part 1 Right hand	35/36	
Ideomotor Apraxia Test - Part 1 Left hand	36/36	
Ideomotor Apraxia Test - Part 2 Right hand	36/36	
Ideomotor Apraxia Test - Part 2 Right hand	36/36	
Token Task	33/35	
Logical Memory		
- Immediate	8	
- Delayed (10 min.)	11	

* Impaired performance by > 2SD's above or below the normal range.

§ Mean (SD) of reference sample score based on N= 30 subjects

MF was assessed with the same battery for spatial neglect used for SV in near as well as in far space (section 3.4.1.2 of this chapter). Clinical assessment revealed mild signs of neglect for cancellation tasks especially for far space compared to near space. MF's line bisection performance was normal in near space but he showed a rightward bisection error above the cut-off (±0.01°) in far space. The patient's performance for the neglect tasks is summarised in Table 3.12.

Table 3.12 MF's results for the clinical assessment of neglect in near and far space

	Space	
Tests	Near	Far
Bells test	32/34[§] (15L / 17R)	28/34 (11L / 17R)
Star cancellation	54/54 (27L / 27R)	51/54 (15L / 17R)
Line bisection	+0.04°	+0.2
Drawing from memory	0[‡]	N.A.
Scene Copying	0	N.A.

[§] Overall number of correctly reported items; L: correct left; R: correct Right

° Deviation in degree of visual angle

[‡] "0": complete and correctly placed

N.A. Not administered

3.4.4.1.3 Experimental tasks and procedure

Both the Balloon task and the Landmark were administrated. Task properties and procedure remained the same as described in pages 72, 91 (Balloon task), 78, 91 (Landmark) and 74 (procedure) of the present chapter. The fundamental difference implemented was the introduction of an additional condition for the two tasks which required subjects to make a ballistic motor response to indicate their response. Therefore, from now onwards the first version of the Balloon and Landmark task described previously will be referred to as "perceptual" while the second version will be called "motor". In the perceptual version, subjects were asked to respond by pressing two different buttons on a keyboard both in near and far space. In the Balloon task they had to press the number "1" key on the keyboard for the "target present" response and the "0" key for the "target absent" response. In the Landmark task, participant were required to press the number "1" key for the responses to the left segment of the line and the number "2" key for the right segment (both for "shorter" or "longer" responses). In the motor version of the tasks, participants were instructed to make a movement with their right arm toward the target (Balloon task) or the segment they have chosen (Landmark task) by touching them with their right index finger in near space and by pointing at them with a laser pen in far space. Only for the visual search task, if they thought that the target was absent they were asked to verbally inform the experimenter who recorded the responses on the computer. It must be acknowledged that technically, the presence of a button press in the perceptual version of the tasks does not make them "purely perceptual". However, the type of movement involvement is fairly minor in comparison to the motor condition. The former (perceptual condition) was indeed meant to emphasize more the perceptual judgement of the stimuli (based mainly on eye centred coordinates) whereas the latter (motor condition) stressed more a specific ballistic motor action toward the stimuli (based mainly on both eye and upper limb centred coordinates). For the perceptual condition, the response times were automatically recorded when the participants pressed the response keys. The response speed for the motor condition was instead recorded by the experimenter who also pressed the same response keys on the keyboard as soon as the participants reached (near) or pointed (far) at the target. As this recording procedure would have added the same degree of error in each participant, the response time data of the motor condition was also included in statistical analyses.

3.4.4.2 Results

3.4.4.2.1 The Balloon task

3.4.4.2.1.1 Perceptual condition

Two control participants were removed from the analysis as their accuracy level was 2 standard deviations below the average of the group. In each space condition (near and far) participants' overall accuracy was calculated by collapsing the mean accuracy data across left and right visual field. MF's overall accuracy was significantly poorer than that of the control group in both near [$t(11) = -7{,}06$, $p < .001$] and far space [$t(11) = -7{,}19$, $p < .001$].

To verify whether there was an abnormal asymmetric pattern of response in MF between the left and the right visual field, the difference in accuracy between the right and the left visual field recorded for the patient was compared with that of the control group for each space condition separately.

In near space, the difference in accuracy between the two visual fields observed in the patient was not significantly different from that of the control group [$t(11) = 0.00$, $p > 0.05$]. However, when performing the task in far space, MF was significantly less accurate in the left than in the right visual field compared to the controls group [$t(11) = 3.54$, $p < 0.01$]. These results are summarised in Table 3.13.

MF's performance changed significantly across the two space distances compared to the controls as he was equally accurate in both hemifields in the near space but more accurate on the right than on the left visual field in far space [$t(11) = 2.37$, $p < 0.05$]. These results are shown in Figure 3.17.

Table 3.13 Balloon task: Mean percentage (SD) of correctly detected targets for MF and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the perceptual condition.

	Near			Far		
	Left	Right	R-L Diff	Left	Right	R-L Diff
MF	67.00	67.00	0.00	67.00	78.00	11.00
NC	96.17 (4.37)	96.17 (4.37)	0.00 (3.62)	98.00 (2.95)	97.17 (4.45)	-0.83 (3.21)

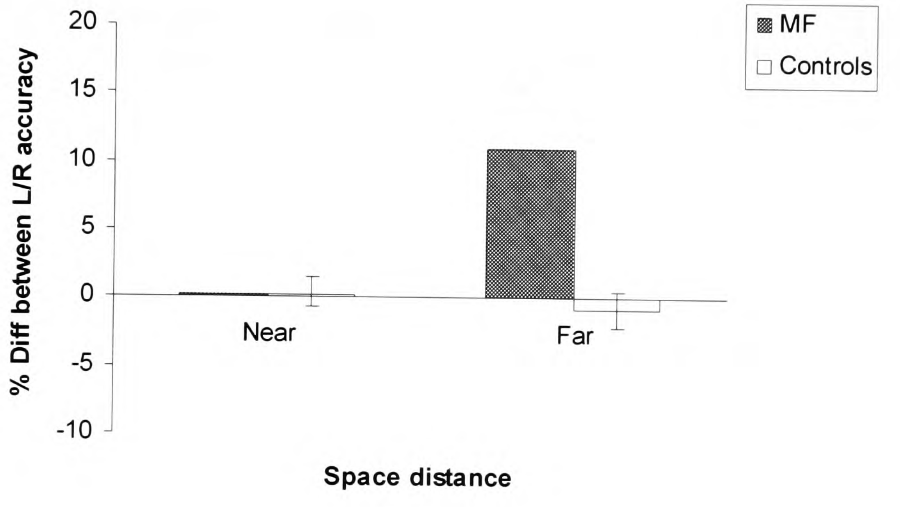


Figure 3.17 Difference in accuracy between the left and right visual field in near and far space for MF and the control group. Positive/negative values indicate a rightward/leftward bias in accuracy in the perceptual condition.

Response times

The overall response time was calculated collapsing the mean RTs scores recorded for the two visual fields for each space condition separately. MF's overall response speed was not significantly slower than that of the control group in near [$t(11) = 1.05, p > .05$] and far space [$t(11) = 0.21, p > .05$].

To compare the difference in response speed between the two visual fields recorded for MF with that of the control group, the difference between the mean response times of the right minus the mean response times recorded for the left hemifield was calculated (Table 3.14). In each space condition, MF showed to be equally fast across the two visual fields compared to the control group [near: $t(11) = -0.25, p > 0.05$; far: [$t(11) = 1.40, p > 0.05$]. MF' response speed across the two visual field did not change significantly between near and far space [$t(11) = 1.27, p > 0.05$].

Table 3.14 Balloon task: Mean response times in seconds (SD) for the correctly detected targets for MF and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the perceptual condition.

	Near			Far		
	Left	Right	R-L Diff	Left	Right	R-L Diff
MF	3.85	3.96	0.11	3.05	4.08	1.02
NC	3.29 (0.53)	3.60 (0.63)	0.31 (0.77)	3.33 (0.60)	3.53 (0.80)	3.43 (0.65)

3.4.4.2.1.2 Motor condition

The same set of analysis was carried out for the motor condition. MF's overall accuracy was significantly poorer than that of the controls in both near [$t(11) = -1{,}877, p < .05$] and far space [$t(11) = -3{,}405, p < .01$].

The difference in accuracy between the right and the left visual field observed in the patient was again compared with that of the control group for each space distance separately (Table 3.15). In near space, MF's accuracy was significantly higher in the right than in the left visual field [$t(11) = 4.48, p < 0.01$]. In contrast, in far space he was equally accurate in both hemifields [$t(11) = -0.12, p > 0.05$].

This change in performance across the two space conditions was significantly different from that shown by the the control group whose difference in accuracy between the two visual fields remained consistent in near and far space [$t(11) = 4.337, p < 0.001$]. These results are shown in Figure 3.18.

Table 3.15 Balloon task: Mean percentage (SD) of correctly detected targets for MF and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the motor condition.

	Near			Far		
	Left	Right	Diff $_{R-L}$	Left	Right	Diff $_{R-L}$
MF	83.00	100.00	17.00	89.00	89.00	0.00
NC	98.08 (3.68)	97.58 (3.80)	-0.50 (3.75)	97.50 (3.09)	98.08 (3.68)	0.58 (4.64)

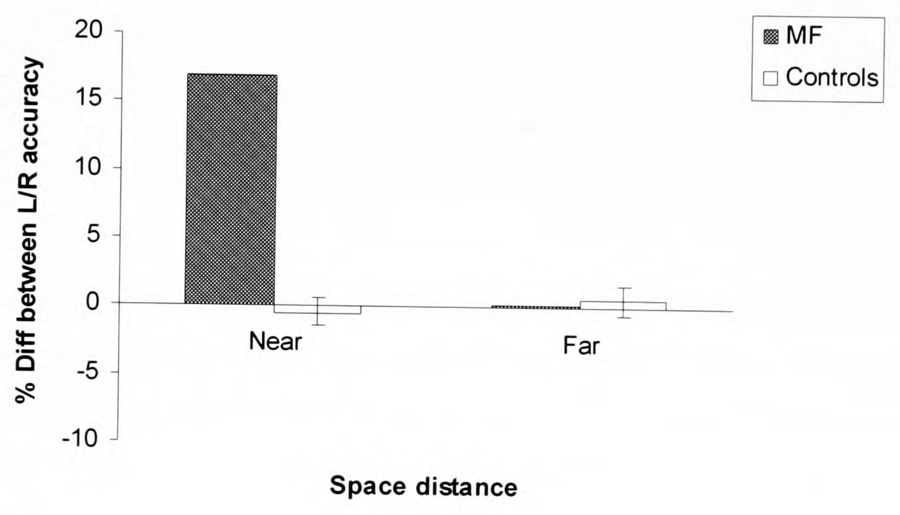


Figure 3.18 Difference in accuracy between the left and right visual field in near and far space for MF and the control group. Positive/negative values indicate a rightward/leftward bias in accuracy in the motor condition.

Response times

By collapsing the mean response times recorded for the left and the right visual field in each space condition, MF's overall response speed was not significantly slower than the controls in both near [$t(11) = 1.75, p > 0.05$] and far space [$t(11) = 1.21, p > 0.05$].

When considering the difference in the response times between the right and the left visual field, MF was significantly slower in detecting stimuli on the left compared to the right hemifield in near space [$t(11) = -2.16, p < 0.05$]. No difference was found in far space [$t(11) = 0.05, p > 0.05$] (Table 3.16).

The difference in MF's response times between the two visual fields changed significantly across near and far space compared to that of the controls [$t(11) = 1.80, p < 0.05$]. His asymmetric pattern of response speed in favour of the right visual field in near space was indeed not present in far space.

Table 3.16 Balloon task: Mean response times in seconds (SD) for the correctly detected targets for MF and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the motor condition.

	Near			Far		
	Left	Right	Diff $_{R-L}$	Left	Right	Diff $_{R-L}$
MF	5.17	4.69	-0.48	5.07	5.34	0.27
NC	3.45 (0.36)	4.41 (0.82)	0.96 (0.64)	3.92 (0.84)	4.14 (1.21)	0.22 (0.90)

Further analysis explored whether MF's accuracy within near and far space was modulated by the type of response required. When he had to make a directional motor response, MF's ability in detecting targets in the left visual field was significantly worse only in near space compared to healthy controls but not in far space [$t(11) = 2.95, p < 0.05$]. In contrast, in the perceptual condition the patient's accuracy on the left visual field was significantly worse than that on the right visual field only in far space and not in near space [$t(11) = 2.69, p < 0.05$].

In far space the opposite pattern was observed as the patient became equally accurate in both visual fields in the motor condition compared to the perceptual condition in which he was significantly more accurate on the right than on the left

3.4.4.2.2 The Landmark task

3.4.4.2.2.1 Perceptual and motor conditions

Following the diagnostic criterion in Toraldo et al. (2004), MF did not show a pathological shift of his PSE in the perceptual condition. The patient's M index was also within the normal range (Table 3.16 and 3.17). In the motor condition, he only showed a rightward response bias in far space which fell just outside the normal range (Table 3.18 and 3.19).

Table 3.16 Landmark results in near space (perceptual condition) for patient MF following Toraldo et al.'s (2004) procedure.

	Near				
	PSE	CI (PSE)	SD	M	(CI) M
MF	-2.50	[-3.61 -1.39]	0.85	0.09	[0.03 0.16]
NC	- 0.79 (1.32)	[1.85 -3.43]	≤ 1.60	-0.01 (0.05)	[0.08 -0.10]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index; * Left neglect.

Table 3.17 Landmark results in far space (perceptual condition) for patient MF following Toraldo et al.'s (2004) procedure.

	Far				
	PSE	CI(PSE)	SD	M	(CI) M
MF	-2.50	[-3.61 -1.39]	0.85	0.09	[0.02 0.16]
NC	-0.81 (1.41)	[2.01 -3.63]	≤ 1.75	-0.01 (0.05)	[0.08 -0.11]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

Table 3.18 Landmark results in near space (motor condition) for patient MF following Toraldo et al.'s (2004) procedure.

	Near				
	PSE	CI (PSE)	SD	M	(CI) M
MF	-0.63	[-1.64 0.39]	1.28	-0.07	[-0.14 -0.01]
NC	-0.38 (1.70)	[3.02 -3.79]	≤ 1.63	-.01 (0.04)	[0.06 -0.09]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

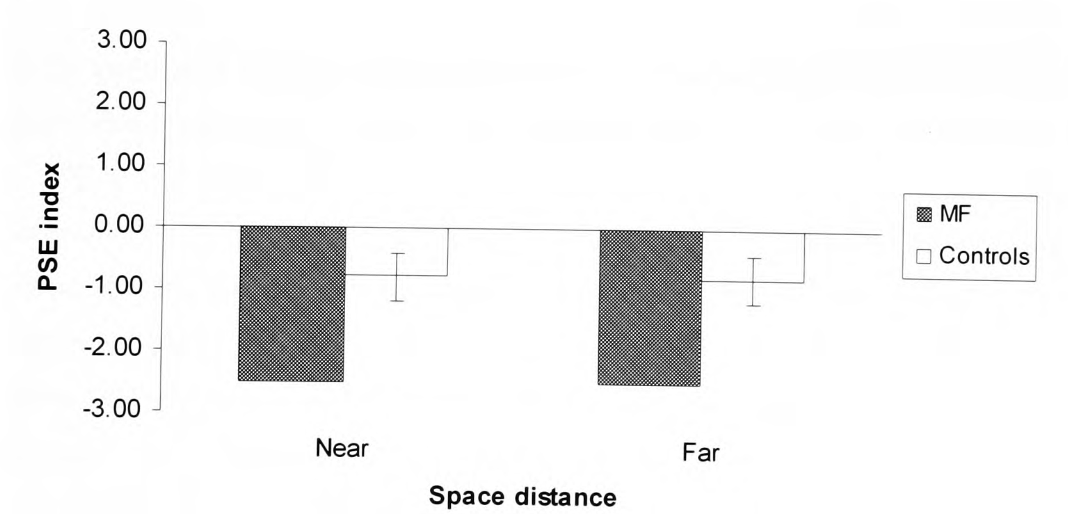
Table 3.19 Landmark results in far space (motor condition) for patient MF following Toraldo et al.'s (2004) procedure.

	Far				
	PSE	CI(PSE)	SD	M	(CI) M
MF	-2.50	[-3.54 -1.46]	0.85	-0.06	[0.44 0.26]*
NC	-1.01 (2.03)	[3.05 -5.06]	≤ 2.42	-0.02 (0.02)	[0.03 -0.07]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

When asked to judge which end of the line was shorter (or longer), MF's leftward perceptual bias was not significantly different from that of the control group in both spatial conditions [near: $t(11) = -1.24, p > 0.05$; far: $t(11) = -1.15, p > 0.05$] (Table 3.16 and 3.17). Similarly, when he was asked to point to one end of the line, no significant difference between the patient's PSE score and the control group was found in both spatial conditions [near: $t(11) = -0.14, p > 0.05$; far: $t(11) = -0.70, p > 0.05$]. MF's PSE amplitude did not change significantly across space distances compared to the control group in both perceptual [$t(11) = 0.07, p > 0.05$] and motor version [$t(11) = 0.76, p > 0.05$] of the Landmark task. In addition, MS's PSE did not change significantly depending on the type of response in both near [$t(11) = 0.83, p > 0.05$] and far space [$t(11) = 0.25, p > 0.05$].These results are summarized in Figure 3.19 A and B.

A



B

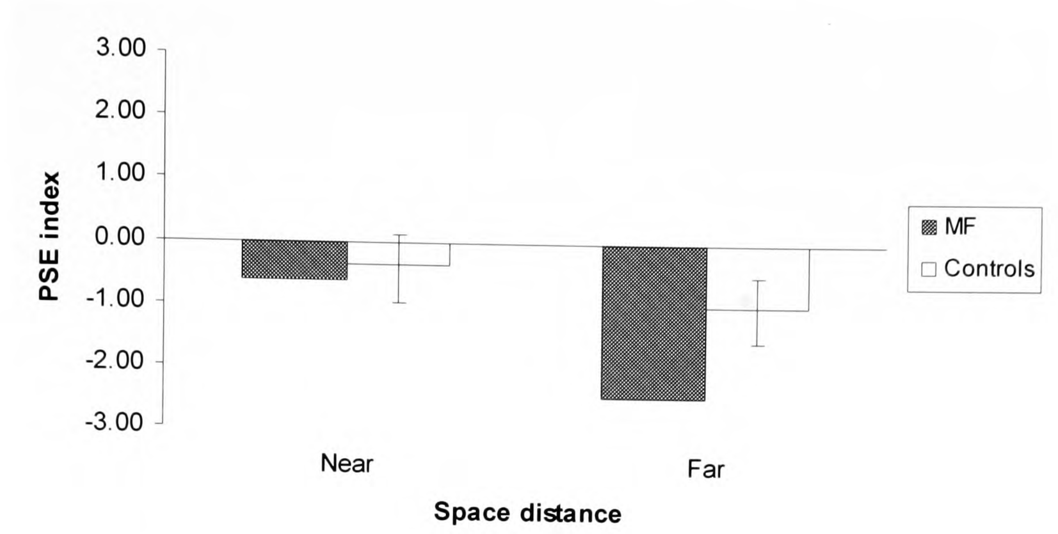
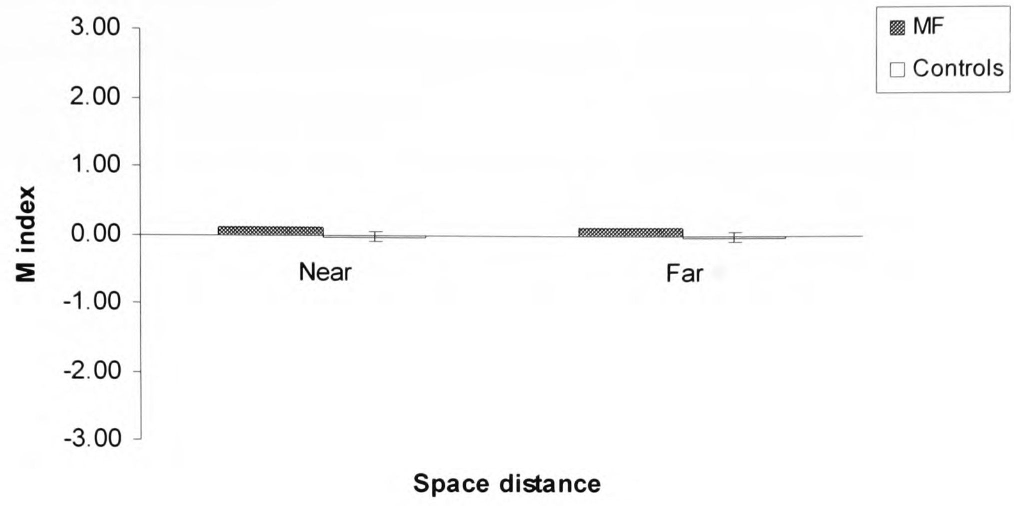


Figure 3.19 Landmark performance as a function of the type of response for MF and the control group. Positive/negative values indicate a rightward/leftward perceptual bias in the (A) perceptual and (B) motor condition in near and far space.

In the perceptual condition, the patient's M score was not significantly different from that of the control group in each space condition [near: $t(11) = 1.92, p > 0.05$; far: $t(11) = 1.92, p > 0.05$]. The same pattern of results was observed for the motor condition [near: $t(11) = -1.20, p > 0.05$; far: $t(11) = -1.92, p > 0.05$]. In addition, the response bias shown by the patient did not change significantly across space distance in both perceptual [$t(11) = 0, p > 0.05$] and motor condition [$t(11) = 0.58, p > 0.05$]. In near space MF tended to make right key presses in the perceptual condition and left key presses in the motor condition compared to the healthy controls that showed a negative M index regardless of the type of response [$t(11) = 2.20, p < 0.05$]. The same pattern was observed in far space [$t(11) = 2.45, p < 0.05$]. These results are shown in Figure 3.20 A and B.

A



B

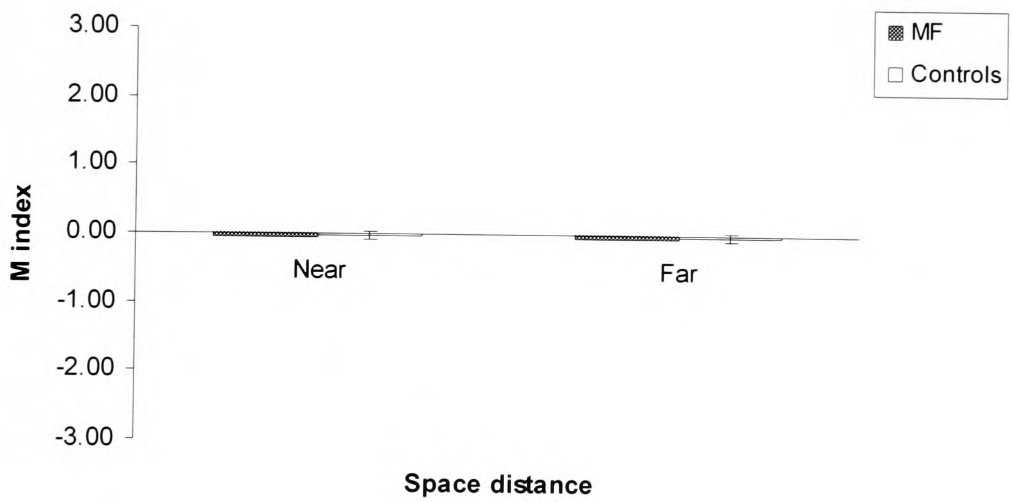


Figure 3.20 Landmark performance as a function of the type of response for MF and the control group. Positive/negative values indicate a rightward/leftward response bias in the (A) perceptual and (B) motor condition in near and far space.

3.4.4.2.3 VBM analysis

Due to the availability of a three dimensional MRI scan for MF, a Voxel Based Morphometry analysis was carried out following the same procedure and parameters used for patient SV (See section 3.4.2.3 -page 114- of patient SV for details). As shown in Figure 3.21, the brain areas of grey matter loss were found in correspondence of the right ventro-temporal cortex (fusiform and inferior temporal gyrus), bilateral putamen and right globus pallidus, midbrain and frontal cortices (See also Table 3.20). Only grey matter was considered in the analysis.

Table 3.20 Brain areas of grey matter loss in patient MF

Brain Areas	R/L	Talairach coordinates
Inferior Temporal Gyrus (BA 20)	R	63, -26, -17
Fusiform Gyrus (BA 20)	R	56, -34, -21
Basal Ganglia		
Putamen	L	-26, 2, 2
	R	27, 0, 1
Globus Pallidus	R	13, 1, -5
Midbrain		
Red nucleus	L	-6, -24, -8
Substantia Nigra	R	8, -20, -12
Superior Frontal Gyrus (BA 6)	L	-6, 3, 65
Orbitofrontal cortex (BA 11)	R	1, 22 -20
	L	-1, 19 -19

R: right L: left

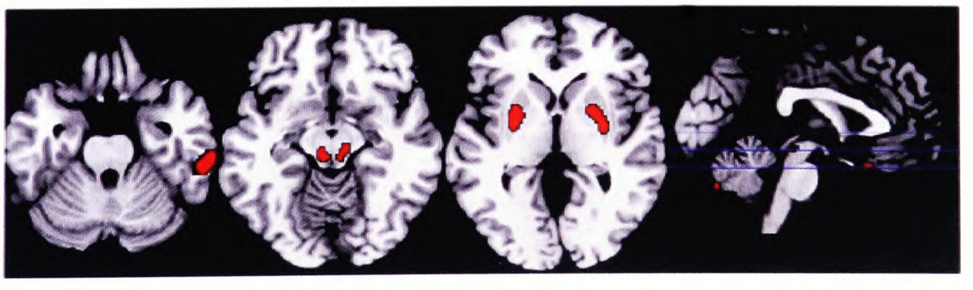


Figure 3.21 Areas of grey matter loss in patient MF. Images are shown in neurological convention (R/R and L/L).

3.4.5 The case of JA

3.4.5.1 Methods

3.4.5.1.1 Subjects

3.4.5.1.1.1 Patient JA

Twenty-seven years old patient JA was allegedly assaulted on December 2001 sustaining a severe closed head injury. He developed a large infarction of the right hemisphere (Figure 3.22) which involved the medial and inferior occipital (BA 18, 19), medial and superior temporal cortex (BA 21, 22), supramarginal and angùlar gyrus (BA 40, 39) and medial frontal areas (BA 44, 46).

