NON-SPATIALLY LATERALIZED MECHANISMS IN HEMISPATIAL NEGLECT

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Hemispatial neglect is a common, disabling disorder that results from brain damage, most frequently stroke. Research on patients with neglect has provided important insights into normal brain mechanisms involved in directing attention, representing space and controlling movement. Although much work has focused on the lateralized components of neglect, recent investigations have also revealed deficits that are not spatially lateralized, consistent with new findings from functional imaging, human neuropsychological and monkey electrophysiological studies. Here we propose that understanding the interactions between spatially lateralized and non-lateralized mechanisms provides important insights into the neglect syndrome and the normal functions of brain structures that are commonly damaged in neglect patients, and will contribute to the development of treatments for the condition.

STROKE
Brain damage that is caused by a lack of blood supply, as a result of either blockage or rupture of a cerebral blood vessel.

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Around the world more than 15 million people suffer a STROKE each year. More than a third of these individuals are left with permanent deficits, including cognitive disorders such as hemispatial neglect. Patients with neglect fail to orientate themselves towards or to detect items on their contralesional side (left side for patients with right brain damage), even though they are not blind to stimuli on that side. Their neglect can be so profound that they are unaware of people or large objects in contralesional space. They might neglect their own contralesional body parts, failing to use or show any interest in them[1], and they can be unaware that they have any of these problems (anosoagnosia)[2].

In one study, two-thirds of patients with either a left- or right-hemisphere stroke suffered from neglect when assessed within three days of being admitted to hospital[3]. Perhaps this is not surprising, given the number of lesion sites, both cortical and subcortical, that are acutely associated with neglect (BOX 1). Although there has been an emphasis on associating neglect with inferior parietal damage (particularly in the region of the temporo-parietal junction, or TPJ)[4], it can also follow localized damage to other parts of the perisylvian region, including the inferior frontal cortex[5,6] and superior temporal gyrus[7] (FIG. 1). Focal subcortical strokes involving the basal ganglia and thalamus can also result in neglect[4,8–10], probably owing to hypoperfusion of the overlying cortex[8,10]. However, stroke patients with neglect typically have large lesions spanning many of these cortical and subcortical regions (FIG. 1b).

Neglect can have a profound impact on the functional capabilities of stroke victims, even if they recover well from paralysis after a stroke. Neglect is more likely to be enduring in patients with right-hemisphere damage than in individuals with left-hemisphere stroke[11,12]. Right-hemisphere patients with neglect often have long-term difficulties on their left with everyday tasks such as bathing, grooming, dressing, eating, reading and social interactions[13–15].

Understandably, much of the research into neglect has focused on its lateralized spatial presentation[16–24]. But recent investigations have also revealed deficits that are not necessarily worse towards one side of space, that is, they are non-lateralized. We argue that an understanding of these components is important

Box 1 | Anatomy of neglect

Neglect is most common after damage to regions that receive blood from the middle cerebral artery (MCA). The cortical regions that have been implicated in neglect are shown in FIG. 1a. Studies that attempt to find the minimal lesion zone that is common to all patients have led to a view of the right temporo-parietal junction (TPJ) as the most common substrate of neglect[4]. However, most neglect patients have extensive brain damage (FIG. 1b), with lesions spanning a number of functionally distinct regions. Hence, individual patients might show different patterns of neglect, depending on the distribution of damage.

Another problem for lesion analysis is that regions that are consistently damaged in neglect patients might reflect the vascular territory of the MCA rather than being directly involved with the syndrome. Ideally, therefore, lesion studies should compare MCA stroke patients who show neglect with those who do not. Identifying regions that are routinely damaged in neglect patients but spared in control patients should lead to a clearer picture of the regions responsible for neglect.

One such study[7] concluded that the superior temporal gyrus (STG) rather than the TPJ is the critical site associated with neglect. However, this result might have been biased by the method of patient selection (see also REF. 106). Moreover, not all the neglect patients in this study had lesions of the STG. Further work is required to determine whether this provocative new account is correct.

'Frontal' neglect is associated with damage to the inferior and middle frontal gyri[5,6]. The zone of maximum overlap of lesions appears to centre on ventral premotor cortex in a region homologous to Broca's area in the left hemisphere, although damage is usually more widespread. These patients tend to recover from their neglect faster than those with posterior lesions, but the reason for this is unclear. Nor is it clear what functional differences distinguish patients with frontal neglect from those with parietal or temporo-parietal neglect[28,107].

The areas associated with disorders of language in the left hemisphere and enduring neglect in the right hemisphere are remarkably similar. The anterior and posterior perisylvian regions, which have been implicated in both hemispheres, might represent higher-order regions that have developed in human brains, but that are absent or less developed in non-human primates. Such a view would be compatible with the finding that although lesions of the inferior parietal lobe, STG and premotor cortex have been implicated in producing neglect, there is little evidence in monkeys for a visual syndrome that is as profound, functionally disabling or long-lasting as that in humans[108,109].

for the development of potential treatments for neglect, and might provide critical insights into the normal functions of the brain regions that are most frequently damaged in patients with neglect. In this review we focus on visuospatial neglect and discuss five key concepts.

First, non-lateralized components might combine with spatially lateralized mechanisms to exacerbate the severity of neglect. Although classical neuropsychology often emphasizes double dissociations of impairments, it is also important to examine the functional consequences of the association of separable component deficits. Second, non-lateralized mechanisms are not necessarily specific to the neglect syndrome: they can occur separately in patients without neglect. This important perspective brings to bear findings from other branches of cognitive neuroscience that have so far been considered unrelated to neglect. Third, brain regions that are typically associated with neglect and that are considered to have spatial functions, such as the parietal lobe, also have non-lateralized functions[25]. Fourth, an understanding of this functional anatomy provides a new way to view the mechanisms driving neglect, with different combinations of spatially lateralized and non-lateralized impairment occurring in individual patients, depending upon the extent and location of brain damage. Finally, non-spatially lateralized mechanisms, when combined with lateralized components, might reduce the potential for recovery from neglect and therefore are potentially important targets for treatment.

