Cognitive Neuropsychiatry
Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/pcnp20

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Published online: 09 Sep 2010.

To cite this article: Masud Husain (2002) Cognitive neuroscience of hemispatial neglect, Cognitive Neuropsychiatry, 7:3, 195-209, DOI: 10.1080/13546800244000067

To link to this article: http://dx.doi.org/10.1080/13546800244000067

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Cognitive neuroscience of hemispatial neglect

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Introduction. Patients with neglect often fail to be aware of stimuli located on their contralesional side—the side of space opposite their brain damage. Some patients show impairments in extrapersonal space; others within personal (body) space; and some in both. Although the neglect syndrome may be associated with a distorted perception of extrapersonal or personal space, recent investigations suggest that attentional, memory and motor deficits may be important additional components. Conclusion. Better understanding of these cognitive impairments holds the key to offering effective treatment for neglect, as well as providing important insights into normal brain function.

The neglect syndrome is a common consequence of unilateral brain damage, most frequently following stroke (Robertson & Halligan, 1999). Although it occurs after both left and right hemisphere damage, neglect appears to be most severe and long-lasting in right hemisphere stroke patients (De Renzi, 1982; Stone, Patel, Greenwood, & Halligan, 1992). These individuals often demonstrate extrapersonal neglect, ignoring or failing to be aware of objects to their left in the world around them, and turning their gaze instead to items on the right. Some right hemisphere patients may demonstrate personal neglect, failing to attend to the left side of their body; while some patients demonstrate both extrapersonal and personal neglect (Beschin & Robertson, 1997; Bisiach, Perani, Vallar, & Berti, 1986; Zoccolotti & Judica, 1991).

The mechanisms underlying neglect have come under considerable scrutiny in recent years for two important reasons (Bisiach & Vallar, 2000; Heilman, Watson, & Valenstein, 1993; Husain, 2001; Robertson & Marshall, 1993). First, there is no effective treatment. With rehabilitation programmes proving to be disappointing, it is increasingly appreciated that effective therapy is only likely to result from a proper understanding of the underlying cognitive mechanisms. Second, it has become apparent that the neglect syndrome offers important...
insights into the nature of normal visual processing: How the brain selects information, represents space, and directs actions toward objects in the world around us.

This essay will not to provide an exhaustive review of the literature on neglect. Rather it will provide an accessible overview of some important principles, using examples from current research and highlighting trends for future investigations.

**CLINICAL FEATURES OF THE NEGLECT SYNDROME**

Patients with neglect orientate towards the side of their lesion—their ipsilesional side—and away from their contralesional side. Thus, a patient with right hemisphere damage and extrapersonal neglect will tend to direct their gaze and interest to the right, neglecting objects toward the left. They may read only the right side of newspapers or books, and leave food untouched on the left side of their plate. When asked to write, they may use only the right side of the sheet of paper. Similarly, if asked to copy an object or draw one—such as a clock—from memory they may neglect to draw elements on the left. Patients who display personal neglect may shave or make-up only the right side of their face, and fail to explore the left side of their body.

Tests for personal neglect include asking the patient to touch the contralesional hand with the ipsilesional one, and pantomiming how they would comb their hair or use a razor to shave (Beschin & Robertson, 1997; Bisiach et al., 1986; Zoccolotti & Judica, 1991). Quantitative bedside tests of extrapersonal neglect include line bisection and cancellation (visual search) tasks (Robertson & Halligan, 1999). In the line bisection task, patients are shown a horizontal line on a sheet of paper, and asked to mark its mid-point. Many patients with left neglect tend to make their bisection mark right of the true mid-point, and this deviation can be used as a measure of the degree of neglect.