Following decompressive surgery and rehabilitation he had been left with a residual left hemiparesis, left homonymus hemianopia, tactile extinction in the upper part of his left arm and trunk and visuospatial neglect. After the accident he developed fluctuant symptoms of depression mostly related to the effects that his disability caused to his everyday life. In fact, because of his hemiparesis, he requires frequent external help even for ordinary tasks such as dressing or showering. The severe left hemianopia coupled with severe left neglect greatly limited JA's ability to navigate successfully and independently in the environment. He has learned to use strategies to compensate for his visual field defect as he voluntarily turns his head and eyes to the left in an attempt to compensate for the losses in the left visual field. His success in doing so, however, was hampered by persistent inattention related to items located within the contralateral hemispace. After seven years from the accident JA's disabling visuospatial deficits were considered as having a chronic nature. The results of JA neuropsychological assessment are summarised in Table 3.21.

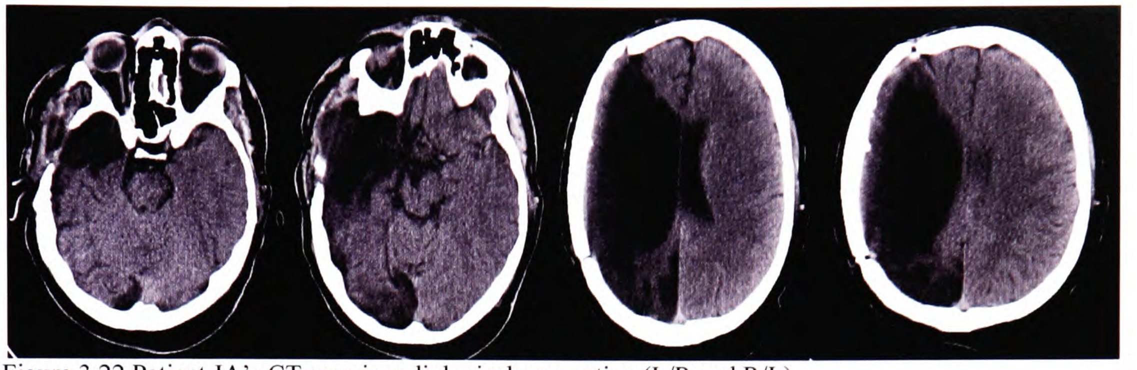


Figure 3.22 Patient JA's CT scan in radiological convention (L/R and R/L)

3.4.5.1.1.2 Controls

JA's performance was compared with that of 8 males matched control subjects (Mean age = 28.2, SD = 1.58; Mean education = 20.5, SD = 1.25). All the participants gave their informed, written consent to take part in the study and had no history of psychiatric disorder, brain damage, epilepsy or drug addiction. None of the control participants were under any medications when testing took place.

3.4.5.1.2 Neuropsychological assessment and neglect tests

JA's neuropsychological assessment revealed normal verbal abilities with scores within the normal range on all tests of verbal reasoning, comprehension, confrontation naming, short and long term verbal memory. Very poor were instead his visuospatial and visuo-constructive skills. He also showed deficit of selective attention in the Stroop task and digit cancellation task (Table 3.21).

Table 3.21 JA's results in the neuropsychological battery

Tests	JA	Reference sample[§]
Mini Mental State Examination (MMSE)	28/30*	29.25 (0.62)
Confrontational naming	20/20	19/58 (0.79)
Verbal Paired Associated	14/24	19.00 (3.36)
Rey's Complex Figure Test		
- Copying	28/36*	35.18 (1.40)
- Delay (10 min.)	14.5/36	19.86 (5.45)
Semantic Fluency	38	61.33 (15.77)
Phonemic Fluency	35	47.42 (12.12)
Digit Span Forward	6	6.83 (1.11)
Digit Span Backward	4	5.42 (1.31)
Raven's Progressive Matrices	22/36*	34.00 (2.04)
Stroop Task		
- Error Interference Effect	0	0.00 (0.00)
- Time Interference Effect	21.5*	10.06 (4.64)
Digit Cancellation		
- Correct Responses	48*	58.08 (1.98)
- False Allarms	0	0.00 (0.00)
- Omissions	12*	2.00 (2.00)
- Execution time (sec)		
- Matrix 1	56*	21.90 (7.37)
- Matrix 2	47*	29.77 (7.18)
- Matrix 3	51	38.22 (7.88)
Visuoconstructive Apraxia Test	9/14*	13.75 (0.45)
Token Task	36/36	
WAIS - Similarities	26/33	
Logical Memory		
- Immediate	21/25	
- Delayed (10 min.)	21/25	

* Impaired performance by > 2SD's above or below the normal range.

[§] Mean (SD) reference sample's scores of N = 30 subjects.

Patient JA was assessed for neglect in near and far space with the same tasks and procedure used to test SV and MF. JA showed a search deficit in cancellation tasks especially with high distractor density (i.e. Bells test) and a severe rightward error in the line bisection. These deficits were more prominent in far than in near space. Milder signs of inattention were instead present when drawing from memory and copying tasks administrated only in near space (Table 3.22).

Table 3.22 JA's results for the clinical assessment of neglect in near and far space

	Space	
Tests	Near	Far
Bells test	28/34§ (4L / 2R)	22/34 (9L / 3R)
Star cancellation	54/54 (27L / 27R)	51/54 (2L / 1R)
Line bisection	+30.09°	+54.4
Drawing from memory	1‡	N.A.
Scene Copying	2	N.A.

§ Overall number of correctly reported items; L: correct left; R: correct Right

° Deviation in degree of visual angle

‡ "1": complete but misplaced on the right; "2": incomplete on the left but correctly placed

N.A. Not administered

3.4.5.1.3 Experimental tasks and procedure

Tasks and procedure were the same as for patient MF (Section 3.4.4.1.3 on page 125).

3.4.5.2 Results

3.4.5.2.1 Balloon task

3.4.5.2.1.1 Perceptual condition

JA's overall accuracy in the Balloon task was significantly lower than that of the control group in far space [$t(7) = -2.83, p < 0.05$] but not in near space [$t(7) = -1.74, p > 0.05$].

The difference in accuracy between the left and the right visual field shown by the patient was significantly larger than that of the control group only in the far space condition [$t(7) = 6.73, p < 0.01$] in which he was more accurate on the ipsilesional (right) compared to the contralateral side of the display. The same comparison did not reach significance for the near space condition [$t(7) = 1.34, p > .05$] (Table 3.23).

When considering the change in left/right accuracy difference across the two space distances, JA showed greater impairment in far space than in near space [$t(7) = 3.06, p < 0.05$]. These results are shown in Figure 3.23.

Table 3.23 Balloon task: Mean percentage (SD) of correctly detected targets for JA and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the perceptual condition.

	Near			Far		
	Left	Right	$_{R-L}$ Diff	Left	Right	$_{R-L}$ Diff
JA	83.00	89.00	6.00	67.00	94.00	27.00
NC	97.13 (4.26)	94.25 (6.02)	-2.88 (6.08)	97.00 (3.21)	94.25 (6.02)	-2.75 (4.17)

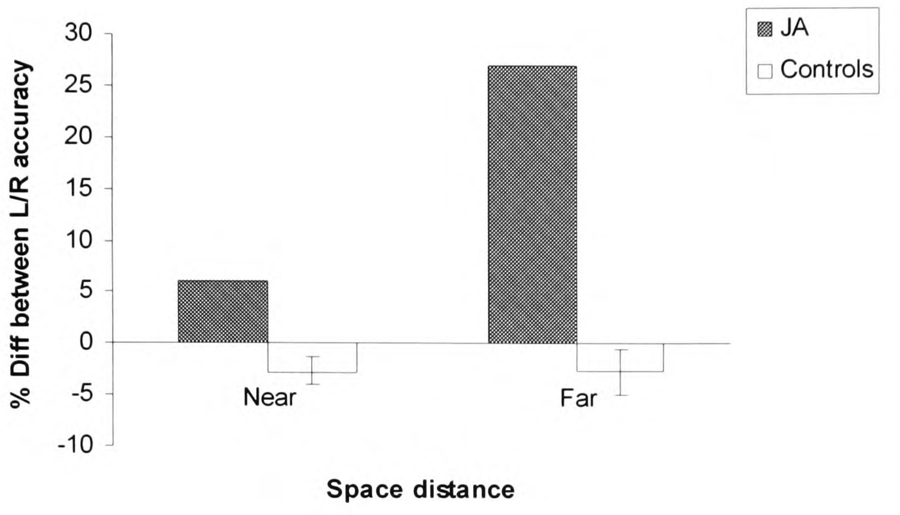


Figure 3.23 Difference in accuracy between the left and right visual field in near and far space for JA and the control group. Positive/negative values indicate a rightward/leftward bias in accuracy in the perceptual condition.

Response times

The analysis of the response times for the perceptual condition revealed that overall, compared to the control group, JA was significantly slower in near space [$t(7) = 5.40$, $p < 0.01$] but not in far space [$t(7) = 1.42$, $p > 0.05$]. However, when considering the difference between the response times for the left and the right visual field, he showed an asymmetric pattern of response speed in each space distance. JA was indeed significantly slower in detecting targets on the left than on the right visual field in far space [$t(7) = -4.87$, $p < 0.01$] but not in near space [$t(7) = -0.95$, $p > .05$]. This change in response speed across near and far space was significantly different from that of the controls [$t(7) = 3.07$, $p < 0.01$] (Table 3.24).

Table 3.24 Balloon task: Mean response times in seconds (SD) for the correctly detected targets for JA and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the perceptual condition.

	Near			Far		
	Left	Right	R-L Diff	Left	Right	R-L Diff
JA	5.32	4.77	-0.55	5.53	3.73	-1.80
NC	3.35 (0.43)	3.74 (0.61)	0.39 (0.93)	3.71 (0.46)	4.08 (0.60)	0.37 (0.42)

3.4.5.2.1.2 Motor condition

When JA was asked to make a ballistic motor response towards the target, his overall accuracy was significantly lower than that shown by the controls in both space distances [near: $t(7) = -3.97, p < 0.01$; far: $t(7) = -2.86, p < 0.05$]. The difference in performance between the two visual fields was not different from that of the control group in both near [$t(7) = 1.77, p > .05$] and far space [$t(7) = 0.17, p > .05$]. JA performance did not change significantly across the two space conditions [$t(7) = 0.42, p > .05$] (Table 3.25). These results are shown in Figure 3.24.

Table 3.25 Balloon task: Mean percentage (SD) of correctly detected targets for JA and the controls (NC) across visual fields (Left/Right) and spatial distance (Near, Far) in the motor condition.

	Near			Far		
	Left	Right	R-L Diff	Left	Right	R-L Diff
JA	78	83	5	83	89	6
NC	100.0 (0.0)	95.75 (4.92)	-4.25 (4.92)	97.00 (3.21)	97.13 (4.26)	0.13 (5.41)

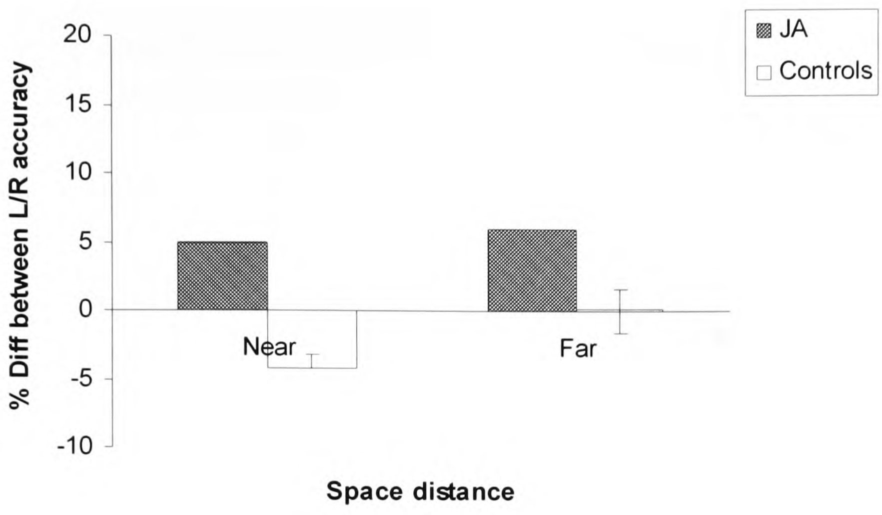


Figure 3.24 Difference in accuracy between the left and right visual field in near and far space for JA and the control group. Positive/negative values indicate a rightward/leftward bias in accuracy in the motor condition.

Response times

The analysis for the response times showed that overall JA was significantly slower than the control group in near space [$t(7) = 3.94$, $p < .01$] but not in far space [$t(7) = 0.40$, $p > .05$].

The difference between the mean response times recorded for the right minus those of the left visual field did not differ significantly from that shown by the control group in both near [$t(7) = -1.70$, $p > .05$] and far space [$t(7) = -1.13$, $p > .05$] (Table 3.26). The same difference between the two visual fields did not change significantly across space distance [$t(7) = 0.44$, $p > .05$].

Table 3.26 Balloon task: Mean response times (SD) in seconds for the correctly detected targets for JA and the controls (NC) across visual fields (Left, Right) and spatial distance (Near, Far) in the motor condition.

	Near			Far		
	Left	Right	R-L Diff	Left	Right	R-L Diff
JA	6.91	5.05	-1.87	5.48	4.20	-1.28
NC	4.19 (0.54)	4.52 (0.88)	0.33 (1.22)	4.27 (0.89)	4.55 (1.44)	0.28 (1.30)

A further analysis compared JA's performance with that of the controls across the two types of response for each space distance separately. JA's accuracy was affected by the type of response required by the task in far space [$t(7) = 3.19$, $p < .01$] but not in near space [$t(7) = 0.22$, $p > .05$]. In far space, indeed, his ability to detect the targets on the left visual field improved in the motor compared to the perceptual condition of the Balloon task.

3.4.5.2.2 The Landmark task

3.4.5.2.2.1 Perceptual and motor conditions

Following the diagnostic criterion of Toraldo et al. (2004), in the perceptual condition JA showed a pathological right PSE indicating a clear tendency to underestimate the length of the left line segment in both space sectors. In far space he also showed a right response bias (M) which fell outside the range of healthy controls (Table 3.26 and 3.27). For the perceptual condition of the Landmark task, JA's SD index was higher than the cut-off for perceptual uncertainty in both near (≤1.66) and far (≤1.85) space. Consequently, his rightward M index was considered as the result of a partial guessing behaviour and not of a genuine ipsilateral motor bias.

In the motor condition, he showed again a pathological rightward perceptual and response bias in far space while in near space only the M index fell outside the normal range (Table 3.29 and 3.30). In this condition, JA's response bias was affected by partial guessing behaviour only in the near space condition. As for patient SV, even in the presence of partial guessing, the patient's PSE estimation can still be considered reliable while the estimation of the M index should be taken with some caution (Toraldo et al., 2004).

Table 3.27 Landmark results in near space (perceptual condition) for patient JA following Toraldo et al.'s (2004) procedure.

	Near				
	PSE	CI (PSE)	SD	M	(CI) M
JA	7.58	[12.06 3.10]*	7.35	0.15	[0.24 0.05]
NC	-0.86 (1.64)	[2.42 -4.14]	≤ 1.66	-0.01 (0.04)	[0.07 -0.09]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

Table 3.28 Landmark results in far space (perceptual condition) for patient JA following Toraldo et al.'s (2004) procedure.

	Far				
	PSE	CI(PSE)	SD	M	(CI) M
JA	13.17	[18.62 7.71]*	7.88	0.17	[0.28 0.06]*
NC	-0.55 (1.32)	[2.10 -3.19]	≤ 1.85	-0.02 (0.04)	[0.06 -0.11]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index;* Left neglect.

Table 3.29 Landmark results in near space (motor condition) for patient JA following Toraldo et al.'s (2004) procedure.

	Near				
	PSE	CI (PSE)	SD	M	(CI) M
JA	5.00	[9.34 0.66]	3.41	0.31	[0.42 0.21]*
NC	-0.64 (1.80)	[2.96 -4.25]	≤ 1.70	-0.02 (0.04)	[0.07 -0.11]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index; * Left neglect.

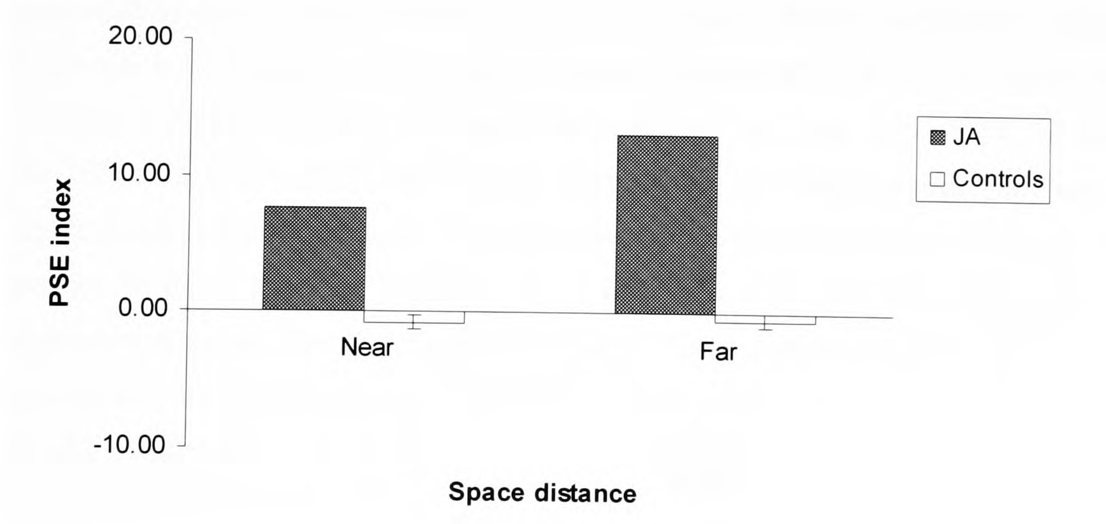
Table 3.30 Landmark results in far space (motor condition) for patient JA following Toraldo et al.'s (2004) procedure.

	Far				
	PSE	CI(PSE)	SD	M	(CI) M
JA	10.00	[14.92 5.08]*	1.71	0.35	[0.44 0.26]*
NC	-1.04 (1.99)	[2.93 -5.02]	≤ 2.95	-0.01 (0.03)	[0.04 -0.07]

PSE: Point of Subjective Equality; M: Motor bias; CI: Confidence Interval; SD: Guessing behaviour Index; * Left neglect

Further statistical analyses revealed that for both spatial distance JA's rightward perceptual bias was significantly larger than the slightly leftward PSE shown by the control group in the perceptual [near: $t(7) = 4.85, p < .01$; far: $t(7) = 9.80, p < .001$] and in the motor condition [near: $t(7) = 2.95, p <.05$; far: $t(7) = 5.23, p < .01$]. In addition, the patient's performance changed significantly across near and far space when compared to the control group in both response conditions [perceptual: $t(7) = 5.63, p < .001$; motor: $t(7) = 3.38, p < .01$]. In near space, JA's perceptual bias reduced significantly in the motor compared to the perceptual condition of the Landmark task [$t(7) = 2.95, p < .05$]. The same pattern was observed in far space [$t(7) = 4.12, p < .01$].These results are shown in Figure 3.25 A and B.

A

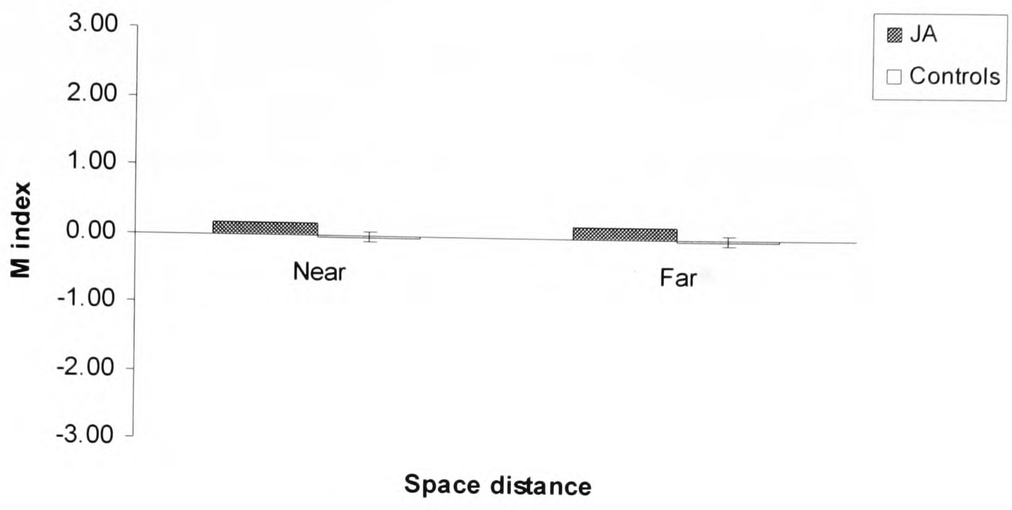


B

Figure 3.25 Landmark performance as a function of response modality for JA and the control group. Positive/negative values indicate a rightward/leftward perceptual bias in the (A) perceptual and (B) motor condition in near and far space.

The analysis of JA's response bias showed that he had a default tendency for "right" responses in both space conditions for the perceptual [near: $t(7) = 3.77, p < .01$; far: $t(7) = 4.48, p < .01$] and the motor version of the Landmark task [near: $t(7) = 7.78, p < .001$; far: $t(7) = 11.3, p < .001$]. This pattern, however, did not change significantly across space distances compared to the controls neither for the perceptual [$t(7) = 0.93, p > .05$] nor for the motor condition [$t(7) = 2.26, p > .05$]. Compared to the control group, JA's rightward response bias was significantly larger in the perceptual than in the motor condition in far [$t(7) = 4.45, p < .01$] but not in near space [$t(7) = 1.74, p > .05$]. These results are shown in Figure 3.26 A and B.

A



B

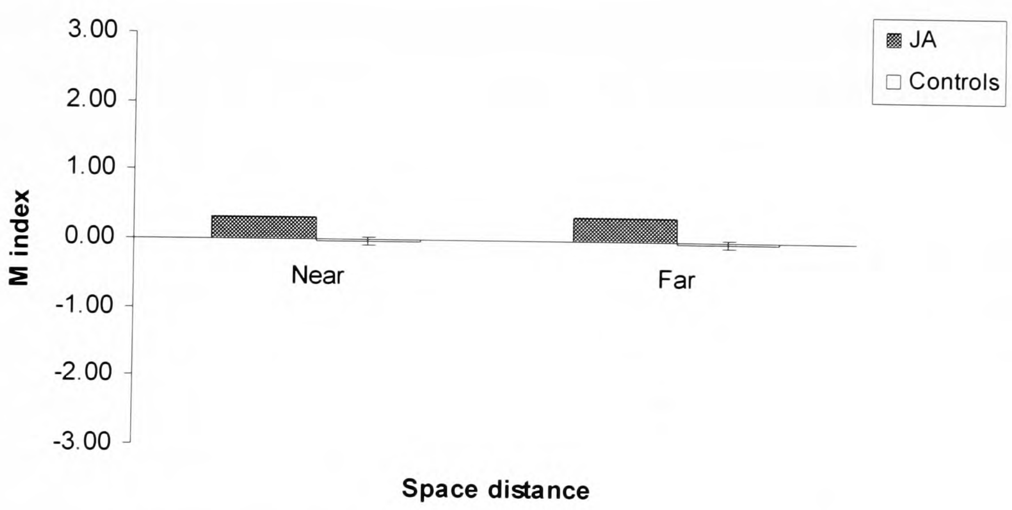


Figure 3.26 Landmark performance as a function of response modality for JA and the control group. Positive/negative values indicate a rightward/leftward response bias in the (A) perceptual and (B) motor condition in near and far space.

3.4.5.3 Discussion

Patient MF and JA showed different neglect deficits across near and far space considering the type of task (visual search vs. line bisection) and the presence/absence of a motor response. MF's deficit was restricted to his ability to effectively explore and detect relevant targets in the environment while his capacity of focusing attention and judging the horizontal extent of a single stimulus was intact. JA on the other hand had impairments in both the visual search and line bisection paradigms. This pattern confirms how different tasks engaging different cognitive mechanisms can be differently affected by brain damage. JA's lesion was considerably more extensive than that of MF and included the right posterior occipital and inferior parietal, as well as medio-temporal and frontal cortices. This severe damage may have destroyed the neuronal networks fundamental to carry out both tasks. MF's lesion on the other hand was restricted to the right basal ganglia, frontal and temporal areas consistent with a major involvement of anterior brain areas in visual exploration tasks. The sparing of posterior occipito-parietal areas may instead explain his unimpaired performance in the line bisection task.

With regard of the patients' performance across space distances, JA's greater deficits in far compared to near space remained consistent in both the Balloon and the Landmark task. This result supports the idea that in some patients neglect for near and far space can occur independently of the task used. The type of response modulated only JA's performance on the visual search task in far space, as his accuracy in the left visual field improved significantly when pointing at the targets compared to when a directional motor response was not required. In the same vein, JA's rightward perceptual bias reduced significantly in the motor compared to the perceptual condition of the Landmark task in both near and far space. The greater impairment shown by JA in far space compared to near space in both versions of the Landmark task may be explained by the fact that a pathological rightward shift of his PSE was coupled with a pathological right response bias. In near space instead this tendency to respond "right longer" (or shorter) was prompted only when a directional motor response was required. Similarly to patient SV, JA showed left homonymus hemianopia but as his performance changed significantly across near and far space, JA's deficits appeared to be more the results of an attentional impairment rather than of a visual field loss.

Patient MF had a totally different behavioural pattern compared to JA. MF showed space specific symptoms only in the visual search task while no sign of neglect was observed for the Landmark task. This behavioural pattern suggested that neglect for near and far space in some patients may affect the specific cognitive mechanisms engaged by the type of task used for the assessment.