CANCELLATION TASK
A bedside clinical task in which patients have to find and mark targets that are usually displayed on a sheet of paper either on their own or with distracting non-targets.

Spatially lateralized mechanisms in neglect

Neglect patients can show spatially lateralized impairments not only in their everyday activities but also on paper-and-pencil tasks such as visual search (CANCELLATION) tasks (FIG. 2). In theory, the behaviour of neglect patients on such clinical tests could be explained by spatially biased sensory, motor, representational or attentional accounts, none of which are mutually incompatible[26].

A sensory account would indicate that neglect patients with right-hemisphere damage do not respond to objects on the left because these stimuli are in a region where the patient is functionally blind (a visual field defect). Although visual field defects can masquerade as neglect, or coexist with neglect, careful clinical testing often reveals that patients with neglect can see objects towards the neglected side, if the stimulus is extremely salient. Furthermore, visual field defects are doubly dissociable from neglect, occurring, for example, in patients with strokes affecting early visual areas in occipital cortex, who do not demonstrate neglect in everyday life or on cancellation tasks because they are able to shift their gaze so that objects appear in their intact visual field. For these reasons, most experts do not consider neglect to be the result of a purely sensory deficit.

According to directional motor models of neglect[27], right-hemisphere patients might perceive stimuli to their left, but have difficulty initiating eye or limb movements in that direction. Studies that have examined leftward and rightward movements to the same sensory stimulus have been used to show that such a directional deficit of motor 'intention' can occur in patients with neglect. However, this type of motor deficit does not, on its own, fully capture the behaviour of neglect patients[28,29].

Representational accounts of neglect emphasize a deficit in the neural representation of space. Many patients with neglect fail to report items that appear on the contralateral side of a scene they are imagining. For example, Bisiach and Luzzatti[30] asked right-hemisphere neglect patients from Milan to imagine that they were standing on the steps of the cathedral in the city's central Piazza (FIG. 2d). When the patients were asked to describe places on or alongside the square, they reported locations that would appear towards their right from this vantage point, neglecting places on the left. However, when the patients were asked to imagine turning around and facing the cathedral, they now neglected places they had previously reported and described only locations on the right, when viewed from this new vantage point. The representation of space that is distorted in neglect seems to operate on

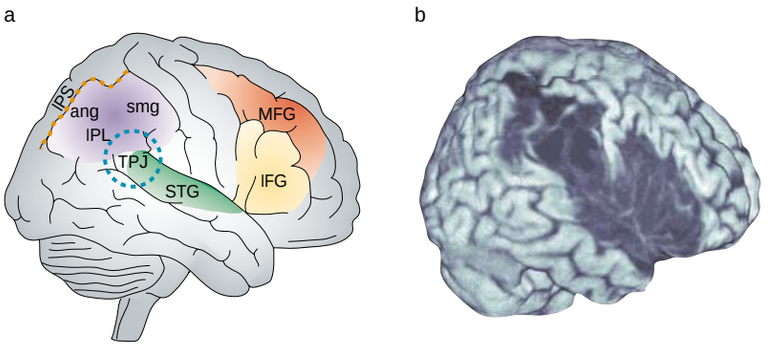

Figure 1 | **Neuroanatomy of neglect. a** | Cortical regions that are damaged in patients with neglect. Posterior areas include the junction of the temporal and parietal lobes (TPJ), the inferior parietal lobe (IPL) which includes the angular (ang) and supramarginal gyrus (smg), the intraparietal sulcus (IPS), and the more recently implicated superior temporal gyrus (STG). Frontal areas include the inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG). **b** | Reconstruction of the cortical areas destroyed by stroke in a patient with neglect. In this patient, all the areas implicated in **a** are affected, but in other patients more focal damage, restricted to one or two of the areas shown in **a**, can occur.

several frames of reference that are not necessarily tied to retinal coordinates[26,31], such as an egocentric representation anchored to the trunk midline[32] or even an object-based (but nevertheless spatially lateralized) frame of reference[33].

Finally, and perhaps most influential, are accounts that propose that neglect is a deficit in directing spatial attention. For example, some models view neglect as a manifestation of a spatially lateralized gradient of attention that is biased away from contralesional space[34,35]. Others consider it to be due to an impairment in the ability to disengage attention and shift it contralesionally[36]. Still others view it as a competitive spatial bias in which items on the contralesional side always lose in the competition for selective attention when there are ipsilesional items[37].

As mentioned, none of these explanations are mutually incompatible[26] and many researchers feel that some, or all, of these components might combine in different patients to give rise to the bewildering array of behavioural dissociations that have been reported in neglect[18,20]. However, there has been little attempt systematically to map such spatially lateralized impairments on to brain structures. The few exceptions include studies that have attempted to localize the attentional disengagement deficit[36,38] or the directional motor impairment[28,39], but these have not always been in agreement, partly perhaps because they were performed using computed tomography (CT) rather than high-resolution magnetic resonance imaging (MRI). Importantly, the spatially lateralized attentional disengagement deficit found in stroke patients appears to be lesion-location-specific rather than neglect-specific[38], showing that even the lateralized components of neglect can exist on their own, without the full-blown neglect syndrome. We show below that the same is true of non-spatially lateralized components that might contribute to neglect in some patients.

