Spatial Neglect and Attention Networks

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\textbf{Abstract}

Unilateral spatial neglect is a common neurological syndrome following predominantly right hemisphere injuries and is characterized by both spatial and non-spatial deficits. Core spatial deficits involve mechanisms for saliency coding, spatial attention, and short-term memory and occur in conjunction with nonspatial deficits that involve reorienting, target detection, and arousal/vigilance. We argue that neglect is better explained by the dysfunction of distributed cortical networks for the control of attention than by structural damage of specific brain regions. Ventral lesions in right parietal, temporal, and frontal cortex that cause neglect directly impair nonspatial functions partly mediated by a ventral frontoparietal attention network. Structural damage in ventral cortex also induces physiological abnormalities of task-evoked activity and functional connectivity in a dorsal frontoparietal network that controls spatial attention. The anatomy and right hemisphere dominance of neglect follow from the anatomy and laterality of the ventral regions that interact with the dorsal attention network.
INTRODUCTION

L.J. is a 58-year-old schoolteacher, who suddenly developed malaise and confusion while at school. He was brought to the hospital for evaluation. On first appearance, his affect was flat and his vigilance reduced; his responses were grammatically accurate but delayed, and when asked “what was the matter” he replied he was not sure why he had been brought in. On exam, his visual fields were normal but his gaze tended to deviate to the right spontaneously when looking ahead. When presented with two objects, one in each visual field, he always looked first to the right object and denied the presence of the object on the left. However, when asked, he was able to move his eyes to the left and reported seeing the object. Overall, he was very slow in reporting stimuli even in his right visual field. When searching blindfolded for objects scattered on a table with either the left or right hand, he explored mainly the right side of the table, and his search progressed to the center only when objects on the right were removed. Touches on the right hand were easily reported and localized, whereas touches to the left hand were inconsistently detected and reported as belonging to the examiner. Motor function was normal in terms of strength, coordination, and dexterity on both sides, but L.J. was reluctant to use his left hand unless asked to do so. Head MRI showed a diffusion restriction in the right inferior and middle frontal gyrus and anterior insula, consistent with an acute ischemic stroke.

This clinical history illustrates some key features of unilateral spatial neglect: a reduction of arousal and speed of processing; an inability to attend to and report stimuli on the side opposite the lesion (contralesional) despite apparently normal visual perception; a spatial bias for directing actions toward the hemi-space or hemi-body on the same side as the lesion (ipsilesional); and several disorders of awareness, including a degree of obliviousness toward being ill and confabulation about body ownership.

Spatial neglect is caused by lesions, typically strokes, in a number of different cortical and subcortical areas. Although acutely both
left and right hemisphere lesions can cause neglect, only right hemisphere lesions cause severe and persistent deficits (Stone et al. 1993), which is the primary basis for the widely held view that the right hemisphere is dominant for attention.

Spatial neglect is unique among the behavioral disorders resulting from focal lesions because its severity can be modulated by behavioral interventions over very short timescales (e.g., seconds). Deficits in attending to and reporting objects in contralesional space can be lessened by (a) encouraging a patient to attend to the previously ignored stimuli using verbal cues (Riddoch & Humphreys 1983); (b) presenting salient sensory stimuli, such as noises (Robertson et al. 1998); (c) asking the patient to perform hand movements controlled by the injured hemisphere (Robertson & North 1992); or (d) training patients to increase their alertness (Robertson et al. 1995). These observations suggest that the neural mechanisms underlying the spatial deficit can be dynamically modulated by signals from other parts of the brain reflecting endogenous or exogenous attention, movement, and arousal. Moreover, in a matter of days or weeks, most patients with spatial neglect recover from the more obvious spatial impairments, which continue to negatively influence their ability to return to a productive life (Denes et al. 1982, Paolucci et al. 2001).

Spatial neglect has attracted tremendous interest as a model for understanding the neurological basis of awareness, cerebral lateralization, spatial cognition, and recovery of function. Yet its neural bases remain poorly understood. Here, we provide a selective review of the vast literature on neglect and present a framework for understanding the disorder.

We propose that neglect is mediated by the abnormal interaction between brain networks that control attention to the environment in the healthy brain (see Heilman et al. 1985 and Mesulam 1999 for other network formulations). Although many authors have emphasized dissociations and subtypes of spatial neglect, we argue for a core set of spatial and nonspatial deficits that match the physiological properties of these networks. The core spatial deficit, a bias in spatial attention and salience mapped in an egocentric coordinate frame, is caused by the dysfunction of a dorsal frontoparietal network that controls attention and eye movements and represents stimulus salience. Core nonspatial deficits of arousal, reorienting, and detection reflect structural damage to more ventral regions that partly overlap with a right hemisphere dominant ventral frontoparietal network recruited during reorienting and detection of novel behaviorally relevant events.

Next, we emphasize that the ventral lesions that result in neglect alter the physiology of structurally undamaged dorsal frontoparietal regions, consistent with the fact that dorsal and ventral attention regions interact in the healthy brain. Physiological dysfunction in dorsal frontoparietal regions is empirically observed not only during task performance but also at rest, and it correlates with the severity of the egocentric spatial bias. Moreover, this dysfunction decreases the top-down modulation of visual cortex, reducing its responsiveness, which can also contribute to neglect. The highly dynamic and plastic nature of the spatial deficits in neglect strongly argues that they are mediated by parts of the brain that still function, even if abnormally. Measurements of the physiology of brain regions, not just of structural damage, are essential for understanding neglect (Deuel & Collins 1983), and we emphasize neuroimaging methods that provide a window on physiological function.

Finally, perhaps the least understood clinical feature of spatial neglect is its right hemisphere lateralization. Brain imaging studies have shown that dorsal frontoparietal regions controlling spatial attention and eye movements are largely symmetrically organized, with each hemisphere predominantly representing the contralateral side of space. In contrast, ventral regions that underlie the core nonspatial deficits observed in neglect patients are strongly
right hemisphere dominant. We argue that lateralization of these latter functions, and their interaction with dorsal regions, rather than asymmetries of spatial attention per se, primarily accounts for the hemispheric asymmetry of neglect.