Cancellation tasks (Figure 1) may be very sensitive measures of extrapersonal neglect, particularly if they require careful discrimination of visual targets from nontargets (Ferber & Karnath, 2001; Halligan, Marshall, & Wade, 1989). These tasks consist of multiple targets distributed on a sheet of paper, and patients are required to mark (‘‘cancel’’) all the targets they can find. Simple cancellation tasks that have only targets, such as Albert’s test (Albert, 1973), are less sensitive than tasks with targets embedded among distractors, such as Mesulam’s shape cancellation test (Mesulam, 1985) or the Bells test (Gauthier, Dehaut, & Joanette, 1989).

A potentially difficult clinical, as well as theoretical, issue concerns the nature of visual fields in patients with neglect. When assessed at the bedside in the traditional way using a 5 mm hatpin, visual fields may, in some neglect patients, appear to be completely intact. Other patients may appear to be blind to
such a stimulus on their contralesional side. However, they may not be completely oblivious to all stimuli on that side. If they are made salient enough, objects may well be reported. For example, it is a common experience to find that a patient fails to perceive a moving hatpin in their contralesional visual field, but is aware of a finger or hand if it is used as a test stimulus instead. Thus, the visual loss in such patients is not an absolute one.

Some patients fail to acknowledge even large salient stimuli, and in such cases it is indeed difficult to distinguish whether such an impairment represents “dense neglect” or hemianopia plus neglect. Despite this failure of neglect patients to be aware of contralesional stimuli, several investigators have shown that these stimuli can nevertheless be processed to some extent by their visual systems (Berti & Rizzolatti, 1992; Marshall & Halligan, 1988; McGlinchey-Berroth, Milberg, Verfaellie, Alexander, & Kilduff, 1993). Moreover, recent functional imaging studies have demonstrated activity in early ipsilesional visual areas in patients who are unaware of contralesional stimuli (Rees et al., 2001; Vuilleumier et al., 2001). Such activity may be responsible for part of the visual processing without awareness that occurs in neglect.
Many patients with neglect, or those who recover from neglect, also demonstrate “extinction”. This refers to unawareness of contralesional stimuli when presented simultaneously with ipsilesional stimuli, even though contralesional stimuli are easily reported when they are presented alone. Both neglect and extinction may be demonstrated in the visual, auditory, and tactile modalities. Neglect may also be “motoric” as well as sensory. “Motor neglect” is the term used to refer to lack of use of a contralesional limb, despite the fact that it may not be weak. By contrast, “directional hypokinesia” is the term used to refer to an impairment in the ability to direct movements in a contralesional direction.

Finally, some patients have also been found to show representational neglect. When asked to imagine a familiar scene from a particular viewpoint (e.g., a landmark in their town), they may fail to report places that would fall on their contralesional side from that particular vantage point (Bisiach & Luzzatti, 1978).

**NEUROANATOMY OF NEGLECT**

Although neglect classically has been associated with damage to the right inferior parietal lobe (Vallar, 2001), some investigators have also drawn attention to the fact that many patients also have damage to the nearby superior temporal gyrus (Karnath, Ferber, & Himmelbach, 2001). Furthermore, lesions of the right inferior frontal lobe alone may result in contralesional neglect (Husain & Kennard, 1996).

All three of these right hemisphere perisylvian cortical areas—inferior parietal, superior temporal, and inferior frontal—closely mirror the language zones in the contralateral left hemisphere. However, this distinction between left and right hemispheres is not an absolute one. Patients with left-sided damage can also suffer from contralesional neglect, although this frequently recovers quickly after insults such as stroke (Stone et al., 1992). Finally, subcortical lesions affecting the thalamus or basal ganglia may also present with neglect. But there is evidence to suggest that such syndromes may result from associated hypoperfusion of overlying perisylvian regions (Vallar, 1993).

**THREE IMPORTANT PRINCIPLES IN NORMAL VISION**

In order to appreciate some of the mechanisms thought to be responsible for extrapersonal neglect it is useful to be aware of three important principles of normal vision.