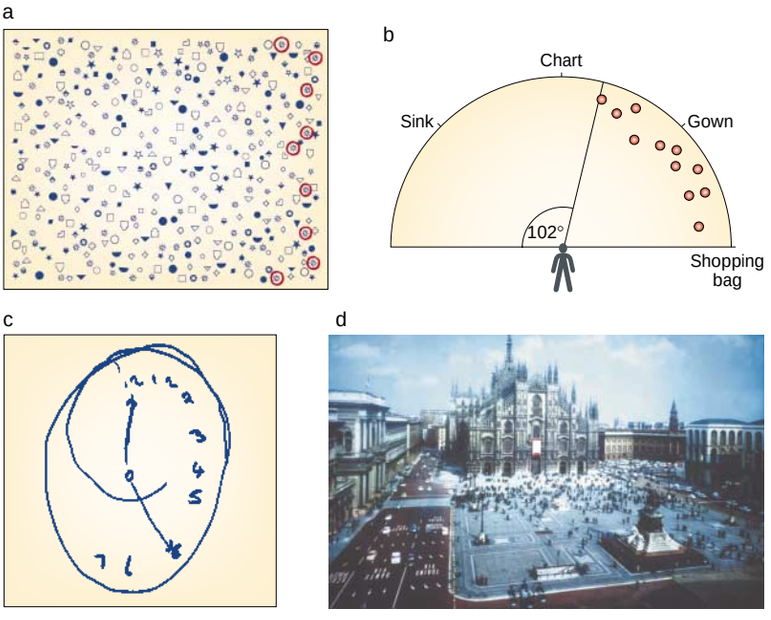

Figure 2 | **Clinical tests for neglect. a** | Cancellation test. The visual search of a typical left neglect patient is restricted to finding and marking targets on the ipsilesional (right) side, and missing those towards the contralesional (left) side. **b** | Naming objects around a room. This simple task reveals that only items to the right were reported. Modified, with permission, from REF. 3 © 1991 BMJ Publishing Group **c** | Clock drawing. Some patients with neglect omit details on the contralesional side of a drawing from memory, such as a clock. **d** | Milan Square. In a famous study, Milanese left neglect patients failed to recollect places on the left of the city's Piazza del Duomo when asked to imagine the square from one vantage point, but were able to report these locations when asked to imagine looking at the square from the opposite side.

Spatially lateralized deficits might not be enough

Although spatially lateralized mechanisms are undoubtedly crucial and might explain neglect in some patients, they might not — on their own — explain the neglect behaviour of all individuals. Moreover, they might not be sufficient to explain why neglect endures in some patients and not in others.

Consider the performance of a right-hemisphere neglect patient on a visual search (cancellation) task (FIG. 2a). A spatially lateralized attentional bias that makes the rightmost items effectively more salient than leftward ones might explain why such a patient starts to search for items on the right. But how does it alone prevent them from moving on towards the left after they have marked targets on the right, when given unlimited time? Although the relative perceived salience of marked items to the right could repeatedly draw a patient's attention back, we argue that this cannot be the full explanation. Erasing the targets (so that they are no longer salient) rather than marking them, improves search performance, but patients continue to show neglect[40].

Similarly, although a directional motor deficit can lead to prolonged reaction times for leftward movements, patients can nevertheless make movements to the left[27–29]. Indeed, on visual search tasks they make just as many leftward SACCADES as rightward ones[41,42]. So why do they not eventually mark targets to the left? A loss of

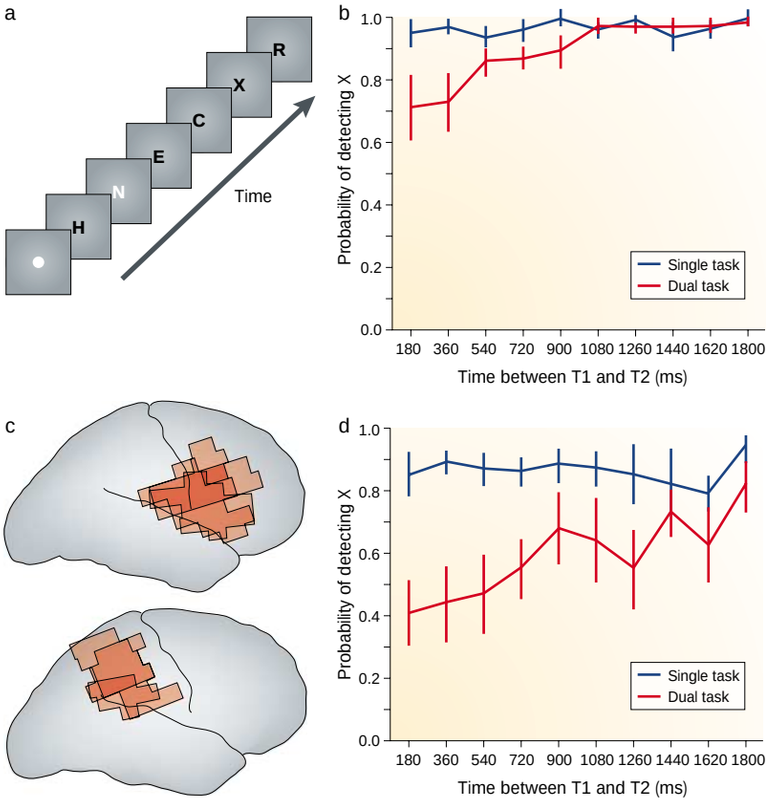

Figure 3 | **Attentional blink measures non-spatial selective attention. a** | The attentional blink protocol. This figure shows only some of the stimuli in a single stream. All stimuli are presented at fixation and observers report both the white letter and whether there was an X following it (dual task), or simply report whether they saw an X (control single task). **b** | Normal performance. On the dual task, subjects are impaired in reporting the X if it is presented within 400 ms of the white letter. This is the 'attentional blink'. Such a dip in performance is not seen on the single task. **c** | Lesions of neglect patients tested on the task. Patients with inferior frontal or posterior lesions were tested using this paradigm. **d** | Performance of neglect patients. Both sets of patients showed a severe and protracted attentional blink, revealing an impairment of non-spatial selective attention in spatial neglect. Modified, with permission, from *Nature* REF. 6 © 1997 Macmillan Magazines Ltd.

SACCADE
A rapid eye movement that brings the fovea (the central retinal area with the highest resolution) to view a point of interest in a visual scene.

BALINT'S SYNDROME
A rare disorder following bilateral parieto-occipital lesions in which the patient has difficulties in directing the eyes to visual objects (ocular apraxia), misreaching to peripheral visual targets (optic ataxia) and perceives only one object at a time (simultanagnosia).