THE CORE SPATIAL DEFICIT: EGOCENTRIC BIAS

A large body of neuropsychological research has tried to characterize the nature of spatial deficits (i.e., involve predominantly one side of space) in neglect. Factor analytic studies have consistently isolated at least one factor associated with impairments in attending/searching/responding to targets in contralateral space, but have yielded inconsistent conclusions with regard to other factors (Azouvi et al. 2002, Halligan et al. 1989, Kinsella et al. 1993, Verdon et al. 2010). Other studies have classified patients based on their performance on different behavioral tasks thought to isolate different subtypes, such as perceptual/attention versus motor/intention deficits (Coslett et al. 1990), but the consistency (Hamilton et al. 2008) and relevance to recovery of these distinctions have been disappointing (Farne et al. 2004, Rengachary et al. 2011). Most patients suffer from perceptual/attention deficits that recover, albeit incompletely, in parallel with recovery from spatial neglect (Rengachary et al. 2011). We argue that at its core, spatial neglect represents a deficit of spatial attention and stimulus saliency that is mapped in an egocentric reference frame.

Gradients of Spatial Attention and Stimulus Saliency

Virtually all patients with spatial neglect manifest a lateralized bias in visual information processing that is evident both clinically and experimentally as a gradient across space (Behrmann et al. 1997, Pouget & Driver 2000). Sensitivity and responsiveness to behaviorally relevant stimuli improve as one moves from contralesional to ipsilesional locations along a continuous spatial gradient. This bias does not reflect abnormal early visual mechanisms, as indicated by normal measures of contrast sensitivity (Spinelli et al. 1990) and image segmentation based on low-level features in the neglected visual field (Driver & Mattingley 1998) and responses in occipital cortex based on visually evoked potentials (Di Russo et al. 2008, Watson et al. 1977) and functional magnetic resonance imaging (fMRI) (Rees et al. 2000).

In contrast, the saliency of objects in the neglected visual field is impaired. Saliency refers to the sensory distinctiveness and behavioral relevance of an object relative to other objects. In a recent study, the saliency of objects in the ipsilesional or contralesional visual field of neglect subjects was measured by indexing the patients’ tendency to look at distinctive but task-irrelevant stimuli or at task-relevant stimuli (Bays et al. 2010). Both kinds of stimuli produced an increased probability of eye movements in their direction along a similar spatial gradient from contralesional to ipsilesional locations, suggesting that exogenous (automatic) and goal-driven components of spatial attention were equally affected (Figure 1a).

The abnormally high salience of ipsilesional stimuli may prevent them from being filtered when they are task-irrelevant (Bays et al. 2010, Shomstein et al. 2010, Snow & Mattingley 2006) or lead to repeated refixations during search tasks (Husain et al. 2001). Importantly, a spatially lateralized bias is observed even in the absence of a stimulus. When neglect subjects searched for a nonexistent object in complete darkness, search patterns as measured by eye or head position were strongly biased toward the ipsilesional field (Hornak 1992). Moreover, gaze deviations are observed tonically at rest, similar to those observed during task performance (Figure 1b) (Fruhmann Berger et al. 2008).

Spatial biases in the dark during target search could reflect a reduced salience of contralesional spatial locations during task performance, but the biases observed at rest also suggest an indwelling imbalance in the mechanisms controlling gaze. These motor biases are likely
Behavioral and lesion analyses of the egocentric spatial bias in neglect patients. (a) Effects of stimulus salience on eye movements of neglect patients. Patients were instructed to saccade to a target letter in an array. A sequence of arrays was presented, some containing a target, some containing a distinctive probe stimulus of a higher luminance or different orientation than the distracter squares, and some containing both a target and a probe. The right graph shows that targets (red line) and irrelevant but distinctive luminance probes (blue line) produced more saccades in the ipsilesional than contralesional visual field with a similar linear gradient along the horizontal position. This indicates a similar ipsilesional bias for automatic and goal-directed orienting (Bays et al. 2010). Lesions are localized in right temporoparietal junction. (b) Neglect patients show an ipsilesional gaze bias while searching for a target letter in a letter array (blue traces) and at rest (green traces). Non-neglect patients (bottom) showed no bias (Fruhmann Berger et al. 2008). (c) Lesions classically associated with neglect involve an ipsilesional bias within an egocentric reference frame, but not biases observed within stimulus-centered or object-centered frames. Each image shows the voxelwise lesion distribution associated with deficits within a particular reference frame (Medina et al. 2008). Panel a is adapted from figures 1, 2d, and 4b of Bays et al. 2010, with permission from the Society for Neuroscience. Panel b is adapted from figure 1 of Fruhmann Berger et al. 2008, with permission from the American Psychological Association. Lesion data in panel c are courtesy of Drs. Medina, Pavlak, and Hillis, Johns Hopkins and University of Pennsylvania, from Medina et al. 2008.

associated with attentional biases because of the functional relationship between the corresponding neural systems (Corbetta et al. 1998, Rizzolatti et al. 1987).

An Egocentric Frame of Reference
Spatial deficits can be separated based on the reference frame in which stimuli are coded. Neglect is often egocentric (viewer-centered),
with left and right hemi-spaces based on the observer’s midline (Figure 1c). Coding of the spatial midline can be further fractionated based on eye, head, or body position. Although these factors have been shown to modulate the severity of neglect in individual cases, no consistent dissociation has emerged between eye-, head-, or body-centered neglect (Behrmann & Geng 2002). These null results have traditionally been explained by the large volume and heterogeneity of lesions in humans. Computational studies and physiological analyses in monkeys, however, indicate an additional factor, namely that activity in many areas reflects combinations of different egocentric reference frames (Chang & Snyder 2010, Pouget & Sejnowski 2001).