**Visual space appears isometric**

First, vision researchers have long appreciated that what is “seen” by the retina is not the same as the percept we experience. For example, although visual resolution falls off sharply away from the fovea, our visual experience does not
mirror what the retina ‘‘sees’’. Normally, we do not perceive vision to be clear at the centre of gaze and blurred at the periphery. Instead, in everyday experience, visual space seems to be isometric—the same size—regardless of whether it is at fixation or in peripheral vision. Visual space perception thus does not seem to depend on representations that are mapped in retinotopic coordinates alone. Instead, space seems to be constructed within the cerebral cortex in nonretinotopic coordinates (Husain & Jackson, 2001).

**Visual objects may be mapped in egocentric coordinates**

Consider what happens to visual space each time we move our eyes—something we do, on average, at a rate of three times a second. How is it that one position on the retina can be associated with many different locations in space in the world around us? For example, if we fixate different objects in the world around us, all the objects will, in turn, come to lie at the fovea. Yet, we are quite aware that these objects all occupy different locations in space. For purposes of discussion, it is useful to refer to this as the ‘‘one-to-many’’ problem because a single locus on the retina (in this example, the fovea) can be associated with many different positions in external space.

Conversely, how is it that many different locations on the retina can specify one particular location in external space? For example, a stationary object can fall on many different locations on the retina as we move our eyes over a visual scene. But although its retinal location can change with every shift of gaze, our percept is that the object has not moved. This is the ‘‘many-to-one’’ problem: Stimulation of many different loci on the retina may be associated with one position in space.

Both the ‘‘one-to-many’’ and the ‘‘many-to-one’’ problem cannot easily be solved by retinotopic information alone. Instead, one simple solution would be to combine retinal information with the direction of gaze (the direction in which the eyes are pointing). Formally, such a combination of retinal and eye position information gives position with respect to the head or head-centric coordinates—one form of so-called egocentric representation.

How would a head-centric representation help? Although one locus on the retina—say, the fovea—may be associated with many different positions in space, all these positions can be distinguished from each other because the direction of gaze varies according to the location of the object. Similarly, as we move our eyes over a visual scene, many different positions on the retina may sequentially be occupied by a single stationary object in the external world. However, the location of the object can be regarded as constant if its position with respect to the head is unchanged across eye movements. Thus, both the ‘‘one-to-many’’ and the ‘‘many-to-one’’ problem can be solved by localising objects in head-centric coordinates.
Of course, the head itself can move with respect to the trunk, as well as with respect to gravity. So the visual system needs also to take into account this information too if stationary visual objects are not apparently to shift their position with every movement of the head. A combination of retinal, eye position, head-position-on-neck, and vestibular signals would effectively encode the location of objects in extrapersonal space with respect to the body orientated in the gravitational field.

Note that similar principles may also apply to representations of the body which may be disturbed in patients with personal neglect. The disposition of body parts with respect to each other are likely to contribute to representations of self. Impairments in encoding contralesional body parts may contribute to a distorted sense of personal space.

**Visual stimuli compete for attention**

The third important principle in normal vision is that very little of the vast amount sensory stimulation of the retina enters visual awareness. The perceptual system appears to have limited capacity and so only stimuli that are salient or are considered to be important capture our attention. Put another way, visual stimuli compete for our attention, and we attend to only a few items in the world around us (Duncan, Humphreys, & Ward, 1997). Many paradigms have been used to probe the capacity limits of the visual attention system. For example, recent studies of the “attentional dwell time” or “attentional blink” suggest that the visual system may be engaged for up to 400 ms when actively attending to and analysing an object in the visual scene (Shapiro, Arnell, & Raymond, 1997). During this period, other visual stimuli may escape awareness altogether.

Where in the visual system do the computations underlying these three important principles occur? It is likely that such processes depend on a distributed network of areas. Nevertheless, it is important to appreciate that greater weight to the peripheral compared to the central visual field (Motter, Steinmetz, Duffy, & Mountcastle, 1987), combination of retinal with eye position signals (Andersen, 1997), and representation of salient objects in the visual world (Constantinidis & Steinmetz, 2001; Downar, Crawley, Mikulis, & Davis, 2002; Gottlieb, Kusunoki, & Goldberg, 1998) are all known to occur in one area—the posterior parietal cortex. This is the area that is also most commonly damaged in patients with neglect.