SIMULTANAGONOSIA
Sometimes also referred to as 'simultagnosia', this is the inability to perceive more than one object at one time.

the representation of left space might ostensibly offer a simpler explanation, because one would not expect a patient to search in a part of space that is not represented in their brain. But patients who do not search towards the left of cluttered cancellation tests nevertheless find the same items to the left if they are presented individually in uncluttered displays[42,43], indicating that objects in that part of space can be represented by these patients.

In our view, each of the spatially lateralized attentional, motoric and representational models has difficulties in fully explaining the performance of unilateral neglect patients on a standard test such as cancellation. Spatially lateralized models also have difficulties in explaining the behaviour of patients with bilateral posterior cortical damage who have BALINT'S SYNDROME. Individuals with this rare condition do not necessarily demonstrate a lateralized bias (presumably because both hemispheres are affected), but nevertheless suffer a profound disorder of visual perception. They report seeing only one thing at a time (SIMULTANAGNOSIA), even if objects such as line drawings are superimposed over each other at one location in space[44,45]. In addition, they have a greatly constricted effective field of vision that prevents them from being aware of all but the most salient stimuli in the periphery of either left or right visual field. Such a 'local bias', albeit in a milder form, might also arise after unilateral damage to the TPJ in patients with and without neglect[22,46].

These considerations suggest that it might be worth considering non-spatially lateralized contributions to neglect. The interaction of spatially lateralized mechanisms with non-lateralized components offers a different way of viewing the behaviour of neglect patients. Furthermore, considering neglect as a failure of non-lateralized as well as spatially lateralized functions might provide a framework for understanding why acute neglect is nearly as common after left-hemisphere stroke as after right-hemisphere damage. Although acute lateralized impairments might be common to both left- and right-hemisphere stroke patients, right-hemisphere patients might recover less swiftly and fully because they also have non-spatially lateralized deficits that combine with their lateralized impairments.

Below, we review more direct evidence for non-lateralized deficits in neglect, and for the consequences of such mechanisms on the severity of neglect. In addition, we discuss the results of imaging studies in healthy humans and electrophysiological studies in monkeys that show that sub-regions within the parietal and frontal cortex have non-lateralized functions.

Non-lateralized selective attention

Only a small fraction of the information captured by the retina normally enters our awareness. The visual system has a limited capacity, so only stimuli that are salient or potentially important capture our attention. One approach that has been used to probe the processing limits of the visual system is to measure the time course of attentional processing[47].

When we identify a visual object, our ability to detect a second object is impaired if it appears within 400 ms of the first. This phenomenon, the 'attentional blink'[48], provides a measure of the temporal dynamics of non-lateralized selective attention: the time taken by the visual system to identify a visual stimulus before it is free to detect a subsequent stimulus. In a typical attentional blink task (FIG. 3a), a stream of black letters is presented in the centre of the screen with one white target letter. In half of the trials, an 'X' follows the white letter at some point in time. After the stream of letters, the participant is asked to report both the identity of the white item and whether an X was displayed. Healthy individuals fail to report the letter X if it occurs within 400 ms of the white letter (FIG. 3b, 'dual task'). In contrast, when participants do not have to pay attention to the form of the white letter, their ability to report the X is not affected by when it is presented in the sequence relative to the white letter (FIG. 3b, 'single task').

Patients with hemispatial neglect have a more severe and protracted attentional blink than healthy individuals[6]. When neglect patients with either anterior or

posterior lesions (FIG. 3c) identify a (white) letter, their ability to detect a subsequent target (X) is impaired for more than 1,200 ms (FIG. 3d). So, they show a deficit in selective attention even on this non-spatially lateralized task. This impairment cannot be attributed to a difficulty in sustaining attention throughout a trial, because their performance on the dual task improves with time. Moreover, their ability to detect the target X in the control single task is excellent, regardless of whether the target is presented early or late in a trial.

Importantly, the level of deficit displayed on this non-spatially lateralized task correlates with the severity of hemispatial neglect[6]. Recent work shows that the impairment might be anatomically specific rather than neglect-specific, as it can occur in patients with lesions of the inferior parietal lobe (IPL) and superior temporal gyrus (STG) who do not have neglect[49]. These findings indicate that a non-lateralized deficit in selective attention can occur independently of neglect, but when combined with a lateralized bias it can exacerbate hemispatial neglect, by prolonging the time spent in processing stimuli on the right, at the expense of those on the left.

Further evidence for a non-lateralized visual deficit in selective attention in patients with neglect comes from studies that have reported impairments on both sides of space in such patients[50,51]. One of these investigations measured the capacity of visual attention and found that neglect patients had reduced capacity for encoding stimuli presented transiently in either visual field[50]. Auditory studies have also begun to find evidence for a non-lateralized deficit in selective attention. Neglect patients have difficulty on a task that requires comparisons between brief, successive central sounds[52], and show a bilateral deficit when stimuli are presented to both ears but with an interaural time difference to act as a localization cue. This deficit correlates with the degree of spatial neglect (F. Pavani *et al.*, submitted).

Functional imaging studies have identified specific locations around the intraparietal sulcus and frontal cortex as being associated with non-spatially lateralized visual processing, for example on the attentional blink task[53–56] (FIG. 4a). These regions are also often damaged in patients with neglect. We propose that damage to these areas causes non-lateralized capacity limits and prolongation of visual processing; when combined with lateralized deficits, these limits exacerbate spatial neglect.

Non-spatially lateralized sustained attention

In addition to selective attention, the ability to maintain attention over periods of time is important[57,58]. Individuals who cannot be vigilant might miss crucial events and this might have a detrimental effect on their performance and behaviour over both the short and long term. For patients with brain lesions, sustained attention might be an important factor in determining the prognosis for recovery[59]. The ability to sustain attention is often tested using tasks that require observers to respond to transient, relatively infrequent stimuli that occur randomly over a protracted period of time. In their simplest and purest forms, these paradigms present observers with only one form of stimulus and the task is to detect that stimulus without having to discriminate it from distractors (compare to 'detecting salience in space and time' below). Importantly, these tasks do not necessarily require stimuli to be presented at different locations in space.