Neglect can also be allocentric, where the midline is defined from the central axis of a stimulus, irrespective of its position in the environment (stimulus-centered, Figure 1c) or of both its position and orientation (object-centered, Figure 1c). The great majority of patients with spatial neglect, however, suffer from egocentric deficits. Marsh & Hillis studied 100 consecutive cases of right hemisphere acute stroke, and found that while 17% and 34% showed visual and tactile egocentric neglect, respectively, the corresponding figures for allocentric neglect were only 4% and 2% (Marsh & Hillis 2008). Allocentric and egocentric neglect rarely co-occur clinically and are dissociated anatomically (Medina et al. 2008, Verdon et al. 2010). While egocentric neglect is associated with regions classically damaged in spatial neglect, i.e., inferior parietal lobule (IPL), superior temporal gyrus (STG), and inferior frontal gyrus (IFG), stimulus- and object-centered neglect is associated with damage of inferior temporal regions (Figure 1c).

Therefore, egocentric spatial deficits in neglect correspond much more closely to the clinical syndrome both behaviorally and anatomically than do allocentric deficits, and represent core features of the syndrome.

### Does Spatial Neglect Involve Only Attention/Salience?

An important question is whether an attention/saliency account of the spatial component of neglect leaves out other impaired perceptual-cognitive functions, particularly visuospatial short-term memory (VSTM) and spatial cognition. An influential account proposes that neglect is a deficit in forming, storing, or manipulating the left side of mental images or information in VSTM, termed representational neglect (i.e., representation within VSTM) (Bisiach & Luzzatti 1978, Della Sala et al. 2004). Most or all of the empirical findings that support an attentional/saliency interpretation of the spatial deficit in neglect patients can also be explained within a representational framework. This duality reflects the fact that mechanisms for spatial attention, VSTM, and imagery are closely related, as shown by psychological and physiological studies (Awh & Jonides 2001, Kosslyn et al. 2001), and entry into VSTM is often considered a normal consequence of conscious perception. Not surprisingly, representational neglect is nearly always observed in association with perceptual neglect (Bartolomeo et al. 1994). The few cases in which a dissociation has been reported (e.g., Guariglia et al. 1993, Ortigue et al. 2001) used pencil-and-paper tasks with lower sensitivity than computerized tasks (Rengachary et al. 2009) and did not control for differences in eye movements (Fruhmann Berger et al. 2008, Hornak 1992) and cognitive load or time-on-task, which affect the direction of spatial attention (Dodds et al. 2008, Rizzolatti et al. 1987). Regardless, both the low frequency of dissociations between perceptual and representational neglect and the likelihood that each is mediated by overlapping neural systems suggest that this distinction, while very important theoretically, may not be critical for first-order identification of the psychological and neural mechanisms that are damaged in the large majority of patients with spatial neglect. Accordingly, in this review, we do not distinguish representational...
and spatial attention formulations of the core egocentric deficit underlying spatial neglect.

Some neglect patients exhibit deficits in VSTM that may not show a contralesional-to-ipsilesional gradient and could be separate from a contralesional attention/salience/VSTM deficit. VSTM deficits are observed for stimuli presented along a central, vertical axis (Malhotra et al. 2005), while a more specialized deficit has also been reported in trans-saccadic spatial memory (Mannan et al. 2005), possibly reflecting saccadic remapping mechanisms (Vuilleumier et al. 2007). When coupled with a bias to attend to ipsilesional locations, full-field VSTM and trans-saccadic deficits can exacerbate contralesional neglect by leading to multiple refixations of already-searched, ipsilesional objects (Husain et al. 2001, Mannan et al. 2005). However, a recent study reported that both VSTM deficits and visual search performance were worse in the contralesional visual field. This result is consistent with the functional similarity and neural overlap of mechanisms for attention/perception and working memory (Kristjansson & Vuilleumier 2010).

In addition to spatial attention, spatial cognition is involved in many tasks used to assess spatial neglect. Line bisection, for example, requires fine judgments of spatial extent or position. Patients with neglect typically show rightward biases in line bisection (Bisiach et al. 1983) or underestimate the size of objects placed on the left side of space (Milner et al. 1998). These perceptual deficits are sometimes thought to reflect a distortion of the horizontal dimension of space (Bisiach et al. 2002). However, extensive investigations of eye movements during line bisection clearly indicate that neglect patients fail to explore the left side of lines, most often judging as midpoint the leftmost position that was fixated (Ishiai et al. 2006). Moreover, their subjective midline judgment is strongly biased by the position of the rightward line endpoint (McIntosh et al. 2005). These findings suggest a more parsimonious explanation of line bisection errors based on the relative saliency of the right versus left side of lines (Figure 1a) and tonic oculomotor biases (Figure 1b). Another aspect of spatial cognition, processing of global stimulus structure, is also impaired in at least some patients (Delis et al. 1986). A resulting local bias could increase the tendency to search near the current focus of attention, exacerbating a bias to attend to ipsilesional locations (Robertson & Rafal 2000).

Overall, the egocentric spatial deficit in neglect reflects impairments in a set of related mechanisms for spatial attention, salience, and VSTM, and perhaps spatial cognition. A recent study has shown that this deficit, when assessed using even a very simple task, is highly associated with clinical judgments of neglect. In a paradigm involving simple reaction time to a cued target, performance differences for left- and right-field targets discriminated acute and chronic neglect patients from healthy controls with better accuracy than a variety of standard neuropsychological tests of neglect (Rengachary et al. 2009). Notably, this task did not involve spatial imagery, spatial cognition (line bisection, clock-drawing, copying tasks), or shape identification in a cluttered field (cancellation tasks), and involved minimal VSTM demands.

Summary

Spatial neglect is characterized by a spatial gradient of impaired attention/saliency/representation within an egocentric reference frame. The saliency deficit reflects both task and sensory factors and is linked with indwelling motor imbalances that produce resting ipsilesional deviations in eye, head, and body movements. Abnormal interhemispheric interactions likely play a role in producing the spatial gradient. The gradient fluctuates depending on arousal and task instructions, suggesting that the underlying neural mechanisms are modulated by signals from other parts of the brain and are dysfunctional rather than obliterated by structural damage.
ANATOMY AND PHYSIOLOGY OF THE EGOCENTRIC SPATIAL BIAS

We next discuss anatomical studies of neglect. The most commonly damaged brain regions do not contain physiological signals that can mediate the egocentric spatial bias. In contrast, physiological studies of spatial attention in healthy adults have highlighted the importance of a dorsal frontoparietal attention network that typically is not structurally damaged in neglect patients. The mismatch between anatomical lesions and physiology may be explained by recent physiological studies of the dorsal network in neglect patients.