MF's only impairment in the visual search task was, however, restricted to far space in the perceptual condition and to near space in the motor condition of the Balloon task. Unlike JA, in which the type of response affected only the patient's performance across tasks, in MF the presence/absence of a directional motor response modulated the patient's performance across space distances. This outcome does not simply suggest that in some patients the magnitude of neglect can be modulated by viewing distance and type of task but rather that a space-related deficit can be affected by the type of response required to carry out the task. This latter pattern has been observed in those studies investigating the effect of tool use in patients with peripersonal and extrapersonal neglect. Berti and Frassinetti (2001), for instance, demonstrated that neglect confined to near space extended also to far space when they asked their patient to perform the task with a stick. Similarly to the animal study of Iriki et al. (2000), the use of a tool resulted in some remapping of what was the intact far space as near space whose representation was instead deficient. The interesting finding in MF was that even without the use of a tool, his space-related dissociation in visual search changed only by introducing or removing a directional motor response of his upper limb. This behavioural pattern might be interpreted within different theoretical frameworks. In proximal space, the operations of grasping and visuomotor coordination have greater importance than in distal space where the ability to visually recognise, explore and discriminate relevant features in the environment appears more relevant as it is not supported by touch (Bjoertomt et al. 2002). This idea is compatible with neurophysiological findings showing that peripersonal space in monkeys is represented mostly by bimodal neurons with visuo-tactile receptive fields (Fogassi et al., 1996; Gentilucci et al., 1988; Graziano and Gross, 1995; Graziano et al., 1994), whereas extrapersonal space representation relies primarily on neurons with visual receptive fields (Goldberg and Brushnell, 1981; Rizzolatti, 1983a). These findings led Berti and Laeng to further develop the original hypothesis of Rizzolatti (1983b, Rizzolatti and Carmandra, 1987) who stated that also in the human brain, peripersonal and extrapersonal space representations may depend on attentional mechanisms which are both action specific (Berti et al., 2001; Laeng et al., 2002). In other words, near space attentional mechanisms would recruit spatial reference frames based mainly on limb/hand movements while far space attention might depend more on oculomotion in the upper visual hemisphace (Laeng et al., 2002). According to this claim, a task requiring not only visual scanning of the stimuli but more critically a directional motor response towards the stimuli (such as for example the motor version of the Balloon task) would be more likely to reveal impairment within the grasping space. On the other hand, when the same task requires mainly visual exploration without a directional motor response (such as for example the perceptual version of the Balloon task), deficits in extrapersonal (far) space would be more detectable. This is indeed the pattern observed in patient MF who had an impaired representation of both sectors of space whose severity did, however, become manifest only when assessed with specific testing procedures. Accordingly it seems, therefore, that a visuospatial impairment for a specific sector of space can be elicited by motor actions engaging different effectors (i.e. limb or eye movements) or a combination of them, through which attention is allocated in space. This interpretation is compatible with the premotor theory of attention formulated by Rizzolatti (Rizzolatti, 1983b; Rizzolatti and Camandra, 1987) which states that the coordinate frames in which space is coded in the brain depends on the motor requirement and the effectors. In this sense spatial attention would thus rely on sensorimotor neuronal networks involved in the transformation of spatial information into a specific action goal (Craighero et al. 1999).

An alternative approach would be to consider MF's asymmetric performance in far space as prevalently perceptual, which then improved in the motor condition with the introduction of additional reference frames based on the visual position of the hand and upper limb. MF's pointing movements could have also acted as an attentional visuo-motor cue which allowed him to overcome his perceptual visusopatial deficit. This idea that a conscious representation of space can be modulated through a combination of visual and motor cueing of attention to the affected side was put forward by Forti and Humphreys (2004). They demonstrated, for instance, that one of their patients showed less severe neglect during a search task when a stick was used but also when he searched with his ipsilesional arm outstretched or with a torch. The authors concluded that motor actions combined with a visual cue (the arm) may enhance attention and detection at the location for which an action is programmed. Accordingly, in the motor condition MF's performance in far space may have improved through the effect of a visuo-motor cue represented by the full view of his arm and the action of pointing with a laser pen. In near space the patient may have beneficed less from this cueing effect as in this condition he could only see his hand and part of his forearm during the reaching action.

The patients' performance could also be interpreted by inferring what mechanisms may have been disrupted based on the location of their brain damage. This approach should provide useful suggestions on the critical areas involved in near and far space representation.
JA had extensive damage to most of the right hemisphere with sparing of the premotor cortex and superior parietal areas (precuneus). This extensive and severe damage compromised his ability to create an effective representation of his proximal as well as distal space. The destruction of polisensory superior temporal areas could potentially generate neglect for near and far space considering that these areas receive neuronal inputs both from the dorsal and the ventral visual streams (Karnath et al. 2001). Consistent with this hypothesis JA had an extensive lesion of the superior and medial temporal gyrus which may indeed justify his poor performance in both space conditions. The patient's visuospatial impairments were, however, significantly more pronounced in far than in near space and his damage in the medio-temporal cortex and ventral occipital areas is in line with clinical, neuroimaging and TMS studies showing a specific involvement of these areas in far space attention (Vuilleumier et al., 1998; Weiss et al. 2000, 2003; Bjoertomt et al., 2002). The brain areas that were still intact in JA's right hemisphere were the superior parietal (precuneus) and premotor cortex. The superior parietal cortex represents one crucial node of the dorsal visual stream for the operations of visuo-motor guidance and coordination of upper limbs movements in near space. Converging evidence suggests that the precuneus is involved in the operation of space representation at both an intentional and perceptual level. This area is indeed involved in directing attention in space not only during the execution of goal-directed actions but also in the absence of an overt motor response (Cavanna and Trimble, 2006). Several neurophysiological studies have demonstrated the presence in the superior parietal areas (7b) of visuo-tactile neurons responding to stimuli only if they are presented within the animal's proximal space (Leinonen et al., 1979; Gentilucci et al., 1983; 1988; Graziano and Gross, 1993; 1994). The superior parietal cortex (7b) has

rich interconnections with the premotor cortex also spared in JA. It has been shown that removal of the inferior premotor area (F4) or a destruction of the neuronal circuit between this area and parietal area 7b causes hemi-inattention restricted to near space in monkeys (Rizzolatti et al., 1983; Rizzolati and Berti, 2002). The involvement of parietal (i.e. intraparietal) and ventral premotor cortex in the representation of near space is also supported by evidence from neuroimaging and TMS studies in humans (Weiss et al. 2000, 2003; Bjoertomt et al., 2002). Accordingly, the sparing of the superior parietal cortex in JA may have played an important role in his deficient, but yet, relatively preserved representation of near space compared to far space.

MF's lesion instead involved the right ventrotemporal area, fusiform gyrus, basal ganglia (putamen and globus pallidus), midbrain, premotor and orbitofrontal cortex. Damage involving the ventrotemporal and fusiform structures may be related to his greater inability to explore and detect contralateral compared to ipsilateral targets in far space. These brain areas represent some of the major components of the ventral high visual stream which is said to play an important role in the representation of distal space (Previc, 1990). In support of this hypothesis, cases of neglect for exploration tasks restricted only to far space have been reported following damage of the right medial and inferior temporo-occipital junction (Vuilleumier et al., 1999).

Damage of the basal ganglia has also been associated with neglect in several studies (Damasio et al., 1980; Healton et al., 1982; Vallar and Perani, 1986; Weiller et al., 1993; Karnath et al., 2002; 2005b). Furthermore, given their anatomical connectivity with one of the critical areas responsible for spatial neglect, namely the STG, the basal ganglia (especially the putamen) have been considered as an integral part of the cortico-subcortical network for spatial awareness in humans (Karnath et al., 2002). Karnath et al. (2001) suggested that neglect can develop after structural damage to any component of this network or functional deactivation of the STG caused by basal ganglia lesion (diaschisis). If the diaschisis hypothesis were true, MF's space-related disorders could be considered related to a metabolic dysfunction of the STC which, as previously hypothesised, may be involved in the representation of near and far space through its connections with both high visual streams. Unfortunately, this assumption cannot be verified without a precise investigation of the patient's cerebral functional activity with a Single Photon Emission Computerised Tomography technique (SPECT) and Positron Emission Tomography (PET). MF's impairment in near space was present only when he was asked to make a ballistic motor response to reach the targets in the contralateral hemifield during the visual search task. This pattern may suggests the presence of a motor impairment in implementing motor acts towards the affected side of space, namely directional hypokinesia, which occurs without any sign of primary motor deficits. This hypothesis could also be supported by the possible presence of unilateral bradykinesia noticeable in the slowness that MF showed during the motor Balloon task. The patient was in fact significantly slower than the controls in carrying out reaching movements towards the contralateral but not the ipsilateral hemifield. If MF had shown the same motor contralateral deficit by repeating the same test also with his left arm, the presence of directional hypokinesia could have been confirmed more thoroughly. The nature of MF's unilateral motor deficit in performing contralateral reaching movements in near space is, however, worth of consideration and it may be probably related to his midbrain (substantia nigra) and basal ganglia damage. Animal studies have indeed demonstrated the presence of unilateral motor deficits after dopaminegic reductions in the nigrostriatal pathway from the substantia nigra to the putamen and caudate nucleus (Carli et al., 1985; Apicella et al., 1991; Milton et al., 2004). Partial reduction of dopamine content in the putamen and caudate nucleus in monkeys, for instance, resulted in slowness in initiating movements with the ipsilesional forelimb towards contralesional stimuli within their immediate visual space (Apicella et al., 1991). In addition, Milton et al. (2004) demonstrated that monkeys with lesioned nigrostriatal dopamine projections exhibited persistent deficits in reaching into contralateral hemispace with both arms (Milton et al., 2004). The authors suggested that the dopamine projections from the substantia nigra to the putamen and caudate nucleus may be part of a cortico-subcortical circuit which determines the mental representation of space for attention and action (Milton et al., 2004) Further evidence supporting the hypothesis that the dopaminergic projections of the basal ganglia may mediate the motor component of neglect are provided also by several studies in humans whose motor intentional neglect decreased following modulation of dopamine transmission by using dopamine agonists (Fleet et al., 1987; Geminiani et al., 1998; Grujic et al., 1998). In addition, a study carried out by Sapir et al. (2007) demonstrated that directional motor deficits during a pointing task in neglect patients were specifically associated with damage of the putamen, caudate nucleus and the white matter underneath the precentral and inferior frontal gyrus. These lines of evidence support the idea that MF's contralateral motor deficit in near space may be associated to his sub-cortical damage in the putamen and substantia nigra. Since his unimpaired performance in far space when pointing may be explained by the compensatory effect of a visuomotor attentional cue (full view of his ipsilesional outstretched arm in action), it is not possible to rule out the possibility that the basal ganglia may play a role also in the operation of far space representation at an output level. It would have been interesting to verify whether the patient's performance in far space had worsened by preventing him from having full view of his arm in action as it was the case for the patient described by Forti and Humphreys (2004). In this way a better evaluation of the possible role played by the basal ganglia in the operations of space representation through action could have been achieved. This aspect has not been explored due to unavailability of patient MF shortly after he took part in the study. The case of this patient showed that damage of the ventral stream results in far space neglect only when space is coded mainly through perceptual information (i.e. visual). On the other hand, a selective reluctance to make contralesional pointing actions in near space but not in far space may be due to lesion of the basal ganglia even without dorsal stream damage. Accordingly, the anatomical results of the single cases described in this chapter support only partially the dichotomy of the dorsal ventral stream for near and far space representation.

CHAPTER 4

Visuo-spatial neglect in near and far space: A group study

4.1. Introduction

Single case studies are particularly effective in detecting distinct patterns of performance which would be otherwise missed in a group study. The clinical dissociations observed in individual patients represent a powerful tool to infer the presence of distinct neuronal modules underneath specific cognitive operations. On the other hand, a group study approach provides the possibility of exploring the frequency of a particular deficit of interest in a specific population of patients. The present study focussed on complementing the findings of the single case studies by examining the incidence of neglect deficits in near and far space in a large group of unselected right brain damaged patients.

To date, most of the group studies that investigated the effect of distance in the manifestation of neglect symptoms drew their conclusions based on the patients' performance on line bisection tasks (Cowey et al., 1994; 1999; Pizalis et al., 2001; Neppi-Mòdona et al., 2007). These studies suggest that overall, in patients with neglect, rightward bisection errors tend to be worse in far than in near space (Cowey et al., 1994; 1999; Pizalis et al., 2001). Butler et al. (2004) replicated this space-dependent pattern of impairment with a cancellation task. Their neglect patients showed a decreasing lateral gradient of target detection from right to left which was significantly worse in far than in near space. Keller et al. (2005) reported the only group study carried out so far in which distance specific deficits in neglect patients were explored with both the line bisection and cancellation tasks. Once again the rightward bisection error of the neglect patients was significantly worse in far compared to near space, while no such distance effect was observed for the cancellation task.

Taken together, these studies suggest that far space representation may be more vulnerable than near space and that visual exploration abilities appear less susceptible to be modulated by space distance than line length judgments. While according to the available findings the former hypothesis seems more likely, the latter still needs to be clarified as only Keller et al. (2005) directly compared cancellation and line bisection performance across near and far space in the same group of neglect patients. The single case studies described in the previous chapter, suggested that in some patients neglect deficits restricted to near or far space may occur independently of the cognitive demand of the task used (cancellation vs bisection). The present study intends to investigate the frequency of this behavioural pattern with a group study approach in a much larger scale. Most group studies with neglect patients explored space related impairments with a relatively small sample size (Cowey et al., 1994; 1999; Pizalis et al., 2001; Butler et al., 2004; Keller et al., 2005). Only two of them recruited a substantial number of right brain damaged patients (N = 70 in Pizzamiglio et al., 1989 and N = 28 in Neppi-Mòdona et al., 2007) but, as no significant effect of distance was observed in the neglect patients' performance between near and far space, they could not provide further evidence on how common space related deficits are within the population of patients with neglect.

The aim of the present study was to explore the occurrence of neglect for near and far space in a large group of unselected right brain damaged patients in order to characterize the predominant behavioural deficit within this population group with respect to space distance. Limitations related to the hospital setting, time restrictions and the patients' availability (due to their medical state and mobility), it was not possible to recreate the same experimental conditions as for the single cases study and use the experimental paradigms devised. Consequently, the additional issue on the effect of the type of motor response which was addressed in the previous chapter could not be examined. As the primary goal of the present study was to recruit and assess a group of right hemisphere damaged patients as much large and representative as possible, the assessment of near and far deficits was carried out with the classical neglect tests frequently used in the clinical setting, namely, the Bells test and line bisection task.

4.2 Methods

4.2.1 Subjects

4.2.1.1 Patients

A group of 46 unselected right hemisphere damaged patients (Mean age = 67, SD = 11.87, mean education = 7.28, SD = 3.19) was recruited from the Neurology Clinic of the Nuovo Ospedale Civile S. Agostino Estense in Modena. Patients were selected only based on their right hemisphere damage and not on their overt symptomatology. In addition, the etiological pattern was related to either neurosurgical intervention or ischemic episode but not to hemorrhagic damage. Hemorrhagic cases were avoided as hemorrhage may potentially cause dysfunctions of cerebral tissues beyond the structural damage resulting in a distortion of the symptomatic picture. All patients were oriented and did not show any sign of cognitive decline. They all provided written informed consent to take part in the study. Testing took place between 4 and 12 weeks after stroke or surgery to assure a stabilization of the symptomatology. The patients were assessed with a neuropsychological battery of four standard clinical neglect tests which included: two cancellation tasks (BIT - Stars cancellation, Albert test), line bisection, scene copying and drawing from memory. Patients failing at least two out of the four tests in the battery were classified as having signs of spatial neglect. According to these criteria, 14 patients were classified as having neglect (N+) while 32 showed no sign of the disorder (N-). Clinical and demographic data are reported in Table 4.1 for the patients with neglect and in Table 4.2 for the right brain damaged patients without neglect.

4.2.1.2 Control sample

Fourteen (six males and eight females) right handed healthy adults matched for age (Mean = 67.93 years, SD = 7.08) and education level with the patients (Mean = 9.79 years, SD = 1.93) were recruited as a control group (C). None of the participants had history of neurological or psychiatric disorder or were under any kind of medication at the time of testing. All of them provided informed consent to take part in the study.

Table 4.1 Clinical and demographic data of the right brain damaged patients with neglect.

Patient	Age	Gender	Education (years)	Lesion site	TIPE* (days)
LR	57	M	8	F-T-I	45
MA	69	M	4	F-T-I	38
NB	57	M	5	F-I-T-BG	52
BC	48	M	11	F-I-P	43
ZR	79	F	13	F	39
VS	78	F	5	O-P-Th	30
CB	71	M	5	T-P	34
BI	85	F	5	F-T-P-BG	41
LC	81	M	5	T-P	30
SG	64	F	16	P-O	43
GL	83	F	8	F-T-P	50
MD	63	M	8	T-O-P-I-F	50
DE	76	M	8	T-P	42
EGF	68	M	8	T-O	48
	69.93 (11.12)	9M/5F	7.79 (3.49)		41.79 (7.08)

Note. F = frontal, P = Parietal; O = occipital; T = temporal; Th = thalamus; BG = basal ganglia, I = insula; *Time interval post event expressed in number of days from the onset of the event (lesion).

Table 4.2 Clinical and demographic data of the right brain damaged patients without neglect.

Patient	Age	Gender	Education (years)	Lesion site	TIPE* (days)
DCG	70	M	17	F-P	39
MG	64	F	8	F-T-P	42
AC	75	M	5	F	49
DA	49	F	13	F	47
PM	78	F	5	P	60
CM	89	M	5	P	32
MR	68	M	8	T	64
RV	81	M	3	I-F	71
RM	52	M	11	T-P-I	76
BL	63	M	8	F-BG	33
CD	63	M	8	F-P	34
SAR	63	F	12	F	34
ZL	85	M	5	F-P	49
CG	66	F	5	F	55
CD	57	F	5	F	55
MG	66	M	5	F-P	59
DRF	60	F	3	Th-BG	36
CR	86	M	5	T-I	42
BV	80	M	5	F-P-I-BG	62
MG	60	M	5	P	55
LS	60	M	3	F-BG	36
MM	59	F	5	F-T-I	44
JH	70	M	10	ACC	42
RR	67	M	6	F	30
BG	61	M	5	F	88
GR	67	M	8	F-P	42
FG	66	M	8	T-P	35
GA	68	F	8	T	32
CAT	68	F	8	F	43
CG	64	M	8	F	37
FG	77	F	8	F	57
FF	65	M	8	F	40
	67.72 (9.49)	21M/11F	7.06 (3.08)		47.50 (14.16)

Note. F = frontal, P = Parietal; O = occipital; T = temporal; Th = thalamus; BG = basal ganglia, I = insula; *Time interval post event expressed in number of days from the onset of the event (lesion).

4.2.2. Screening tasks

Some of the clinical tasks for neglect used in the present study have already been described in the previous chapter (see section 3.4.1.2 page 105) such as star cancellation, line bisection, copying and drawing from memory. The cut-off criteria for neglect remained the same as for the single cases studies: star cancellation (3 omissions, 2L>R), line bisection (±6.5 mm of deviation from the true midpoint), copying and drawing from memory (>0; 3 = incomplete and misplaced to the right, 2 = incomplete on the left but correctly positioned, 1 = complete but misplaced on the right, 0 = complete and correctly placed). Note that the line bisection task used for the screening of neglect in the present study consisted of one unique horizontal line (20 cm x 0.1 cm) presented centrally on a 4A sheet. The screening battery for this group study included also the Albert test which consists of 41 short lines randomly distributed on an A4 spread sheet (Albert, 1973). There are 18 targets in each half of the page plus 5 lines placed on the central column which were not considered on the calculation of the individual scores. Patients were asked to cross out all the lines they could find without any time limit. The maximum score was 36 and a number of left omissions greater than 2 were considered as the cut-off level for this test (Mark and Heilman, 1997). As for the other cancellation tasks, in the case of right sided omissions, only the instances in which there were at least 2 omissions more on the left than on the right were considered to fulfil the criterion for left neglect.

4.2.3 Apparatus and procedures

In the experimental session two tests were administrated: the Bells test (Gauthier et al., 1989), which is considered as a particularly sensitive cancellation tests for neglect, and the line bisection task from the Behavioural Inattention Test (BIT) (Wilson, Cockburn, and Halligan, 1987). Both tasks were carried out in near and far space respectively. In the near space condition, the stimuli were presented in front of the patient on a horizontal A4 paper sheet at a distance of 40 cm. The centre of the sheet was aligned with the patients' body midline. Far space performance was assessed by projecting the stimuli onto the wall with an overhead projector at 320 cm distance between the patients' body midline and the stimuli. The visual angle of each array (43° x 31°) was kept constant during both conditions. Patients performed the tasks by using a pen in near space and a laser pointer in far space.

4.2.4. Experimental tasks

The Bells test

The Bells test (Gauthier et al., 1989) has been described in the previous chapter (see section 3.4.1.2 for details). Patients were asked to detect 35 bells presented on A4 paper sheet, along with 280 distractors (objects). In the near space condition, patient performed the task by crossing out the targets with a pencil whereas in far space the experimenter recorded the patients' responses by crossing the detected targets on the transparent spreadsheet which contained the stimuli projected onto the wall. The cases with more than 6 left-sided omissions were taken to indicate left neglect (Azouvi et al., 2006). As well as for the cancellation tasks used during the screening session, in case of right sided omissions only the cases presenting at least 2 omissions more on the left than on the right were considered pathological for left neglect. For each patient, a laterality index (LI) was calculated using the following formula: [(CR-CL)/(CR+CL)]*100 in which CR and CL correspond to the number of targets detected on the right and on the left respectively. Targets located in the central column were not considered in the formula. A positive LI indicated predominantly left sided target omissions while a negative LI indicated a tendency to miss stimuli on the right. Accordingly, a LI of 0 indicated an unbiased performance between the left and the right visual field.

The line bisection task

In the line bisection task patients were asked to mark the middle of three lines (20 cm length and 1 mm width) placed respectively on the right, on the centre and on the left of an A4 sheet. Also in this case, in the far space condition the experimenter recorded the patients' performance by drawing the bisection mark on the acetate spreadsheet. Deviation from the true centre was measured in mm, with a positive sign indicating rightward deviations and a negative sign for leftward deviations. The values for each line were averaged and each mean score was then converted into degree of visual angle for near and far space.

4.3 Results

For each task, a repeated measures ANOVA with distance (near, far) as within and group (neglect, no neglect, healthy controls) as between subject factors. Significant results were followed-up by Bonferroni-corrected t-test for multiple comparisons.

Bells test

The analysis for the Bells test revealed significant main effects of distance [$F(1,57) = 18.84$, $p < 0.01$] and group [$F(2,57) = 21.15$, $p < 0.01$]. Overall, subjects showed a positive laterality index which was higher in near than in far space. This tendency indicated that subjects were more accurate in detecting right targets than left targets in near compared to far space. The significant main effect of group instead indicated that regardless of space distance, the three groups differed in the level of accuracy across the two visual fields. Post-hoc analysis [$p = .02$] revealed that the positive laterality index shown by the neglect group was significantly higher from that of the no neglect group which was also positive [$t(90) = 4.82$, $p <.001$]. The negative laterality index of the controls differed significantly from that of the neglect group [$t(54) = -3.77$, $p <.001$] but not from that of the no neglect group [$t(90) = -1.15$, $p >.01$].

There was also a significant distance x group interaction [$F(2,57) = 24.59$, $p < 0.01$] which indicated that the level of accuracy across the two visual field was different in each group depending on the distance from the stimuli. Post-hoc analysis [$p = .02$] showed that the neglect group was significantly more accurate in far than in near space [$t(13) = 4.02$, $p < .01$]. No difference between the two space sectors was observed for the no neglect group [$t(31) = -1.54$, $p > .05$] and the healthy controls [$t(13) = -1.09$, $p > .05$].

Line bisection

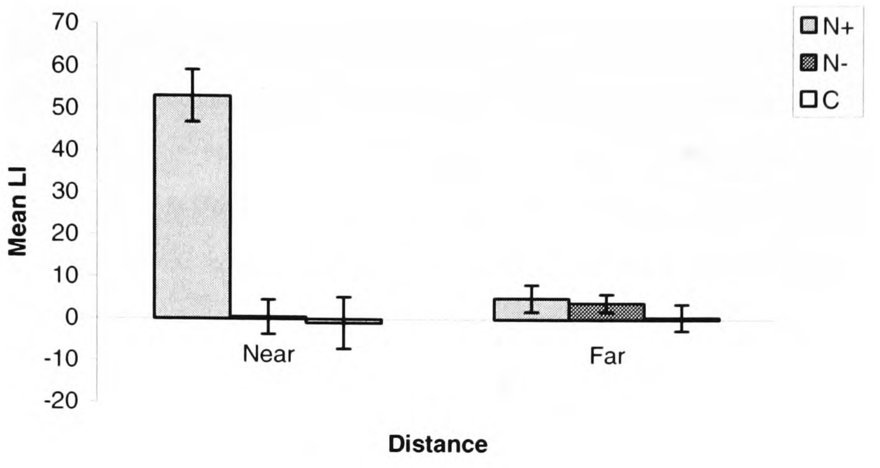
The analysis for the line bisection task showed a significant main effect of group [$F(2,57) = 18.80$, $p < 0.01$] but not of distance [$F(1,57) = 1.71$, $p > .05$]. Post-hoc analysis [$p = .02$] showed that the mean rightward bisection error of the neglect group was significantly larger than that of the no neglect group [$t(90) = 4.22$, $p <.001$] and the controls [$t(54) = 3.93$, $p <.001$]. The control group showed a slight tendency to bisect the line on the left of the true centre (pseudoneglect) and this error differed significantly from the small rightward bisection error of the no neglect group [$t(90) = 4.39, p < .001$]. A significant distance x group interaction was also observed [$F(2,57) = 18.98, p < 0.01$] which indicated that the mean bisection error of each group differed from each other depending on space distance. Post-hoc analysis [$p = .02$] revealed that the rightward bisection error of the neglect group was significantly larger in near than in far space [$t(13) = 2.94, p < 0.01$]. No difference in the bisection error was observed for the patients without neglect across space distance [$t(31) = 1.49, p > 0.05$] while healthy controls demonstrated a larger leftward error in near than in far space[$t(13) = -3.25, p < 0.01$]. These results are shown in figure 4.1 (A and B) and table 4.3 summarizes the descriptive results of the experiment.

Table 4.3 Mean laterality index (SD) for the Bells test and mean deviation error (SD) in the line bisection task in the (N+) neglect, (N-) no neglect and (C) control groups across near and far space.

	Bells test*		Line bisection#	
Groups	Near Space	Far Space	Near Space	Far Space
N+	53.07 (46.53)	5.09 (12.06)	3.98 (4.97)	0.38 (0.42)
N-	0.18 (8.62)	4.08 (14.06)	0.17 (0.59)	0.03 (0.06)
C	-0.89 (2.82)	0.00 (2.06)	-2.35 (2.73)	-0.01 (0.50)
Total	12.28 (32.14)	3.36 (11.85)	0.47 (3.48)	0.10 (0.35)

Note. N+ = neglect; N- = no neglect; C = healthy controls; *Laterality index, #Degree of visual angle.