Human lesion studies have implicated the right frontal lobe as a key site in mediating sustained attention. For example, patients with damage to this region are poor at counting non-lateralized monotonous auditory tones[60], detecting a visual target at the centre of a screen[61] or detecting tactile stimuli presented to either hand[60]. More recently, sustained attention deficits have been reported in patients with posterior lesions using a visual vigilance task[62]. In all these investigations, the patients were not noted to show signs of unilateral neglect at the time of testing. So, deficits of sustained attention can occur independently of neglect. On the other hand, patients with neglect can show impaired sustained attention on tasks that do not use spatially lateralized stimuli, or that present stimuli only in the 'good', ipsilesional side of space.

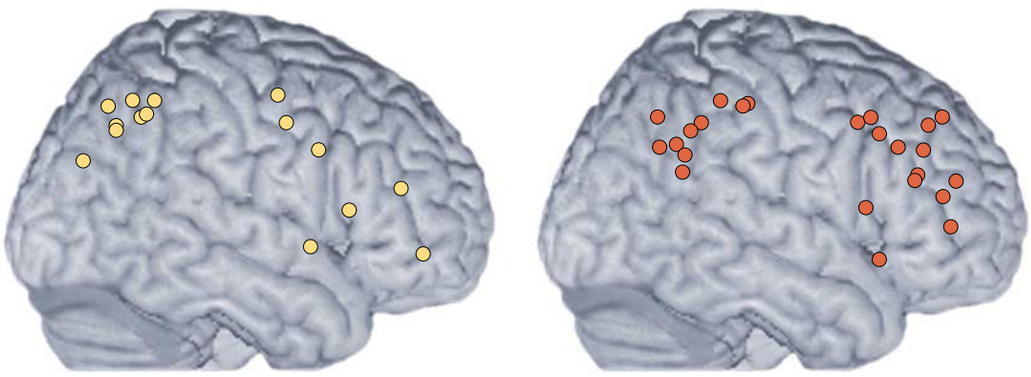

Figure 4 | **Lateral parietal and frontal areas involved in non-spatial visual selective and sustained attention in healthy individuals. a** | Visual selective attention. Most of the parietal activations are near to or in the depths of the intraparietal sulcus. The frontal regions include an area in the insula which is projected onto the surface (and not actually in the temporal lobe). **b** | Visual sustained attention. The areas activated include the inferior parietal lobe and predominantly middle frontal gyrus.

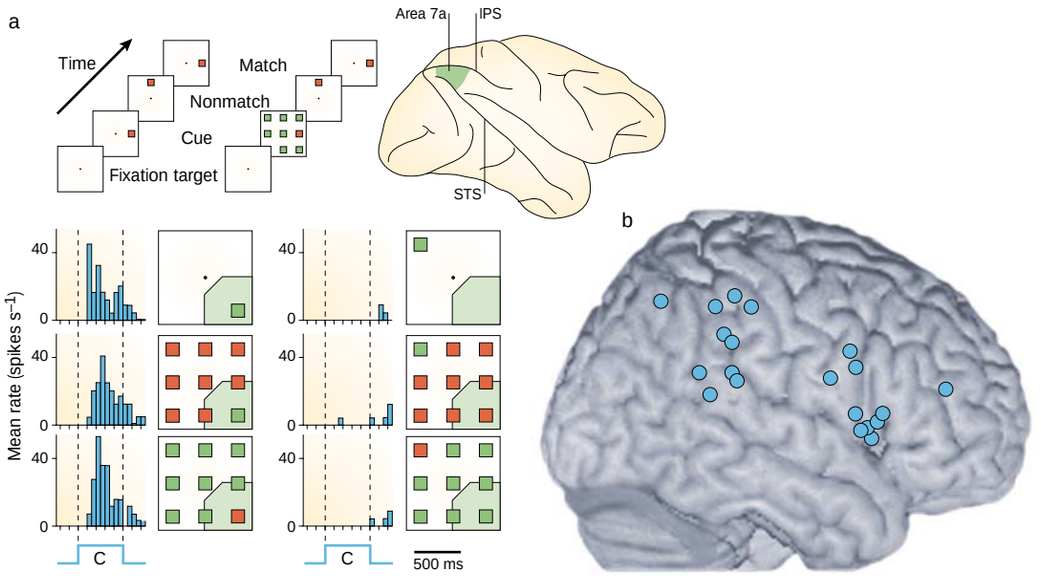

Figure 5 | **Encoding salience in space and time. a** | Salience encoding in monkey parietal cortex[73]. Monkeys were trained to attend to the location of a salient stimulus (cue phase) and to release a lever when a subsequent display contained that stimulus in that location. Cues were red or green squares presented alone or with distractors of the opposite colour. The activity of one cell during the cue phase is shown. The light green area represents the neuron's spatial receptive field. This cell fires when there is a salient stimulus (green or red) presented either alone or with distractors. Note that it is not activated by either a green or red stimulus if they are not the salient stimulus in the array (right column). IPS, intraparietal sulcus; STS, superior temporal sulcus. Modified, with permission, from REF. 73 © 2001 Oxford University Press. **b** | Lateral temporo-parietal and frontal areas encoding non-spatial visual salience in human brain. Activations include the temporo-parietal junction (TPJ) and inferior frontal regions.

Robertson and colleagues[63] found that right-hemisphere stroke patients with neglect performed significantly worse on a tone-counting task than did stroke patients without neglect. Moreover, there was a strong correlation between the severity of hemispatial neglect and the degree of impairment on the non-spatially lateralized sustained attention task. Further analyses indicated that the deficit in sustained attention was an independent predictor of performance on clinical measures of visual neglect, such as cancellation. Other studies have shown that patients with persistent spatial neglect continue to be impaired on sustained attention tasks[59,64,65], whereas patients who recover from neglect show improvements in sustained attention[59]. The performance of patients who fail to recover from neglect cannot be attributed simply to lesion volume[59,64]. Lesion location might be more important — the results of one CT study implicated the paraventricular white matter in the temporal lobe[59] — but the correlates of poor sustained attention in neglect have not been specifically investigated using high-resolution MRI.

