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THE ROYAL SOCIETY

Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events

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CONTENTS

The syndrome of contralesional neglect reflects a lateralized disruption of spatial attention. In the human, the left hemisphere shifts attention predominantly in the contralateral hemispace and in a contraversive direction whereas the right hemisphere distributes attention more evenly, in both hemispaces and both directions. As a consequence of this asymmetry, severe contralesional neglect occurs almost exclusively after right hemisphere lesions. Patients with left neglect experience a loss of salience in the mental representation and conscious perception of the left side and display a reluctance to direct orientating and exploratory behaviours to the left. Neglect is distributed according to egocentric, allocentric, world-centred, and object-centred frames of reference. Neglected events can continue to exert an implicit influence on behaviour, indicating that the attentional filtering occurs at the level of an internalized representation rather than at the level of peripheral sensory input. The unilateral neglect syndrome is caused by a dysfunction of a large-scale neurocognitive network, the cortical epicentres of which are located in posterior parietal cortex, the frontal eye fields, and the cingulate gyrus. This network coordinates all aspects of spatial attention, regardless of the modality of input or output. It helps to compile a mental representation of extrapersonal events in terms of their motivational salience, and to generate 'kinetic strategies' so that the attentional focus can shift from one target to another.

Keywords: sensorimotor integration; limbic; cognition; neural networks

1. INTRODUCTION

Nearly 25 centuries ago, Empedocles reflected on the nature of God and likened it to 'a circle of which the centre is everywhere and the circumference nowhere'. The omnipresence that Empedocles envisaged would have engendered an all-encompassing awareness: nothing would be ignored, nothing could be brought into sharper focus, all events would be registered in parallel, everything would have full access to instantaneous action, and the global would be identical to the focal. Anything short of such omnipresence creates the need for choosing which of many suitable mental or external events will have preferential access to the narrow portals of consciousness and action. 'Attention' is a generic term that can be used to designate the entire family of processes that mediate these choices. At the psychological level, attention implies a preferential allocation of the limited processing resources and response channels to events that have become behaviourally relevant. At the neural level, attention refers to reversible modulations in the selectivity, intensity and duration of neuronal responses to such events.

No neuron is exclusively dedicated to attention, and yet nearly every neuron displays some attentional modulation. Such modulations are least noticeable in primary sensory areas and become increasingly more prominent in downstream association, heteromodal and limbic cortices (Mesulam 1998). Conceptually, attentional modulations can be divided into those that are domain-specific and domain-independent. Visual neurons, for example, mediate domain-specific attentional responses to visual stimuli, face neurons to faces, posterior parietal neurons to spatial targets, Wernicke's area to words, and so on (Spitzer *et al.* 1988; McCarthy & Nobre 1993; Treue & Maunsell 1997; Wojciulik *et al.* 1998). Domain-independent modulations are exerted predominantly through the bottom-up influence of the ascending reticular activating system (ARAS) and the top-down influence of the cerebral cortex, especially the frontal lobes and the limbic system. Through the influence of these channels, domain-specific modulations become responsive to variations in arousal levels, motivational valence and cognitive state (figure 1). The domain-independent attentional functions of the ARAS, frontal lobe, and limbic system have been discussed elsewhere (Mesulam 1998). This review focuses on a domain-specific attentional system which directs attention to behaviourally relevant targets in the extrapersonal space.

2. THE NEUROPSYCHOLOGY OF NEGLECT

The syndrome of contralesional neglect reflects a severe disruption in spatial attention and is caused by lesions which damage the dorsal parieto-frontal streams of sensory processing. Severe contralesional neglect occurs almost exclusively after right hemisphere lesions so that the clinical examples below will be confined to patients with left neglect. When neglect is severe, the patient may behave almost as if one-half of the universe had abruptly ceased to exist in any meaningful form. One patient may shave, groom, and dress only the right side of the body; another may fail to eat food placed on the left side of the tray; another may omit to read the left half of each sentence or even the left side of every word printed anywhere on the page; still another may fail to copy detail on the left side of a drawing and may show a curious tendency to leave an uncommonly wide margin on the left side of the paper when asked to write. Even without specific stimulation, some patients display a tonic rotation towards the right side of the bed, as if responding to the irresistible magnetism of everything that is on the right. Hemianopia and gaze paresis are neither necessary nor sufficient for the emergence of visual neglect (figure 2). Manual exploration of the left side is impaired even when the intact right limb is used, indicating that hemiparesis is not an essential factor either. Neuropsychological tests help to classify neglect behaviours into sensory-representational, motor-exploratory and limbic-motivational components (Mesulam 1985). Although, no test is absolutely specific for assessing a single component of neglect, each test emphasizes one component more than the others.

(a) *Representational (perceptual) component of neglect: extinction, line bisection, covert shifts of attention*

Patients with unilateral neglect behave as if sensory events within the left extrapersonal hemispace have lost their salience, especially when competing events are concurrently occurring on the right side. This aspect of neglect can be probed with tests of extinction, line bisection, and covert attentional shifts. Extinction is said to exist when patients who respond accurately to unilateral stimulation from either the left or the right side, consistently ignore the stimulation on the left under conditions of bilateral simultaneous stimulation. If extinction occurs in only one modality, it can conceivably reflect a subtle disruption of relevant sensory pathways or even a callosal disconnection syndrome (Sparks & Geschwind 1968; Eidelberg & Schwartz 1971). Multimodal extinction, however, almost always reflects the representational aspect of neglect. Extinction can be cross-modal. For example, contralesional tactile extinction in the hand may be elicited by ipsilesional visual stimulation, especially if the visual stimulation is presented close to the hand (Di Pellegrino *et al.* 1997).

In the traditional version of the line bisection task, patients are asked to mark the midpoint of a horizontal line drawn on a sheet of paper. Neurologically intact subjects tend to place the bisection mark slightly left of the true centre. Patients with left hemineglect tend to place their mark substantially rightward of centre, suggesting that the representational impact of the left side

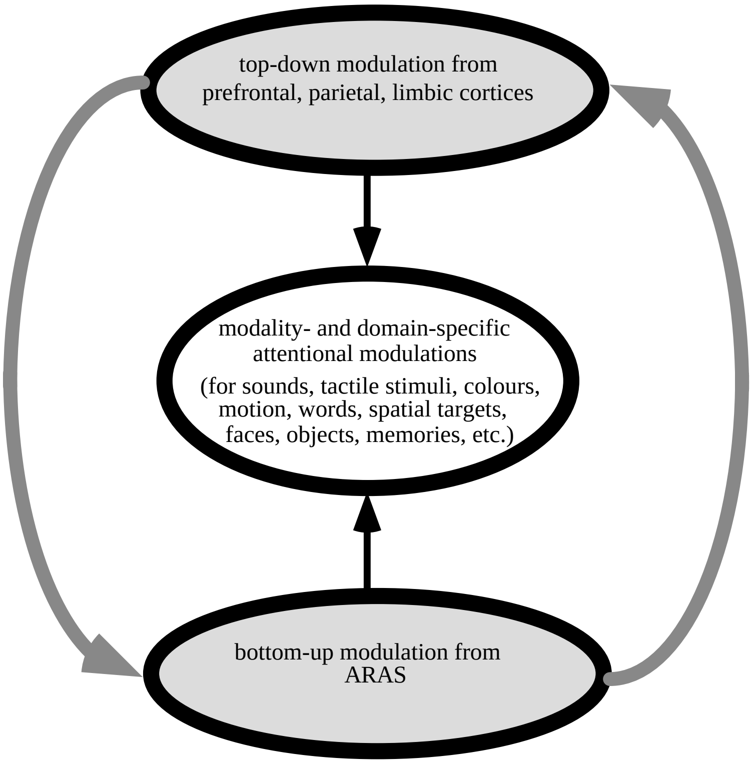

Figure 1. A schematic representation of the three compartments that regulate the attentional matrix.

becomes diminished and that it takes a longer segment on the left to balance the salience of a shorter segment on the right. Confirmation for this interpretation comes from the 'landmark' variant where the task is to point to the shorter side of a correctly pre-bisected line. Patients with left hemineglect choose the left side as the shorter, indicating its lesser salience (Harvey *et al.* 1995). The magnitude of the rightward deviation in the traditional version of the test is monotonically related to the length of the line, although the proportionality constant varies from patient to patient (Mozer *et al.* 1997; Monaghan & Shillcock 1998). This relationship to total length implies that the sensory information from the entire line is being apprehended and that the neglect is a post-sensory phenomenon directed to an internal representation.

The field of unilateral neglect was thrown into considerable turmoil by reports which showed that bisection of lines shorter than 5 cm led to a crossover effect whereby the longer side fell on the right (Marshall & Halligan 1989). According to one explanation, the orientation of patients with left neglect is automatically directed to the rightmost point of the line from whence it is volitionally pulled back and moved as far to the left as the excessive attentional pull of the right permits. The patient then places the bisection mark at the subjective midpoint of the segment between the right end of the line and the 'attentional horizon' reached on the left (Halligan & Marshall 1988; Ishiai *et al.* 1989). If the line is long enough, its left end remains beyond the attentional horizon and the bisection mark is placed rightward of true centre. If the line is shorter, the attentional horizon on the left extends beyond the end-point of the line and induces the confabulatory insertion of an incremental segment on the left. The subsequent bisection of the distance between the right end-point of the line and the left end-point of the confabulated segment leads the patient to place the midpoint leftward of true centre. Such confabulatory completion on the left has, in fact, been noted in the context of neglect dyslexia, especially for very short words (Chatterjee 1995). According to a less elaborate interpretation, bisection errors diminish with decreasing line length so that the inconsistent and small crossover effect for short lines could represent the resurfacing of the normal tendency for making bisection errors slightly leftward of centre (Mozer *et al.* 1997). Mathematical and computational models of line bisection have been described, some of which also account for the crossover effect elicited by short lines (Chatterjee 1995; Anderson 1996; Mozer *et al.* 1997; Monaghan & Shillcock 1998).