**MULTIPLE COGNITIVE MECHANISMS IMPAIRED IN NEGLECT**

Recent investigations suggest that the neglect syndrome may be a heterogeneous disorder with multiple possible underlying components (Bisiach & Vallar, 2000; Heilman et al., 1993). For example, some patients have been found on clinical testing to have only extrapersonal neglect, whereas others demonstrate only
personal neglect (Beschin & Robertson, 1997; Bisiach et al., 1986; Zoccolotti & Judica, 1991). However, a systematic study of a range of potential impairments has not been conducted in a large series of patients, partly because of the practical difficulties associated with extensive and prolonged testing of patients who are often frail and fatigue easily. Nor has there been much work on mapping functional component deficits to lesion location. Nevertheless, several possible components have been identified, and in some cases, there has been some progress towards mapping such components to brain regions (Vallar, 2001).

Note that a component deficit on its own, for example, impaired spatial working memory (see below), may not lead to neglect, but when combined with other deficits it may exacerbate the neglect syndrome (Husain et al., 2001). Furthermore, it is possible that different neglect patients suffer from different combinations of such component deficits. This may, in part, explain why some neglect patients (e.g., those with left hemisphere damage) recover so quickly, whereas others are left with persistent neglect. A major focus of future research must be an attempt to characterise the spectrum of component deficits within single patients, and relate this to recovery and possible treatment. Broadly speaking, the mechanisms that have been identified to date may be divided into spatial and nonspatial mechanisms.

**SPATIAL MECHANISMS UNDERLYING EXTRAPERSONAL NEGLECT**

**Impaired egocentric representation**

It has been suggested that the primary disorder underlying neglect is a failure to represent spatial locations in egocentric coordinates rather than in purely retinal coordinates. For example, Karnath and his colleagues have shown that the ability to report left stimuli is modulated by the location of stimuli with respect to the trunk mid-line in patients with right hemisphere lesions (Karnath, Schenkel, & Fischer, 1991). In their task, the retinal locations of stimuli were kept constant but their positions were shifted with respect to the trunk. When stimuli appeared left of the trunk mid-line they were more likely to be incorrectly reported than when they were presented to the right of the trunk mid-line.

Karnath has proposed that there is effectively a rotation of the mid-sagittal plane around the body axis towards the ipsilesional side, and away from the neglected side (Karnath, 1997). Others have argued that the egocentric spatial representation may be translated or compressed (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996; Halligan & Marshall, 1991; Milner & Harvey, 1995). Clearly, there is a distortion of perceptual space in neglect, and many studies suggest that part of this distortion may be explained by impairments in egocentric representation. But such impairments may not capture an important aspect of
neglect: In patients with right sided lesions, stimuli to the left are neglected at the expense of those on the right, regardless of whether they are to the left of the fovea, head or trunk (Robertson & Halligan, 1999). Furthermore, the degree of left neglect is modulated by the number of salient stimuli on the right; the more stimuli on the right, the greater the degree of neglect (Eglin, Robertson, & Knight, 1989; Husain & Kennard, 1997; Mark, Kooistra, & Heilman, 1988). Such modulation is not really explained by accounts that propose there is impaired mapping of egocentric space.

Competitive bias toward ipsilesional stimuli

Normally, visual stimuli appear to compete for selection (Duncan et al., 1997). Not all stimuli may capture our attention; we may be unaware of many aspects of the visual scene around us unless they become salient. Left neglect after right hemisphere damage could be envisaged to be a pathological extreme of this competition process, with stimuli on the right always winning in the competition for selection over those on the left.