In healthy individuals, the results of several functional imaging studies (FIG. 4b) point to locations in the right IPL and predominantly in the right mid-frontal lobe as being vital for sustained visual attention[66–71]. Damage to these regions might be necessary to produce deficits in sustained attention after stroke, and these areas are also often involved in neglect after right middle cerebral artery (MCA) territory stroke. In such patients, a lateral spatial bias (initially directing attention to the right) combined with a non-lateralized deficit in sustained attention might exacerbate leftward neglect[63], with patients experiencing difficulty in continuing to search from their initial rightward starting position.

Detecting salience in space and time

Whereas sustained attention tasks probe the ability to maintain attention over time, other paradigms have been developed to investigate the brain mechanisms involved in detecting salient stimuli among distractors. Neuronal recording studies have found activity relating to the spatial location of salient stimuli in monkey parietal cortex[72,73]. Remarkably, some neurons in the inferior parietal cortex respond only when a particular stimulus is salient among distractor objects, but not when the same stimulus acts as a distractor in a different visual array[73] (FIG. 5a). Such studies have led to the view that neural representation in the posterior parietal cortex might be very sparse, with only salient stimuli, or those relevant to behaviour, being encoded there[72].

In humans, evidence that stimulus salience is represented in a similar way has been obtained using the 'oddball' paradigm. Typically, a sequence of standard stimuli is presented over time. Embedded in this stream are infrequent target stimuli, familiar non-targets or novel non-target deviant stimuli. ERP (evoked response potential) studies reveal a consistent posterior P3 or P300 positive waveform that occurs ~400 ms after the presentation of either targets or novel non-targets, but not after familiar non-targets. The P3

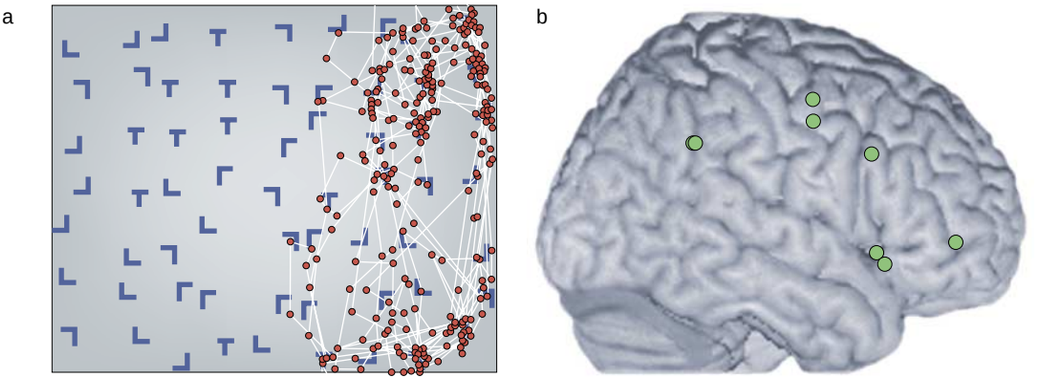

Figure 6 | **Trans-saccadic spatial working memory. a** | Eye movements of a right-hemisphere patient with neglect. The red dots show the fixation points (where the patient looks) while he searches for targets (Ts) among distractors (Ls). The white lines show his scan path. Note how he recursively revisits locations he has searched before. Modified, with permission, from REF. 43 © 2001 Oxford University Press. **b** | Green dots represent lateral parietal and frontal areas activated in double or triple memory-guided saccadic paradigms. These tasks are considered to require updating of spatial representations across saccades.

might be a marker of salient stimuli that draw attention, regardless of whether the stimulus is a target or a novel non-target (although some investigators have distinguished between an earlier P3a component in response to novelty and a slightly later P3b wave evoked by a target[74]). Unilateral lesions of the TPJ eliminate P3a and P3b components in both cerebral hemispheres[74], indicating that this region might be at least one of the crucial sites for their generation. There is also evidence of prefrontal involvement in salience encoding, as unilateral lesions of the lateral prefrontal cortex also reduce P3b amplitude bilaterally over posterior regions[75].

Functional imaging researchers have also adopted the 'oddball' paradigm. The results of their studies point to a key role for the TPJ region, as well as inferior frontal regions, predominantly in the right hemisphere[76–81] (FIG. 5b). Note that, unlike tasks that require spatially lateralized or non-lateralized selective attention, visual 'oddball' paradigms do not consistently activate the posterior intraparietal sulcus, indicating that there might be segregation of different attentional functions within the posterior parietal and TPJ regions (see below).

Both the posterior and anterior brain regions that have been implicated in detecting salience are damaged in many patients with neglect. One would anticipate, given the ERP and fMRI (functional MRI) data, that the detection of salience would be compromised in these patients. Lack of awareness of stimuli that are often salient is a hallmark of the neglect syndrome, but until now research efforts have been directed towards understanding only the spatially lateralized distribution of salience encoding in neglect patients. However, the data from healthy individuals and focal lesion patients without neglect indicate that there should also be a deficit in encoding salience even when stimuli are presented centrally at one location in space. Such a specific non-lateralized deficit, which can be distinguished from an impairment of selective or sustained attention, has yet to be identified.

SPATIAL WORKING MEMORY
The ability to hold 'on-line' and manipulate information regarding the location of an object.

Trans-saccadic spatial working memory

A common observation is that patients with neglect often re-inspect items they have already studied. For example, when right-hemisphere neglect patients perform a cancellation task, some of them repeatedly re-examine rightward targets that they have already found[82]. Although the relative perceived salience of items on the right, compared with those on the left, might be one explanation for such behaviour, a failure to keep track of object locations across saccadic eye movements might be an important independent contributing factor in some patients[42,83,84].