A



B

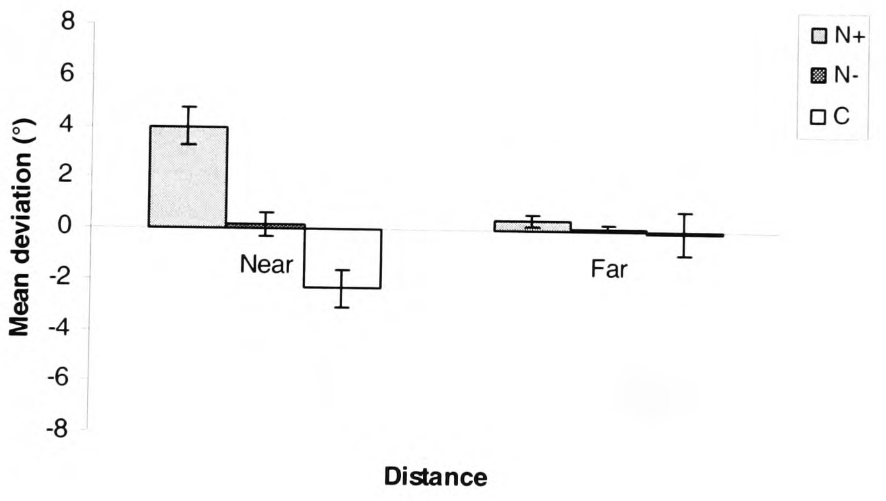


Figure 4.1 Performance of patients with neglect (N+), patients without neglect (N-) and healthy controls (C) in the (A) Bells test and in the (B) line bisection task as a function of spatial distance. LI (laterality index); ° (visual angle).

Frequency analysis

Based on the performance of all the patients in the experimental tasks across near and far space, 24 individuals were classified as showing neglect according to the cut-off criteria specified previously. A descriptive frequency analysis was carried out to explore within this group of 24 patients, the number of individuals showing neglect in each task within in near or far space (Table 4.4). The frequency analysis revealed that by taking into account both tasks, only eight patients showed a space related dissociation (N = 4 near only; N = 4 far only). More than half (N = 16) out of 24 cases showed neglect in both near and far space. However, a closer inspection revealed that this latter pattern was primarily due to line bisection performances as the vast majority of patients impaired in this task showed a large rightward bisection error irrespectively of space distance (14 out of 18). In contrast, those cases with a visual search deficit in the Bells test (N =16), tended to be selectively impaired only in near (N = 9) or in far space (N = 4). In this task, only three individuals were classified as having a visual exploration impairment in both space sectors.

Table 4.4 Frequency table with the number of neglect patients with neglect showing selective deficits depending on the spatial distance and the type of task.

	Distance	Bells test	Line bisection
Near only	4/24 (17%)	9/16 (56%)	2/18 (11%)
Far only	4/24 (17%)	4/16 (25%)	2/18 (11%)
Both	16/24 (67%)	3/16 (19%)	14/18 (78%)

4.4 Discussion

The present study showed that in a large group of right hemisphere damaged patients, only the performance of the individuals with neglect was modulated by space distance in both cancellation and line bisection tasks. In these patients, left omissions on the Bells test and rightward line bisection errors appeared indeed more severe in near than in far space. Overall, the cancellation test seemed to be more sensitive in detecting space related deficits compared to line bisection.

In the Bells test, the greater ipsilateral bias shown by the patients with neglect in near compared to far space is not consistent with the findings of Butler et al. (2004). In their study neglect patients showed the opposite behavioural pattern in a cancellation task carried out in both space sectors. The differences between the findings of these studies may be related to the different task procedure used. In the present study, the patients performed the task manually with a pencil in near space and a laser pointer in far space, while Butler et al.'s (2004) patients were required to read out loud all the targets they could find in both space distances. Accordingly, it appears that visual search abilities in far space may be more impaired than in near space when removing a manual motor response to perform the task. This is the same behavioural pattern observed in patients MF and JA described in the previous chapter whose visual search deficit in far space improved when they performed the motor version of the Balloon task. The cancellation task used in Keller et al. (2005) also required a motor response but their neglect patients did not perform differently between near and far space. The authors instructed neglect patients to detect the targets manually with a pen in near and a stick in far space. Although the task required a directional motor response, the lack of distance effect observed by Keller et al. (2005) in their cancellation task could have been due to the use of the stick which may have remapped the patients' far space as near space (Berti and Frassinetti, 2000; Ackroyd et al., 2002). Hence, an impaired representation of near space in Keller et al.'s (2005) neglect patients could have extended their visuospatial deficit also in far space through the use of the stick, leading to an equivalent performance in both space sectors. The above evidence seems to indicate that, at least for cancellation tasks, the presence of a directional motor response may have the effect of improving neglect patients' visual search abilities in far space.

The results of the line bisection task in the present study revealed that patients with neglect had a larger rightward bisection error than the individuals without neglect in both near and far space. As for the Bells test, the neglect patients' performance in the line bisection task, although still pathological, improved in far space compared to near space. This result is not in line with the prevalent pattern that emerges from other group studies on distance related deficits in neglect which indicate that patients tend generally to make larger bisection errors in far space compared to near space (Cowey et al., 1994; 1999; Pizalis et al., 2001). This discrepancy can not be fully explained by methodological differences related to the type of response, since previous studies found an effect of distance with both motor (i.e. pen and laser pointer) and "perceptual" (verbal response with pre-bisected lines) tasks. However, given the evidence from single case studies supporting the occurrence of the opposite dissociation (Halligan and Marshall, 1991; Berti and Frassinetti, 2000; Mennemeier et al., 1992), it is entirely conceivable that both phenomena are observable in the neglect population.

It is worth noticing that the group studies that observed a smaller bisection error in near compared to far space recruited a relatively small sample size of neglect patients (N = 5 and 13 in Cowey et al., 1994; 1999 and N = 29 in Pizalis et al., 2001). They may have therefore captured only partially the frequency with which some distance related deficits (i.e. bisection errors) in the neglect population occur. In addition, the discrepancies with some of the previous studies' findings may also be related to the different selection criteria used to recruit the patients.

Cowey et al. (1994; 1999), for example, selected their patients based on their performance on neglect tests and assessed them while they were still in the acute phase after stroke. In the present study instead, one fundamental criterion of patients recruitment was lesion site (right) and not the overt presence of neglect symptoms. By recruiting the patients' based on their clinical assessment with neglect tests, one would have missed all those cases with a selective impairment in far space which was not ideal given the purposes of the study. In addition, as the assessment of all the patients in the present study took place after a time window of at least four weeks, probably their specific and stable behavioural impairments may have been isolated more effectively than in Cowey et al.'s study (1999). Different observations regarding instead the different types of patients recruited could be made for another group study carried out by Pitzalis et al. (2001). The authors included in their sample not only ischemic patients but also hemorrhagic cases whose diagnostic profile may often be distorted by the functional damage related to the hemorrhage. In the present study, the effect of unknown confounds on the patients' cognitive profile was minimised by selecting only the patients with ischemic or chirurgical aetiology and not with hemorrhagic damage. Overall, the larger sample size and stricter recruitment criteria may have allowed for a clearer picture of the frequency of space related neglect deficits amongst right hemisphere damaged patients.

The descriptive frequency analysis for both experimental tasks revealed that more than half of the total patient sample had visuospatial deficits in both near and far space and only eight showed neglect restricted to one of the two space sectors. This pattern reflects the rarity of those patients whose selective brain damage results in distance specific neglect deficits. Only the availability of a large group of right brain damaged patients allowed the detection of these singular clinical cases. The clinical dissociation shown by these patients was detected by the cancellation task in six out of eight cases. This finding suggests that cancellation tasks may be more sensitive than line bisection in identifying space-specific dissociation in neglect. This possibility needs to be explored more extensively as, except for of Vuilleumier et al.'s (1999) study, almost all single cases of neglect restricted to near or far space described to date have been assessed with line bisection tasks. The sensitivity of cancellation tasks in detecting space related deficits in neglect appears to be supported also by the overall pattern of performance shown by the whole group of patients for both experimental tasks. While the majority of individuals showed impaired line bisection performance in line bisection in both near and far space (78%), visual exploration deficits were more likely to occur in one space sector only. In fact, only a small percentage (19%) of those patients with a visual search deficit in the Bells test had an impaired performance in both near and far space. In this test, more than half (56%) showed the deficit in near space only and four patients out of sixteen (25%) in far space only.

The findings from the case series study (i.e. SV and JA) suggested that in some patients, neglect for near and far space can occur independently of the cognitive demand of the task used. The results of the group study, which investigated the same issue on a larger scale, reinforced this behavioural pattern. The frequency analysis, however, showed that in comparison to line bisection, cancellation tasks may be a better tool to detect distance related deficits in neglect patients.

However, it is important to clarify whether space related dissociations in neglect arises because of discrete damage which selectively affects the relevant brain areas which is strongly associated with the specific representation of a given space sector. A way to clarify this issue is that of analysing in details the brain structures that were damaged in those patients with and without neglect and with space specific deficits. Furthermore, examining in detail the brain structures that when damaged result in a task specific deficit in cancellation or line bisection should help to identify the critical regions supporting performance in those tasks within near and far space.

4.5 Group lesion overlap analysis

4.5.1 Methods

4.5.1.1 Subjects

A total of 37 patients out of 46 were included in the lesion analysis. The remaining 9 patients were not considered as it was not possible to obtain their brain scan.

The criteria for including the patients in the critical groups were based on their performances on the experimental tasks (the Bells test and the line bisection task). In brief, the cut-off for left neglect in the Bells test was set at more than 6 left-sided omissions plus two more omissions in case of concurrent right-sided omissions (Azouvi et al., 2006). The cut-off for the line bisection was of ± 6.5 mm of deviation from the true midpoint or 13% of the line length (Azouvi et al., 2006). In order to qualify for a specific neglect group, an individual patient was required to show impaired performance in at least one of the two tasks. According to these criteria, the following main critical groups were defined: Neglect (N = 22), No neglect (N = 15), Neglect in near space only (N = 4), Neglect in far space only (N = 4).

4.5.1.2 Lesion analysis

Lesion mapping was carried out using a digital adaptation of the method devised by Damasio and Damasio (1989). For each patient, lesions were drawn manually with the free software MRIcro (Rorden and Brett, 2000; www.mricro.com) in their own native space (CT scan) and superimposed onto the specific template that best matched the orientation of the tomographic image. The CT scans were resliced to obtain the same number of slices as the template. A digital fitting of each lesion onto the template was carried out for each patient to convert lesions from native space into the template space. The lesioned brain areas were identified using the labelling of the Brodmann areas (BAs) marked on each template. Subsequently, the lesions of all the patients showing a specific deficit of interest (for example, Neglect in near space only group) were superimposed on a unique general template (Damasio and Damasio, 1989). In this way the brain regions of maximal overlap for that specific group of patient could be defined. The region of maximum overlap for every group of patients was then considered to be critical for the occurrence of the symptom shown by the group.

In addition, to verify which brain area was uniquely involved in one particular deficit (for example, near space only neglect) and not in another (for example, far space only neglect), a graphical pixel-based subtraction procedure was carried out between the general templates of the specific groups of interest.

4.5.1.2.1 Anatomical correlates of neglect vs. no neglect

The first anatomical subtraction carried out was between the general template of those patients showing neglect (Neglect group) and those that did not show any sign of the disorder (No neglect group). This subtraction was carried out to verify whether the findings of previous anatomical studies that have investigated the neuronal substrate of the disorder could be replicated. In this way, the method used to identify the location of the lesions in this study could be validated. For the Neglect group, it was irrelevant if some patients showed the deficits also in far space as the critical factor in this case was the presence of neglect at least in near space. However, the patients whose neglect was restricted to far space only were not included in this group. This criterion was applied to make this first comparison more comparable with that of other anatomical studies which typically assessed the presence of the syndrome only in near space.

Separate general templates were constructed for the neglect and the no neglect group which included the brain areas damaged in each member for each group. For both groups, only the regions of maximal overlap within each group were reported on the general templates. To visualize the brain structures critically damaged in neglect, the areas involved in the lesion of the non neglect group were graphically subtracted from those of the neglect group. The opposite subtraction was used to obtain the areas that were not associated with neglect.

4.5.1.2.1.1 Results

Anatomical subtraction between the neglect and no neglect group

After the subtraction analysis between the neglect and the no neglect group, the brain areas specifically involved in the syndrome for the present group of patients were: primary motor and somatosensory cortices (BA 4, 3, 2 and 1), premotor cortex (BA 6), middle temporal gyrus (BA 37), superior temporal gyrus (BA 22), anterior cingulate gyrus (BA 24), supramarginal gyrus (BA 40), angular gyrus (BA 39), superior parietal cortex (BA 7 and 5). The brain lesions obtained after the subtraction are displayed in Figure 4.2.

The brain structures that appeared instead not involved in neglect were: primary motor and somatosensory cortices (BA 4, 3, 2 and 1), premotor and supplementary motor area (BA 6), anterior ventral cingulate (BA 32), prefrontal cortex (BA 9 and 8), temporal pole (BA 38), middle temporal gyrus (BA 21), auditory cortex (BA 41 and 42), supramarginal gyrus (BA 40). (Figure 4.3).

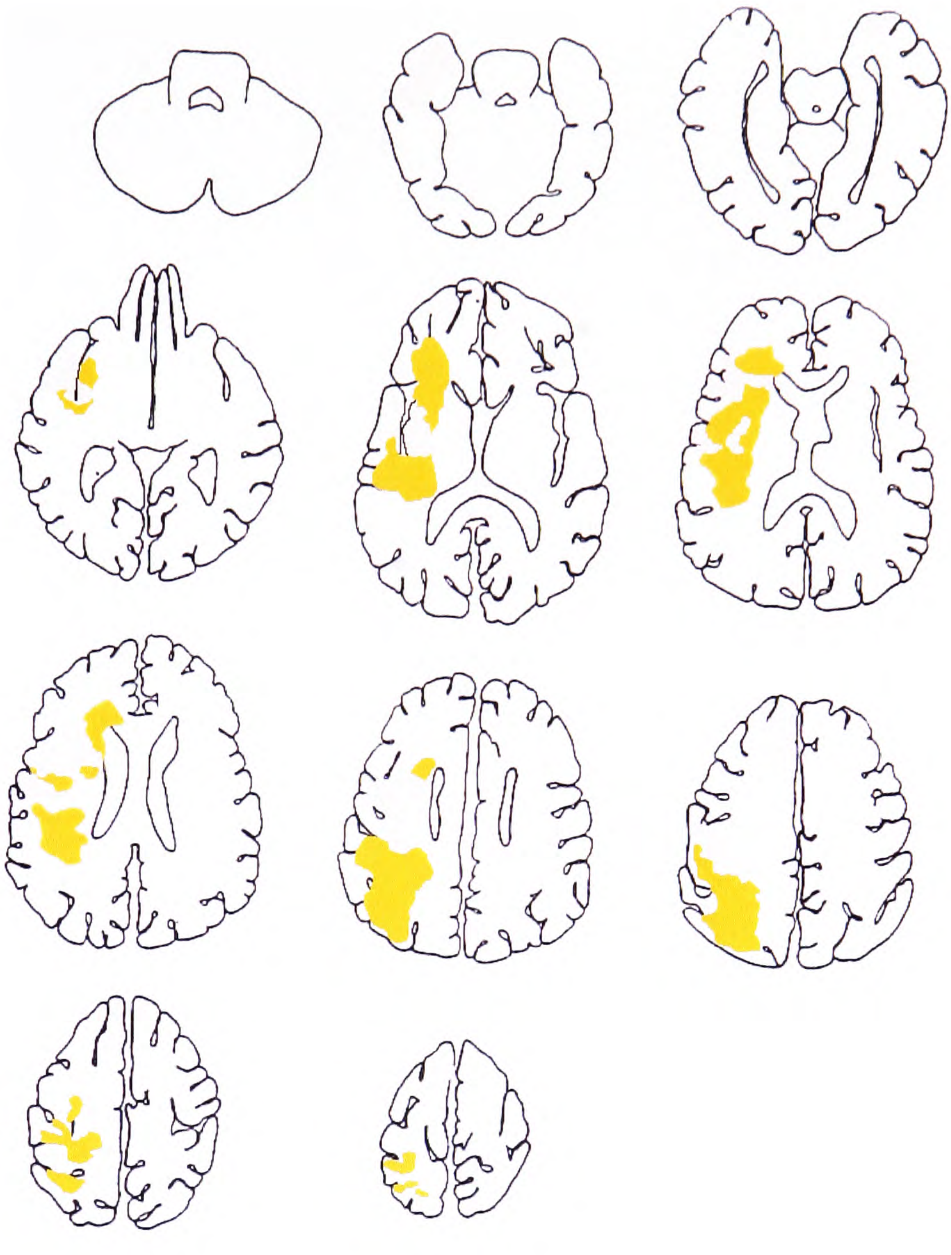


Figure 4.2 Template showing the brain areas obtained after the subtraction of the no neglect general template from the neglect general template. The images are oriented in radiological convention (R/L and L/R).

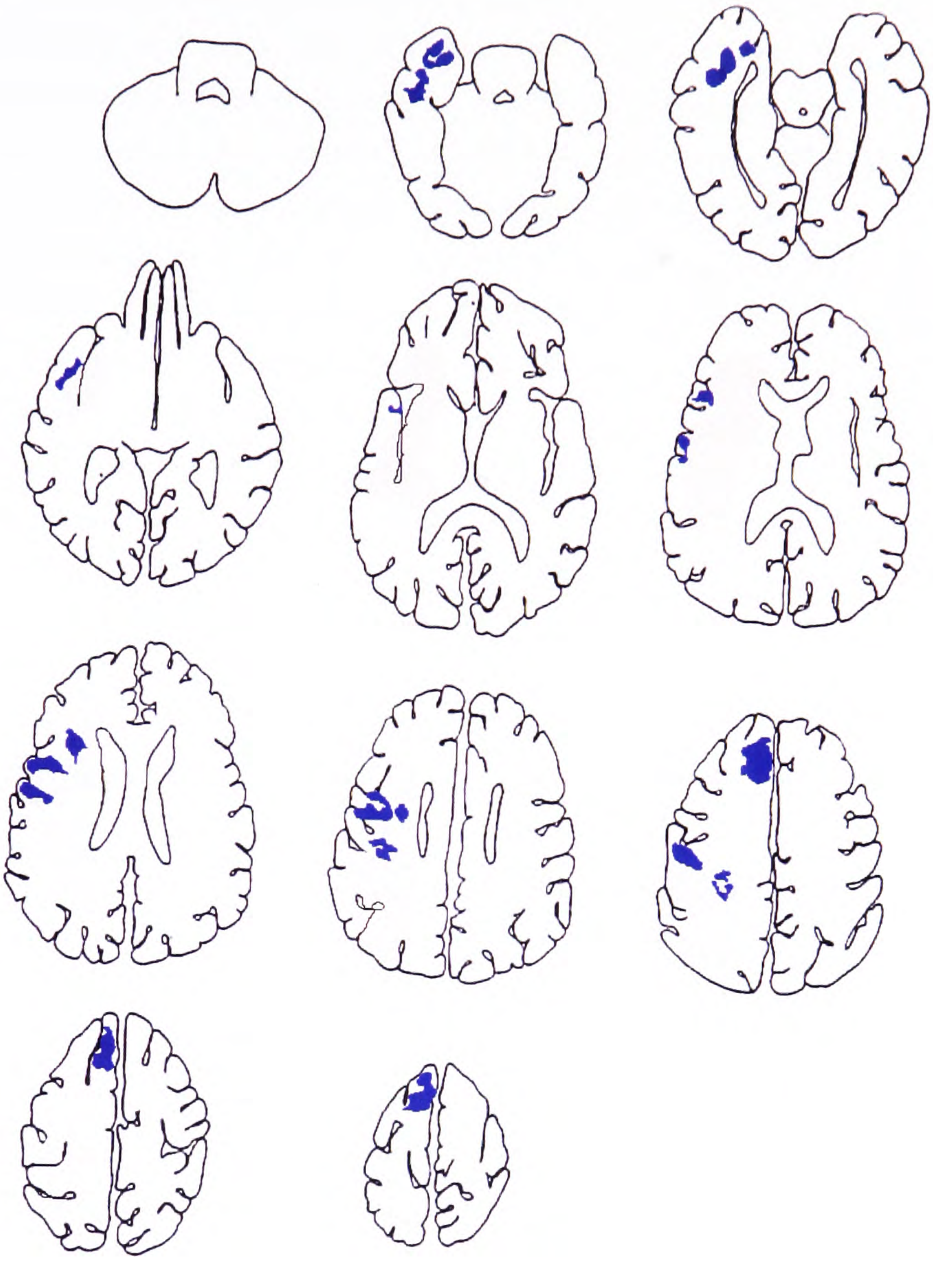


Figure 4.3 Template showing the brain areas obtained after the subtraction of the neglect general template from the no neglect general template. The images are oriented in radiological convention (R/L and L/R).

4.5.1.2.2 Anatomical correlates of neglect in near only vs. far space only

To visualize the brain areas that when damaged result in neglect for near and far space, the patients showing a clear-cut dissociation between the two space sectors were included in the critical groups of near only (N = 4) and far only (N = 4) neglect. For each of these groups, a separate general template was constructed including the brain regions compromised in each member belonging to each critical group.

To visualise the brain areas that were in common in both near only and far only neglect, the lesions of both groups were firstly superimposed on one unique template. In this way, the regions of overlap between near and far space neglect could be located. Secondly, to obtain the brain areas that were instead selectively involved in those patients whose neglect was restricted to near space only, the lesions of the far space only general template were graphically subtracted from those of the near space only general template. The same logic was applied to obtain the brain regions uniquely involved in those patients with neglect for far space only.

4.5.1.2.2.1 Results

Anatomic areas of overlap for near only and far only neglect groups

The general templates of the near only and far only groups showed no region of overlap specific for each group of patients. The brain areas damaged in those patients with neglect for near space only were: primary motor and somatosensory cortices (BA 4, 3, 2 and 1), premotor cortex (BA 6), inferior frontal gyrus (BA 44 and 45), dorsolateral prefrontal cortex (BA 9 and BA 46), mesial prefrontal (BA 10) and orbitofrontal areas (BA 11 and 12), anterior cingulate gyrus (BA 32 and 24), superior and middle temporal gyrus (BA 22, 21 and 37), supramarginal gyrus (BA 40), angular gyrus (BA 39) and superior parietal cortex (BA 7 and 5). (Figure 4.4).

In contrast, the brain areas damaged in those patients showing neglect for far space only were: primary motor and somatosensory cortices (BA 4, 3, 2 and 1), premotor cortex (BA 6), inferior frontal gyrus (BA 44 and 45), anterior cingulate gyrus (BA 32 and 24) and superior and middle temporal gyrus (BA 22 and 21). (Figure 4.5).

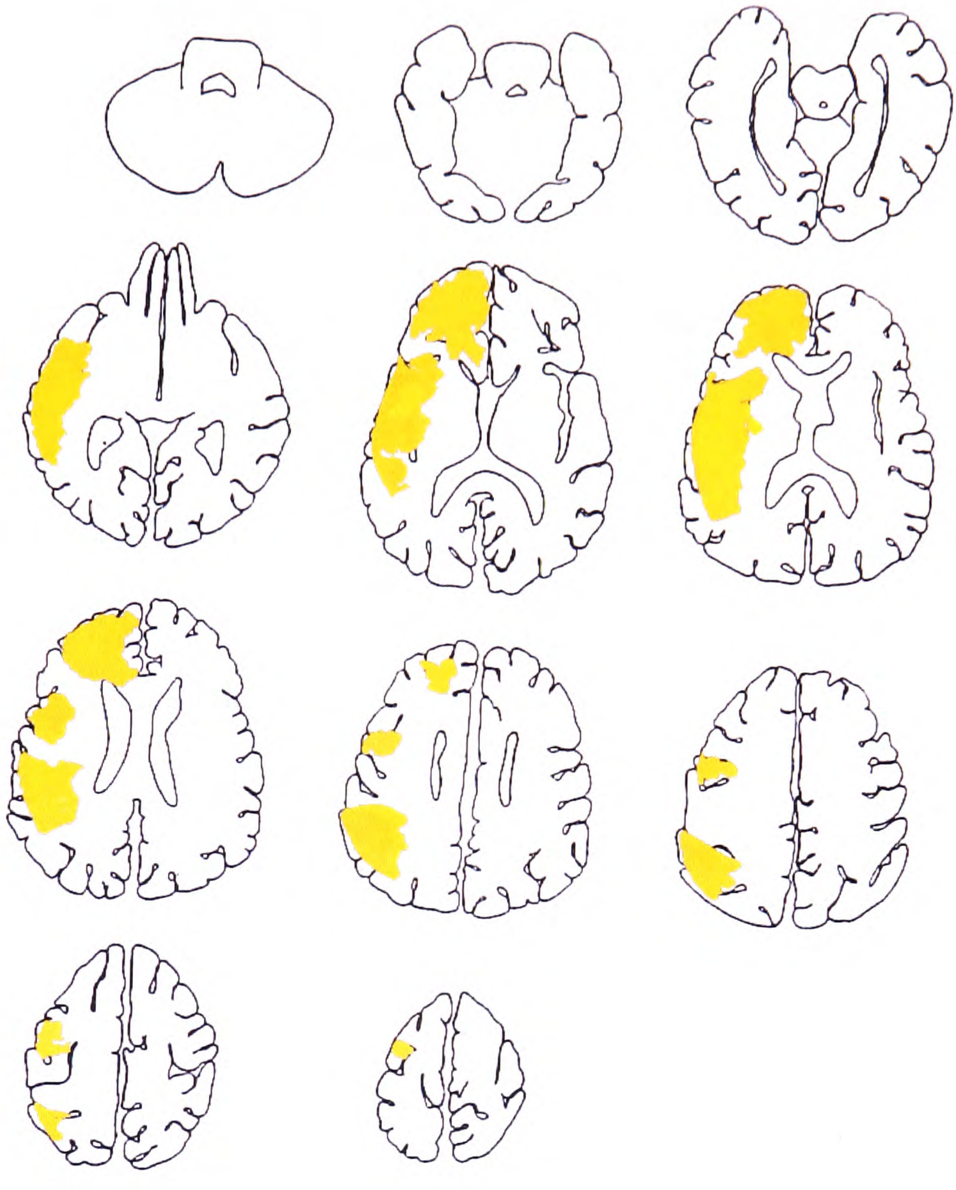


Figure 4.4 Template showing the brain areas damaged in those patients with neglect for near space only. The images are oriented in radiological convention (R/L and L/R).