Such an account would be similar in many ways to models that suggest that extinction is due to competition between ipsi- and contralesional stimuli, with the latter losing in the competition if presented simultaneously with an ipsilesional stimulus (Driver, Mattingley, Rorden, & Davis, 1997). However, when there is no competing stimulus, the contralesional stimulus would be attended to.

Some evidence for the validity of such a model in neglect comes from studies that have manipulated the number or salience of ipsilesional stimuli. A particularly good illustration is a study by Heilman’s group. These investigators asked neglect patients to cancel out stimuli and, as expected, found that the patients neglected targets on their contralesional side. But when they asked patients to erase stimuli rather than simply cancel them, they found that the degree of neglect was significantly reduced: They were able to search further over to their contralesional side (Mark et al., 1988). One interpretation of this result is that rubbing out stimuli effectively excludes ipsilesional stimuli from competing for attention, and therefore allows stimuli to the left to capture attention.

Gradients of attention

Although the competitive bias account captures the modulation of neglect by ipsilesional stimuli, some have argued that competition may not be an essential component of neglect. In some patients, the degree of neglect is unchanged regardless of ipsilesional stimulus density or salience (Husain & Kennard, 1997). Moreover, it has been shown that gaze in neglect patients may be directed ipsilesionally in the dark—when there are no visual stimuli (Karnath & Fetter, 1995). Thus, following unilateral brain damage, there may be a gradient of attention biased toward the ipsilesional side (Kinsbourne, 1993).
A number of studies have presented evidence for such a gradient using, for example, simple reaction time measures in response to visual stimuli presented at different locations in space (Smania et al., 1998). Some investigations have also suggested that neglect patients may demonstrate more attention than normal—“hyperattention”—to stimuli on their ipsilesional side (De Renzi, Gentilini, Faglioni, & Barbieri, 1989).

**Constriction of the effective field of vision**

There are few detailed reports that focus only on formal visual testing in patients with neglect. Nevertheless, many investigators acknowledge that the effective visual field is constricted in neglect, with impaired awareness of peripheral visual stimuli. Such constriction may be evident on the (good) ipsilesional side of space as well as the neglected contralesional one. An example of the visual field obtained using standard automated perimetry from one patient is shown in Figure 2. Note that such constriction means that far more attention is directed towards stimuli at the centre of vision—near the current point of regard—than toward new events occurring in the periphery. It is possible that the effective field of vision is even more constricted when neglect patients perform tasks that require careful discrimination at fixation. When a limited capacity visual system has to engage in a task that has “high load” at fixation (e.g., discriminating between letters, or targets, from distractors) the processing capacity that can be devoted to peripheral objects is likely to be reduced and constricted. Such constriction may account for the performance of patients with right temporoparietal junction lesions on Navon figures (Halligan & Marshall, 1994; Robertson, Lamb, & Knight, 1988). These figures have both a global form (the letter M shown in Figure 3), which is made up of local constituent forms (the letter Z in Figure 3). Patients with right temporoparietal junction damage show a local bias, being able to report the local constituent forms (Zs) but not the global shape (M).

**Impaired spatial working memory in visual search**

When neglect patients perform cancellation tasks it is a frequent observation that they search over territory on the ipsilesional side that they have searched before. Such behaviour might be due to a failure in remembering where they have looked before. To test this hypothesis, Husain and colleagues presented displays containing multiple targets (Ts) embedded among distractors (Ls)—rather like a cancellation task—to patients with neglect, who were asked search for all the Ts they could find. Eye movements were monitored during the search. At the same time, a measure of memory for previously searched items was obtained by asking patients to click a response button whenever they found a new target, emphasising they should not re-click on targets they had found before.
Figure 2. Visual field measured by automated perimetry in one eye of a patient with left neglect. Note that, effectively, only stimuli on the right are perceived, but the constriction means that even peripheral stimuli on the right may not reach awareness.