To examine this issue, a task has been developed to probe memory for previously inspected spatial locations during visual search[42]. Subjects are asked to find targets (Ts) among distractors (Ls), and to click on a response button only when they find a new target — one they have not found before. At the same time, their eye movements are recorded so that it is possible to know exactly where they are looking when they press the response button. Using this system, it has been confirmed that many neglect patients refixate targets they have previously found (FIG. 6a). Crucially, analysis of the click responses shows that many neglect patients mistake targets they have previously found for new discoveries, indicating that they do not remember inspecting them[42,85].

Importantly, for the purposes of the structure–function correlations we have sought to make, high-resolution MRI shows that this SPATIAL WORKING MEMORY deficit across saccades is associated with specific lesion sites near the right intraparietal sulcus and inferior frontal gyrus[86]. Functional imaging studies in healthy individuals also reveal the importance of specific regions within inferior parietal and frontal lobes in keeping track of spatial locations across saccades[87,88] (FIG. 6b). These studies used double- or triple-step saccade paradigms, which have also been used to demonstrate trans-saccadic spatial updating impairments in patients with parietal or frontoparietal lesions, some of whom had neglect[89,90] (BOX 2). Note that such an

Box 2 | Keeping track of spatial locations across saccades

Perceiving the spatial location of an object might at first seem to be a trivial problem: we know where something is because we know where its image falls on the retina. However, representing visual space might not be quite so straightforward[110]. As our eyes move, the retinal image is displaced so that a stationary object can occupy many retinal positions but is still perceived as being in the same location. Conversely, many different locations in space can occupy a single retinal position. Representing the spatial location of an object requires the brain to take into account eye movements as well as retinal information.

Electrophysiological studies of monkey parietal cortex[102,111,112] have begun to reveal how the brain might dynamically remap retinal information, or use eye position, across saccades, to represent the locations of objects in space. Central to the development of these ideas has been the double-step saccade paradigm. Observers look at a central fixation point and are shown, in quick succession, two different targets. These are extinguished before the subjects make two saccades, in turn, to the remembered locations of the first and second targets. To make the second saccade accurately, observers need to take into account where their eyes have moved to after the first saccade. The initial retinal locus of the second target (as seen from the fixation point) alone is insufficient.

Patients with lesions involving the right parietal lobe are impaired on the double-step saccade task[89,90]. Although many of them have some degree of left neglect, they can nevertheless make a first saccade to the remembered position of a left target. However, unlike normal subjects, they find it very difficult to saccade to the remembered location of a second target to the right. They seem to be unable to take into account the first leftward eye movement when computing the direction and amplitude of the second saccade. Although this deficit seems to be worse when the first target is presented to the left and the second to the right, right parietal patients are also impaired when the sequence is reversed, with this effect not being fully explained by neglect of left stimuli[90]. These patients seem to have difficulty in updating representations of spatial location across saccades, regardless of the spatial location of targets. Such an impairment, when combined with a spatially lateralized bias, would be expected to lead to problems in keeping track of object locations across saccades, as is required on cancellation tasks[42].

impairment is not neglect-specific but rather seems to be related to lesion location, with the vital parietal region being within the IPL[90].

Across neglect patients, the severity of the working memory deficit correlates with the degree of hemispatial neglect[85]. The greater the difficulty in keeping track of previously inspected locations to the right, the more likely it is that patients will not shift their search towards the left. Furthermore, the trans-saccadic spatial working memory deficit is not spatially lateralized, as neglect patients are impaired even when required to keep track of locations in a vertical array[86]. The combination of a lateral bias and a (non-lateralized) failure to remember which locations have already been searched offers a new explanation for the inability of these patients to direct their search to the contralesional side.

Combining non-lateralized and lateralized

The non-spatially lateralized mechanisms that have been implicated in neglect correlate well with functional imaging evidence that the inferior parietal and lateral frontal cortices are involved in these functions in the normal brain (FIGS 4–7). Within the parietal and frontal cortices, there might be regional specialization for these non-lateralized processes. Although we must be circumspect when comparing imaging data across different subjects, paradigms and scanners, different non-lateralized functions seem to activate different parts of the parietal cortex, extending from the intraparietal sulcus down to the IPL and TPJ (FIG. 7a).

In addition, there is some evidence that spatially lateralized and non-lateralized functions might be anatomically segregated. Several functional imaging studies show lateralized attentional mechanisms localized in the superior parietal lobe (SPL)[70,91], whereas the non-lateralized ones we have reviewed cluster in the IPL (FIG. 7). Regions within the intraparietal sulcus (between the SPL and IPL) seem to participate in both lateralized and non-spatially lateralized functions[53,54]. This specialization within parietal cortex might explain why different patients show different symptoms, depending on the extent and location of their lesion (see REF. 92 for a different perspective). We argue that the combination of spatially lateralized and non-lateralized deficits leads to persistent neglect. According to this model, although SPL lesions might lead to a lateralized bias, they would not lead to lasting neglect. By contrast, damage to the IPL (including the intraparietal sulcus and TPJ) would lead to severe and protracted neglect, with both lateralized and non-lateralized deficits.

Of course, it is possible that the distinction between spatially lateralized and non-lateralized processes is not dichotomous, at least for some component processes. Indeed some have argued that a left–right spatial gradient in, for example, the attentional blink might underlie part of the lateralized bias in neglect[93,94]. Further work will be required to investigate this possibility. What is clear, however, is that studying lateralized and non-lateralized component deficits and their interaction might be an important way to improve our understanding of neglect.

The argument for combined deficits in neglect is itself not new, and there is experimental evidence that, for example, spatially lateralized attentional impairments can combine with spatially lateralized motoric deficits in some patients[28,29]. Our proposal is therefore an extension to non-lateralized components of the idea that multiple components interact to exacerbate neglect. Behavioural studies indicate that the greater the non-lateralized deficit, the worse the severity of hemispatial neglect.