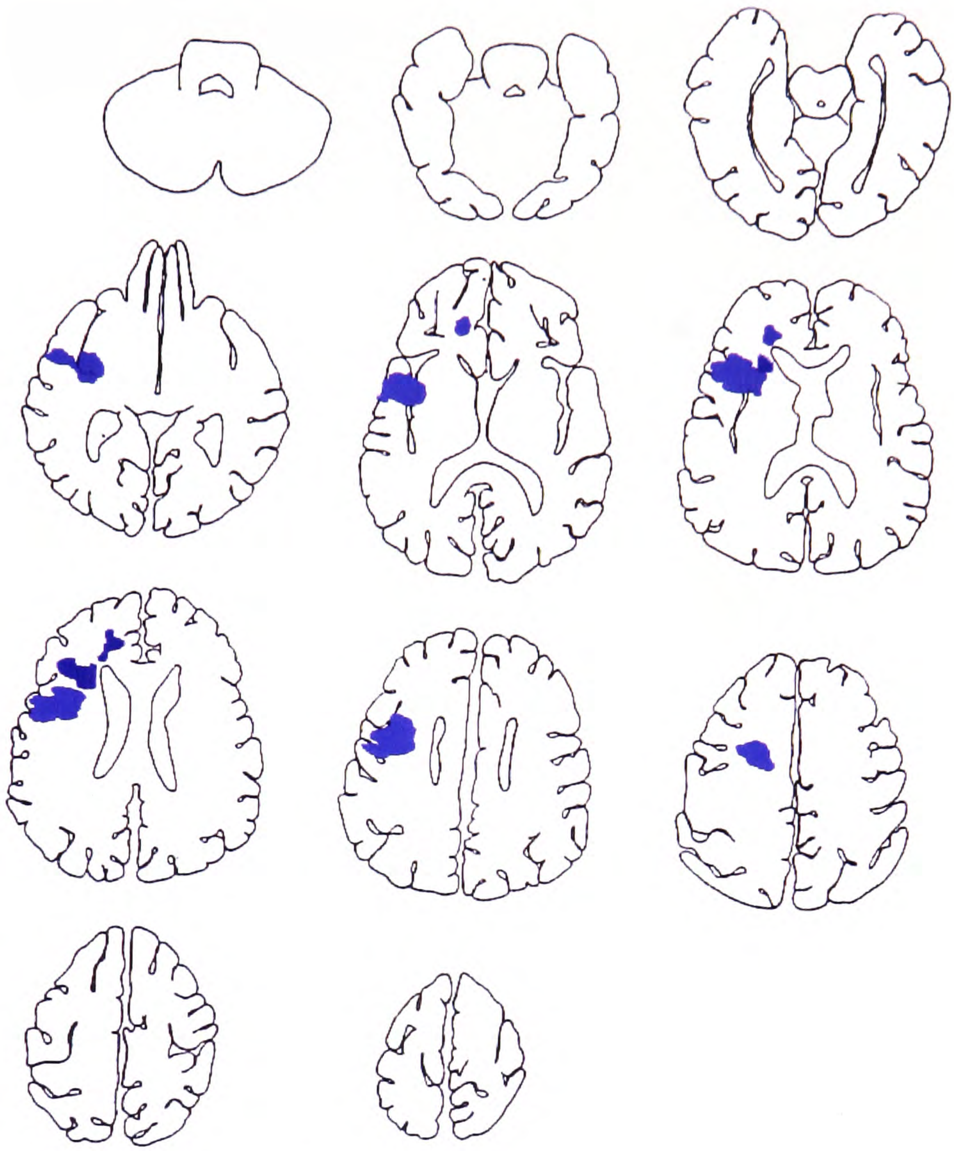


Figure 4.5 Template showing the brain areas damaged in those patients with neglect for far space only. The images are oriented in radiological convention (R/L and L/R).

By superimposing the lesions of both groups into one unique template (Figure 4.6), the brain structures that appeared commonly damaged in near only and far only neglect were: primary motor and somatosensory cortices (BA 4, 3, 2 and 1), premotor cortex (BA 6), inferior frontal gyrus (BA 44 and 45), anterior cingulate gyrus (BA 32 and 24) and superior and middle temporal gyrus (BA 22 and 21).

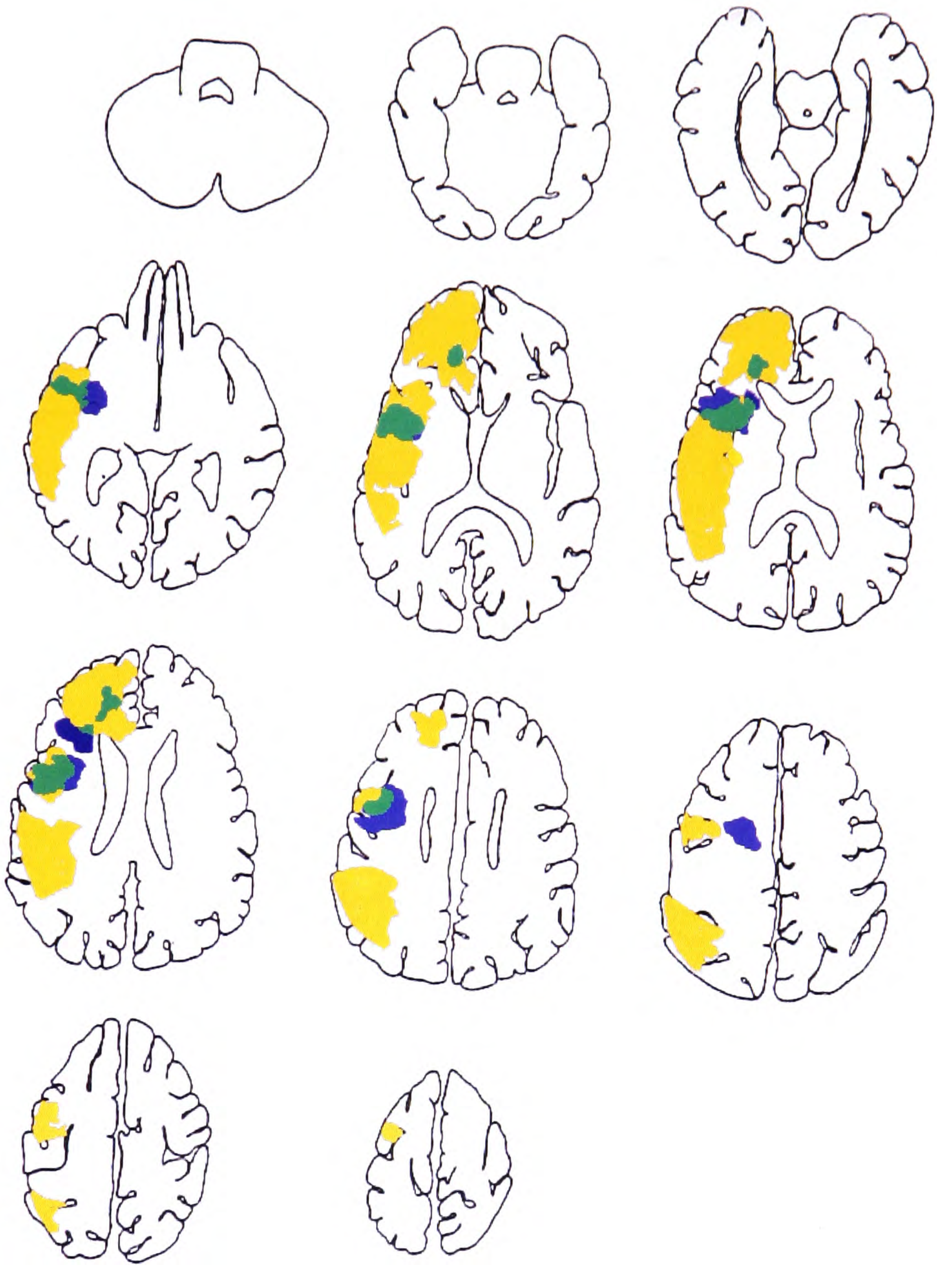


Figure 4.6 Template showing the brain areas of overlap (green regions) between the lesions of those patients with neglect for (yellow) near and (blue) far space only. The images are oriented in radiological convention (R/L and L/R).

Anatomical subtraction between near only and far only neglect groups

By subtracting the brain areas damaged in the far only group from those of the near only group, the brain structures uniquely damaged in those patients with neglect for near space only were: superior parietal cortex (BA 7 and 5), supramarginal gyrus (BA 40), angular gyrus (BA 39), mesial prefrontal (BA 10), orbitofrontal (BA 11 and 12) and dorsolateral prefrontal cortex (BA 9 and BA 46). Although compromised in both critical groups, damage in correspondence of the superior and middle temporal gyrus (BA 22 and 21) was larger in the near only compared to the far only neglect group. As a consequence even after the subtraction analysis, parts of these brain structures were still present on the template for near only neglect. The brain lesions obtained after this subtraction are displayed in Figure 4.7.

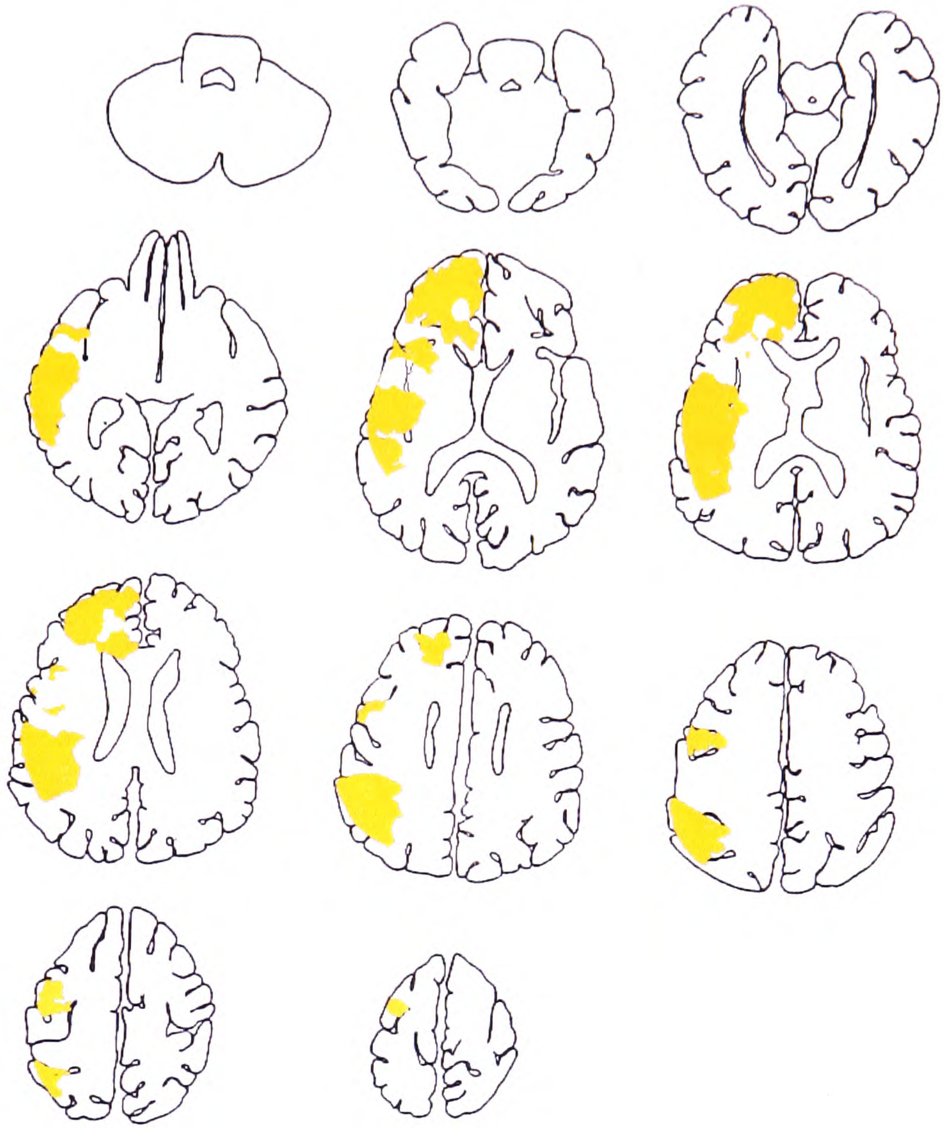


Figure 4.7 Template showing the brain areas obtained after the subtraction of the far only general template from the near only general template. The images are oriented in radiological convention (R/L and L/R).

Anatomical subtraction between far only and near only neglect groups

As the brain damage sustained by the patients with near only neglect was larger than that shown by the patients with the opposite dissociation, the subtraction of the brain areas of the near only general template from the far only general template showed no specific areas selectively compromised in the patients group with far space only neglect. In fact the subtraction revealed an involvement of the the superior temporal gyrus (BA 22), premotor cortex (BA 6) and frontal operculum (BA 44 45) which were also compromised in the near only group. Although lesioned in both groups, different areas within these brain regions were, however, damaged in the far only neglect group. For example, only the anterior portion of the middle and superior temporal gyrus was damaged in the far only neglect group, while the near only neglect group showed damage prevalently in the posterior area of the same gyrus. In addition, the patients with far only neglect presented damage in the ventral portion of the frontal operculum whereas only the dorsal portion of the same brain region was damaged in those patients with neglect for near space only. The lesions are displayed in Figure 4.8.

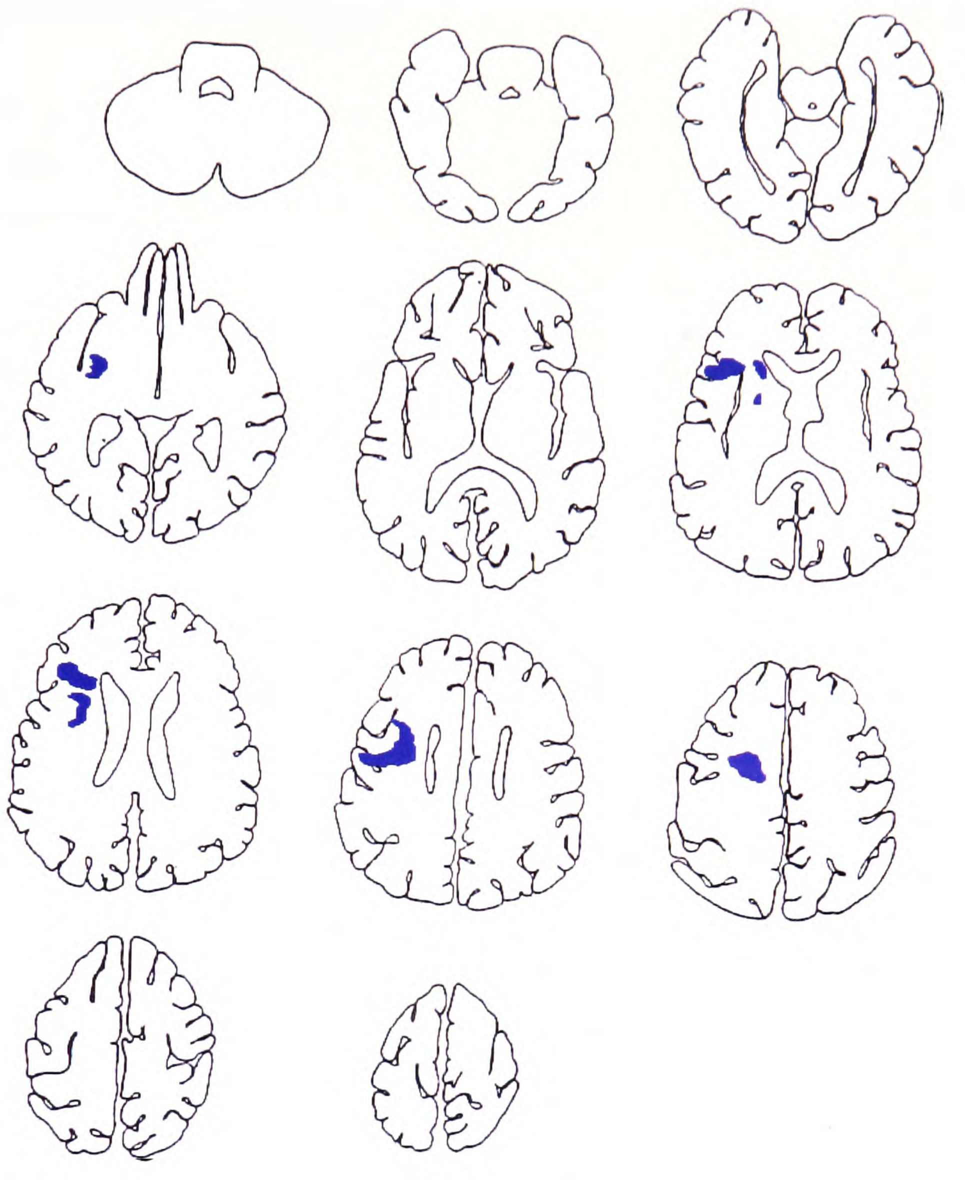


Figure 4.8 Template showing the brain areas obtained after the subtraction of the near only general template from the far only general template. The images are oriented in radiological convention (R/L and L/R).

4.6 Discussion

Along with the behavioural analysis of the patients' performances in near and far space, a further investigation aimed at identifying the presence of gross anatomical differences between those patients showing space specific neglect deficits in near and far space.

Firstly, to verify whether the brain structures associated with neglect in the present patient group were similar to those highlighted by previous findings, the initial anatomical analysis focussed on the comparison between those patients with and without clinical signs of neglect in near space.

Most of the brain regions damaged in the present neglect group such as the superior temporal gyrus, anterior cingulate cortex, angular gyrus and supramarginal gyrus have been considered critical for the occurrence of the syndrome also by previous anatomical studies (Karnath et al., 2001; Mort et al., 2003; Vallar and Perani, 1989). Damage of the primary motor and somatosensory areas in both the neglect and no neglect group was probably related to hemianestesia and hemiplegia for the ipsilesional hemi-soma. However, some of the areas considered related to spatial neglect were also compromised, to a lesser extent, in the group of patients who did not show any sign of the syndrome, namely, the supramarginal gyrus and the anterior cingulate cortex. Although it is beyond the scope of the present study to investigate which brain structure can be considered fundamental for the occurrence of the disorder, one possible explanation for this pattern of results could refer to the size of the lesions and the destruction of more than one crucial area responsible for the syndrome in the neglect group. Overall, the extent of the brain damage present in the patients without neglect was indeed less prominent compared to those who showed the symptoms. In addition, if the brain areas considered so far strongly associated with neglect are part of a large distributed network for spatial awareness, it could be argued that damage to only one component of the network (i.e. neurons of the supramarginal gyrus) might not be sufficient for the occurrence of the syndrome as there might be the opportunity for compensation from other critical areas part of the same network.

Accordingly, given the concomitant lesion of the posterior superior temporal gyrus and inferior parietal lobule in the neglect group, it is likely that in those patients another essential brain area associated with neglect, namely the temporal parietal junction, may have been also damaged. This region represents a multimodal "detection area" and is fundamental for orienting attention toward novel and behaviourally relevant stimuli in the environment (Downar et al., 2000, 2001, 2002; Corbetta and Shulman, 2002). The additional destruction of this area and of the superior temporal cortex in the neglect group may have led to a more severe dysfunction of the neuronal network for spatial awareness. The replication of previous findings on the anatomical substrates of spatial neglect confers external validity to the procedure adopted in the present study to locate the brain areas of interest possibly associated with more specific types of neglect.

With regard to space specific attentional deficits, in the present study the anatomical substrates of neglect for both near and far space overlapped in correspondence of the superior and middle temporal gyrus (BA 22 and 21), medial frontal cortices (BA 44 and 45) and anterior cingulate (BA 32 and 24).

As the superior temporal cortex is located at the transition between the dorsal and the ventral streams, it has been suggested that this brain structure may represent an important cortical site where information from both pathways is integrated (Karnath, 2001). In support of this hypothesis, Oram and Perrett (1996) demonstrated, for instance, that the cells of the superior temporal cortex in monkeys code for both objects properties (i.e. shape) and their direction of motion. The superior temporal cortex may thus play a relevant role in the operations of reconstruction of the surrounding space as a coherent whole by integrating object-related features with their position relative to the viewer. Within this framework, it could be possible to consider the superior temporal area equally involved in the representation of peripersonal (near) and extrapersonal (far) space.

There is evidence supporting the involvement of the right medial and inferior frontal gyrus in neglect for near space (Husain and Kennard, 1996; 1997; Binder et al., 1992; Husain et al., 1997). In the present study, these frontal structures appear also related to far space neglect. In this study eight patients showed space related neglect, in four of them the deficit was restricted to near and in the other four to far space. Six out of these eight patients were impaired in the cancellation task which seemed to be more sensitive than the line bisection task in detecting the dissociation. Some studies found that neglect patients with frontal damage perform poorly on high density cancellation tasks with a relatively preserved performance in line bisection tasks (Binder et al., 1992; Husain and Kennard, 1997; Maeshima et al., 1995). This pattern can be explained by the pivotal role played by the right inferior frontal lobe in target selection and information filtering (i.e. irrelevant distractors in the cancellation task). Damage to the frontal cortex in both critical groups may thus justify the high vulnerability to high distractor load in visual search observed in near as well as in far space. In addition, it has been suggested that the prefrontal cortex may be one of the critical brain sites where the integration of information carried by both high visual pathways may take place (Boussaoud et al., 1996). There are indeed cells in the prefrontal cortex that, as well as the polysensory superior temporal cortex, code both for the identity of visual stimuli (ventral stream inputs) and their spatial location (dorsal stream inputs) (Rao et al., 1997; Rainer et al., 1998). If the hypothesis on the dichotomy between near space/dorsal stream and far space/ventral stream were true, the combination of the inputs from both streams that takes place in the prefrontal cortex may justify its involvement in both near and far space representation.

A further brain structure that appeared related to both near and far space neglect was the anterior cingulate cortex. This region has been shown associated with neglect and more generally with attentional mechanisms (Heilman and Valenstein, 1972; Watson et al., 1973; Posner et al., 1988; Vogt. 1992; Mesulam 1999). The patient described by Heilman and Valenstein (1972), for instance, following a right anterior cingulate lesion, developed visual and personal contralateral neglect, anosognosia for left hemiparesis and depression. The cingulate areas commonly damaged in those patients with neglect for near space only and far space only were BA 32 and 24. These regions are included in both the rostral (rACC) and the dorsal (dACC) subdivision of the anterior cingulate cortex and are associated with several cognitive and emotional functions (Mohanty et al., 2007). Through its reciprocal connections with dorsolateral prefrontal cortex (BA 46/9), parietal (BA 7), premotor and supplementary motor areas (BA 6), the dorsal component appears involved in attention modulation and executive functions by influencing sensory and response selection, complex motor control, error detection, covert shift of attention and anticipation of cognitively demanding tasks (Posner and Petersen 1990; Frith et al. 1991; Paus et al. 1993). In contrast, the rACC in light of its rich connections with the limbic system and orbitofrontal cortex, is prevalently implicated in affective behaviour and contributes to the motivational drive underlying those attentional and motor processes which engage more typically the dorsal division.

With regard to space representation and neglect, the anterior cingulate component may play a role in such cognitive functions as attention control and response selection, and at the same time recognising the potential behavioural implications and motivational relevance of surrounding events which are essential in both peripersonal and extrapersonal space.

The mesial prefrontal cortex (BA 10) and orbitofrontal cortex, were also damaged (BA 11 and 12) in both critical groups with near only and far only neglect. Through its connection with the anterior cingulate cortex, supplementary motor area and inferior parietal lobule, the mesial prefrontal cortex constitutes part of the neuronal network for inhibitory motor control while the orbitofrontal cortex is more prominently associated to emotional rather than motor inhibition (Rubia et al., 2001). These two structures may thus not be directly related to the occurrence of neglect deficits.

A part from those brain areas that were damaged in both groups, the patients with neglect restricted to near space showed additional damage in the dorsolateral prefrontal cortex (BA 9 and 46) and inferior and superior parietal cortices, namely the supramarginal (BA 40), angular gyrus (BA 39) precuneus (BA 7) and the dorsal part of BA 5.

Functional imaging studies have specifically linked dorsolateral prefrontal cortex with target selection processes, particularly when the item selected is guided by information stored in working memory (Rowe et al., 2000; de Fockert et al., 2001; Rowe and Passingham, 2001; Iba and Sawaguchi, 2002). The dorsolateral prefrontal cortex (BA 9 and 46) represents one of the major cortical sites receiving abundant neuronal inputs predominantly from the dorsal stream and the motor cortex while the ventral stream projects especially to the ventrolateral (BA 44 and 45) and orbitofrontal cortex (Boussaoud et al., 1996). The dorsal stream seems to be particularly involved in near space attention because of its special role in the "on line" visual guidance of manual actions. Within these processes, the dorsolateral prefrontal cortex may participate in the operations of target selection and top-down modulation of actions according to the outcomes of the external context in which they are implemented.

The inferior parietal cortex has been classically considered one of the critical brain sites which, when damaged, can cause spatial neglect (Vallar and Perani, 1989). Different areas of the inferior parietal cortex are believed to subserve different types of spatial computations. The angular gyrus seems to participate in the operations of voluntary visual orienting of attention and corporeal awareness in maintaining a stable representation of one's own body (Doricchi and Tomaiuolo, 2003; Danckert and Ferber, 2005). In contrast, the supramarginal gyrus contributes to disengage attention from its current focus and reorienting it towards a new location after invalid spatial cueing (Lepsien and Pollmann; 2002). In addition, both areas participate in the operations of space encoding according to an egocentric frame of reference and in exploratory goal-directed motor behaviours (Committeri et al., 2006; Danckert and Ferber, 2005; Doricchi and Tomaiuolo, 2003). Selective damage of these structures can, therefore, impair specific spatial abilities which constitute part of the symptomatology of neglect. Lesion of the superior parietal cortex instead is not directly related to the syndrome but it could generate additional attentional and motor deficits when also one of the crucial areas associated with neglect is lesioned. The superior parietal lobule and adjacent intra parietal sulcus are indeed involved in selective visuospatial attention mechanisms and visuomotor control of spatially guided behaviour such as reaching and grasping (Milner, 1997). In addition, area BA 7 is strongly interconnected with the pulvinar nucleus of the thalamus and participates in encoding the behavioural salience of relevant stimuli in the surrounding environment.

With respect to the operations of space representation, the results of the present study are compatible with those lines of evidence that show a pivotal role to the parietal cortex in multimodal coding of peripersonal (near space). For instance, many neurons of the ventral intraparietal area (VIP) of the macaque respond most strongly to incoming targets approaching near space especially in proximity of the animal's face (Colby, 1998). This pattern applies to visual, tactile or auditory stimuli (Bremmer et al. 2001). The VIP and the anterior intraparietal areas (AIP) are both nodal parts of the neuronal circuit responsible for visual guided reaching, pursuit tracking, gaze shifting to relevant targets and global perception (Previc, 1998). These mechanisms are fundamental for the reconstruction of proximal space and effective allocation of attentional resources upon it.

Further evidence of the involvement of parietal areas in the representation of near space is provided also by human neuroimaging research and TMS. PET studies showed parieto-occipital junction (POJ), inferior parietal sulcus and inferior parietal lobule activation in near space over far space during a line bisection task (Weiss et al., 2001; 2003). A fMRI study carried out by Quinlan and Culhan (2007) demonstrated that the dorsal parieto occipital sulcus responds particularly to stimuli presented within peripersonal space compared to far space and is engaged during planning and execution of reaching movements.