Structural Damage Does Not Explain the Ego Centric Spatial Bias

Spatial neglect was first associated with damage to parietal cortex (Critchley 1953), especially IPL (Mort et al. 2003, Vallar & Perani 1987). However, subsequent studies have also emphasized STG (Karnath et al. 2001) and IFG (Husain & Kennard 1996), and convincing evidence exists that damage to other regions, including anterior insula and middle frontal gyrus (MFG), sometimes produces neglect. Interestingly, the distribution of cortical damage is similar irrespective of the behavioral criteria (e.g., neglect severity, clinical diagnosis, comparison of neglect versus no-neglect individuals) used to group the lesions (Figure 2a). Importantly, neglect patients, especially in severe cases, have white matter fiber damage, which can disconnect frontal, temporal, and parietal cortex (Bartolomeo et al. 2007, Gaffan & Hornak 1997, He et al. 2007, Thiebaut de Schotten et al. 2005). White matter damage most commonly involves a dorsal region lateral to the ventricle where arcuate and superior longitudinal fasciculi (II and III) run parallel in an anterior-to-posterior direction (Figure 2c) (Doricchi & Tomaiuolo 2003). Finally, neglect also can be caused by damage to subcortical nuclei (pulvinar, caudate, putamen) (Karnath et al. 2002a, Vallar & Perani 1987) that cause cortical hypoactivation of regions important for the genesis of neglect (Karnath et al. 2005, Perani et al. 1987).

While the detailed profile of behavioral deficits undoubtedly depends on the site of the lesion (Medina et al. 2008, Verdon et al. 2010), and some lesion sites are more likely than others to produce neglect, the striking fact remains that neglect of the left field can be caused by many different right hemisphere lesions.
Attempts to identify a critical region based on structural damage alone inevitably must explain away a large number of reported lesions that produce neglect and yet do not involve the supposedly critical region.

Moreover, regions that are commonly damaged in spatial neglect do not contain the physiological signals expected based on deficits in spatial attention, eye movements, and coding of salience. These regions are not usually recruited in neuroimaging experiments that isolate those processes, and none have yet been shown in humans to contain maps of space. Right ventral frontal cortex (VFC), for example, has been associated with target detection (Stevens et al. 2005), task control and error detection (Dosenbach et al. 2006), and response inhibition (Aron et al. 2004).

To resolve this paradox, we propose that the heterogeneity of lesions in spatial neglect patients masks a greater uniformity at the level of physiology, with common physiological abnormalities in remote neural systems specialized for spatial processing (Corbetta et al. 2005, He et al. 2007). Next, we review evidence in healthy subjects for a dorsal frontoparietal attention network that houses the physiological signals impaired in spatial neglect.
A Dorsal Frontoparietal Network for Spatial Attention, Stimulus Salience, and Eye Movements

Regions in dorsal frontal and parietal cortex, including bilateral medial intraparietal sulcus (mIPS), SPL, precuneus, supplementary eye field (SEF), and frontal eye field (FEF), respond to symbolic cues to shift attention voluntarily to a location (e.g., Corbetta et al. 2000, Hopfinger et al. 2000, Kastner et al. 1999) (Figure 3a). In some studies, additional responses are reported in lateral prefrontal cortex, including the inferior frontal sulcus/junction (IFS/IFJ) (Sylvester et al. 2007) and MFG (Hopfinger et al. 2000). The standard regions are also recruited when attention is shifted to salient objects based on task relevance and sensory distinctiveness (Shulman et al. 2009) (Figure 3b), consistent with the idea that these regions are involved in coding the saliency of objects under both goal-driven and stimulus-driven conditions. Dorsal frontoparietal regions (mIPS, precuneus/SPL, FEF, SEF, DLPCF) are also recruited during visually and memory-guided saccades, with almost complete overlap of attention- and eye movement–related activations (Corbetta et al. 1998), and in some regions sensory signals are remapped during eye movements (Merriam et al. 2003). Both body-centered and stimulus-centered coding has been reported in IPS/SPL (Galati et al. 2010).

We previously proposed that these frontoparietal regions constituted a dorsal cortical network for the control of spatial and featural attention and stimulus–response mapping (Corbetta & Shulman 2002). Subsequent work demonstrated that at rest, many of these regions show highly correlated activity (Figure 2b), consistent with the notion that they represent a separate functional-anatomical network analogous to sensory and motor systems (Fox et al. 2006, He et al. 2007). Importantly, these dorsal frontoparietal regions are not generally damaged in neglect patients.