Figure 3. A Navon figure. The global shape here is an M; the local elements consist of Zs.
Neglect patients re-fixated items on their ipsilesional side at a greater rate than healthy individuals (Husain et al., 2001; Kennard et al., 2001). Critically, they also re-clicked on targets they had previously visited at a rate significantly higher than controls, demonstrating an impairment in spatial working memory. When combined with a spatial gradient or competitive bias to the ipsilesional side and a constriction of the effective visual field, such a memory deficit would be expected to lead to recursive search over ipsilesional targets, just as is observed at the bedside. Pharmacological interventions that are known to improve spatial working memory, for example, dopamine D$_1$ agonists (Williams & Goldman-Rakic, 1995), may therefor be one potential treatment for patients with neglect.

**Directional hypokinesia**

A number of researchers have proposed that some patients with neglect, particularly those with frontal (rather than parietal) damage, may be impaired in directing their movements toward the contralesional side (Heilman, Bowers, Coslett, Whelan, & Watson, 1985). This directional deficiency in exploring space may effectively lead to neglect of that side. Several interesting methods, including mirrors (Tegner & Levander, 1991) and pulleys (Bisiach, Geminiani, Berti, & Rusconi, 1990), have been used to dissociate the direction of visual stimuli from the direction of movement in an attempt to dissect out such directional hypokinesia. More recent evidence suggests that a motor impairment may interact with a visual deficit in different ways in neglect patients with parietal and frontal lesions (Husain, Mattingley, Driver, Rorden, & Kennard, 2000).

**NONSPATIAL MECHANISMS UNDERLYING NEGLECT**

**Limited capacity**

As we have seen, studies of the normal visual system have revealed that it has a limited capacity to process visual information (Duncan et al., 1997). Although a myriad of visual information hits the retina, only a fraction of this appears to reach our awareness. Recent studies have revealed that in neglect, processing capacity—even for stimuli presented at fixation—is extremely limited (Duncan et al., 1999; Husain, Shapiro, Martin, & Kennard, 1997). For example, the “attentional dwell time” or “attentional blink” may be significantly protracted, with patients’ visual systems taking more than a second to process a simple shape, for example, a letter, at fixation (Husain et al., 1997).

Such an extremely limited nonspatial capacity when combined with a spatial bias would lead to a very impaired visual processing system, with stimuli fixated even in ipsilesional space taking long to process. An alternative view might be
that the non-spatial limited capacity reveals an important—possibly even a core—deficit in neglect. A recent study of an extinction patient found that the attentional dwell time was significantly more prolonged for stimuli in contralesional space than in ipsilesional space, suggesting there may be a gradient of visual processing capacity from ipsi-to contralesional space (di Pellegrino, Basso, & Frassinetti, 1998). Such a gradient in processing capacity may explain why ipsilesional stimuli win in the competition for selection over contralesional ones (i.e., the competitive spatial bias), because ipsilesional objects are processed much faster than contralesional ones.

Impaired sustained attention

Studies of focal brain damaged patients without neglect have revealed that regions within the right frontal and posterior parietal lobe may have a special role in maintaining attention (Rueckart & Grafman, 1996, 1998). Robertson and his colleagues have argued that difficulties in sustaining attention over time might contribute significantly also to the spatial neglect syndrome. They have shown that patients with neglect are impaired on tasks such as counting monotonous nonspatially lateralised auditory tones presented through headphones (Robertson et al., 1997). Moreover, they have shown that alerting tones may improve report of contralesional stimuli in neglect (Robertson, Mattingley, Rorden, & Driver, 1998).

CONCLUSIONS

The neglect syndrome appears to be a heterogeneous condition with multiple components—both spatial and nonspatial, extrapersonal and personal. The study of these components is helping to uncover some of the normal mechanisms involved in the localisation of visual stimuli, selection of salient objects, awareness of peripheral visual events, control of limb movements, as well as memory of spatial locations and sustaining attention. Moreover, they point towards rational treatment for neglect, directed towards specific component deficits. It is possible that these deficits may combine in a number of different ways in different patients. Future treatments for neglect may therefore need to target specific combinations of deficit in individual patients.

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