Makin et al. (2007) investigated the brain areas that selectively responded to a visual stimulus when approaching the immediate space surrounding the hands (perihand space) by providing visual and/or proprioceptive information about the hand itself. The authors showed that neuronal activity in the precuneus (BA7) was modulated by purely visual aspects of hand position while activation in the supramarginal gyrus (BA 40) was sensitive to both proprioceptive and visual information regarding hand position. These two parietal areas seem, therefore, to deal with different information useful in coding near space around one's hand. In addition, Bjoertmont et al. (2002) demonstrated that repetitive pulse TMS (rTMS) over the posterior parietal cortex can generate impaired line bisection performance in healthy adults in near but not in far space.

The subtraction of the brain lesions of the near only from the far only general template showed no specific brain areas uniquely involved in far space neglect. The brain regions obtained after this subtraction were also damaged in those patients whose neglect was restricted to near space, however, the extent and the location of damage were different. For example, damage of the middle frontal gyrus was found in both groups (BA 44 and 45) but the patients with far space only neglect had greater involvement of the ventral portion of area 44 while the frontal lesion of the other group included more the dorsal component of the same gyrus (BA 45 and 46). As stated previously, the ventral stream projects predominantly to the ventrolateral portion of the prefrontal cortex and the dorsal stream to the dorsolateral component of the prefrontal cortex (Boussaoud et al., 1996). More extensive damage to the ventrolateral prefrontal cortex in those patients with far only compared to those with near only neglect supports, therefore, the hypothesis that the neuronal networks shaping the ventral stream are prevalently involved in the representation of distal space.

The above analysis represented a preliminary investigation which intended to verify the presence of gross anatomical differences between those patients showing dissociation between neglect for near and far space. The region of common overlapping approach has, however, the intrinsic limitation that manual drawing of the patients' lesions can inevitably add a certain degree of error in the identification of the brain structures of interest. In the next chapter a voxel-based morphometry (VBM) technique was used to explore more thoroughly the anatomical correlates of space related deficits in a group of right hemisphere damaged patients.

The analysis approach used in this chapter was not adequate to identify subtle anatomical differences between groups with discrete spatial deficits. but most importantly it was not possible to clarify whether brain structures underlying performance on cancellation and bisection task differ. The number of patients showing dissociated performance in one task only was too small to yield any reliable result. Space and task related anatomical dissociations could be more readily explained by trying a more sophisticated image analysis approach which is that of Voxel-based morphometry of 3D structural MRI scans. The following chapter includes the findings of this study.

CHAPTER 5

Near and far space attention: A VBM correlation study

5.1. Introduction

The single case series and the group study of the present dissertation, demonstrated that visual exploration tasks are more sensitive in detecting neglect for near and far space. Indeed, search abilities seem to be differently affected depending on the spatial distance they are assessed while line length estimation appears less susceptible to distance. Cancellation and line bisection tasks have been shown to tap into different cognitive mechanisms and rely on different neuronal substrates but there are currently no studies that explored whether performance on these tests is supported by distinct areas when executed in near and far space.

To date, all the neuroimaging and TMS studies that investigated the anatomical correlates of near and far space attention used line bisection paradigms. In the two PET studies carried out by Weiss et al. (2000; 2003), far space attention evoked activation of the ventral occipital and medial temporal cortex while in near space occipito-parietal and premotor cortex activation was observed. Bjoertomt et al. (2002) demonstrated that magnetic stimulation of the posterior parietal cortex yielded a rightward bisection error in near space whereas stimulation of the ventral occipital area selectively generated the same error in far space. These latter findings are in line with the hypothesis that near and far space representation appear to be neuronally associated with the dorsal and ventral high visual streams respectively (Previc, 1990). However, while Bjoertomt et al.'s results (2002) support the findings of clinical studies on near and far space neglect by showing a direct involvement of the right hemisphere in near and far space attention, Weiss et al.'s studies (2000; 2003) reported a left hemisphere activation for near space and a bilateral activity in far space. As a result, to date neuroimaging techniques have not yet provided substantial evidence for the understanding of space specific deficits in neglect patients and their neuroanatomy. In addition, as Weiss et al. (2000; 2003) and Bjoertomt et al.'s (2002) limited their investigation only to line bisection, it is still unknown whether different visuo-spatial abilities, such as visual exploration, engage different neuronal substrates which are specific for near and far space.

By using both line bisection and cancellation tasks, the aim of the present study was to explore those brain structures that, when damaged, can result in a task-specific visuo-spatial deficits within near or far space. To achieve this goal, a Voxel Based Morphometry (VBM) correlation study was carried out to define those brain structures whose grey matter loss is associated with a space-specific symptom of interest (i.e. bisection errors or left/right asymmetric accuracy in visual search) in a group of unselected right brain damaged patients. As the patients were selected based only on their right hemisphere damage, the whole range of symptom severity for both tasks was taken into consideration in the analysis. The VBM technique is generally used to identify automatically in a objective manner regional differences in grey matter and white matter density in structural MRI scans (Ashburner and Friston, 2001; Salmond et al., 2002). This procedure allows every area of the brain to be considered in an unbiased way, with no a priori region of interest (Salmond et al., 2002).

5.2 Methods

5.2.1 Sample

Eighteen right hemisphere damaged patients were recruited form the Neurology Clinic in the Nuovo Ospedale Civile S. Agostino Estense in Modena (Mean age 59, SD = 15; education 7.56 SD = 3). None of them showed signs of cognitive decline and all provided written informed consent prior to taking part in the study. Clinical and demographic data are reported in table 5.1.

5.2.2 Tasks and procedure

The patients carried out the Bells test and the line bisection task in near and far space respectively following exactly the same procedure as outlined in the previous chapter (section 4.2.4 at page 163). Again the individual results in the Bells test were transformed into laterality index (LI - see chapter 4 for the formula). A positive LI indicated left sided target omissions while a negative LI indicated right sided omissions. Accordingly, a LI of 0 indicated an unbiased performance between the left and the right visual field.

In the line bisection task, for each patient the average deviation from the true centre of the three lines was measured in mm, with a positive sign for rightward deviations and negative for leftward deviations. Each score was converted in degrees of visual angle. Both tasks were carried out in near (40 cm) and far (320 cm) space respectively.

5.2.3 Structural MRI scanning: acquisition and analysis

Three dimensional T1-weighted MRI images were acquired on a 3T Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1 x 1 x 1 mm and field of view was 256 mm with a matrix size of 256 x 256 x 124. Total acquisition time was 4 minutes 41 seconds (TR 9.9 msec, TE 4.6 msec and flip angle 8°). A number of preprocessing steps were followed to isolate the grey matter from the 3D T1-weighted structural scans before performing the statistical analysis using SPM5 (Welcome Department of Imaging Neuroscience, UCL, London, UK). To correct for global differences in brain shape, structural images were warped to standard stereotactic space and segmented to extract grey matter, white matter and cerebrospinal fluid. The grey matter segments were then modulated to correct for changes in volumes introduced by nonlinear normalization and smoothed using a Gaussian filter set at 12 mm to reduce the possible error from between-subject variability in local anatomy and render the data more normally distributed. Finally, smoothed grey matter segments were entered into a voxel-based multiple regression analysis to investigate linear correlations between grey matter concentration and a specific performance of interest considering the type of test (Bells test and line bisection) and space distance (near and far). Four different models were designed considering the patients' laterality index for the Bells test in near (1) and far space (2) as well as the deviation in degrees of visual angle in the line bisection task also in near (3) and far (4) space. Age, number of years of education and gender were included in each model as covariates. Height threshold was set at $p < 0.01$ with a small volume correction. The criteria used to apply a small volume correction was the presence of an a priori hypothesis on specific areas of interest which have been shown involved in neglect for near and far space. The x, y, z coordinates of the areas of significant correlation obtained from the analysis were first converted into Talairach coordinates and then identified using Talairach Demon Client (http://ric.uthsca.edu/projects/tdc/).

5.3 Results

Behavioural results

For the Bells test, patients showed a rightward laterality index that was overall larger in near compared to far space. In some cases a positive laterality index in near space became negative in far space and vice versa. A similar pattern was observed for the line bisection task. In this task, the rightward bisection error showed by the group in near space was reduced in far space. In both tasks, neglect appeared less severe in far compared to near space which was also reflected in the lower variability of the individual scores in far space. Given this pattern of lower variability in far space together with the relatively small number of cases with neglect, the results of the subsequent regression analyses must be interpreted with some caution. The scores of the patients for both tests are reported in Table 5.1.

Table 5.1 Demographic, clinical data and performances of the patients for both line bisection and the Bells test in near and far space.

Patients	Age/gender	Education	Lesion site	Line Bisection‡		Bells test#	
				Near	Far	Near	Far
1	57/M	8	F-T-I	3.44	0.67	100.00	0.00
2	49/F	13	F	-0.24	-0.03	3.70	0.00
3	81/F	3	I-F	0.48	0.05	0.00	0.00
4	52/M	11	T-P-I	0.62	0.07	0.00	0.00
5	63/F	12	F	0.00	0.00	-3.45	0.00
6	57/M	5	F-I-T-BG	1.10	0.17	4.35	-11.11
7	57/F	5	F	0.48	0.05	8.33	0.00
8	48/M	11	F-I-P	1.67	0.21	76.47	0.00
9	86/M	5	T-I	1.05	0.09	0.00	0.00
10	80/M	5	F-P-I-BG	1.10	0.13	0.00	0.00
11	78/F	5	O-P-Th	19.35	1.69	100.00	15.79
12	59/F	5	F-T-I	0.24	0.24	-3.45	47.37
13	63/M	8	T-O-P-I-F	5.02	0.37	7.69	12.00
14	66/M	8	T-P	-0.76	0.02	0.00	-7.14
15	44/M	8	F	0.24	0.05	0.00	0.00
16	40/F	8	F	1.48	0.06	0.00	0.00
17	37/F	8	F	0.48	0.02	-11.11	0.00
18	40/F	8	F	-0.96	0.02	-7.14	0.00
Mean	58.72	7.56		1.93	0.22	15.30	3.16
SD	14.97	2.81		4.57	0.40	35.97	12.44

#Values show laterality index and ‡deviation errors in degree of visual angle. F = frontal, P = Parietal; O = occipital; T = temporal; I = insula; Th = thalamus; BG = basal ganglia.

Neuroanatomical results

Near space

For the near space condition, the voxel-based multiple regression analysis showed that high positive LI values on the Bells test were significantly correlated with low grey matter density in the right middle temporal gyrus (BA 21 and 39), inferior frontal gyrus (BA 47) and insula (BA 13) (Fig. 5.1 A and B). In contrast, a significant negative correlation was found between low grey matter density values in the right lingual gyrus (BA 19) with large rightward errors in the line bisection task (Fig 5.2 A and B). (See also Table 5.2). Figures 5.3 and 5.4 show the scatterplots with the distribution of individual values of laterality indexes and deviation in degree of visual angle in the line bisection task plotted against the level of grey matter density in the middle temporal gyrus and lingual gyrus respectively.

A B

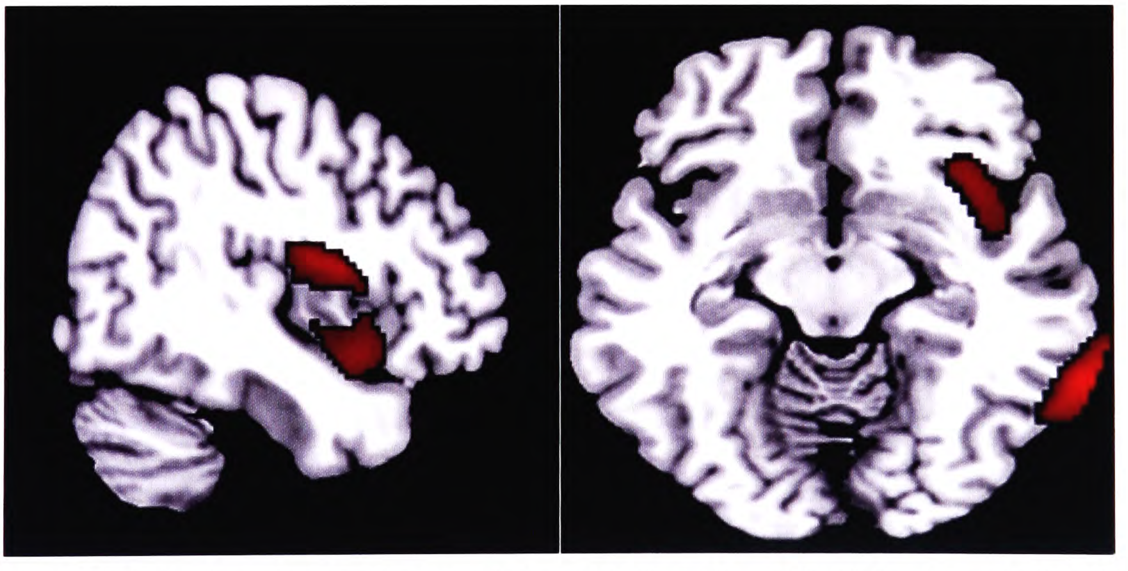


Figure 5.1 Areas of negative significant correlation with high number of left-sided omissions in the Bells test for near space with (A) the right inferior frontal gyrus (sagittal view) and (B) insula and middle temporal gyrus (axial view). The images are presented in neurological orientation (R/R).

A B

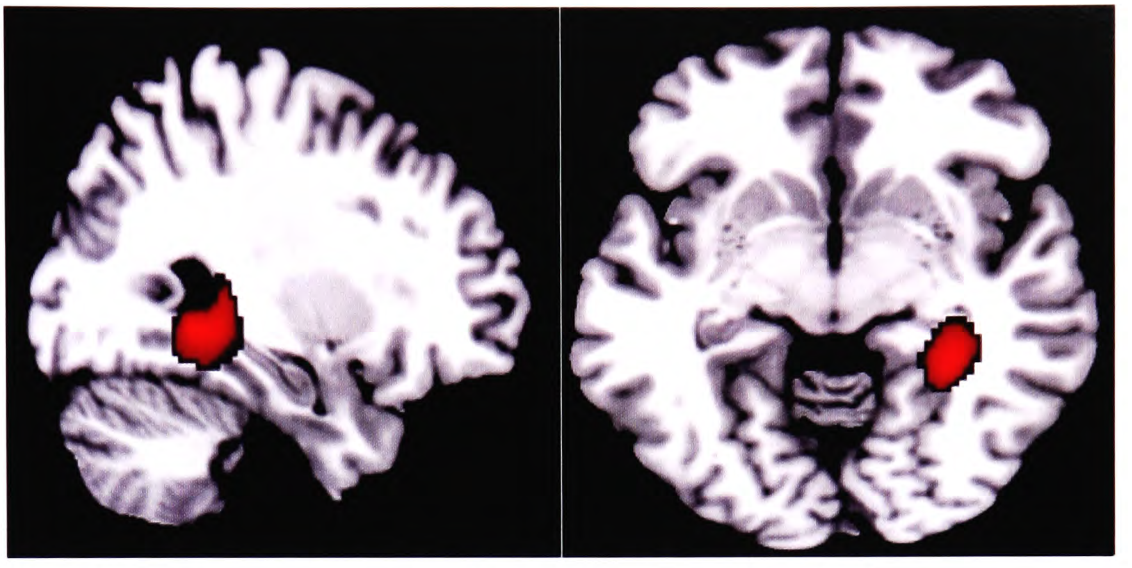


Figure 5.2 Sagittal (A) and axial (B) view of the right lingual gyrus where a significant negative correlation with rightward bisection errors for near space was found. The images are presented in neurological orientation (R/R).

Table 5.2 Areas of significant correlation between GM density values and the LI indexes in the Bells test and deviations of visual angle in the line bisection tasks in near space.

Brain area	Right/Left	Brodmann's area	Talairach Co-ordinates			Z-value at local maximum
			X	Y	Z	
Bells test						
MiddleTemporal Gyrus	R	21	67	-49	-4	4.24
		39	57	-69	24	3.03
		39	59	-69	11	2.98
Insula	R	13	40	4	11	3.25
Inferior Frontal Gyrus	R	47	34	17	-16	3.25
		47	32	25	-3	3.11
Line bisection						
Lingual Gyrus	R	19	32	-45	-1	3.60

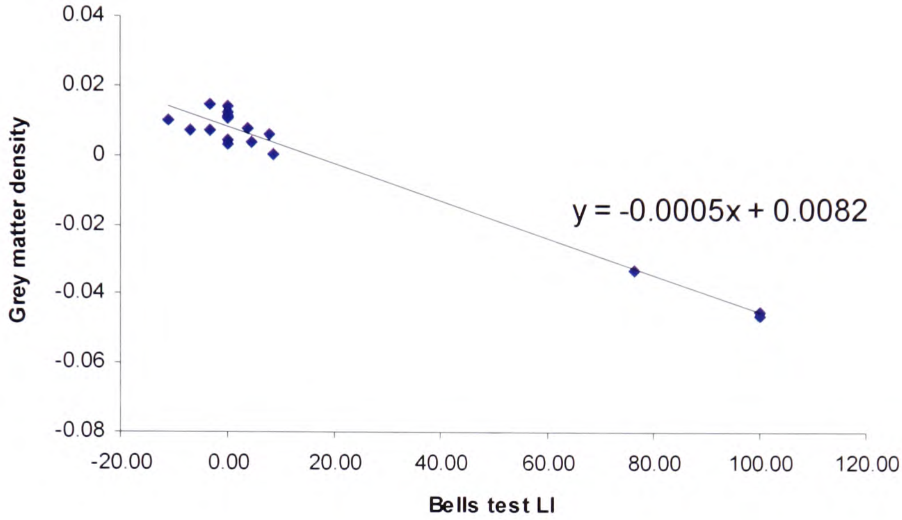


Figure 5.4 Laterality index plotted against grey matter volumes in the middle temporal gyrus [67, -49, -4].

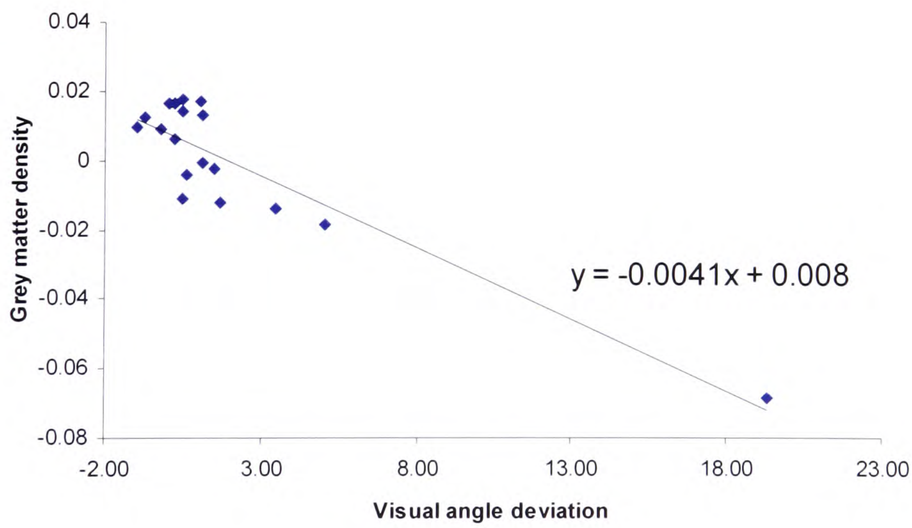


Figure 5.3 Deviation of visual angle plotted against grey matter volumes in the lingual gyrus [32, -45, -1].

Far space

In the far space condition, high positive LI values for the Bells tests correlated significantly with low grey matter density in the right middle temporal gyrus (BA 21). Large rightward deviations errors in the line bisection task were instead significantly correlated with low grey matter density values in the right middle and inferior temporal gyrus (BA 21 and 37). (See Figure 5.5 A and B and Table 5.4). Figures 5.6 and 5.7 show the scatterplots with the distribution of individual values of laterality indexes and deviation in degree of visual angle in the line bisection task plotted against the level of grey matter density in the middle and inferior temporal gyrus respectively.

A B

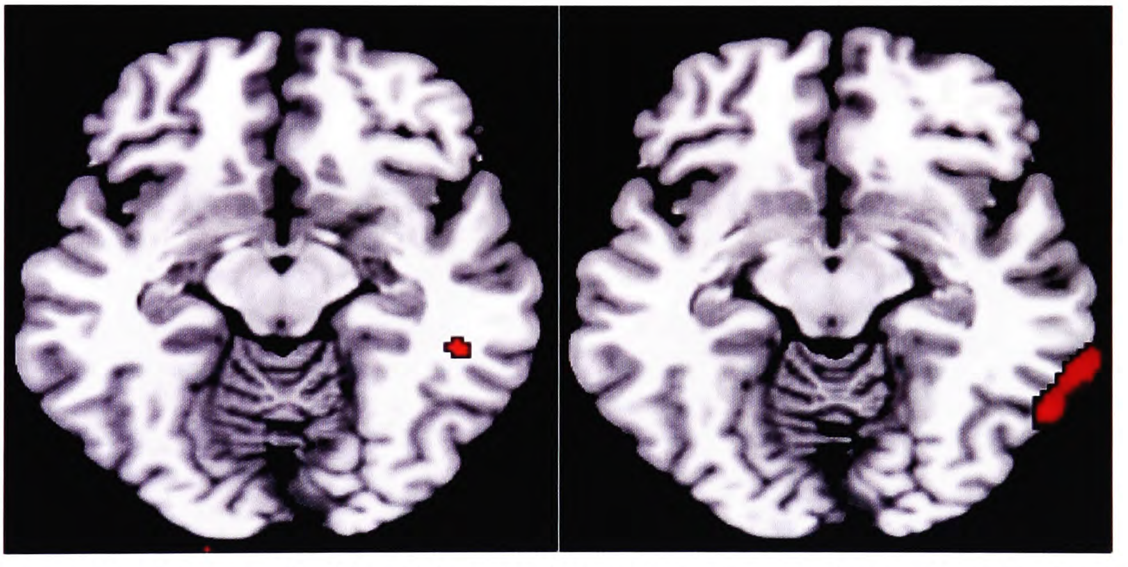


Figure 5.5 Axial view of the right middle temporal gyrus whose grey matter loss correlates significantly with a high number of left-sided omissions on the Bells test in far space (A). Axial view showing the right middle and inferior temporal gyrus which correlated negatively with rightward bisection errors for the line bisection task in far space (B). The images are presented in neurological orientation (R/R).

Table 5.4 Areas of significant correlation between GM density values and the LI indexes in the Bells test and deviations of visual angle in the line bisection tasks in far space.

Brain area	Right/Left	Brodmann's area	Talairach Co-ordinates			Z-value at local maximum
			X	Y	Z	
Bells test						
Middle Temporal Gyrus	R	21	48	-37	-8	2.61
Line bisection						
Middle Temporal Gyrus	R	21	69	-50	6	3.04
		21	65	-45	-6	2.84
Inferior Temporal Gyrus	R	37	57	-59	-7	2.84

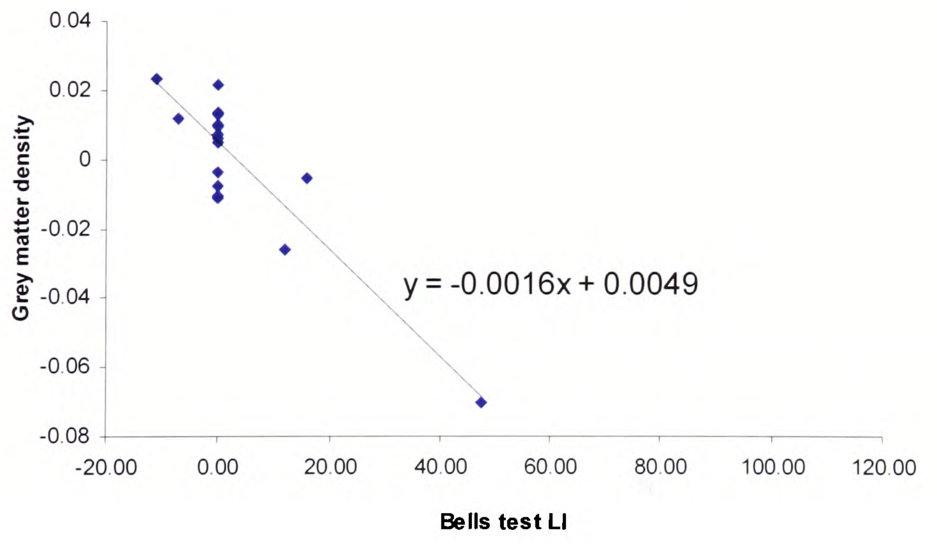


Figure 5.6 Laterality index plotted against grey matter volumes in the middle temporal gyrus [48, -37, -8].

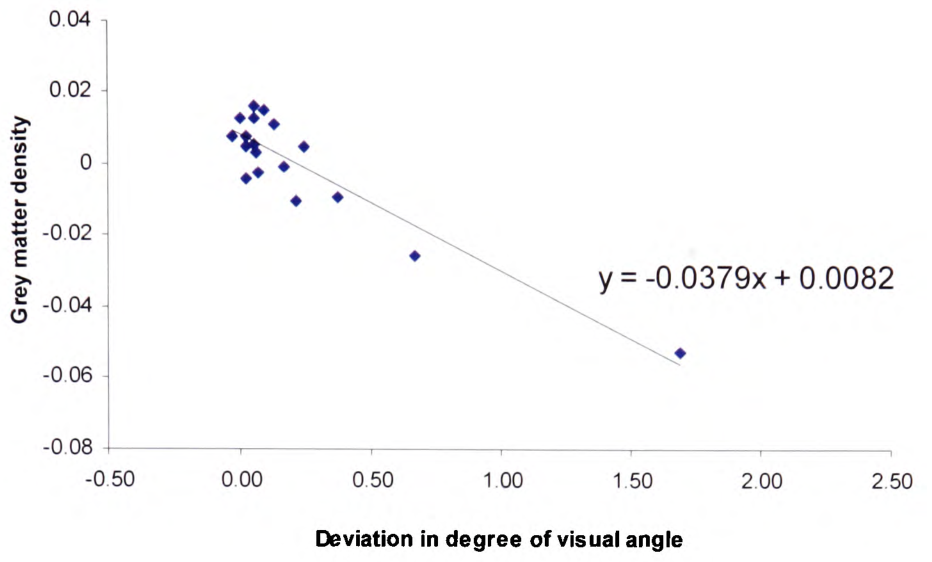


Figure 5.7 Deviation of visual angle plotted against grey matter volumes in the inferior temporal gyrus [57,-59, -7].

5.4 Discussion

The present investigation intended to explore the association between the degree of grey matter loss and the severity of neglect as assessed with both line bisection and cancellation tasks in near and far space.