In studies of non-spatially lateralized selective attention[6], sustained attention[63] and trans-saccadic spatial working memory[85], the degree of non-lateralized impairment correlates with neglect severity across patients. Interestingly, recovery from neglect is associated with improvements on both sides of space[95]. Of course, correlation is not causality, but these findings are consistent with the view that non-lateralized deficits interact with spatially lateralized biases to keep patients' attention towards their 'good' ipsilesional side and away from contralesional space.

Evidence for the effect of non-lateralized factors on spatially lateralized bias within individual patients comes from a study performed by Robertson and co-workers[96]. They asked right-hemisphere patients with left neglect to judge whether a visual stimulus

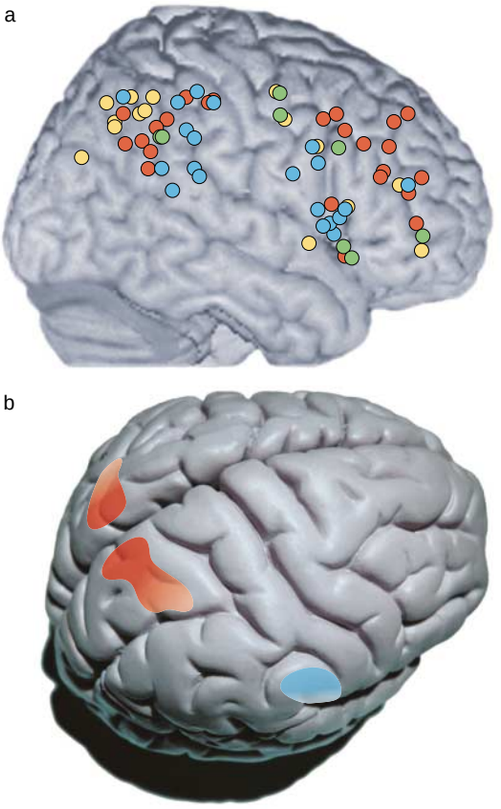

Figure 7 | **Non-spatial and spatial visual attention.** **a** | Lateral parietal, temporo-parietal and frontal regions activated in non-spatial visual selective attention (yellow), sustained attention (red), salience (blue) and spatial updating across saccades (green). There appears to be some segregation of these functions within the brain, although conclusions regarding this must be limited until further studies are performed using these different paradigms in the same subjects. More importantly these areas, activated in non-spatial tasks, are also the regions commonly damaged in neglect patients. **b** | Regions associated with shifting attention (red) and sustaining attention (blue) in posterior brain regions. The superior parietal lobe was activated by spatial shifts of attention whereas the inferior parietal lobe was active during the sustained attention task[70]. Modified, with permission, from REF. 70 © 2001 Academic Press.

presented on the left preceded one presented on the right, or vice versa. They found that patients became aware of the left stimulus more than half a second later than the right one. Remarkably, this rightward spatial bias was abolished when patients heard a central auditory warning sound, suggesting that a tonic deficit in sustained attention normally contributes to the lateralized bias in these neglect patients. These findings also have significance for potential treatments of the neglect syndrome.

Therapy and future directions

There is no established treatment for neglect. Conventional methods that have targeted the spatially lateralized deficit have been singularly unsuccessful. For example, efforts to improve visuospatial neglect by getting patients to track stimuli towards their neglected side[97] might improve tracking behaviour on a particular paradigm, but these improvements have repeatedly failed to generalize to everyday settings. More recently, the use of short bursts of prismatic adaptation[98] have produced intriguing results, with patients showing long-lasting benefits for weeks after the intervention on tasks that test more everyday functions[99]. Although prism treatment looks promising, our review of the potential contribution of non-lateralized factors in neglect suggests that, for successful treatment, both lateralized and non-lateralized mechanisms might need to be targeted.

One behavioural intervention aimed at improving sustained attention has shown some promise. Patients with neglect were trained to perform a variety of tasks and periodically had their attention drawn to the task by a loud noise coupled with a verbal instruction to attend. With time, the patients were trained to alert themselves sub-vocally. Such training led to improvements not only in non-lateralized sustained attention but also in lateralized spatial neglect[100]. However, not all patients might be suitable for this type of treatment. Instead, pharmacological interventions directed towards improving sustained attention are likely to be the next step.

For impairments of sustained attention, one possible pharmacological target might be the cholinergic system, which is likely to have a role in this function[57,101]. The use of acetylcholinesterase inhibitors, which increase postsynaptic concentrations of acetylcholine and are already used to improve cognition in Alzheimer's disease, would be a natural first step. By contrast, the dopaminergic system might be an important target for treatments aimed at improving trans-saccadic spatial working memory. Neurons in monkey frontal cortex, like those in the intraparietal sulcus, encode the remembered locations of saccadic targets[102,103]. Both the activity of these neurons and the monkeys' memory of saccadic targets are modulated by dopamine D1-receptor agents[103]. Some clinical studies used the dopamine agonist bromocriptine, reporting both favourable and adverse effects on neglect[104,105]. The variation in response might be due to the heterogeneity of the component deficits in the patients that were studied, as well as the fact that bromocriptine acts mainly at dopamine D2 receptors. Future dopaminergic treatment might need to be aimed selectively at D1 receptors, specifically in patients with a trans-saccadic spatial working memory deficit.

It is likely that over the next decade several behavioural and pharmacological strategies, perhaps in combination, will be deployed to treat the neglect syndrome. However, for such interventions to be successful, a clear understanding of the component deficits underlying the disorder — both lateralized and non-spatially lateralized — will be essential. Greater insight into the heterogeneous nature of neglect, and its fine-grained anatomical basis, might be the key to unlocking the syndrome, tailoring treatment to deficits in individual patients, and revealing the functions of the brain regions that are commonly damaged in neglect.

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Online links

FURTHER INFORMATION
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MIT Encyclopedia of Cognitive Sciences: http://cognet.mit.edu/MITECS/
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