The rightward skewing of the spatial representation in left neglect was demonstrated directly when patients were asked to mentally retrieve prominent features along the Piazza del Duomo in Milan as they imagined themselves looking towards the cathedral. The patients were more accurate in listing details situated on the right side of the square as viewed from that vantage point. Upon being asked to imagine looking at the square while facing away from the cathedral, however, the same patients showed better recall of the items that had been omitted when assuming the former vantage point. Thus, the impaired evocation of left-sided details in the first part of the experiment was not due to an obliteration of the information but to an inability to activate the part of the representation which fell to the left of the imaginary perspective (Bisiach *et al.* 1981). In addition to this difficulty in activating the left side of existing representations, patients with left neglect also display a relative deficit in constructing a mental representation of the left side of sensory events, even when all the relevant sensory input is presented centrally (Bisiach *et al.* 1979). The

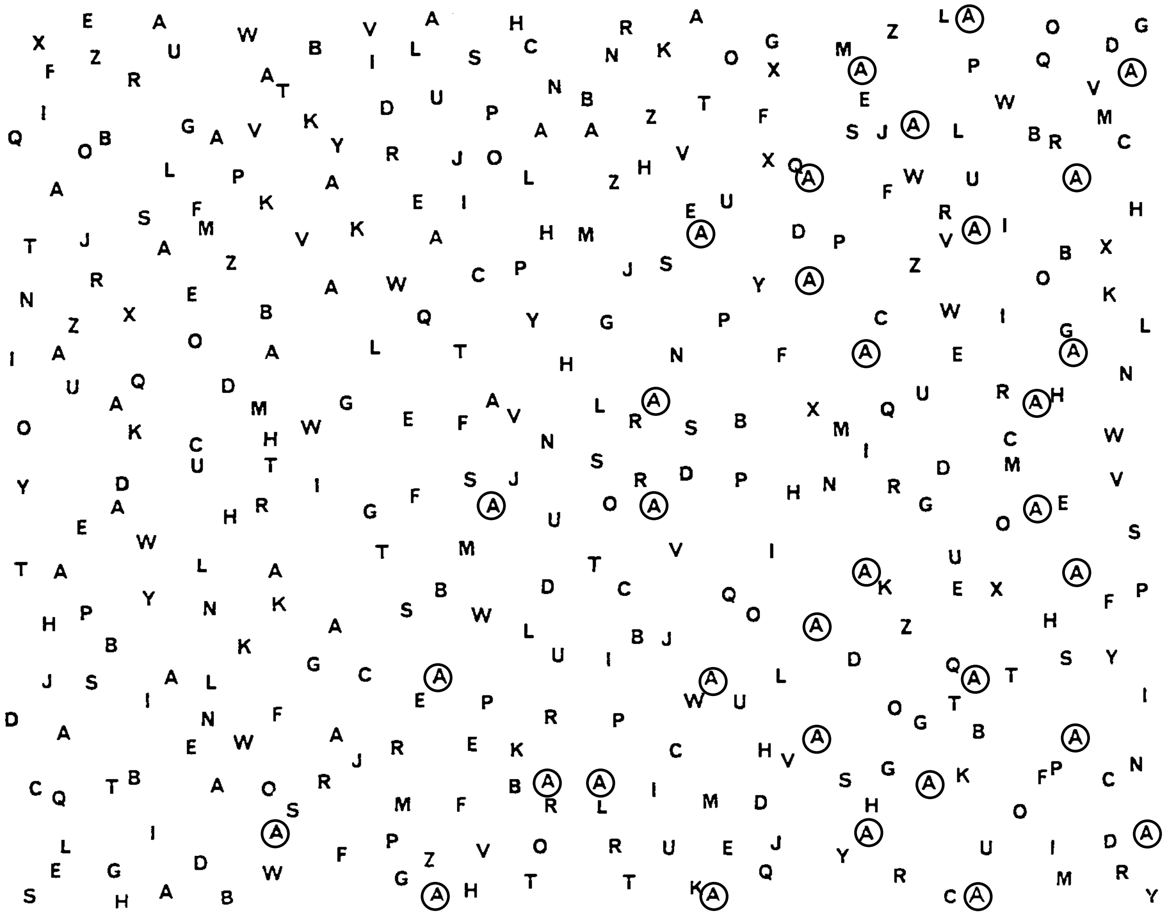

Figure 2. This figure shows the performance of a 70-year-old woman in a target cancellation task after a right hemisphere lesion. An 8 inch × 10 inch (approximately 20 cm × 25 cm) sheet of paper is placed directly in front of the patient, who is then asked to check or encircle all the 'As' without moving the sheet of paper. The patient had no visual field deficit. However, she has marked neglect for targets on the left.

resultant mental devaluation of the left side has many manifestations: when patients with hemineglect develop delirium, their hallucinations remain confined to the right side of space; when they dream, their rapid eye movements are directed to the right; and when they are exposed to a small stationary spot of light in the dark, the illusory movement they report is almost always directed to the right (Battersby *et al.* 1956; Mesulam 1981; Doricchi *et al.* 1991).

A task developed by Posner and colleagues has played a very influential role in this field of investigation (Posner 1980). No eye movements are allowed, central fixation is required at all times, and the attentional focus is shifted covertly within a mental representation of the ambient visual scene. These shifts are triggered exogenously through sensory priming or endogenously through foveally presented arrows which induce directional expectancy. Patients with left hemineglect show much longer reaction times when responding to targets in the left. They also display an excessive difficulty disengaging attention from a cue in the right hemispace when the task requires a subsequent leftward shift of covert orientation to targets on the left (Posner *et al.* 1984). This resistance to disengagement is partially analogous to the phenomenon of extinction.

(b) *Motor-exploratory aspects of unilateral neglect: visual and tactile search*

Patients with neglect display a reluctance to scan and explore the left hemispace even in the absence of obvious gaze or limb paresis. The impairment of search behaviour is readily elicited by tasks which require the patient to circle or check targets on a sheet of paper (Albert 1973; Weintraub & Mesulam 1988; Aglioti *et al.* 1997). Patients with left hemineglect omit many more targets on the left, need more time to find left-sided targets, use a disorganized scanning strategy, make fewer and lower-amplitude eye movements to the left and have longer visual fixation times on right-sided targets (Weintraub & Mesulam 1988; Behrmann *et al.* 1997). The use of a 90° mirror, which reverses the direction of a manual movement needed to reach a target from the direction of the shift in visual attention that leads to its detection, shows that target cancellation impairments reflect a failure to look left in some patients and a failure to reach to the left in others (Tegnér & Levander 1991). In some types of tasks, detection performance follows the power function [targets cancelled $= K(\text{targets presented})^{B}$] where the constant and exponent are derived empirically (Chatterjee *et al.* 1992). This relationship implies that the patient has some covert awareness of the total number of targets and that the neglect is a post-sensory phenomenon that occurs after an initial low-level encoding of the stimulus field.

The frequent observation that targets orientated randomly on the page are far less efficiently detected than targets organized into rows and columns, implies that an inability to endogenously impose an orderly scanning strategy contributes to the severity of the neglect. In some patients, neglect of left-sided targets is also more severe if the target identification requires 'attentive' serial search (as in the detection of an individual letter embedded among other letters) than if it can be based on 'pre-attentive' pop-out features (as in the detection of a slanted line embedded among straight lines), suggesting that global attention may be less impaired than focal search (Aglioti *et al.* 1997). If patients are given two versions of a cancellation task, one where they have to mark the detected targets and another where they have to erase them, performance is considerably better in the second version, probably because it gradually eliminates the hypersalience of the right-sided targets which are also the first to be detected and erased (Mark *et al.* 1988).

Patients with left unilateral neglect also display difficulties in manual exploration and tactile target detection. Blindfolded search for small objects by manual palpation is intact on the right side of the table not only with the right hand but also with the left hand (in non-hemiparetic patients) whereas it becomes ineffective on the left side of the table even when the intact right hand is being used (Weintraub & Mesulam 1987). These observations show that left neglect is associated with impaired tactile exploration within the left hemispace regardless of the limb that is being used. Thus motor programmes involved in exploration appear to be organized not according to the muscle groups that are being activated but according to the hemispace within which the movement is to be discharged (Wallace 1972; Anzola *et al.* 1977).

There may also be a reluctance to direct movements into the left side, whether or not such movements have any exploratory purpose. This has been designated hypokinesia and contributes to the emergence of intentional neglect (Heilman *et al.* 1985). In a group of patients with left neglect, for example, response times to left-sided visual targets improved considerably when the hand had to move rightward to reach the response button (Driver & Mattingley 1998). In another group of patients, however, where the stimulus sheet had to be moved by the subject under a fixed central slit (so that targets on the right were exposed under the slit by moving the sheet to the left), more targets were detected on the right side, indicating that hypokinesia towards the left was not an important factor in causing the manifestations of left neglect (Mijovic 1991). In the context of left neglect, 'hypokinesia' and 'intentional neglect' are used to designate general impairments of leftward movements whereas 'exploratory deficit' refers to more complex breakdowns of systematic search strategies within the extrapersonal space.

(c) *Motivational aspects of unilateral neglect*

A major role of any attentional system is to shift the attentional spotlight towards extrapersonal sites that harbour actual or expected events of emotional and motivational significance. While expecting a phone call or knock on the door, for example, the relevant segment of space becomes hypersalient so that otherwise insignificant stimuli in the vicinity of the phone or door assume an enhanced ability to attract attention. Patients with unilateral neglect devalue the left side of the world and behave not only as if nothing is actually happening in the left but also as if nothing of any importance could be expected to emanate from that side. The influence of this factor can be probed by varying motivational valence. For example, a patient showed marked improvement in detecting targets on the left when he was promised one penny for each accurate detection (Mesulam 1985). Although several alternative explanations may come to mind, one possibility is to attribute this improvement to a reward-induced motivational enhancement of targets on the left. Another patient with severe left hemineglect failed to reach for food on the left side of the tray and would bitterly complain that his tea had been left out. On a day when the nurse was instructed to withhold breakfast, the patient became unusually hungry by noontime but did not show any change in the severe neglect of left-sided targets in a letter cancellation task. When his lunch tray was brought, however, he had no reluctance to reach for his tea on the left side of the tray. These anecdotal observations suggest that a devaluation of sensory events on the left may contribute to the emergence of neglect and that the relationship between neglect and motivation may be material-specific so that hunger decreases the spatial distribution of neglect for edible items but not for letters on a test sheet.

(d) *The gating in neglect is central not peripheral*

Many aspects of neglect are based on top-down processes which impose a spatially determined bias upon a percept that is already encoded. In patients with extinction, for example, reaction times to unilateral right-sided stimuli are longer than those to bilateral stimuli, although both are reported as unilateral right-sided stimulation by the patient, indicating that the extinguished stimulus gains access to the central nervous system and exerts a covert influence on behaviour (Di Pellegrino & De Renzi 1995). In other patients, neglected sensory stimuli can even elicit cortical evoked potentials (Vallar *et al.* 1991). In one experiment, left-sided objects which were easily identified when presented alone, became ignored through the process of extinction when paired with meaningless patterns on the right. Nonetheless, the patients were much faster in detecting centrally presented words which were semantically related to the extinguished object, showing that the stimulus had been able to trigger covert semantic priming (McGlinchey-Berroth *et al.* 1993). Furthermore, a patient with left hemineglect who was shown line-drawings of two houses, one of which had flames coming out of the left side, judged the two drawings to be visually identical but chose the one without flames when asked to select the house she would prefer to live in (Marshall & Halligan 1988). Another patient who was shown two banknotes, one of which was torn on the left, could not tell that the two were different but preferred the intact one without being able to explain the reasons for the choice (Cantagallo & Della Sala 1998).