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**Figure 3**

Physiology of spatial attention in healthy adults. (a) Dorsal frontoparietal regions are activated following a central cue to shift attention. The statistical map shows the z-map from a meta-analysis of four experiments (n = 58) in which BOLD activity was measured following a central cue to shift attention to a peripheral location (Astafiev et al. 2003, Corbetta et al. 2000, Kincade et al. 2005). The time course of the response to the cue shows bilateral activity from right (R) IPS with a contralateral preponderance indicating spatial selectivity. (b) Occipital and dorsal frontoparietal regions show spatially selective attentional modulations following a stimulus-driven shift of attention [from a meta-analysis of two experiments (n = 47) (Shulman et al. 2009; A. Tosoni, G.L. Shulman, D.L.W. Pope, M.P. McAvoy, and M. Corbetta, unpublished data)]. Subjects were cued to attend left or right to detect targets in a rapid-serial–visual-presentation (RSVP) stream presented among distracter streams. The z-map indicates voxels showing contralateral activity > ipsilateral BOLD activity following a shift of attention to the peripheral cue (red square). Note the strong spatially selective response in right IPS and visual cortex for shifting and attending to contralateral rather than ipsilateral stimulus streams. Also, maps for purely goal-driven (Panel a) versus stimulus-driven (Panel b) shifts of attention are very consistent with a role of these regions in coding stimulus saliency under both conditions. (c) Contralateral topographic maps in dorsal parietal cortex. The left image shows five contralateral polar angle maps along R IPS. The right image shows the activations in these maps during a VSTM task in which subjects remembered the orientation and location of target lines presented among distracters. The bottom graph shows a comparison of the magnitude of contralateral and ipsilateral activations in left and right IPS maps as a function of VSTM load. Although left and right IPS contains contralateral polarangle maps (left IPS not shown), right IPS was equally activated by VSTM load in the contralateral and ipsilateral hemifields and left IPS was only modulated by load in the contralateral hemifield (Sheremata et al. 2010). This pattern of activity matches that postulated by the standard model for neglect (Mesulam 1981). (d) Interhemispheric coding of spatial attention. BOLD activity was measured following an auditory cue to attend to a peripheral location. The top right graph shows the magnitude of activity in left (L) and right (R) IPS activity on a trial-to-trial basis following leftward (blue dots) and rightward (red dots) cues. Activity in L and R FEF is highly correlated across trials, but a contralateral signal is superimposed on the positively correlated noise (i.e., blue dots plot above red dots). This correlated noise is partly explained by the presence of strong correlations at rest (bottom graph) between homologous regions (e.g., left-right FEF) or parts of maps (e.g., left-right fovea in V1). The locus of attention is only weakly predicted (AUC value = ~0.50) by reading out activity only from the portion of the map in visual cortex or area (e.g., FEF) coding for the attended location. The prediction increases significantly (AUC = ~0.80) when subtracting activity from the attended-minus-unattended homologous portion of map or area in the two hemispheres (Sylvester et al. 2007). Figure 3c is adapted from figures 3a, 3b, and 5b of Sheremata et al. 2010, with permission from the Society for Neuroscience.
as shown in the comparison of Figure 2a and 2b. Recent physiological studies of these dorsal frontoparietal regions, discussed next, have suggested two mechanisms for coding the locus of behaviorally relevant stimuli that may provide insights into the pathogenesis of spatial neglect.

**Topographic maps of contralateral space.** Computational theories show that the co-occurrence of topographic maps, eye/attention, and saliency signals is useful for stimulus selection (Koch & Ullman 1985). Correspondingly, many dorsal frontoparietal regions modulated by spatial attention, eye movements, and salience also contain polar angle maps of the contralateral hemifield (Figure 3, left image) (Hagler & Sereno 2006, Sereno et al. 2001, Swisher et al. 2007): medial IPS, precuneus, medial parieto-occipital cortex, SPL, FEF, and IFS/IFJ. Polar angle maps of the ipsilateral hemifield, however, have not been reported, indicating no evidence for separate topographic representations of both visual fields within a hemisphere, a longstanding explanation for the right hemisphere dominance of neglect (see below).
Conversely, topographic maps have not been reported in ventral regions typically damaged in neglect patients, consistent with the lack of evidence for their involvement in spatial attention. However, this null result should be treated cautiously. Maps in these regions may only be imaged with appropriate tasks or may be masked by a larger-scale organization involving other variables, such as eye position (Siegel et al. 2003). Moreover, the absence of a topographic map does not imply null spatial coding, as in rat hippocampus and entorhinal cortex (O’Keefe 2006). Spatial coding in ventral regions may occur at a scale and organization that are amenable to multivariate analyses of activation patterns, but not to standard retinotopic mapping procedures.

Interhemispheric control of the locus of attention. Interhemispheric competition may play a key role in the efficient control of spatial attention by the dorsal network (Kinsbourne 1987). Sylvester and colleagues (Sylvester et al. 2007) found that attention-related blood oxygenation level–dependent (BOLD) activity in dorsal frontoparietal and occipital regions contralateral to an attended location was only modestly predictive of whether a left- or right-field location had been cued on that trial. However, predictability was greatly increased by subtracting the activity of homologous left and right hemisphere regions, largely because activations in the two hemispheres showed strong positive trial-to-trial correlations (Figure 3d, right graph). Differenting the signals between the two hemispheres eliminated this common noise (Figure 3d, left). High interhemispheric correlation of activity also occurs at rest (Figure 3d, bottom), indicating tonic interhemispheric interactions.

Computational studies show that when signals in two brain regions are negatively correlated, as is the case with spatially selective signals in the two hemispheres, positive correlations in the noise increase the amount of information that is encoded by the corresponding neurons (Averbeck et al. 2006). The locus of attention may be efficiently coded by the two hemispheres through a difference signal implemented by interactions via either the corpus callosum (Innocenti 2009) or subcortical routes. Enhanced prediction of the locus of attention based on an interhemispheric difference signal also has been observed with electroencephalography (Thut et al. 2006) and single-unit recordings in monkey posterior parietal cortex (Bisley & Goldberg 2003).

A prediction of this model is that abnormalities in the computation of the locus of attention should correlate with abnormal interhemispheric interactions or response imbalances between the left and right hemisphere dorsal attention network. The next section discusses the physiological activity of these regions in neglect patients.