The results indicated that grey matter loss in the inferior and middle temporal gyrus was associated with rightward line bisection errors and an asymmetric visual search performance in favour of ipsilesional targets in far space. The inferior temporal area has long been considered one of the major cortical sites shaping the ventral pathway which seems to play a special role in the representation of far space (Previc, 1998). Generally this temporal structure, together with the ventral occipital areas (i.e. V4) with which it is tightly connected, is particularly involved in visual search, scanning, high visual features analysis and visual attention (Desimone and Duncan, 1995; Previc, 1990). The clinical deficits that follow inferior temporal lesions in humans are usually associated to object, colour and facial recognition impairments as well as high distractibility during visual search in neglect patients. This deficiency may underlie a more general inability to attend to and integrate local features of the surrounding stimuli, while sparing visuo-motor reaching faculties (Damasio, 1995; Previc, 1990; Levine et al., 1985; Arguin et al., 1996; Valenza, 2005).

The involvement of the right medial temporal regions instead in visuospatial attention has been observed by Maguire and Ogden (2002), who showed how this area can be related to chronic neglect together with damage in the basal ganglia and dorsolateral prefrontal cortex. The patients showing persisting symptoms of neglect in this study were assessed with a comprehensive battery which included not only line bisection and cancellation tasks but also reading, scene copying and visuoconstructive tasks.

More specifically, in accordance with the results of the present VBM study, neuropsychological evidence supports the role of the inferior as well as medial temporal regions in neglect especially for far space. For instance the patient described by Shelton et al. (1990), following bilateral medial and inferior temporal and occipital damage, had greater rightward line bisection error for distal stimuli compared to those within proximal space. The same structures were damaged in Vuilleumier et al.'s (1998) patient whose damage was, however, confined to the right hemisphere. This patient showed neglect restricted to far space in both line bisection and cancellation tasks. This latter evidence would imply that inferior and medial temporal lesions may not only be associated with a space specific ability in focusing attention along the physical extent of one single object but also with the capacity of actively explore and select multiple items in the environment. This hypothesis is supported by the significant correlation between the degree of grey matter loss in the inferior and medial temporal areas observed for the present group of patients with poor performance in both line bisection and the Bells test in far space. The involvement of the right medial temporal cortex in extrapersonal space attention is also consistent with the findings of two PET studies carried out by Weiss et al. (2001, 2003) who compared neuronal activation associated with line bisection performance in healthy participants in near and far space.

In this study, the VBM correlation analysis showed that middle temporal gyrus damage is also associated with impaired visual search abilities in the contralateral side of space within proximal space. The coordinates obtained for this area in the correlational analysis with the Bells test scores in near space were, however, closer more to superior temporal regions and included also part of the angular gyrus (67, -49, -4 and 57, -69, 24) in comparison to those associated with the same test in far space which involved, instead, more inferior portions of the middle temporal gyrus (48, -37, -8). This pattern appears consistent with the hypothesis that the dorsal and ventral streams are differentially involved in near and far space representation (Previc, 1990). The dorsal stream projects to more superior portions of the temporal lobe (MT and SMT), while the ventral stream sends its neuronal inputs prevalently to inferior temporal regions.

Some lesion studies with neglect patients provide further evidence on the involvement of the middle temporal gyrus in visual exploration abilities for near space.

Karnath et al. (2005) assessed patients with basal ganglia stroke and the presence of neglect was defined based on their everyday orienting behaviour and performance on typical cancellation tasks. In the group of patients with neglect, one of the brain areas with maximum abnormal perfusion following structural basal ganglia damage was the right middle temporal gyrus. In addition, Commiteri et al. (2006) investigated the neuronal substrates underpinning neglect for personal space (body surface) and peripersonal (near) space with a neuropsychological battery of neglect tests which included cancellation but not line bisection tasks. While personal neglect was mainly related to inferior parietal damage, neglect within proximal space was associated with right superior and middle temporal gyrus as well as middle frontal areas.

In support of the results of the present study, Karnath et al. (2005) and Committeri et al.'s (2006) findings indicate that both dysfunction or structural damage of the middle temporal area contributes to generate visual exploration deficit in neglect as assessed in near space.

The VBM analysis revealed that poor performance on the Bells test was related to grey matter loss in correspondence not only of the middle portion of Brodmann's area 21 but also of the more posterior part of Brodmann's area 39 in the middle temporal gyrus. This result leads to consider the possibility that the region along the border between the temporal and the parietal lobe, namely the temporal parietal junction, may also be compromised and, as such, involved in asymmetrical visual exploration in near space. The temporal parietal junction has been considered as having the function of a salience detector for novel stimuli in the environment by numerous neuroimaging studies (He at al., 2007). This region cannot be defined as a functionally distinct area and its involvement in visual exploration for near space in the present study can only be inferred given the observed grey matter loss in correspondence of Brodmann's area 39 in the middle temporal gyrus. If this assumption is correct, the involvement of the temporal parietal junction in cancellation tasks within proximal space would be consistent with the role of this brain region in visual search and stimulus driven orienting of attention which is commonly impaired in patients with neglect.

The right inferior frontal gyrus was also damaged in those patients with relatively poor performance in the Bells test for near space. This region, in connection with the right temporal parietal junction, represents the critical nodes of the ventral bottom-up attentional network for target detection and reorienting towards novel unexpected events as described by Corbetta and Shulman (2002). Several neuroimaging studies observed signal increase in the inferior frontal gyrus in association with activation of the temporal parietal junction during visual search tasks (Downar et al., 2000; 2001; 2002; Serences et al., 2005). Structural damage or functional disconnection of the neuronal components shaping the ventral attentional network, namely the temporal parietal junction and inferior frontal cortex, has been considered critical for the occurrence of neglect (He at al., 2007).

Further support for the role played by the inferior frontal gyrus in visual search abilities is provided by several neuroimaging studies. Himmelbach et al., (2006) investigated in healthy participants the activity of those brain structures typically associated with neglect during free visual search by using a task which closely resembled a classical cancellation test as those used in the clinical assessment of neglect.

The authors showed that the inferior frontal gyrus, together with the temporal parietal junction and superior temporal gyrus, were critically involved in voluntary visual orienting and exploration and, therefore, represent important candidates in the genesis of biased visual search deficits in neglect patients (Himmelbach et al., 2006). Furthermore, Anderson et al., (2007) showed that the inferior frontal cortex is specifically active during inefficient conjunction search while Aron and co-workers (2003; 2004) demonstrated that this region may play a role in filtering out irrelevant stimuli in association with its involvement in response inhibition of distractor items. These findings are in accordance with clinical studies showing that isolated frontal lesions are frequently associated with neglect for target cancellation tasks with a relatively preserved ability to perform line bisection tasks (Binder et al., 1992; Hussain and Kennard, 1996; Maeshima et al., 1995).

The above evidence regarding the special role played by the inferior frontal cortex in visual search and exploration deficits in neglect is consistent with the finding of the present VBM correlation analysis which indicated an association between low grey matter density in the inferior frontal gyrus and ipsilesionally biased performance on the Bells test in near space.

A further region whose grey matter loss correlated significantly with impaired visual exploration abilities in near space was the insula. By integrating vestibular, proprioceptive, visual, auditory and olfactory inputs, this structure is considered an area of multimodal integration fundamental for a stable internal representation of one's own body position and movements in space. Several anatomical findings provided by Karnath et al. (2001, 2004, 2006) on neglect patients suggest that the insula, together with the superior temporal cortex and basal ganglia, represents one of the critical structures responsible for the occurrence of neglect. In their studies, a part from the overt behavioural signs shown by the patients (i.e. spontaneous ipsilesional deviation of the head and eyes), one of the fundamental criteria adopted by Karnath et al. to assess the presence of neglect was performance on cancellation tasks which they believe reflect the symptomatology of the disorder more specifically in comparison to line bisection tasks. In accordance with the results of the present study, damage of the insula appears therefore especially related to exploration deficits in neglect, as assessed within cancellation tasks, within the patients' peripersonal space.

Finally, for the near space condition, a pathological rightward error in the line bisection task correlated significantly with low levels of grey matter density in correspondence of the occipital right lingual gyrus (BA 19). This result is consistent with those group studies on neglect patients showing that abnormal performance on line bisection tasks is usually associated with posterior brain damage including the occipital and the parietal cortex (Binder et al., 1992; Rorden et al., 2004). Cancellation tasks instead seem to engage more anterior structures such as the insula, temporal and middle frontal cortex as performed within the patient's proximal space (Weintraub et al., 1988; Ishiai et al., 1989; Binder et al., 1992; Rorden et al., 2004). Several neuroimaging studies consistently reported the involvement of occipital areas during line bisection paradigms probably because of their involvement in those operations of selective object perception, from their basic features elements (i.e. orientation) to a more complex holistic representation (Fink et al., 2002; Screnences and Yantis; 2007). In addition, striate and extrastriate cortex has been shown to play a role in top-down visuospatial selective attention processes (Yantis et al., 2002; Kincade et al., 2005; Hahn et al., 2006 Corbetta et al., 1990; Fink et al., 1996). Numerous neurophysiological studies reported near-space preference in early visual areas in macaque and Quinlan and Culham (2007) suggested that this over representation of near-tuned neurons seems to be present also in humans. The authors used fMRI to investigate whether specific posterior brain areas would show a stronger response for a stimulus located in near over far space and they showed a general preference for near space presentation over much of the occipital lobe (Quinlan and Culham, 2007). Two PET studies carried out by Weiss et al. (2000; 2003) investigated whether a line bisection task evoked a different pattern of activation depending on the stimulus distance. Their results revealed that dorsal occipital areas were associated with line bisection performed in near space while ventral occipital activation was observed for far space. This pattern is consistent with the neuronal organization of the occipital cortex between the magnocellular (dorsal) and parvocellular (ventral) pathways from which the dorsal and the ventral high visual streams generate. In accordance with the hypothesis which suggests a dorsal ventral stream dichotomy for near and far space attention, different regions of the occipital cortex may be involved in the representation of specific space sectors. Markin et al. (2007) for instance, demonstrated that the occipital region in correspondence of Brodmann's area 19 showed activation for near over far space object presentation (a ball), independently of the subject's hand position with respect to the object. The above evidence together with the findings of the present study support thus an association between BA 19 and near space representation.

In summary, the present anatomical investigation suggests that far space attention relies on ventro-temporal structures regardless of the cognitive demand evoked by the task. This finding has been demonstrated clinically in a single case report (Vuilleumier et al., 1999) and the present morphometric group study reinforces this anotomo-clinical association. In addition, the results of the present study provide also further support to the role of the ventral stream in far space coding.

In contrast, the type of task used seems to be more relevant in near space attention for which the segregation of different neuronal substrates supporting specific visuospatial abilities appears more distinct compared to that observed for far space. Damage of anterior brain regions such as the insula and the inferior frontal cortex was specifically related to visual exploration impairments within near space, whereas the inability to focus attention along the physical extent of the line was associated with damage to more posterior occipital structures. While this pattern is consistent with the anatomical trend of those clinical studies of neglect patients with specific deficits in cancellation or line bisection tasks, it does not support the selective involvement of the dorsal stream in near space representation. This outcome may be due to the lower presence of patients with posterior parietal damage over those with more anterior temporal and frontal injury in the sample. However, note that the clinical cases of neglect described to date whose deficit was restricted to near space only, had selective occipito-parietal damage with the additional involvement of temporal and frontal structures (Mennemeier et al., 1992; Halligan and Marshall 1991; Berti and Frassinetti; 2000). Therefore, in accordance with this evidence and the findings of the present study, it may be possible that deficits restricted to peripersonal space are not associated only with damage of the dorsal stream. Lesion of different brain structures located outside the neuronal territory shaping this pathway can indeed be sufficient to generate neglect deficits restricted to peripersonal space.

SUMMARY

The aim of the present research was to explore whether neglect for near and far space is modulated by the type of task (cancellation vs. bisection) and the type of response required (perceptual vs. motor). At an anatomical level, it has been suggested that near and far space representations are mapped on the dorsal and ventral visual streams respectively. Neglect for either near or far space following specific damage to brain areas within these two high visual pathways was, therefore, investigated.

Following extensive pilot work, a series of single case studies with right brain damaged patients was carried out using a visual search and a line bisection paradigm. In the perceptual condition of both tasks, patients were asked to respond only by pressing a response button to indicate their answer while in the motor condition they had to point toward the stimuli with their arm at full stretch. The results showed that in some patients neglect for near and far space was consistent across the two tasks (patient SV, JA) whereas in other cases, neglect was seen only in visual search either in near or far space (patient MF). In addition, in some cases the presence/absence of a directional motor response was found to modulate significantly the magnitude of neglect in near and far space. For example, JA's neglect deficits were more severe in the perceptual than in the motor condition regardless of type of task. In contrast, patient MF showed neglect only in the visual search task with his deficit being restricted to far space in the perceptual condition and to near space in the motor condition. An evaluation of the three patients' brain lesions revealed that neglect for near space was associated with damage of the right insula, posterior cingulate and possibly basal ganglia while neglect for far space resulted from damage in ventral and middle temporal areas. This preliminary anatomical outcome showed that the dichotomy between the dorsal and the ventral stream for near and far space representation was not clear-cut.

A subsequent study was carried out to explore the frequency of neglect for near and far space in a large group of unselected right brain damaged patients. Patients with and without neglect and a group of neurological healthy controls performed a traditional cancellation task (Bells test) and line bisection task, in both space distances. The results showed that in both tasks, only the neglect patients performed significantly poorer in near compared to far space but not the other two groups. However, frequency analysis yielded a differential impact of spatial distance on neglect in both tasks. Those neglect patients who were impaired in the cancellation task were more likely to show the deficit in one space sector only, while those that made large rightward line bisection errors tended to be impaired in both near and far space although the level of severity was different. The Bells test appeared to be, therefore, more sensitive in detecting dissociations in distance related neglect.

A lesion overlap analysis carried out on the CT scans of those patients with neglect restricted to either near or far space showed that the anatomical substrates shared by these two critical groups were the superior and middle temporal gyrus, medial frontal cortices and anterior cingulate. A lesion subtraction analysis between the CT scans of the two critical neglect groups (near only minus far only neglect) demonstrated that neglect restricted to near space was associated with damage in the dorsolateral prefrontal cortex and inferior and superior parietal cortices, namely the supramarginal gyrus, angular gyrus, precuneus and the dorsal part of BA 5. In contrast, the opposite lesion subtraction (far only minus near only neglect) revealed that there were no specific brain areas uniquely involved in neglect restricted to far space. The patients with far only neglect, however, showed greater involvement of the ventral portion of the middle frontal gyrus (BA 44), while the frontal lesion of the group with near only neglect included more the dorsal component of the same gyrus (BA 45 and 46).

A final study focussed on identifying those discrete anatomical structures within the near and far space attention network that, when damaged, result in lateralised visual search and line bisection behaviour. This goal was achieved by using a Voxel-based morphometry correlation approach, a technique which is able to identify those brain areas whose grey matter loss was associated with a specific symptom of interest in an unbiased way. An unselected group of right brain damaged patients was assessed for visuospatial neglect in near and far space with a cancellation task (Bells test) and a line bisection task. A Voxel-based multiple regression analysis between grey matter density values extracted from patients' 3D MRI scans and their behavioural performance on each test within near and far space was carried out. In near space, left omissions on the Bells test were significantly correlated with low grey matter density in the right middle temporal gyrus, inferior frontal gyrus and insula. In contrast, large rightward errors in the line bisection task were significantly correlated with low grey matter density values in the right lingual gyrus. In far space, left omissions in the Bells tests correlated significantly with low grey matter density in the right middle temporal gyrus. Large rightward deviations errors in the line bisection task were instead significantly correlated with low grey matter density values in the right middle and inferior temporal gyrus. These results, together with the lesion analysis of the single case series and of the overlap study showed that neglect for near and far space can indeed result from damage of some of the anatomical structures forming part of the dorsal and the ventral streams. However, lesions of additional brain areas (i.e. insula, middle frontal cortex, cingulate and basal ganglia) located outside the main territories of the two visual streams can also generate neglect deficits restricted to near or far space.

CHAPTER 6

General discussion

6.1 General findings

The present research showed that neglect does not always affect the whole contralesional space as the behavioural patterns observed in the group study and in the single case series demonstrated that the disorder can be confined or more pronounced within the patient's near or far space. In addition, it emerged that within each of these space sectors the phenomenology of neglect symptoms can vary according to several factors such as the type of task and the presence/absence of a directional motor response when performing the task. Most importantly, the specificity of these space related deficits was crucially related to damage of particular brain structures which appeared to be especially recruited for near or far space coding. Finally, the brain areas engaged during different visuospatial tasks (cancellation or bisection) can vary depending on the space sector in which they are performed.

Taken together, the above results suggest that the observed severity of spatial neglect is a result of the interaction between type of task, motor response, spatial distance and specific brain damage which may vary across individual patients.

6.2 The effect of task

The results of the group study described in chapter 4 showed that amongst a large sample of right brain damaged patients, both contralateral omissions during visual search and rightward line bisection errors were more severe in near than in far space. However, left neglect in cancellation tended to occur only in one space sector or the other while rightward line bisection errors were more likely to be present in both space sectors. To date, space related deficits in neglect have been investigated mainly with line bisection paradigms and the above findings indicate that cancellation tasks may be instead more sensitive in detecting neglect deficits confined to either near or far space. The results of the single case series complemented those of the group study as they suggested that although near and far space neglect can be present independently of the cognitive demands of different tasks, there are cases in which distance related neglect can be observed only in one specific task but not in another (i.e. visual search or line bisection).

In contrast to previous findings (Cowey et al., 1994; 1999; Pizalis et al., 2001), the results of the group study indicated that overall neglect seems to impair more near than far space attention. While it has been shown that both space sectors can be selectively affected in neglect patients (Halligan and Marshall, 1991; Berti and Frassinetti, 2000; Mennemeier et al., 1992; Vuilleumier et al., 1999; Shelton et al., 1990; Barrett et al., 2000), this discrepancy can be explained by the fact that earlier group studies recruited a smaller number of patients and used different selection criteria. Most importantly, they restricted their observations only to line bisection performance, explaining therefore why no particular behavioural trend has been so far highlighted regarding space related visual exploration deficits in neglect.

The findings of the present study indicated that visual exploration abilities can be more vulnerable to space distance than line length estimation in neglect patients. However, very few studies explored whether, although with a lesser extent, this space related pattern observed for visual search tasks is consistent also across neurologically intact subjects. For example, Previc and Blume (1993) suggested that there are asymmetries in the search abilities of healthy right-handed subjects across the three dimensions of space which may reflect a differential speed in shifting focal attention. Indeed, visual search performance appears biased towards the lower left quadrant in near space and to upper right quadrant in far space (Previc, 1990; 1991). The authors predicted also that between the two space sectors, visual search accuracy in healthy subjects may be higher in far than in near space due to the special role played by the neurons of the ventral stream in visual exploration behaviour (Burkhalter & Van Essen, 1986; Previc, 1990; Previc and Blume, 1993). It would be interesting to investigate the consistency of this hypothesis per se and across different visual search tasks evoking specific patterns of efficiency (feature and conjunction search). The findings on the possible presence of search asymmetries across space sectors in healthy subjects may be integrated and interpreted along with those indicating significant differences also in line bisection performance between near and far space (Bjoertomt et al., 2002; McCourt & Garlinghouse, 2000; Varnava et al., 2002; Longo and Lourenco, 2006).

6.3 The effect of response

The present study investigated also the effect of the presence/absence of a manual motor response in the manifestation of near and far space neglect. The single case studies showed that distance related deficits in neglect can vary depending on the type of response required by the task used. Several findings suggested that a directional manual response such as bisecting a line with a pen in near space or with a stick in far space can be determinant in detecting neglect impairments restricted to near or far space (Halligan and Marshall, 1991; Mennemeier et al., 1992; Vuilleumier et al., 1999; Shelton, 1990; Cowey et al., 1994; 1999; Pizzamiglio et al., 1989). This idea was reinforced by the studies on tool use which in some patients seemed to trigger a dynamic remapping between space sectors (Berti and Frassinetti, 2000; Ackroyd et al., 2002). For example, far space can be coded as near space and included within it as the use of a tool (i.e. stick) can act as an extension of the subject's arm. However, more recent studies demonstrated that space distance can modulate neglect deficits even without a direct contact between the observer and the stimuli (Pitzalis et al. 2001; Butler et al., 2004). In addition, a PET study in healthy volunteers showed that the activation pattern associated with a line bisection task did not change depending on the presence/absence of a motor response across near and far space (Weiss et al. 2003).

The results of the single case studies suggested that in some cases the patient's space specific deficit was consistent regardless of the presence/absence of a motor act toward the stimuli. This finding does not support the idea that tasks involving an overt motor act are generally more effective in detecting dissociations between near and far space neglect. In addition, this pattern demonstrated that space is not only coded on the basis of the intention or execution of possible motor acts upon it (i.e. grasping, oculomotions) but is also defined through various sensory inputs (i.e. visual, proprioceptive). Accordingly, the integration of both perceptual and output related information concurs to create a coherent representation and awareness of the three-dimensional space. In this dissertation, the performance of one patient with mild neglect, however, demonstrated that in some cases the specific motor act required to perform the task can modulate the manifestation of space specific deficits. Patient MF showed poorer visual search accuracy on the left compared to the right visual field in far space and not in near space only when no ballistic movement was required to perform the task. Conversely, when he had to point overtly at the target during the same task, his visual search abilities improved in far space but became deficient in near space. This behavioural pattern can be interpreted within the framework of the premotor theory of attention (Rizzolatti, 1983b, Rizzolatti and Camarda, 1987) which considers the mechanisms of spatial attention and space coding as dependent on the preparation and execution of particular motor acts (i.e. limb, eye movements) which are specific for each sector of space. Hence, for instance, eye exploration and oculomotion may be more specifically linked to far space coding while action based mechanisms of attention specialised in the control of limb/arm movements may be primarily associated to near space processing. In line with this hypothesis, MF showed a deficit in far space only when the task required exploring visually the display without a direct manual contact between the viewer and the stimuli while when he had to reach for the target with the upper limb his attentional impairment was evident only in near space. This interpretation of MF behaviour would lead to consider the mechanisms of space encoding as primarily actions-based and the perceptual information would only be functional to the preparation and execution of motor acts toward specific sectors of space.

An alternative explanation for MF's deficits can be found in the hypothesis formulated by Forti and Humphreys (2004) who considered the possibility of modulating the processes of space representation by using visuomotor cues. In other words, MF's visual search impairment in far space recovered when he had to point at the targets because a directional motor movement and the full view of his ipsilesional outstretched arm in action may have acted as a visuomotor cue enhancing the deployment of attention in space. As he could not see his upper limb while performing the same search task in near space, MF did not benefit of the same cue effect which may have instead helped him to overcome his visuospatial impairment in the far space condition. This interpretation may be further supported by the fact that in the group study patients' visual search performance improved in far space compared to near space with a motor cancellation task while in the study of Butler et al. (2004) the performance of neglect patients became worse in far than in near space with a perceptual visual search task. Unfortunately, given that in both studies the patients carried out the task only with one type of response (motor or perceptual) it was not possible to explore further Forti and Humphreys's (2004) hypothesis on space representation.

Alternatively, to verify the effectiveness of the visuomotor cues account in explaining MF's behavioural pattern, it would have been interesting to repeat the same motor task by preventing the patient to have full view of his outstretched arm. While the latter possibility may be considered for future research, the case of MF demonstrated that the presence of space related disorders can vary not only depending on the type of test used, but in some cases also on the types of assessment procedure stressing prevalently perceptual or motor mechanisms which define space distance. In line with the above findings, it emerged that in some patients with distance related neglect, both the perceptual and the motor operations shaping spatial awareness processes can be compromised, while in others one component may be more impaired than the other and can be detected only under specific testing conditions. Accordingly, it seems that the classical dichotomy between perceptual and motor aspects of neglect can not only be observed along the horizontal dimension (left /right) but is consistent also along the radial (near/far) axis.

The findings of the present study on the effect of the presence/absence of a motor response in the manifestations of space related deficits in neglect were only based on the behavioural patterns showed by the single cases whose frequency needs to be further explored in a larger population of right brain damaged patients. As all the tasks used for the behavioural group study required a manual motor response, the patients whose neglect deficits resulted from an impaired space specific representation at a pure perceptual level may have not been identified. Difficulties related to patient availability, hospital setting and time restrictions limited the possibility of exploring the effect of both perceptual and motor factors in the expression of distance related disorders in neglect in a larger scale which should be considered for future research.

According to the present findings on the effect of the presence/absence of a motor response in the manifestation of space related neglect deficits, it could be hypothesised that spatial awareness and attention for near and far space may rely on discrete perceptual and motor mechanisms that are specific for each space sector. As in the present study, the specific contribution of perceptual and motor mechanisms in space related neglect could be disentangled, for example, by asking the patient to perform the same task with or without a directional motor act toward the stimuli. Alternatively, several experimental procedures may be able to differentiate the influence of each of these components by dissociating the subject's action space from the task viewing space (i.e. TV monitor) or by exploiting the properties of mirrors as shown in the study of Laeng et al. (2002). The use of a range of visuospatial tasks as wide as possible in both near and far space may allow exploration of whether other visuospatial abilities, different from those evoked by line bisection or cancellation tasks, are more or less affected by space distance.

A neglect patient described by Humphreys and Riddoch (2001) was able to search and detect specific contralesional targets when they were defined by the action they afforded (e.g. "find the object you could drink from") but not by their name or their salient visual features (e.g. "find the red object" or "find the red cup"). In addition, the patients' accuracy was higher when the objects were oriented in such a way to afford actions (e.g. a cup was less likely to afford action when the handle faced away from the subject). From these results the authors suggested that search abilities can be influenced by intended actions and affordances offered by the target objects independently of their perceptual properties. Accordingly, spared action templates defined by intended actions enabled their patient to detect targets on his affected side of space while perceptual templates to define the characteristics and identity of the objects were disrupted.

One question that arises in this case is whether the patient's ability to detect contralesional targets increased because the objects were located within his peripersonal space and afforded specific actions that are normally carried out in near space (e.g. picking up the cup) or whether the action templates can be active independently of the distance between the patient and the targets? It would be interesting to know whether the patient's performance would have changed if the target object that afforded "near space actions" had been located in far space in which those same intended actions were no longer functional to their scope. In other words, when a typical near space action evoked by a particular object is not "affordable" in extrapersonal space does the patient's performance change in any way or the action templates are not affected by distance? In addition, since far space attention relies heavily on the fine features analysis of the targets more than near space attention, would the perceptual templates be more relevant in far space and therefore reverse or worsen the patient's performance for those items defined by their colour or name rather than by the action they evoke? This latter possibility could be investigated in the future as it would contribute to elucidate the relationship between the perceptual and motor mechanisms shaping the representation of peripersonal and extrapersonal space. In addition, by using ordinary objects as stimuli, similar to the ones chosen by Humphreys and Riddoch (2001), the patients' deficits in near and far space could be assessed based on more "ecological" activities and their everyday behaviour.