3. DETERMINANTS OF NEGLECT: THE COST OF BEING ON THE LEFT

In the preceding account, the word 'left' has deliberately been used without further qualification, as if it constituted a fixed attribute such as colour or texture. This is clearly not the case since there is no left or right without a specific frame of reference. At least four frames of reference can define the leftness of an extrapersonal event: *egocentric* (defined with respect to the observer), *allocentric* (defined with respect to another extrapersonal event), *world-centred* (defined with respect to a fixed landmark in the environment), and *object-centred* (defined with respect to a principal axis in the canonical representation on an object). Since the eyes, head and trunk can rotate and tilt with respect to each other, the egocentric frame of reference contains *retinocentric*, *cephalocentric*, *somatocentric* and *gravitational* coordinates so that an event which is in the left according to one egocentric coordinate could be on the right according to another. Furthermore, perceptual and conceptual factors influence the segmentation of the stimulus field into individual clusters with their own left and right sides. In general it can be said that a location in one of the egocentric lefts, in the environmental left, in the canonical or object-centred left, in the allocentric left, and in the segmentational left blunt perceptual salience and weaken the probability of influencing action. A location on the right side of any of these frames of reference has the opposite effect of promoting salience and access to action.

(a) *Egocentric coordinates*

Since the retina is the obligatory entry zone for all visual information, almost all visual neglect displays some retinotopic mapping which then interacts with other egocentric frames of reference. Turning the eyes to the right, for example, brings more of the right hemispace into the left visual field and can depress the detection of targets within the right somatocentric hemispace. Conversely, turning the head and eyes into the left or vestibular and proprioceptive stimulation that promote such rotations can reduce the number of target detection failures on the left side of a test sheet placed in front of the patient (Rubens 1985; Karnath 1997). These effects are also seen in accessing mental representations. Thus, one patient displayed a dramatic improvement in naming cities on the western coast of an imagined map of France upon left vestibular stimulation with cold water, a procedure that would induce leftward deviations of the head and eyes (Perenin 1997).

The somatocentric and cephalocentric frames of reference also influence the distribution of neglect. Thus, detection of stimuli presented to the left visual field improves when the subject looks 30° to the right so that the stimuli (still directed to the same part of the retina) become located in the right side of the somatocentric coordinates (Kooistra & Heilman 1989). Errors in line bisection and tactile exploration improve when the line or tactile maze is placed on the right side of the body, and saccadic reaction times to targets in the left visual field improve if the trunk is rotated to the left so that all visual stimuli (even those directed to the left visual field) fall on the right of the body midline (Heilman & Valenstein 1979; Karnath *et al.* 1991; Beschin *et al.* 1997*b*). The rightward line bisection error indicative of left neglect is less prominent when the patients are tested in the supine position (Pizzamiglio *et al.* 1997), suggesting that the boundaries between left and right may be sharper in the erect posture and thus illustrate the influence of the gravitational frame of reference in determining the extent of neglect.

(b) *Allocentric factors and relative leftness*

In experiments where double simultaneous stimulation is confined to a single visual hemifield, the leftmost of two stimuli presented in either the left or right field becomes extinguished in patients with left neglect (Gazzaniga & Ladavas 1987; Di Pellegrino & De Renzi 1995). Furthermore, tactile information emanating from the same spot of skin, located on the right arm, becomes heeded or ignored depending on whether it is located on the left or right of another simultaneously administered stimulus (Moscovitch & Behrmann 1994). It appears, therefore, that being on the left of another event increases the probability of neglect, even when both events are in the right hemispace or hemifield.

Target detection also displays allocentric effects as shown in an experiment where patients with left extinction were asked to attend to horizontally aligned peripheral target sites with different eccentricities. All target sites were visible throughout the experiment but only one contained the stimulus that needed to be detected in any given trial and all trials were initiated during central fixation. In contrast to normals who are slower in detecting eccentric targets, patients with left extinction displayed faster reaction times to the right-sided targets with the greater eccentricity, presumably because they were located in the allocentric right of the other targets (Làdavas 1990). The influence of relative leftness explains why the left side of words and chimeric faces become neglected even when the experimental paradigm is designed to ensure that the entire stimulus falls within the right visual field (Behrmann *et al.* 1990; Young *et al.* 1992).

Allocentric coordinates also influence the effectiveness of motor responses. In one experiment, subjects saw a '1' or a '2' in the centre of the visual field and had to press a key with the right index finger for one of the numbers and the right middle finger for the other. In the conventional position of the hand, the index finger was on the left of the middle finger. In a second condition, the keyboard was rotated by 180° so that the relative position of the two fingers with respect to each other was reversed. In each condition, responses were slower with the finger on the relative left position. Thus, the effectiveness of performance was based on the relative leftness of the responding digit rather than on a change in the location of the sensory input (Làdavas *et al.* 1994). It should be noted, however, that none of these experiments has totally dissociated allocentric from egocentric factors since events located to the left of other events in these tasks were also located further to the left within egocentric coordinates.

(c) *Effect of eye movements: the global and focal work-spaces*

In testing patients with neglect, the eyes are usually allowed to move, creating complex interactions between retinotopic and other egocentric coordinates. A test sheet placed in front of the patient defines the global work-space. As the eyes move, the point of regard defines a focal work-space with its own allocentric left and right. Depending on the task, the focal work-space may include each face, word or other target placed within the global work-space. Left neglect operates within both the global and focal work-spaces. Thus, as the patient looks at a face or word on the right side of the test sheet, the face or word constitutes the focal work-space and its left side becomes vulnerable to neglect.

In drawing and copying tasks, the point of the drawing implement defines the centre of the focal work-space. Thus, the patient tends to omit detail on the left of each item even when all the activity is confined to the right side of the test sheet and even when the right side of items further to the left are drawn quite accurately. One patient with left neglect who was asked to draw a map of the British Isles from memory, for example, omitted the west coast of England and Scotland while including Ireland in his map (Halligan & Marshall 1992).

(d) *World- and object-based coordinates*

In a target detection experiment done in patients with left neglect, the position of the targets remained the same but the subjects were asked to do the task when sitting and when reclining to the left. As expected, target detection in the sitting position was least effective in the two quadrants located in the somatocentric left. While reclining, however, subjects continued to neglect targets in the same two quadrants although one of these (the former upper left quadrant) was now in the right visual field and within the right somatocentric hemispace of the subjects (Calvanio *et al.* 1987). These results may reflect the tendency to represent the work-space with respect to the canonical gravitational vantage point of the erect posture. Alternatively, the work-space may be mapped with respect to a fixed environmental landmark so that stimuli on the left side of this representation are neglected even when they are no longer on the left side with respect to egocentric coordinates.

An analogous phenomenon can be seen at the level of individual objects. Thus a patient failed to draw the detail on the left side of the canonical vertical axis of a tower, even when the model was inclined 45° to the right so that part of the detail on the left of the canonical axis fell on the right side of the patient (Halligan & Marshall 1994). In another experiment, the ability to determine if two irregular tower-like shapes were identical or different deteriorated when the critical detail was on the left side of the canonical axis even when the object was inclined to the right and the canonical left entered the egocentric right (Driver & Halligan 1991). These observations indicate that the definition of left and right in the neglect syndrome is also influenced by the subjective representations of the environment and of the objects within it.

(e) *Segmentation and conceptualization effects*

The distribution of neglect is also influenced by the perceptual (gestalt) and conceptual (top-down) segmentations of the stimulus field. Thus, four black circles with a missing quadrant resisted extinction when they collectively formed an illusory Kanizsa rectangle and were presumably processed as a single entity rather than as four distinct stimuli (Mattingley *et al.* 1997). Furthermore, asking a patient to copy a pot containing two daisies joined by a common stem led to the omission of the entire left flower whereas erasing the convergence into a common stem and the pot below it (so that the patient saw two separate unattached daisies) led to a drawing where both daisies were copied but each with details missing on its left half (Halligan & Marshall 1993). In another setting, when a target cancellation task was administered in conventional form and also after erasing the central targets so as to give the impression of two distinct clusters of targets, the patient omitted targets on the left of the right-sided cluster although the same targets were detected when they were part of a single array (Driver & Halligan 1991). This experiment further emphasizes the influence of the focal work-space in determining the distribution of neglect within the larger global work-space.

Top-down conceptual processing of the sensory input also influences the distribution of neglect. Thus, neglect of the left side of a letterstring is less likely if the letters form a word than a non-word (Sieroff *et al.* 1988), and the ability to use information from the left side of a chimeric face increases if the information on the right side is degraded (Young *et al.* 1992). In these cases, the knowledge that the stimuli are words and faces, and that their identity cannot be resolved without access to further left-sided information is likely to have triggered a top-down pressure to push the attentional horizon further to the left. This is consistent with the notion that neglect represents an impairment in the 'automatic' allocation of attention to the left but that this bias can be overcome, at least partially and transiently, under specific 'cognitive' conditions.

(f) *Far-space versus near-space*

Unilateral neglect represents a distortion in the lateral distribution of attention along the x-axis. Some component of vertical neglect along the y-axis can also be identified, suggesting that patients with neglect have greater difficulty with the detection of targets in the lower quadrants (Pitzalis *et al.* 1997). However, vertical neglect is much less pronounced than lateral neglect and its clinical and anatomical determinants remain to be clarified. Several observations indicate that the distribution of neglect may also show variations along the z-axis and that there may be dissociable states of neglect for peripersonal, near- and far-spaces. Thus some patients have left neglect only for the near-space within an arm's reach, whereas others neglect only left-sided events in far-space, beyond an arm's reach (Halligan & Marshall 1991; Vuilleumier *et al.* 1998).