Physiological Correlates of the Egocentric Spatial Bias in Neglect

Patients with spatial neglect following lesions to right ventral cortex and underlying white matter have shown two types of physiological abnormalities in the structurally intact, dorsal attention network. First, at three weeks post-stroke, a widespread cortical hypoactivation during a spatial attention task was observed in both right and left hemispheres (Figure 4a), a finding consistent with other studies in the literature (Pizzamiglio 1998, Thimm et al. 2008). The cortical hypoactivation was associated with a large interhemispheric imbalance of activity in dorsal parietal cortex (Figure 4b). The interhemispheric imbalance normalized at the chronic stage (9 months poststroke) in parallel with an overall improvement of cortical activity and spatial neglect (Figure 4a,b) (Corbetta et al. 2005). Interestingly, activity in ipsilesional occipital visual cortex was also imbalanced, showing reductions in magnitude and spatial selectivity (Corbetta et al. 2005) that were particularly marked under high attentional loads (Vuilleumier et al. 2008). These impairments in sensory-evoked activity, possibly reflecting abnormal top-down control from...
Physiology of egocentric spatial bias in neglect patients. (a) Statistical map of BOLD activations during a Posner spatial attention task (same as in Figure 3a), in which subjects are cued to a peripheral location and detect a subsequent target. Right hemisphere acute neglect patients show hypoactivation of both hemispheres (right>left) that partly recovers at the chronic stage. The dark shading in the anatomical image indicates the distribution of structural damage (Corbetta et al. 2005). (b) As a result of right hemisphere hypoactivation, acute patients show a large imbalance of BOLD activity in IPS/SPL, with relatively greater left than right hemisphere activity, even though activity in both hemispheres is lower than normal. This imbalance normalizes at the chronic stage. The left columns show statistical maps of activity in parietal cortex, the right column shows the averaged time course of activity time-locked to the presentation of the cue over a trial of the Posner task in left (blue line) and right (red line) parietal cortex (Corbetta et al. 2005). (c) Acute neglect patients (top graph) show low correlations in BOLD spontaneous activity between homologous regions of left (blue lines) and right (red lines) parietal cortex, but the correlation recovers at the chronic stage (bottom graph) (He et al. 2007). (d) Abnormal physiological signals in the dorsal attention network of acute neglect patients are functionally significant. (Left graph) Left parietal activity was stronger in subjects with more severe neglect, as indexed by longer response times (RTs) to contralesional versus ipsilesional visual targets. (Right graph) Reduced interhemispheric correlation within frontoparietal regions of the dorsal attention network correlates with the severity of neglect of the left visual field, as indexed by longer RTs to contralesional versus ipsilesional visual targets (Carter et al. 2010).
Functional connectivity: the correlation over time of the spontaneous activity between different brain regions.

Frontoparietal cortex (Bressler et al. 2008), may further lessen the saliency of contralesional stimuli.

Second, neglect patients have shown anomalies in the pattern of spontaneous activity fluctuations within the dorsal attention network (Figure 4e). Coherence between left and right parietal regions was disrupted three weeks post-stroke and improved over time in parallel with the improvement of neglect (Figure 4e) (He et al. 2007).

Dorsal frontoparietal abnormalities in both task-evoked activity and resting coherence are functionally significant. Left parietal activity is stronger in subjects with more severe neglect, as indexed by the difference in response times to contralesional versus ipsilesional visual targets (Figure 4d) (Corbetta et al. 2005). Stronger left than right hemisphere activation of parietal and occipital regions may reflect a biased representation of stimulus salience and the locus of spatial attention (Bisley & Goldberg 2003, Sylvester et al. 2007). This interpretation is consistent with trans-cranial magnetic stimulation studies, in which inactivation of left posterior parietal cortex reduced left-field neglect (Brighina et al. 2003, Koch et al. 2008). At rest, significant correlations are found throughout the dorsal attention network between reductions in interhemispheric coherence and the magnitude of the spatial bias (Figure 4d) (Carter et al. 2010, He et al. 2007).

The anomalies in spontaneous activity may underlie the lateral rotation of the eyes, head, and body in neglect patients at rest (Fruhmann Berger et al. 2008), which likely reflect biased coding of the locus of attention and salience, and contribute to the observed abnormalities in task-evoked responses.

Therefore, in structurally intact regions of the dorsal attention network, ventral lesions induce changes in BOLD resting functional connectivity and task-evoked activity that reflect abnormal interhemispheric interactions and response balances (Kinsbourne 1987), which plausibly explain the egocentric spatial bias in neglect. Recent studies of resting blood perfusion, which assess physiological function, have associated spatial deficits in neglect patients with hypoperfusion of right IPL (Hillis et al. 2005), STG (Zopf et al. 2009), and IFG/anterior insula (Medina et al. 2008), but not of dorsal frontoparietal regions. However, these studies did not assess the functional relationship or coherence between regions, corresponding to the resting BOLD measure of the dorsal network that shows abnormalities, and did not measure task-evoked signal changes, corresponding to the other BOLD measure of dorsal network function that shows abnormalities. Moreover, the task-evoked changes measured in BOLD studies are quite small, well under 1% (Corbetta et al. 2005), and may not be detected with less-sensitive perfusion methods.

Summary

The extant literature strongly supports the presence of physiological signals (spatial attention, eye movement, saliency, maps of contralateral space, interhemispheric interactions, egocentric frame of reference) in the dorsal frontoparietal network that are likely highly relevant to the pathogenesis of spatial neglect. Recent neuroimaging results potentially resolve the paradox that ventral regions traditionally associated with neglect do not contain physiological signals that could account for an egocentric spatial bias, whereas dorsal frontoparietal regions that contain these signals are not typically damaged in strokes that cause neglect. However, only a few BOLD imaging studies have been conducted, involving relatively small patient samples. Further studies will be necessary to determine if similar changes in dorsal network physiology are observed across the different lesions that cause spatial neglect.

The above neuroimaging results, moreover, do not explain why lesions that cause neglect occur ventrally and in the right hemisphere. After more than 50 years of research, the right hemisphere dominance of spatial neglect remains the most puzzling aspect of this syndrome. These issues are considered next.
RIGHT HEMISPHERE DOMINANCE OF SPATIAL NEGLECT

Right Hemisphere Lateralization of Spatial Deficits

The right hemisphere dominance of neglect might reflect a corresponding asymmetry for spatial attention, the primary mechanism underlying the egocentric spatial deficit, and for related functions of VSTM and spatial cognition. Perhaps the most widely accepted, standard theory of neglect postulates that the right hemisphere controls shifts of attention to both sides of space, while the left hemisphere only controls attention to the right side (Mesulam 1981). Damage to the right hemisphere impairs attention to the left hemifield, whereas damage to the left hemisphere can be compensated. A second, opponent-process theory proposes that each hemisphere promotes orienting in a contralateral direction, but the strength of this bias is stronger in the left than right hemisphere (Kinsbourne 1987). Left hemisphere lesions cause only mild right spatial neglect because the unopposed orienting bias generated by the right hemisphere is relatively weak.