6.4 Anatomy of neglect for near and far space

The behavioural results of the present study suggested that the expression of a particular neglect disorder restricted to a specific sector of space resulted form the combination of several factors related, for example, to the type of task used or the type of response. However, some of the key components which ultimately seemed to influence the manifestation of particular neglect symptoms were the location and the extension of the patient's brain damage.

Several neurophysiological studies in animals and some neuroimaging and TMS studies in healthy humans document how the representation of near and far space could be broadly mapped onto the dorsal and ventral high visual streams (Previc, 1990; Bjoertomt et al., 2002; Weiss et al., 2000; 2003). This association is supported by the special role played by the dorsal stream in the operations of visuomotor coordination for reaching and grasping behaviour which takes place primarily within proximal space while the mechanisms of fine stimulus analysis and recognition subserved by the ventral stream appear predominantly needed in far space. The results of the present study are in line with this dichotomy but at the same time indicated that other brain areas, located outside the territory of the dorsal and ventral stream, may play a role in the visuospatial mechanisms restricted to near or far space.

6.4.1 Near space

Near space impairments resulted from right hemisphere lesion of both occipital and parietal areas, but also of medio-temporal structures (patient SV, overlap analysis and VBM) which is consistent with the lesion pattern reported in previous single cases studies with patients whose neglect was confined to near space (Halligan and Marshall, 1991; Mennemeier et al., 1992; Berti and Frassinetti, 2000). The prevalent involvement of dorsal occipital and parietal areas in near space over far space coding is also supported by several neuroimaging studies which used both line bisection paradigms and looming objects (Weiss et al., 2000; 2003; Markin et al., 2007; Quinlan and Culham, 2007). Visusospatial attention operations in patient JA were more preserved in near space than in far space probably because of the sparing of dorsal superior parietal regions. Neurophysiological studies have shown that the neurons of specific areas of the parietal cortex such as VIP and AIP respond selectively for stimuli presented within the animal's proximal space (Colby, 1998). Given the above evidence and the pivotal role that the dorsal parietal cortex plays in the operations of visuospatial attention and visual guided actions (i.e. reaching and grasping), this brain structure appears as a critical cortical site for near space encoding.

The VBM study and the lesion overlap analysis indicated that also the superior portion of the middle temporal gyrus is especially involved in near space attention. This finding is consistent with the results of Karnath et al. (2005) who indicated the right middle temporal gyrus as one of the areas of maximum abnormal perfusion following basal ganglia stroke in a group of neglect patients with visual exploration impairment in near space. In addition, the involvement of the middle temporal gyrus in near space attention is also documented by a lesion overlap study carried out by Committeri et al. (2006) which showed an association of this temporal structure with the occurrence of neglect symptoms within peripersonal space.

In the present study, neglect for near space only was also associated with damage of the insula. The multimodal neurons of this area integrate several sensory inputs to generate a stable representation of the surrounding space and of one's own body position. Several lesion studies demonstrated that the insula is one of the brain sites that when damaged can cause visual exploration impairments in neglect patients as assessed in near space (Karnath et al., 2001; 2004; 2006). This pattern is confirmed by the results of the VBM correlation study for the Bells test in near space and the greater visual search impairment shown by patient SV (with insular lesion) in peripersonal compared to extrapersonal space.

The single case studies demonstrated that subcortical damage of the basal ganglia (putamen) and posterior cingulate may also play a selective role in near space attention. Basal ganglia damage in patients MF was considered associated with his deficient performance in the motor version of the visual search task which occurred only in the near space condition. This hypothesis is in line with the findings of several studies supporting the idea that disruption of the dopaminergic projections of the basal ganglia may result in contralateral motor deficits in neglect (i.e. directional hypokinesia) especially during pointing tasks as performed in near space (Sapir et al., 2007; Milton et al., 2004; Apicella et al. 1991; Carli et al., 1995; Fleet et al., 1987; Geminiani et al., 1998; Grujic et al., 1998). The evidence of only one single case, however, can not rule out the possibility that basal ganglia lesions may disrupt also output-related visuospatial mechanisms in distal space and further investigations are needed to explore more thoroughly this possibility.

The posterior cingulate region was instead damaged in patient SV whose neglect was more prominent in near than in far space. This brain structure could participate in the mechanisms of peripersonal space coding through its interconnections with the dorsal stream via the parietal cortex (Vogt et al., 1992) for the monitoring of hands movements during reaching, pointing and grasping of salient spatial targets (Grafton et al., 1996; Inoue et al., 1998). As the occurrence of posterior cingulate damage was not consistently seen in any of the other group studies of the present research, its selective contribution to near space over far space attention still needs further clarifications.

A further pattern that emerged from previous case studies and that was confirmed by the present results is that neglect restricted to far space is more likely to result from a focal damage of selective medial and ventro temporal structures as shown in the VBM study for both cancellation and line bisection tasks in addition to ventral prefrontal cortex. In contrast, hemi-inattention for near space only seemed associated to more severe damage which can involve several brain areas at a cortical (parietal, temporal, insula, frontal) and subcortical level (basal ganglia and posterior cingulate). Accordingly, the better performance shown in far space by the patients of the group study in both cancellation and line bisection task may be due to the fact that there are more brain areas associated with near space than those selectively recruited for far space attention. As a consequence, there may be a higher probability that brain damage may disrupt one of the crucial brain sites responsible for the occurrence of neglect for near space compared to the ones causing neglect for far space only which are fewer and more circumscribed.

6.4.2 Far space

Neglect deficits in far space were found consistently associated with right middle and inferior temporal damage as shown in both group studies (overlap analysis and VBM) and in the single case series (i.e. MF and JA). The involvement of the right middle temporal cortex in extrapersonal space attention is supported by the results of PET studies with healthy participants who performed a line bisection task in near and far space (Weiss et al., 200, 2003). In the present study, this area appeared associated not only with mechanisms of line length estimations but also with visual exploration abilities in distal space. This pattern is consistent with the symptoms shown by Vuilleumier et al.'s (1998) patient who, following inferior and medial temporal damage, developed neglect restricted to far space evident in both line bisection and cancellation tasks. The inferior temporal area instead represents one of the major constituents of the ventral visual stream whose damage can result in the inability to analyse and integrate local features of the surrounding objects and visual exploration deficits especially in far space (Previc, 1998). The right ventral prefrontal cortex was also compromised in some of the patients with neglect for far space only. The fact that this area receives rich projections from the ventral stream support the idea that the neuronal network shaping the ventral stream may be especially involved in the spatial attention mechanisms required in extrapersonal space.

6.4.3 Anatomical areas involved in both near and far space representation

The present study demonstrated also that some brain areas may be equally involved in the representation and allocation of attentional resources in both peripersonal and extrapersonal space. The first candidate in this respect was the superior temporal gyrus, followed by the medial prefrontal cortices and anterior cingulate.

The superior temporal and medial prefrontal cortices receive rich projections from both the dorsal and the ventral visual stream (Karnath et al., 2001; Boussaoud et al., 1996; Young, 1992). Within the framework on the dichotomy between dorsal and ventral stream for near and far space attention, the integration of both types of information conveyed by the two pathways may justify why damage of those brain structures can result in peripersonal and extrapersonal neglect.

The anterior cingulate was also lesioned in those patients with neglect restricted to either near or far space. Indeed this brain area is involved in a range of cognitive functions that are essential in both space sectors such as attention modulation, event anticipation and analysis of their behavioural and motivational relevance.

6.4.4 Near and far space anatomy for cancellation and line bisection task

The lesion overlap approach did not allow exploring whether deficits on cancellation and line bisection tasks are related to damage of specific brain areas depending on whether they are carried out in near or far space. This issue was instead addressed in the VBM correlation study which permitted identifying a significant association with low grey matter density in discrete brain structures and selective deficits on those tasks in near and far space respectively.

Rightward bisection errors were found associated in near space with high levels of grey matter loss in the right lingual gyrus and in far space with the middle and inferior temporal gyrus. In contrast, an asymmetric performance in favour of ipsilesional targets in the Bells test correlated instead in near space with a high degree of grey matter loss in the middle temporal gyrus, insula and inferior frontal cortex and in far space with ventral portions of the middle temporal gyrus. These results showed that the neuronal substrates associated with line bisection for near and far space are located to specific brain sites that are fairly proximal to each other and, as such, more likely to be both affected by brain damage. In contrast, the brain structures whose damage appeared related to visual exploration deficits in near space were rather far apart from the one subserving the same function in far space. Consequently, the more defined segregation of the brain regions supporting visual search abilities compared to line bisection judgments may justify why poor accuracy on the contralateral hemifield observed for the cancellation task in right brain damaged patients was more likely to occur in one sector of space than the other, while rightward line bisection errors tended to be present in both space sectors.

The VBM study indicated a correlation between the degree of grey matter loss in specific parts of the brain with specific space related neglect symptoms in right hemisphere damaged patients. However, this association does not imply a link of causality between the two phenomena. To provide more robust support for the results of the VBM study it may be interesting to evaluate the performance in near and far space of neglect patients with more focal damage in those brain structures found associated with visual search and line bisection deficits for each space sector. As patients with neglect usually have fairly large lesions that can involve more than one brain structure, sometimes can be very difficult to recruit those types of patients to verify specific anatomo-clinical hypotheses. Transcranial magnetic stimulation of a particular region of interest in healthy subjects may represent an alternative solution to verify the possible presence of a causal relationship between specific space related attentional mechanisms and the integrity of those brain areas found associated with near and far space neglect in the VBM study. By using rTMS in healthy subjects Bjoertomt et al. (2002) explored the involvement of the dorsal parietal and ventral occipital cortex in line bisection abilities for near and far space respectively, but there are no TMS studies which investigated space related performance in a visual search task with a specific anatomical hypothesis. A study of this kind on visual exploration abilities has never been carried out also with neuroimaging techniques. The integration of different research methodology and the evaluation of recurrent pattern of results across studies can help to unveil the neuronal substrates of near and far space attention in humans.

Attentional mechanisms for near and far space could also be investigated by studying patients with optic ataxia. This condition usually results form dorsal stream damage and is characterised by specific impairments of manual goal-directed movements towards visual targets in the immediate proximal space. Reaching errors are not evident when the patient maintains eye fixation on the target stimulus. If the deployment of attention within near space is especially dependent on the integrity of the motor programs for reaching and grasping, then patients with optic ataxia may demonstrate a worse performance in near space compared to far space during visuospatial attention tasks with or without a manual response.

Overall the anatomical results of the present research partially confirmed the dichotomy between the dorsal and the ventral stream for near and far space representation. Damage of some of the brain areas part of the ventral stream was indeed consistently associated with neglect in far space. In contrast, the role of the dorsal stream in near space attention was not exclusive as also restricted damage of several brain structures namely, the insula, medio-temporal and frontal cortex were sufficient to generate neglect confined to near space.

6.5 Conclusion

In conclusion, the present research provided further support on the multicomponential phenomenology of neglect which can vary not just with respect to modality, task and reference frames but also to the sector of space the patient is assessed in. From a clinical point of view, in light of the present findings, it is important to stress the necessity of examining the presence of neglect also beyond reaching space which remains often dismissed during conventional clinical assessments. Neglect for far space can easily lead to spatial misjudgements which may increase the risk of accidents in daily life. Therefore, neglect in far space should be taken into more consideration during clinical evaluations.

The results of the present study suggested that in some patients the presence/absence of a manual motor response can modulate the expression of the disorder in a specific space sector. In addition, the type of task can be determinant in detecting distance specific dissociations which implies that the specific cognitive operations evoked by each task can be differently affected by distance. The latter pattern can be explained by the fact that different brain structures have been found associated with visual exploration and line bisection abilities within near and far space. Cancellation tasks appeared to be more sensitive in detecting space related deficits in neglect patients compared to line bisection tasks. This outcome may reflect the fact that the neuronal correlates supporting visual search abilities in near and far space appeared more segregated than those involved in line length estimation. Overall, the present study provided partial support for the hypothesis that considers near and far space representation and attention as mapped on the territory of the dorsal and the ventral stream respectively. The anatomic results showed indeed the involvement of additional cortical and subcortical structures in the cognitive mechanisms of spatial attention across near and far space. The dorsal and ventral stream dichotomy for near and far space coding is by no means absolute as information processed by both pathways is needed in near as well as in far space. However, it is the prevalent use of the input from one stream over the other that ultimately differentiates the cognitive reconstruction of peripersonal and extrapersonal space, each of which associated with specific behavioural goals.

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APPENDIX

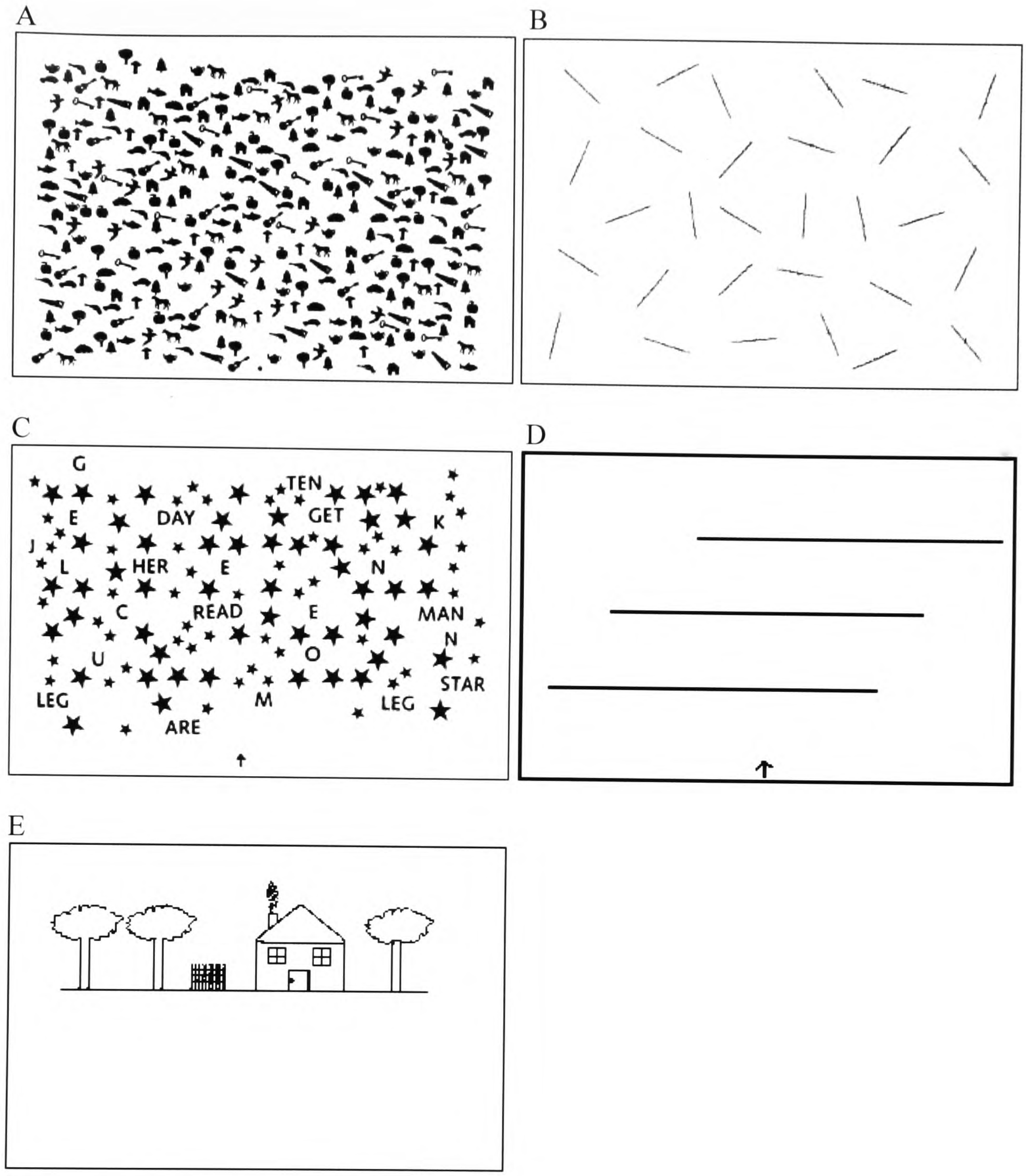

Figure 1 Tests used for the clinical assessment of neglect: (A) Bells test, (B) Albert test, (C) Stars cancellation, (D) line bisection and (E) scene copying. All tests were presented on an A4 sheet of paper.

A

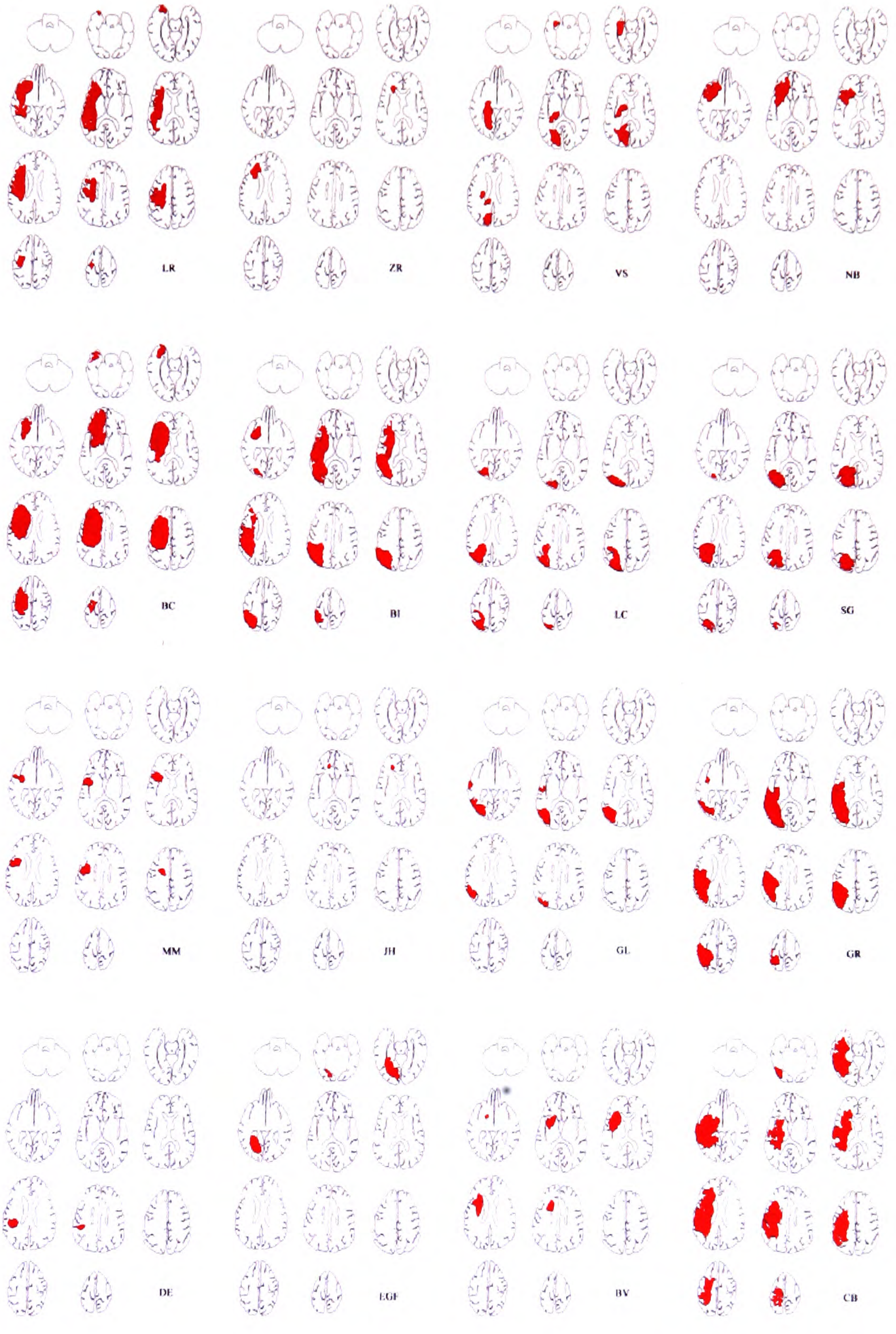

Figure 2 Individual lesion templates (Damasio and Damasio, 1989) of the 37 patients included in the region of overlap study. (A) Neglect, (B) No neglect.

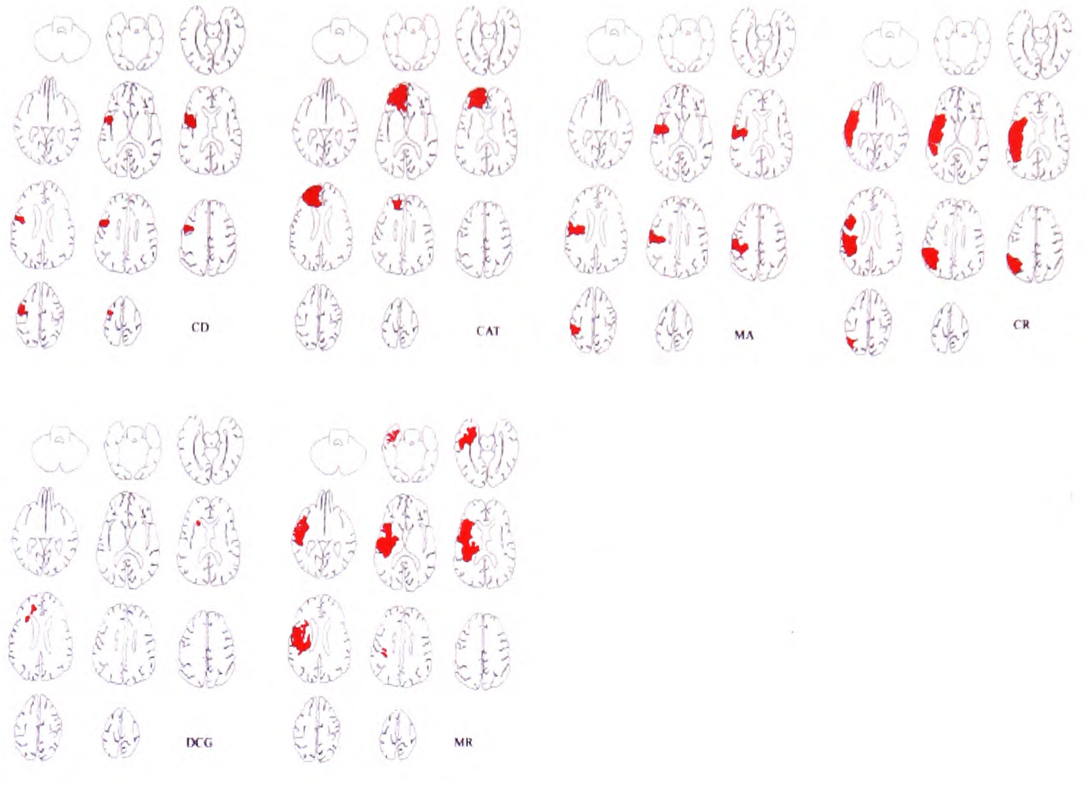

Figure 2 Continuation.

B

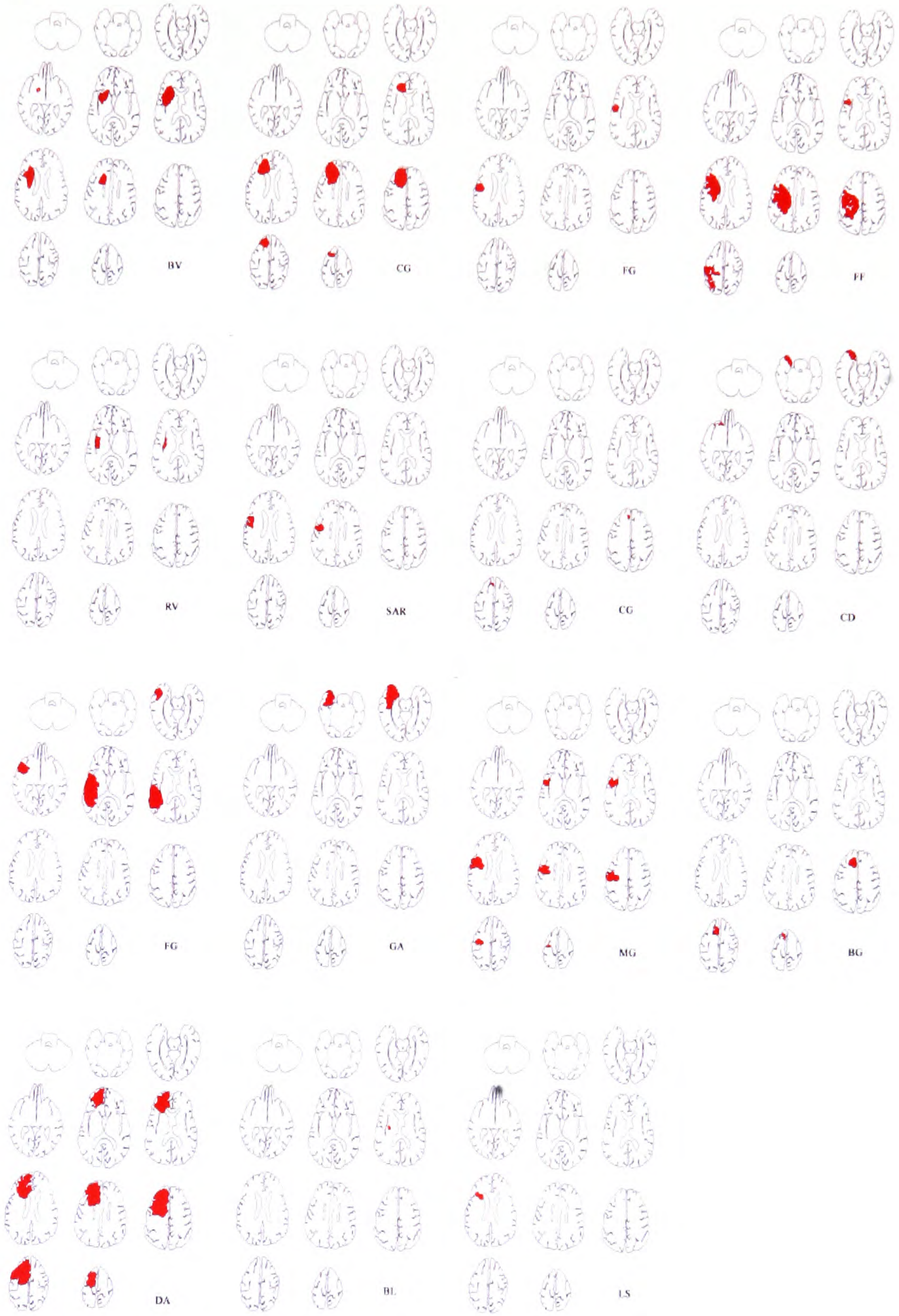

Figure 2 Continuation.