4. RIGHT HEMISPHERE DOMINANCE FOR SPATIAL ATTENTION

Clinical evidence based on thousands of patients shows that right hemisphere lesions elicit more frequent, severe and lasting contralesional neglect than equivalent lesions in the left hemisphere (De Renzi *et al.* 1970; Gainotti *et al.* 1972; Oxbury *et al.* 1974; Chain *et al.* 1979; Denes *et al.* 1982; Weintraub & Mesulam 1987). Furthermore, when the same set of subjects underwent a reversible inactivation of

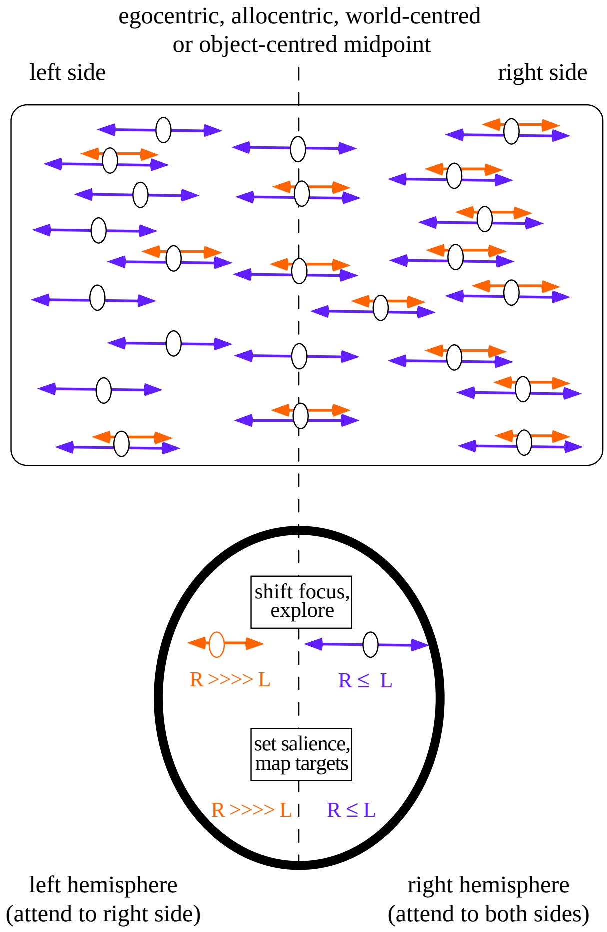

Figure 3. A right hemisphere specialization model for shifting spatial attention and representing salience. The large rectangle corresponds to the global work-space and the small ovals represent multiple focal work-spaces (such as individual faces, words or stimulus clusters) distributed within the global work-space. The arrows depict the directional probability of attentional shifts and representational salience, orange for the left hemisphere, purple for the right hemisphere. Within a given work-space, global or focal, the left hemisphere attentional mechanisms are more likely to endow the right side of events with salience, and tend to coordinate the distribution of attention almost exclusively within the right hemispace, especially in a contraversive direction. In contrast, right hemisphere attentional mechanisms are more likely to distribute salience and attentional shifts more equally within both hemispaces and in both directions, although there is a slight leftward predominance. In the normal brain all points in the extrapersonal space have an equal probability of claiming salience and attentional shifts although there may be a slight leftward bias because of the greater right hemisphere involvement in attentional tasks. When the left hemisphere is damaged, a mild leftward bias emerges but does not cause neglect because attention and salience can still be distributed in all directions. When the right hemisphere is damaged, a strong rightward bias emerges and keeps pushing the attentional focus rightward. The setting of salience and the mapping of extrapersonal targets for intended foveation, attentional grasp and exploration are more closely allied with the function of neurons in posterior parietal cortex, whereas the selection, sequencing and execution of attentional shifts and exploratory behaviours are more closely allied with the functions of neurons in the frontal lobe.

each hemisphere through sodium amytal injections, visual neglect and tactile extinction occurred only after the inhibition of the right hemisphere (Meador *et al.* 1988; Spiers *et al.* 1990). Several explanations have been proposed to account for this asymmetry (Heilman & Van den Abell 1980; Mesulam 1981; Kinsbourne 1987). The neural model shown in figure 3 incorporates some of these explanations and introduces additional characteristics. This model postulates that (i) the left hemisphere attributes salience predominantly to the right side of events, coordinates the distribution of attention mainly within the right hemispace, and shifts attention mostly in a contraversive rightward direction; (ii) the right hemisphere attributes salience to both sides of events, coordinates the distribution of attention within both hemispaces, and shifts attention in both the contraversive and ipsiversive directions, with only a slight contraversive bias; and (iii) the right hemisphere devotes more neuronal resources to spatial attention so that attentional tasks are more likely to engage right hemisphere mechanisms.

According to this model, each hemisphere has a greater tendency to shift attention in a contraversive direction and within the contralateral hemispace but the asymmetry is more pronounced in the left hemisphere. In the intact state, the attentional spotlight can be shifted to any motivationally relevant location but there may also be a slight bias favouring the left because the right hemisphere is more likely to be engaged by attentional tasks. Left hemisphere lesions are not expected to give rise to much contralesional neglect since the ipsiversive attentional shifting ability of the right hemisphere and its capacity to coordinate the distribution of attention within both hemispaces are likely to compensate for the loss. On the other hand, right hemisphere lesions are likely to yield severe contralesional neglect because the left hemisphere has relatively little capacity for endowing left-sided events with salience, triggering leftward attentional shifts, or coordinating the distribution of spatial attention within the left side. Following right hemisphere lesions, left-sided events would thus lose representational salience and the focus of attention would keep being pushed rightward, towards the rightmost boundary of the global work-space, under the unopposed influence of the left hemisphere. The constitutive role of the right hemisphere in the ipsilateral distribution of attention and the paucity of left hemisphere mechanisms for shifting attention ipsiversively, even within the right hemispace, raises the expectation that right hemisphere damage should also give rise to mild but detectable attentional impairments within the ipsilesional right hemispace.

One prediction of this model is that the right hemisphere should participate in encoding the representational salience of sensory events throughout the extrapersonal space whereas the left hemisphere should show a more limited response confined to contralateral right-sided events. In fact, the left hemisphere displays event-related potentials, electroencephalogram desynchronizations and metabolic activation only after right-sided sensory stimulation, whereas the right hemisphere shows these changes after stimulation from either side (Desmedt 1977; Heilman & Van den Abell 1979; Reivich *et al.* 1983; Pardo *et al.* 1991). Retrieval of spatial information also leads to greater right hemisphere activation, regardless of the location of the information that is being retrieved, suggesting that the right hemisphere plays a more prominent role in activating the mental representation of both sides of space (Moscovitch *et al.* 1995; Maguire *et al.* 1998). This organization is consistent with a proposed dichotomy according to which the field of view and perceptual style of the right hemisphere is 'global', whereas that of the left hemisphere is more 'focal' (Robertson *et al.* 1988). Furthermore, the line bisection errors in patients with left hemineglect can be described by a mathematical model where the right hemisphere encodes salience in both hemispaces whereas the left hemispace encodes salience in only the contralateral left hemsipace (Anderson 1996).

The model summarized in figure 3 leads to two predictions concerning cerebral activation in tasks that involve attentional shifts: (i) the right hemisphere should show relatively greater activation when attention is equally shifted to the right and to the left, and (ii) the left hemisphere should be activated mostly when attention shifts within the contralateral right side, especially in a contraversive direction, whereas the right hemisphere should be activated when attention shifts within either hemispace and in either direction. Both predictions are supported by the available evidence: functional imaging experiments where neurologically intact subjects were asked to shift attention equally to the left and to the right showed greater activation in the right hemisphere (Nobre *et al.* 1997*a*; Gitelman *et al.* 1999), increased cortical activation in the left hemisphere was noted only after covert attentional shifts within the contralateral right side whereas activations in the right hemisphere were seen after shifts within either hemispace (Corbetta *et al.* 1993), and a blindfolded manual exploration task showed right hemisphere activation even when the exploration occurred on the ipsilateral right side (Gitelman *et al.* 1996*a*). Furthermore, damage or transcranial magnetic stimulation of the right hemisphere diminished the speed and accuracy of saccades to actual and remembered targets in both directions whereas left hemisphere damage had a much more modest effect, confined to saccades made in the contralesional direction (Pierrot-Deseilligny *et al.* 1991; Oyachi & Ohtsuka 1995). In keeping with these observations, left hemisphere dysfunction did not impair target detection even in the right hemispace, whereas right hemisphere dysfunction caused severe target detection failures in the left hemispace and lesser but statistically significant target detection failures in the right hemispace (Weintraub & Mesulam 1987; Spiers *et al.* 1990).

The model depicted in figure 3 suggests that the attentional functions of the two hemispheres can be classified not only on the basis of a 'place code' which signals the location of the attentional focus but also on the basis of a 'vector code' which signals the direction of attentional shifts from any point of origin. Experimental support for this vectorial organization is somewhat mixed. A functional imaging study found that the laterality of cerebral activation depended on the hemispace within which attention was being shifted rather than on the direction of the shifts within the hemispace (Corbetta *et al.* 1993). However, other experiments showed that unilateral brain damage interferes with contraversive shifts of covert attention irrespective of the hemispace or field within which the shift occurred, although the effect is more pronounced in the contralesional field (Posner *et al.* 1987; Arguin & Bub 1993).

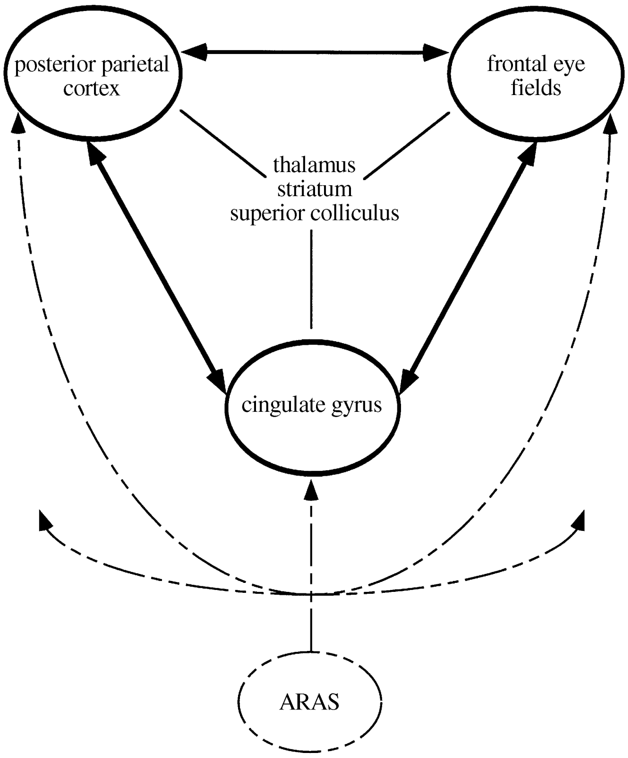

Figure 4. A large-scale distributed network for spatial attention.

5. FUNCTIONAL ANATOMY OF UNILATERAL NEGLECT

The most common lesion site associated with neglect is located in posterior parietal cortex. In view of this relationship, textbooks of neurology have tended to encourage the diagnosis of parietal lobe pathology in all patients with this syndrome. However, left neglect has also been described in patients with lesions in the frontal lobes, cingulate gyrus, striatum and thalamus. The availability of rhesus monkey models for behaviours related to neglect helped to show that each one of these areas made a specific contribution to the neural organization of spatial attention, and that they collectively formed an interconnected network organized according to the principles of selectively distributed processing (Mesulam 1981). It is therefore no longer accurate to designate left neglect as a 'parietal syndrome'. The more accurate designation would be to characterize it as an 'attentional network syndrome', realizing that the responsible lesion can be anywhere within this network (figure 4).