Empirical support for each theory from neuroimaging studies is surprisingly modest. Mapping studies have reported contralateral retinotopic maps in both hemispheres but no evidence of ipsilateral maps in the right hemisphere. Most neuroimaging studies of cueing paradigms have reported largely bilateral dorsal frontoparietal activations for directing spatial attention to locations in either visual field (e.g., Hopfinger et al. 2000, Kastner et al. 1999, Shulman et al. 2010, Sylvester et al. 2007). Several studies, however, have reported larger activations for contralateral than ipsilateral stimuli (contralateral bias) in some left than right dorsal regions (e.g., Szczepanski et al. 2010, Vandenberghe et al. 2005). These asymmetries in contralateral bias are consistent with either the standard or opponent process theory, depending on whether the bias in the right hemisphere was completely absent (standard theory) or was simply present to a lesser degree (opponent process). Given the large number of discrepant findings, however, it will be important to identify the factors controlling when the specific hemispheric asymmetry postulated by either theory is observed.

A recent study suggested that one factor might involve high loading of VSTM (Sheremata et al. 2010). Under conditions that involved high VSTM load and spatial filtering of distracters, left and right hemisphere activations in regions of IPS, which contained strictly contralateral polar angle maps, nevertheless showed the postulated visual field profile (Figure 3e). Despite this intriguing result, however, the presence of the standard visual field organization under high VSTM load does not satisfactorily explain the laterality of neglect. Contralesional neglect is correlated with conditions that do not involve high VSTM loads, such as simple detection of a single visual target (Rengachary et al. 2009). Similarly, gaze biases that correlate with contralesional neglect are present even at rest.

Finally, the laterality of contralesional neglect could partly reflect a similar laterality for aspects of spatial cognition. Variants of line bisection tasks qualitatively produce right-dominant activity in IPS/SPL after they are referenced to control tasks that largely subtract out activations from shifting and maintaining attention (Fink et al. 2001). Similarly, Sack and colleagues observed right hemisphere dominance during variants of a clock task, in which subjects judge the angle formed by hour and minute hands (Sack 2009). To explain the laterality of contralesional neglect, however, mechanisms of spatial cognition must also show the visual field organization postulated by the standard attention theory, for which there is only limited evidence (Kukolja et al. 2006).

Most importantly, right lateralization of spatial attention, VSTM, and spatial cognition has primarily been observed in dorsal parietal regions, leaving unanswered the critical question of why ventral (e.g., IFG or IPL) rather than dorsal (e.g., IPS/SPL) right hemisphere lesions cause neglect.
Right Hemisphere Lateralization and Anatomy of Core Nonspatial Deficits

An alternative explanation that addresses this question, and is fully compatible with either the presence or absence of hemispheric asymmetries in dorsal visuospatial mechanisms, links the laterality of neglect to several nonspatial behavioral deficits that are commonly observed in neglect patients (Heilman et al. 1987, Husain & Rorden 2003, Robertson 2001). Nonspatial refers to deficits that are nominally present across the visual field (e.g., the putative full-field VSTM and global processing deficits discussed above). In practice, a nonspatial deficit is rarely if ever shown to be of equal severity in the two hemifields, and measurements across the visual field are often not made, mainly because of the difficulty of separating nonspatial deficits from the egocentric spatial bias (but see Duncan et al. 1999). More commonly, conclusions are based on finding a deficit relative to control subjects for stimuli located centrally or in the ipsilesional field, although this procedure does not control for spatial gradients that extend across the visual field (e.g., Figure 1).

Below, we briefly review three core nonspatial deficits consistently observed in neglect patients. These deficits are of particular interest because, unlike the egocentric spatial mechanisms discussed above, their physiology maps closely onto the anatomy of neglect, with clear involvement of ventral right hemisphere regions. We discuss evidence for the interaction of these ventral regions, damaged in neglect, with the dorsal attention network, a critical link for understanding the pathophysiology and right hemisphere dominance of the neglect syndrome.

Reorienting of attention. Michael Posner and colleagues reported that neglect patients are impaired in reorienting to unexpected events (Posner et al. 1984). Patients showed especially large deficits in detecting contralateral targets when they were expecting an ipsilesional target, suggesting a deficit in disengaging attention from the ipsilesional field. A comparison of temporoparietal junction (TPJ)/STG versus SPL patients originally localized disengagement/reorienting deficits to right TPJ/STG (Friedrich et al. 1998). A recent study confirmed that a reorienting deficit was stronger for contralesional than ipsilesional targets following TPJ lesions, but the magnitude of the ipsilesional deficit was substantially increased following VFC lesions (Rengachary et al. 2011) (Figure 5a), indicating a bilateral deficit in reorienting.

Detection of behaviorally relevant stimuli. Right hemisphere and neglect patients show deficits in target detection in even the simplest paradigms. Simple auditory reaction time (RT), for example, is much slower following right than left hemisphere damage (Howes & Boller 1975). Related differences have been reported for auditory stimuli presented at ipsilesional locations in right hemisphere patients with neglect versus those without neglect (Samuelsson et al. 1998), indicating that the RT slowing may reflect damage to right hemisphere brain regions specifically associated with neglect (Figure 5b). Impairments are sometimes reported even for accurate detection of suprathreshold stimuli presented centrally (Malhotra et al. 2009) or ipsilesionally (although only acutely (Rengachary et al. 2011)), indicating that RT slowing likely does not reflect motor difficulties with the ipsilesional or good hand. RT slowing could reflect deficits in arousal and processing capacity (Duncan et al. 1999, Husain et al. 1997), although the latter effects occur following both left and right hemisphere damage (Peers et al. 2005).

Arousal and vigilance. Reduced arousal and vigilance is an important component of the neglect syndrome following right hemisphere injury. Clinically, patients with neglect and right hemisphere injuries suffer from lower arousal than patients with similar lesions in the left hemisphere. Arousal refers to the combination of autonomic, electrophysiological, and behavioral activity that is associated with an alert
Behavioral analyses of nonspatial deficits in neglect patients. (a) Reorienting deficits in neglect patients with VFC and TPJ lesions (Rengachary et al. 2011). Patients detected a visual target (asterisk) that occurred in a validly cued location (dotted circle) or at an invalidly cued location (shown in the figure). Both TPJ and VFC patients showed large contralesional deficits in reorienting, as indexed by longer response times (RTs) to unattended (invalid) than attended (valid) targets. The VFC group additionally showed reorienting deficits in the ipsilesional field and larger overall detection deficits. Similar results were observed for accuracy (not shown), but the TPJ group showed evidence of a small reorienting deficit in the ipsilesional field. (b) Detection deficits in neglect patients. Neglect patients show abnormally slow simple RTs to an ipsilesional auditory stimulus (Samuelsson et al. 1998). Controls were healthy age- and gender-matched subjects. The mild and severe groups consisted of non-neglect patients with minor and major right hemisphere strokes. (c) Arousal deficits in neglect patients. Parietal neglect patients show a vigilance decrement (red curve) in a task that involved detection of letter targets in two locations (arrows) within a central column. No deficit is observed in right hemisphere stroke controls without neglect (blue curve). The anatomical images show the association of damaged voxels in right TPJ with the vigilance decrement, with darker areas indicating a weaker association (Malhotra et al. 2009). Panel b is adapted from Samuelsson et al. 1998, with permission from Taylor & Francis. Panel c is adapted from figures 5a, 6c, and 7 of Malhotra et al. 2009, with permission from Oxford University Press.