(a) *The parietal component of the attentional network*

The human posterior parietal lobe has four major components: the superior and inferior parietal lobules, the intraparietal sulcus and the medial parietal cortex. It is situated at the confluence of visual, auditory, somatosensory and vestibular unimodal areas and contains an extensive heteromodal sector which supports multimodal integration. In addition to these rich sensory associations,

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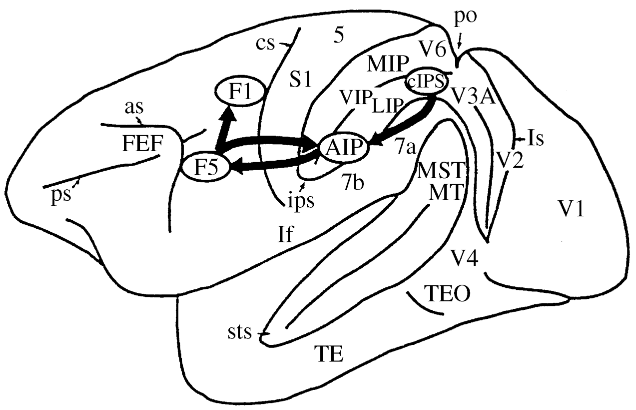

Figure 5. The location of cortical areas related to spatial attention in the macaque brain. Modified from Sakata *et al.* (1997). Abbreviations: as, arcuate sulcus; cIPS, caudal intraparietal sulcus; cs, central sulcus; FEF, frontal eye field; F1, primary motor area; F5, hand region of ventral premotor cortex; ips, intraparietal sulcus; lf, lateral (Sylvian) fissure; LIP, lateral intraparietal area; ls, lunate sulcus; MIP, medial intraparietal area; po, parieto-occipital sulcus; MT (V5), MST, motion-sensitive visual areas of the superior temporal sulcus; ps, principal sulcus; sts, superior temporal sulcus; S1, primary somatosensory area; TE and TEO, infero-temporal visual association areas; VIP, ventral intraparietal area; V1–4, V6, the primary, secondary, third, fourth, and sixth visual areas; 5, 7a, 7b, Brodmann areas.

experiments in monkeys lead to the inference that the posterior parietal cortex is also interconnected with premotor cortex, the frontal eye fields (FEF), the superior colliculus, and several paralimbic areas including the cingulate gyrus, insula, orbitofrontal cortex and perhaps the parahippocampal region (Mesulam *et al.* 1977; Mesulam & Mufson 1985; Pandya & Yeterian 1985; Morecraft *et al.* 1992). The cingulate gyrus provides the strongest of these paralimbic connections.

Persistent and severe neglect in the context of parietal lobe damage almost always indicates a large lesion with considerable subcortical extension. Neurologically intact subjects engaged in tasks of covert visuospatial attention (Corbetta *et al.* 1993; Nobre *et al.* 1997*b*), tactile exploration (Gitelman *et al.* 1996*a*), oculomotor search (Gitelman *et al.* 1997) and auditory target detection (Medvedev *et al.* 1997) displayed cortical activation in the superior and inferior parietal lobules, the banks of the intraparietal sulcus and, less frequently, medial parietal cortex. The one component of the posterior parietal cortex that is most consistently activated in all of these tasks lies within the banks of the intraparietal sulcus and in its immediate vicinity (Nobre *et al.* 1997*b*; Gitelman *et al.* 1999). The banks of the intraparietal sulcus may thus constitute the parietal core of the attentional network in the human brain although the adjacent parts of the inferior, superior and medial parietal lobules are also likely to participate in the integration of related neural activities.

As in the human brain, the posterior parietal cortex of the macaque includes the superior parietal lobule, the inferior parietal lobule, the intraparietal sulcus, and medial parietal cortex (figure 5). The cortex along the intraparietal sulcus of the macaque brain has been subdivided into a mosaic of functionally distinct regions known as LIP, MIP, VIP, AIP and PIP (for definition of abbreviations, see caption to figure 5) (Sakata *et al.* 1997). Among these areas, the posterior part of the inferior parietal lobule (BA 7a in the monkey) and area LIP show the closest relationship to visuospatial attention whereas the superior parietal lobule (BA 5), the anterior part of the inferior parietal lobule (BA 7b), MIP, VIP and AIP are more closely related to manual reaching and grasping. In the monkey, damage to the inferior parietal lobule causes contralesional extinction and reaching deficits whereas damage to the banks of the immediately adjacent superior temporal sulcus causes neglect of contralesional stimuli (Lynch & McLaren 1989; Watson *et al.* 1994). Lesions involving the inferior parietal lobule also impair the ability to solve tactile visuomotor mazes and to determine allocentric spatial relations among objects (Ungerleider & Brody 1977; Petrides & Iversen 1979). These observations indicate that the posterior parietal cortex in the monkey and in the human display considerable similarities of behavioural affiliation.

Recording of neural activity in awake and behaving monkeys shows that posterior parietal areas display two properties relevant to spatial attention: (i) they form representations of the external space based on motivational salience rather than shape, colour or object identity, and (ii) they enable the mapping not of absolute spatial position but of 'kinetic plans' for exploring, grasping and foveating salient events, either covertly or overtly. Neurons in the posterior inferior parietal lobule and adjacent intraparietal sulcus, for example, increase their firing rates when the animal detects, looks at, or reaches towards a motivationally relevant object such as food when hungry or liquid when thirsty (Hyvärinen & Poranen 1974; Mountcastle *et al.* 1975; Robinson *et al.* 1978; Lynch 1980; Bushnell *et al.* 1981). These neurons are not as responsive if the visual event has no motivational significance or if equivalent eye and limb movements are performed passively or spontaneously rather than being directed towards the stimulus (Lynch 1980; Gottlieb *et al.* 1998). Furthermore, some neurons are more active before a targeted saccadic eye movement whereas others are more active before a reaching movement towards the same stimulus, indicating that the encoding is contingent on the nature of the intended action rather than on spatial position alone (Snyder *et al.* 1998*a*).

Area LIP, located in the lateral bank of the intraparietal sulcus, is known as the 'posterior eye field' because of its critical role in coordinating eye movements. It is closely interconnected with the FEF and the superior colliculus, triggers saccadic eye movements in response to microstimulation, and gives directionally tuned responses prior to saccadic eye movements directed to visual targets or their remembered sites (Andersen 1995). Neurons in LIP have sensory, motor and memory fields. They respond when the monkey intends to make a saccade that will bring a behaviourally relevant stimulus (or its remembered site) into their receptive fields (Duhamel *et al.* 1992). Area 7a of posterior parietal cortex is monosynaptically interconnected with LIP. The 7a neurons have fewer connections with FEF, give fewer presaccadic responses and tend not to trigger saccadic eye movements upon stimulation (Snyder *et al.* 1998*b*). They have large receptive fields, relatively little sensitivity for colour, shape, orientation or object identity and respond to behaviourally relevant events whether or not such events become targeted for reaching or foveation (Bushnell *et al.* 1981). These neurons may therefore play a major role in encoding a representational map of salience which can be used by LIP to generate motor plans.

Eye movements induce constant shifts in the correspondence between the retinal projection of visual targets and their actual spatial locations. These shifts need to be integrated into the neural computations related to attention because visual input enters the brain in retinocentric coordinates but action has to be targeted in egocentric and spatial coordinates. Translations from one frame of reference to another occur at various sites within posterior parietal cortex, especially in areas 7a and LIP. Neurons in these two regions have visual receptive fields with strong gradients of excitability distributed according to foveal eccentricity. The gradient is retinotopic but the base level of excitability is gaze-dependent. Groups of these neurons can thus encode spatial position in a head-centred frame of reference by combining retinotopic information with information about eye position (Andersen *et al.* 1985). Some of these neurons can also use proprioceptive information related to head position to create a body-centred representation, and vestibular information to create a world-centred representation of visual events (Andersen 1995). There are even some neurons which encode events in environment-centred coordinates based on external landmarks rather than proprioceptive or vestibular inputs (Andersen *et al.* 1997).

Many LIP neurons with presaccadic activity for movements towards sources of sound display directional preferences that move with the eyes, indicating that they can bring auditory and visual spatial perception into a common frame of reference in a way that may promote the holistic sense of a single spatial dimension (Andersen *et al.* 1997). There may also be a segregation of neurons sensitive to different frames of reference. For example, LIP is more closely involved in constructing a body-centred representation based on proprioceptive input whereas area 7a is more closely involved in constructing a world-referenced representation based on vestibular input and environmental landmarks (Snyder *et al.* 1998*b*). Posterior parietal cortex thus has the computational capacity for the multimodal mapping of salient events in multiple frames of reference. Damage to these neurons may account for the multimodal aspects of neglect and their manifestations according to multiple coordinate frames.

Neurons in 7a and LIP also support covert shifts of attention. Many neurons in these regions are excited by the appearance of the cue which initiates the initial shift of covert attention. The subsequent appearance of the target excites area 7a neurons only if it is at a location different from that of the cue (Robinson *et al.* 1995; Steinmetz 1998). Thus neurons of area 7a and adjacent intraparietal sulcus provide signals for redirecting the attentional focus even when the shift is covert, without head or eye movements. The lack of response to targets located at the site of the preceding cue indicates that these neurons may be more involved in shifting the attentional focus (overtly or covertly) than just registering the presence of a significant event.

Neurons in posterior and medial parietal cortex play an important role in additional aspects of spatial attention such as reaching, grasping, tactile search and manual exploration. For example, neurons in BA 5 give responses that are more closely related to the significance of the stimulus and the motor planning that it elicits than the actual execution of the movement (Kalaska & Crammond 1995; Caminiti *et al.* 1996). Neurons in area MIP, located in the posterior portion of the medial bank of the intraparietal sulcus, project to premotor areas which encode motor programmes in arm-centred coordinates and fire optimally when the animal reaches towards a visual target (Colby & Duhamel 1996). Area AIP, located in the anterior part of the lateral bank of the intraparietal sulcus, is interconnected with premotor area F5 and coordinates the manual grasping of complex visual objects. Area 7b also contains neurons with corresponding tactile and visual receptive fields. For example, if the tactile field is on the hand the visual field is also near the hand, even when the hand moves but the eyes do not (Graziano & Gross 1998). Such neurons would be expected to play an important role in behaviours where tactile search is conducted under visual guidance. Neurons medial and posterior to LIP, in a sector known as the parietal reach region, fire during visually guided arm movements and may play a role for manual grasping and tactile exploration in a manner that is analogous to the role of LIP in visual search and gaze (Snyder *et al.* 1998*a*). Posterior parietal cortex thus contains many areas which coordinate manual reaching and potentially also tactile exploration. Damage to these areas may be responsible for hypokinesia, intentional neglect and tactile exploration deficits.

These observations suggest that the brain does not have a unitary ‘spatial map’. Instead, posterior parietal cortex contains several parallel mappings of behaviourally relevant targets in terms of the motor strategies that would be needed to reach or foveate them. Posterior parietal cortex plays a relatively minor role in identifying the perceptual or semantic nature of the stimulus that has been chosen as the target of attentional focusing. This function is carried out by cortical areas along the ventral streams of sensory processing. The two streams of processing become integrated through multiple interconnections, including those that have been described between infero-temporal cortex and area 7a (Mesulam *et al.* 1977).

(b) *The temporo-occipito-parietal area, the superior temporal sulcus and the encoding of visual motion*

In a world where sensory stimuli and the observer can move with respect to each other, the neural mechanisms that direct attention to extrapersonal targets must be sensitive to self- and target-motion. In the macaque, motion-sensitive neurons are located in the banks of the superior temporal sulcus, in areas known as MT (V5), MST and FST. On topographical grounds, these areas, especially MST and FST can be considered as part of the inferior parietal lobule. Neurons in MST and FST have larger receptive fields than those in MT and have response properties which suggest they use information about real or inferred motion to generate signals for smooth pursuit eye movements (Dürsteler & Wurtz 1988; Ilg & Thier 1997). The neurons of MST have preferred movement directions, encode complex motion patterns, enhance their responses to behaviourally relevant stimuli, and show a reduction of directional selectivity if attention is attracted to a point outside their receptive fields (Treue & Maunsell 1997). Neurons in MST are also responsive to optic flow so that they can encode self-motion and the direction of heading (Lappe 1997). These neurons may help to direct attention towards targets that are in motion, select a heading for approaching targets, and navigate the body among solid objects in the environment.

Some of these motion-sensitive areas may have been damaged as part of the superior temporal sulcus ablations that cause contralesional neglect in the macaque (Watson *et al.* 1994). In the cat, the reversible inactivation of an area equivalent to MT (V5) causes severe contralesional visual neglect (Payne *et al.* 1996). Tasks of covert attentional shifts have led to activations at the confluence of the temporal, parietal and occipital lobes, in the most posterior aspects of the middle temporal gyrus (Gitelman 1999; Kim 1999). This activation falls within a region designated as MT+, which probably includes the human homologues of MT (V5), MST and FST (DeYoe *et al.* 1996). Clinical cases with lesions limited to this region are rare. However, in one patient, damage confined to this region led to left-sided target cancellation deficits even four years after the cerebrovascular accident and even in the absence of any visual field cut (Hasselbach & Butter 1997). It appears, therefore, that this temporo-occipito-parietal motion-sensitive area may play an important role in the attentional network, at least for certain types of spatial attention.

(c) *The frontal connection in neglect*

Lesions confined to the right frontal lobe can cause states of contralesional neglect which are just as severe as those caused by parietal lesions (Silberpfenning 1941; Heilman & Valenstein 1972; Daffner *et al.* 1990; Husain & Kennard 1996). Many functional imaging experiments based on tasks of either overt of covert shifts of directed attention report activation in the region of FEF, usually extending into adjacent premotor and prefrontal cortex (Corbetta *et al.* 1993; Gitelman *et al.* 1996*a*; Nobre *et al.* 1997*b*; Kim 1999). As opposed to the FEF of the monkey, which is located in the posterior part of BA 8, the human FEF corresponds to BA 6 and is located at the junction of the precentral and superior frontal sulci (Barbas & Mesulam 1981; Darby *et al.* 1996; Paus 1996).

Activation in the FEF has been seen during covert attention shifts even when potentially confounding factors such as working memory, intense foveal fixation, inhibition of eye movements and the conditional go–no-go aspects of the task have been controlled (Gitelman 1999). A definitive demonstration of attention-related FEF activation in the total absence of eye movements has been hampered by the inability to monitor oculomotor activity during the imaging. This has posed a potential dilemma since occasional eye movements, either reflexive or blink-induced, do occur even when the subject is instructed to keep the eyes still and could conceivably account for the observed FEF activation. As an indirect test of this hypothesis, we compared a covert attentional task with a task where the subjects were instructed to make saccadic eye movements to the left and right. When the activation in the saccade task was subtracted from the activation in the covert attentional shifting task, residual FEF activation was still seen (Nobre *et al.* 1998). Since the surreptitious and rare saccades in the covert task could not have involved more eye movements than the deliberate saccades, the residual activity in this experiment suggested that at least some of the FEF activation must have been related to the attentional shifts rather than the eye movements. These sorts of considerations have supported the conclusion that the FEF is likely to constitute the frontal core of the attentional network. In addition to FEF, the frontal component of the attentional network may also include adjacent parts of premotor and perhaps prefrontal cortex.

The FEF of the monkey is interconnected with posterior parietal cortex, peristriate and infero-temporal cortex, the cingulate gyrus, other premotor and prefrontal areas, the dorsomedial and medial pulvinar nuclei of the thalamus, the subthalamic nucleus, and the superior colliculus (Arikuni *et al.* 1980; Barbas & Mesulam 1981). These projections provide direct access to pathways that control head, eye, and limb movements necessary for scanning and exploratory activities. Up to 51% of all the afferent cortical input into the caudal portion of the FEF originates in unimodal visual association areas in the peristriate and infero-temporal regions (Barbas & Mesulam 1981). This pattern suggests that the FEF may be profoundly influenced by (and probably also profoundly influences) visual information at a relatively early stage of analysis. Parts of the FEF also receive auditory input, and this connection may mediate orientation to auditory stimuli (Barbas & Mesulam 1981). Posterior parietal cortex and the FEF receive inputs from overlapping groups of cingulate neurons (Morecraft *et al.* 1993). This arrangement would ensure that the frontal and parietal components of the attentional network receive similar information about the distribution of motivational relevance.

In the macaque monkey, lesions in the area of the FEF have been known to result in marked contralateral neglect (Bianchi 1895; Kennard 1939; Welch & Stuteville 1958; Watson *et al.* 1978). Animals with such lesions do not orientate towards the contralateral hemispace, fail to retrieve motivationally relevant objects from the contralesional side even with the intact arm, and show poor orientation and exploration within the contralesional hemispace even in the absence of competing stimuli from the intact side. As in humans, the lack of response to events in the neglected hemispace may be so profound that it may be difficult to distinguish hemianopia from neglect (Kennard 1939).

In the monkey, many FEF neurons give a burst of activity just before a saccade to a behaviourally relevant target or to its remembered site. Spontaneous saccades not directed towards a relevant object do not elicit such bursts. These neurons have relatively large and mostly contralateral visual fields. The direction of a saccade that will occur upon microstimulation of a particular neuron is independent of orbital eye position and can be predicted by mapping its visual field (Goldberg & Bushnell 1981). As in the case of LIP with which it is tightly interconnected, the FEF can thus play a crucial role in foveating and exploring behaviourally relevant visual targets. Neurons in the FEF also participate in the on-line retention of spatial information in tasks that require saccadic eye movements towards the remembered location of events that had occurred in the immediate past. These neurons may thus support the type of sensorimotor working memory which is essential for the systematic exploration of a visual scene.

Unilateral inactivation of the FEF leads to a selective impairment of contraversive saccades. After such inactivation, the same spot in head-centred contralateral space is more successfully targeted by ipsiversive saccades originating from an eccentric contralateral fixation point than by contraversive saccades originating from central fixation points (Sommer & Tehovnik 1997). The deficit is for making contraversive saccades anywhere in the extrapersonal space, not just for saccades made within the contralateral space, showing that the FEF uses a 'vector' code signalling the direction of saccades rather than a strictly 'place' code signalling their destination (Sommer & Tehovnik 1997). These properties of FEF neurons fit the characteristics of the right hemisphere specialization model illustrated in figure 3.

The supplementary eye field (SEF) is an oculomotor area on the dorsomedial surface of the frontal lobe. Its relationship to eye movements is slightly more complex than that of the FEF and shows a dependency on the position of the eyes in the orbit. In a task where macaque monkeys were required to make eye movements to the right or left of a horizontal bar, SEF neurons fired differentially as a function of the end to which the eye movement was made regardless of the direction of the movement (Olson & Gettner 1995). Thus, neurons in the SEF appear to have motor action fields defined relative to an object-centred frame of reference and may contribute to the emergence of the object-centred aspects of neglect.

Neurons of the ventral premotor cortex respond preferentially to visual stimuli in the space near the arms and face whereas FEF neurons respond to more distant stimuli, thus providing a potential neural substrate for the distinction between near and far neglect. Neurons in ventral premotor cortex encode the egocentric location of objects, even after the light is turned off, in a way that may underlie the ability to reach towards or avoid objects in the dark (Graziano *et al.* 1997). Dorsal premotor neurons respond to cues that reorientate direction of intended limb movements (Kermadi & Boussaoud 1995). The numerous premotor areas intercalated between M1 and FEF may thus mediate attention-related reaching and grasping behaviours in near-space, whereas FEF may be more closely involved in mediating orientating and exploratory responses in far-space.

The LIP and FEF have neurons with visual as well as saccade-related discharges, trigger saccades when stimulated, and project to the intermediate layers of the superior colliculus. However, the FEF projection to the superior colliculus arises predominantly from saccade-related neurons, whereas the LIP projection comes predominantly from neurons with visual activity (Paré & Wurtz 1997). It appears that the FEF signal conveys a more extensive sensorimotor transformation, which may therefore exert a greater influence upon the collicular encoding of eye movement commands (Segraves & Goldberg 1987; Paré & Wurtz 1997). Neurons with exclusively sensory responses are more common in LIP whereas neurons that display exclusively presaccadic discharges are more common in FEF. Although this information appears to imply that LIP is more 'sensory' and FEF more 'motor', both areas support sensorimotor integration, explaining why frontal as well as parietal lesions lead to neglect syndromes with sensory as well as motor manifestations.

(d) *The limbic connection in neglect*

Patients who develop neglect on the basis of lesions confined to the cingulate gyrus are rare (Heilman *et al.* 1983). Functional imaging studies in neurologically normal subjects engaged in tasks of covert shifts of attention, overt oculomotor exploration, and manual search have consistently shown an anterior cingulate focus of activation (Nobre *et al.* 1997*b*; Gitelman *et al.* 1999; Kim 1999). When performance is also taken into account, subjects who are most effective in shifting attention show significantly greater activation in the posterior cingulate gyrus (Kim *et al.* 1998). The cingulate component of the attentional network may thus have two parts: an anterior part related to general motivational engagements, and a posterior part related to more differentiated lateralized displacements of attention.

The behavioural affiliations of the cingulate gyrus are predominantly limbic in the ventral cingulate, visuospatial in the posterodorsal cingulate, and somatomotor in the anterodorsal cingulate. Monosynaptic connections link the limbic as well as non-limbic parts of the cingulate to the FEF and BA 7a (Mesulam *et al.* 1977; Barbas & Mesulam 1981). The limbic component of this input may enable FEF and BA 7a neurons to recognize the behavioural relevance of extrapersonal events. In cats, stimulation of the cingulate region causes a cessation of spontaneous activity and the onset of searching head and eye movements towards the contralateral side (Jansen *et al.* 1955). In monkeys, unilateral lesions of the cingulum bundle and adjacent cingulate cortex result in contralateral somatosensory extinction (Watson *et al.* 1973).

Neurons in the dorsal part of the anterior cingulate fire in response to behaviourally relevant cues and during the planning and execution of arm movements (Olson *et al.* 1993). The activity of posterior cingulate neurons increases immediately following saccadic eye movements and is sensitive to the direction of displacement rather than the spatial location of the target (Olson *et al.* 1993). Since their activity is post-saccadic, these neurons are likely to be monitoring rather than controlling the saccadic shifts in the direction of overt visual attention. The predominance of post-saccadic activity is reminiscent of neuronal activity in BA 7a whereas the vectorial encoding is reminiscent of neuronal activity in FEF.

(e) *Subcortical neglect*

Unilateral neglect in the human has been reported after lesions of the thalamus (Watson & Heilman 1979; Cambier *et al.* 1980; Schott *et al.* 1981). The deficit has been attributed to an impairment in engaging the contralesional target and has been contrasted to the disengagement deficit associated with parietal lesions (Rafal & Posner 1987). Functional imaging during tasks of attentional shifts has shown activations in the ventral lateral nucleus and in a region that is intermediate between the medial pulvinar and the mediodorsal nucleus (Gitelman *et al.* 1999). Pulvinar activation is also seen in tasks of selective attention to objects and seems to encode the behavioural salience or relevance of stimuli (LaBerge & Buchsbaum 1990; Morris *et al.* 1997). Pulvinar neurons may help to generate visual salience by increasing the signal-to-noise ratio (Petersen *et al.* 1985; Robinson 1993). In concert with BA 7a, with which it is interconnected, the pulvinar nucleus may thus participate in establishing a representational map of salience.

Unilateral striatal damage has also been associated with contralateral neglect (Luria *et al.* 1966; Damasio *et al.* 1980; Healton *et al.* 1982). Functional imaging has shown caudate and putaminal activation during overt and covert shifts of spatial attention (Gitelman *et al.* 1996*a*, 1999). Some neurons in the caudate and putamen of the macaque monkey are sensitive to the behavioural relevance of the cue but not to its colour and participate in the construction of spatial plans for the sequential distribution of oculomotor and limb movements (Kermadi & Joseph 1995; Miyashita *et al.* 1995). In humans, the neglect syndromes associated with subcortical lesions may also reflect the destruction of cortico-cortical connection pathways running in the white matter and the remote cortical hypometabolism caused by diaschisis. In fact, neglect-causing subcortical lesions have been reported to induce distal hypometabolism in frontal and parietal cortex (Fiorelli *et al.* 1991).

The intermediate layers of the superior colliculus play a critical role in initiating eye movements, foveating visual targets, and releasing ocular fixation when a new target must be foveated (Dorris *et al.* 1997). The superior colliculus receives input directly from the retina, from primary visual cortex, from LIP, from the FEF, and probably from the cingulate gyrus (Künzle 1995). Lesions of the superior colliculus can lead to contralesional neglect in the cat (Sprague & Meikle 1965). There are no analogous human cases. Functional imaging shows more superior colliculus activation in tasks of overt oculomotor exploration than in those of covert attentional shifts (Gitelman *et al.* 1997).

Several functional imaging studies had detected cerebellar activation even in tasks of covert attentional shifts, suggesting that the cerebellum may play an important role in spatial attention. However, an experiment which employed stringent controls for all motor activities involved in the task failed to show cerebellar activation associated with covert shifts of attention (Gitelman *et al.* 1999). This is consistent with studies which show that cerebellar lesions do not cause deficits in covert shifts of attention (Yamaguchi *et al.* 1998). The cerebellum could conceivably play a more prominent role in tasks that require active exploration.

The intralaminar thalamic nuclei, the brainstem raphe nuclei, the nucleus locus coeruleus, the ventral tegmental area-substantia nigra, and the nucleus basalis project to each cortical component of the attentional network. These projections from the ARAS modulate the activation state of other network components. In keeping with this relationship, unilateral lesions in the intralaminar nuclei and even in the mesencephalic reticular formation trigger contralateral neglect in the cat and in the rhesus monkey (Orem *et al.* 1973; Watson *et al.* 1974, 1978).

6. DISSOCIATIONS AND SUBTYPES: IS THERE PARIETAL VERSUS FRONTAL NEGLECT?

The symptoms and signs of neglect are so numerous that no individual patient manifests them all. Dissociations among the behavioural components are the rule rather than the exception. Some patients display extinction but no other symptom of neglect while others display most of the other manifestations of neglect except for extinction (Weintraub & Mesulam 1987; Daffner *et al.* 1990; Liu 1992). Additional dissociations have also been reported, including those of clock drawing from target cancellation (Weintraub & Mesulam 1988), visual extinction from tactile or auditory extinction (De Renzi *et al.* 1984; Stone *et al.* 1998), directional hypokinesia from neglect of mental representation (Bisiach *et al.* 1990; Mijovic 1991), and neglect of mental representation from target cancellation (Manoach *et al.* 1996; Beschin *et al.* 1997*a*; Coslett 1997).

These dissociations could conceivably represent clinical 'subtypes' of neglect, each with a different anatomical substrate within the attentional network. Some evidence suggests that reaching deficits, extinction and extinction-like phenomena (such as attentional disengagement in tasks of covert attentional shifts) may be associated with superior parietal lobule lesions whereas the distortions of spatial representation and perhaps other manifestations of neglect may be associated with inferior parietal lobule lesions (Posner *et al.* 1984; Vallar 1993; Milner 1997). However, functional imaging experiments have not yet supported this correlation and clinical reports indicate that directional reaching may be impaired after inferior parietal lesions as well (Gitelman *et al.* 1996*a*, 1999; Mattingley *et al.* 1998).

A relatively attractive hypothesis revolves around the possibility that 'parietal neglect' might be predominantly perceptual whereas 'frontal neglect' might be predominantly motor. In support of this possibility, several studies have shown that 'perceptual' tasks such as extinction and line bisection are more likely to be associated with parietal lesions whereas 'motor' tasks such as target cancellation are more likely to be associated with frontal lesions (Daffner *et al.* 1990; Binder *et al.* 1992; Liu 1992). Ingenious experiments with pulleys and mirrors have shown that errors in line bisection and target detection tasks can be attributed to representational biases in patients with parietal lesions and to directional hypokinesia in patients with frontal lesions (Bisiach *et al.* 1990; Tegnér & Levander 1991). Other studies, however, have not been able to confirm the presence of a relationship between directional hypokinesia and frontal lesions (Mattingley *et al.* 1998), or have identified behavioural subtypes without being able to fit them into anatomical subtypes (McGlinchey-Berroth *et al.* 1996). A definitive study based on the testing of patients with lesions confined to the parietal or frontal lobes, with tasks that isolate the representational versus exploratory aspects of spatial attention, remains to be done.

Even if such a study were done, however, it is unrealistic to expect a strict distinction between parietal and frontal neglect. The frontal and parietal components of the attentional network subserve a level of sensorimotor integration where the boundaries between action and perception become blurred (Mesulam 1981). Furthermore, the strong interconnectivity between the frontal and parietal components of this network raises the possibility that damage to one may induce distal hypometabolism in the other through the process of diaschisis. The most that could be expected is to find a relative (and probably quite subtle) predominance of representational neglect in parietal lesions and a relative predominance of exploratory (not just intentional) neglect in frontal lesions.

7. A NEURAL NETWORK FOR THE DISTRIBUTION OF SPATIAL ATTENTION

The evidence reviewed above has led to the hypothesis that directed attention is organized at the level of a distributed large-scale network revolving around three cortical epicentres (or local networks), each providing a slightly different but interactive and complementary type of neural encoding so that behaviourally relevant targets in the environment can be represented mentally and become the targets of further action and exploration (Mesulam 1981). Lesions to any of the components of the resultant large-scale network in figure 4 or to their interconnections can result in contralesional neglect. In general, lesions involving network epicentres are likely to cause multimodal deficits whereas lesions that disconnect the network from other areas of the brain could cause modality-specific attentional disorders.

The network depicted in figure 4 is organized according to the computational principles that apply to large-scale networks in other cognitive domains (Mesulam 1998). This organization allows the network to undertake very rapid surveys of motivational salience, perceptual representations, multiple coordinate systems, and motor strategies, so that attention can be shifted adaptively from one target to another. Assigning an identifiable 'task' to each component of this network raises the spectre of anthropomorphism but also serves a heuristic purpose. Thus, the posterior parietal component (centred around the intraparietal sulcus but including adjacent cortex of the inferior and superior parietal lobules and perhaps the MT+ region in parieto-occipito-temporal cortex) may enable the mapping of salient events in multiple coordinates. The resulting mental representation allows behaviourally relevant environmental events to be encoded with respect to each other and with respect to the observer, so that they can be targeted for covert shifts of the attentional focus, overt foveation, oculomotor scanning, tactile exploration, reaching and manual grasp. The dual functional role of the parietal component would be to compile a dynamic representation of salient landmarks and to compute provisional strategies for shifting attention from one salient target to the other.

The parietal component of the attentional network is likely to act as a critical gateway for the domain of spatial attention in ways that are analogous to the critical role of Wernicke's area in language and of the hippocampo-entorhinal cortex in declarative memory (Mesulam 1998). Wernicke's area, for example, assumes a critical role in language comprehension, not as the convergent site of a mental lexicon, but as a transmodal gateway for linking word-forms in multiple sensory modalities into the distributed associations that encode their meaning. The hippocampo-entorhinal area assumes its critical role in declarative memory, not as the site of memory storage, but as a gateway for binding distributed fragments of events and experiences into coherent entities that can support declarative recall. In a similar fashion, posterior parietal cortex would seem to play its key role in spatial attention not as the repository of a multimodal spatial map, but as a critical gateway for linking distributed channels of spatially relevant information with each other and with multiple channels of motor output related to orientating, reaching, grasping, scanning and exploration. When the parietal component of the attentional network is destroyed, the individual input and output channels may remain quite intact but they cannot be integrated into a coherent template that can sustain flexible shifts of spatial attention.

The frontal component of the attentional network (centred around the FEF but including adjacent premotor and perhaps prefrontal cortex) may play its critical role in the attentional network by converting strategies for attentional shifting into specific motor acts. If posterior parietal cortex sculpts a salience- and trajectory-based template of the attentional landscape, the FEF selects and sequences the individual acts needed to navigate and explore the resultant landscape. There is no single set of spatial codes upon which all kinetic strategies for exploration, foveation and grasping converge. Instead, there are multiple circuits, such as LIP–FEF and AIP–F5, each specialized for specific input–output relationships such as those related to looking, grasping, searching and so on. The parietal and frontal components provide gateways for accessing and coordinating these circuits. They also constitute 'bottlenecks' where lesions have the most severe impact on the integrity of directed attention. The role of the cingulate component is the least well understood. As a limbic component of the attentional network, the cingulate gyrus may play a critical role in identifying the motivational relevance of extrapersonal events and in sustaining the level of effort needed for the execution of attentional tasks.

At a macroscopic level of analysis, the network in figure 4 supports all activities related to spatial attention, regardless of modality of input or output (figure 6). The frontal and parietal components of this network have a collective mechanism for specifying whether an event in ambient or imagined space will participate in the compilation of mental representations and how attention will be shifted to it. Each of the three cortical components in figure 4 serves a dual purpose; that is, it provides a local network for regional neural computations and also a nodal point for the linkage of distributed information. Functional imaging experiments suggest that all three core components are probably engaged simultaneously and interactively by attentional tasks (figure 6). The phenomenon of spatial attention is not the sequentially additive product of perception, motivation and exploration but an emergent (that is, relational) quality of the network as a whole.

8. OVERLAP WITH OTHER NETWORKS: EYE MOVEMENTS, WORKING MEMORY AND TEMPORAL EXPECTATION

Advanced primates interact with the environment predominantly through visually guided behaviours. Even

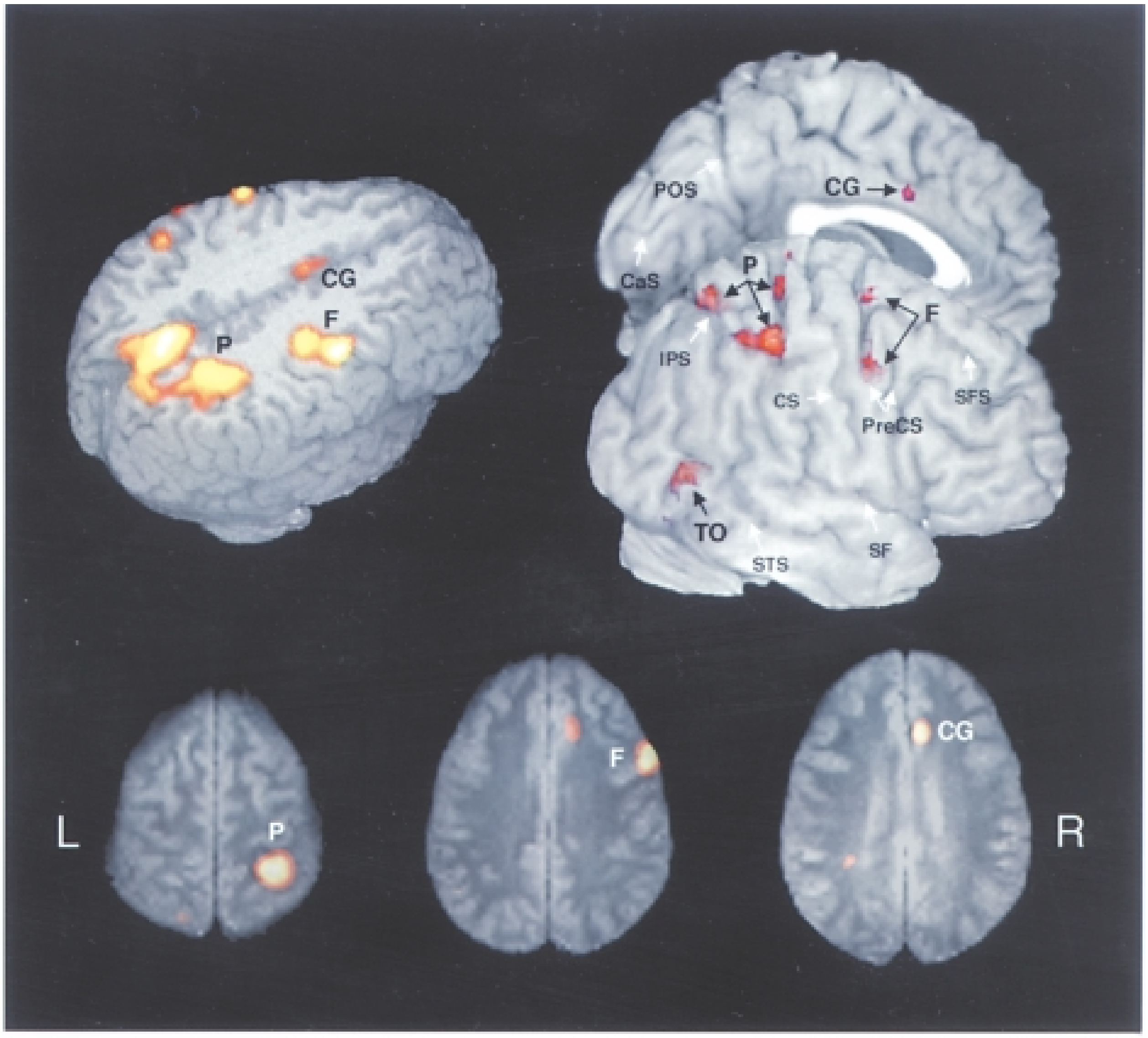

Figure 6. Functional imaging with fMRI. Top left: functional MRI of a subject engaged in a task of covert shifts of spatial attention. All three cortical components of the attentional network (parietal (P), FEF (F) and cingulate (CG)) are activated, and there is more activation in the right hemisphere although the task required symmetrical attentional shifts to the left and right. Top right: another subject performing the same task. The parietal component (P) is centred around the banks of the intraparietal sulcus (ips). There is activation in a temporo-occipito-parietal (TO) area functionally corresponding to MT+ (Gitelman *et al*. 1999). Bottom: functional PET study in a subject engaged in a task of manual exploration of the right hemispace with the right hand. As in the case of tasks based on covert shifts of visuospatial attention, this task of overt manual exploration leads to the activation of the same cortical epicentres of the attentional network, parietal (P), FEF (F) and cingulate (CG). The activations are almost exclusively right-sided although the task was being performed in the right hemispace with the right hand, a result which is consistent with the model depicted in fig. 10 (Gitelman *et al*. 1996*a*). Additional abbreviations: CaS, calcarine fissure; CS, central sulcus; POS, parieto-occipital sulcus; PreCS, precentral sulcus; SF, Sylvian fissure; SFS, superior frontal sulcus; STS, superior temporal sulcus.

auditory, tactile and olfactory stimuli attract reflexive visual orientation. In fact, the direction of gaze is almost always aligned with the direction of attention, except when there is a need to attend to multiple locations simultaneously, or a conscious intent to deceive an observer. It is therefore reasonable to expect a close relationship between the network for spatial attention and the network which controls eye movements. All components of the attentional network shown in figure 4, the FEF, posterior parietal cortex, cingulate gyrus, superior colliculus, striatum, pulvinar and mediodorsal nucleus, have been implicated in either the control or monitoring of eye movements (Segraves & Goldberg 1987; Robinson & McClurkin 1989; Alexander *et al.* 1990; Andersen *et al.* 1997; Dorris *et al.* 1997). The functional overlap of the two networks is quite extensive, even for completely covert shifts of spatial attention. Thus, when a covert spatial attention task was compared with a task of non-attentional repetitive saccadic eye movements, a conjunction analysis showed that the components of the attentional network were activated by both tasks (Nobre *et al.* 1998). It appears, therefore, that the network for spatial attention is embedded within an oculomotor network, irrespective of whether the attentional task involves any eye movements. In keeping with this formulation, the covert shifting of attention was shown to elicit a contralateral deviation of vertical saccades, suggesting that shifts of spatial attention may automatically engage oculomotor mechanisms, even when the attentional shifts do not involve eye movements (Sheliga *et al.* 1995).

A second type of overlap occurs with the networks subserving working memory and temporal expectancy. A conjunction analysis of two tasks, one based on covert shifts of spatial attention and the other on working memory for letters, showed that the frontal and parietal epicentres of the attentional network displayed a nearly complete overlap with the areas activated by the working memory task, although the working memory task also led to additional frontal activation, and the attentional task to additional parieto-temporo-occipital activation (LaBar *et al.* 1998). Furthermore, a task that manipulated temporal expectancy by directing attention to different temporal intervals led to the activation of all three cortical epicentres of the attentional network (Nobre *et al.* 1997*a*).

One common denominator for the functions subserved by these overlapping networks is that they move attention: from one location to another, from one point in time to another, and from an external source of input to its internal on-line representation. It appears, therefore, that the network shown in figure 4, may subserve a general function of shifting the attentional focus in space, in time and in mental domains. In comparison, the attentional function of the ventral visuofugal stream of processing is based on locking onto a target and filtering out irrelevant input rather than moving from one target to another (Moran & Desimone 1985).

9. OVERVIEW AND CONCLUSIONS

Under normal circumstances, the probability of attracting attention is determined by the novelty or significance of an event, irrespective of its location. Left neglect erects an inertial barrier to the leftward movement of the attentional focus in all frames of reference even in the absence of primary sensory or motor deficits. Neglect is not a disorder of seeing, hearing, or moving but one of looking, detecting, listening and exploring. It is said to exist when the conscious impact of real or imagined events displays a spatially addressed bias in all frames of reference, including the egocentric, allocentric, world-centred, object-centred and conceptual.

Many accounts of neglect have been published, ranging from the phenomenological to the computational. Few, if any, have been able to account for the entire spectrum of clinical manifestations, leading some authors to question the existence of an identifiable neglect syndrome. This review aims to show that 'neglect' is no less unitary than 'aphasia' or 'amnesia'. Contrary to some proposals that have been advanced in the past, it is becoming increasingly clear that neglect cannot be attributed to a unitary deficit of arousal, orientation, representation or intention. Instead, it represents the collective and interactive outcome of multiple impairments in each of these processes. As in the case of aphasia and amnesia, neglect is a 'network syndrome'. It represents damage to one or more interactive components of a distributed network where each component has a different pattern of physiological and anatomical specialization.

The distributed network which controls spatial attention, revolves around cortical epicentres in the posterior parietal cortex, FEF and the cingulate gyrus. This network displays sensorimotor as well as cognitive affiliations. It enables behaviourally relevant extrapersonal events to be represented in the form of targets for attentional shifts and exploration. In the human brain, the attentional network displays a distinctly asymmetrical organization so that the left hemisphere directs attention mostly within the right hemispace and in a predominantly contraversive direction whereas the right hemisphere directs attention more evenly within both hemispaces and in both directions. Prominent contralesional neglect is therefore seen almost exclusively after right hemisphere lesions.

The computational features of the attentional network are similar to those of the networks associated with other cognitive domains such as language and memory. The advent of functional imaging, the availability of animal models for the attentional network, and the very substantial advances already made in investigating the anatomical and physiological properties of the corresponding areas in the monkey brain, provide unprecedented opportunities for exploring the organizing principles of large-scale neurocognitive networks in the human brain.

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