state, whereas vigilance refers to the ability to sustain this state over time.

Kenneth Heilman and colleagues have argued that neglect patients have decreased arousal due to hypoactivation of the right hemisphere (Figure 4a) (Corbetta et al. 2005, Heilman et al. 1987). For instance, patients with right as opposed to left hemisphere damage do not show the typical slowing of heart rate following a cue that signals a subsequent target (Yokoyama et al. 1987) and show reduced galvanic skin responses to electrical stimulation (Heilman et al. 1978). Lesions studies have associated right frontal damage with decreased arousal (Wilkins et al. 1987) and a decrement over time in sustaining attention and detecting targets (vigilance decrement) (Rueckert & Grafman 1996).

Importantly, there is evidence for interaction between arousal/vigilance and spatial deficits. A nonspeeded, auditory counting test of arousal discriminated neglect from non-neglect patients in a right hemisphere group with heterogeneous lesions, indicating a strong linkage between arousal and spatial deficits in neglect (Robertson et al. 1997). A recent study reported a specific association between damage to right TPJ cortex and vigilance decrements, but only when attention had to be sustained to a spatial location, not for targets presented at random locations (Figure 5c) (Malhotra et al. 2009). The interaction between mechanisms underlying nonspatial and spatial deficits is likely critical for the pathogenesis and right hemisphere lateralization of spatial neglect (see below).

Right Hemisphere Lateralization and Physiology of Core Nonspatial Deficits

The above results indicate that neglect patients show nonspatial deficits in reorienting,
target detection, and arousal that are likely right hemisphere dominant. We next show that, correspondingly, physiological signals mediating these functions in the healthy brain are right lateralized and occur in ventral regions typically damaged in neglect (IPL, STG, and IFG). Interestingly, the lateralization of these processes is supported by similar findings in other species (see Right Hemisphere Dominance in Vertebrates sidebar).

**Reorienting of attention.** Neuroimaging studies of healthy adults have shown that reorienting to stimuli in either visual field that are presented outside the focus of attention (stimulus-driven reorienting) recruits a right lateralized ventral attention network in TPJ (including separate foci in SMG and STG) (Shulman et al. 2010) and VFC (insula, IFG, MFG), in conjunction with the dorsal network (Figure 6a) (Corbetta & Shulman 2002). While TPJ is uniformly activated by stimulus-driven reorienting, VFC is mainly activated when reorienting is unexpected and requires cognitive control (Shulman et al. 2009) or is coupled to a response. Because one or both conditions usually apply in real-world situations, the two regions are typically coactivated and a similar network is observed in the resting state (Figure 2b) (Fox et al. 2006, He et al. 2007).

Importantly, the cortical anatomy of the ventral attention network includes the primary regions damaged in neglect (Figure 2b, Figure 6a) and matches the localization of the reorienting/disengagement deficit (Figure 5a), indicating a clear convergence between studies in neglect patients and healthy adults (Fox et al. 2006, Friedrich et al. 1998, He et al. 2007, Rengachary et al. 2011, Shomstein et al. 2010, Shulman et al. 2010).

**Detection of behaviorally relevant and novel stimuli.** The ventral (and dorsal) attention network is activated by detection of behaviorally relevant stimuli that are unattended or unexpected with respect to a wide range of attributes, not just their location, as demonstrated by oddball tasks in which subjects report infrequent targets that differ in some feature (e.g., color, tone frequency) from a standard stimulus (Corbetta & Shulman 2002). Oddball detection, however, activates not only the ventral attention network but also additional regions

**RIGHT HEMISPHERE DOMINANCE IN VERTEBRATES**

While right lateralization in humans is often considered a byproduct of left hemisphere dominance for language, comparative studies suggest the basic specification of each hemisphere may have been present early in vertebrate evolution. MacNeilage and colleagues (2009), summarizing this work, write “...the right hemisphere, the primary seat of emotional arousal, was at first specialized for detecting and responding to unexpected stimuli in the environment.”

The latter sentence describes the human ventral attention network (Corbetta et al. 2008, Corbetta & Shulman 2002). When visual input is confined to the left eye/right hemisphere of chicks, their behavior is greatly affected by salient or novel stimuli (Rogers & Anson 1979). Feeding behavior, for example, is disrupted by the presence of brightly colored pebbles scattered among grains (Rogers et al. 2007). Similarly, during feeding, a simulated hawk is detected faster when it appears in the left than right monocular field (Rogers 2000).

Behavioral asymmetries in chicks arise partly from asymmetric light exposure prior to hatching. Following exposure, connections from the ipsilateral visual field innervate more the right than left hyperstriatum (Rogers & Sink 1988), reminiscent of the standard neglect theory. This physiology, however, varies widely across avian species. In pigeons, the asymmetry is reversed and is mediated by tectofugal rather than thalamofugal pathways (Valencia-Alfonso et al. 2009).

In mammals, right hemisphere dominance for several nonspatial functions may partly reflect asymmetric brainstem projections. The locus coeruleus/noradrenergic system in rats shows an asymmetric organization (Robinson 1985) that Posner & Petersen (1990) have linked to right lateralization of arousal. Recent evidence also points toward locus coeruleus/noradrenergic involvement in reorienting and target detection, two other lateralized, nonspatial functions associated with neglect (Aston-Jones & Cohen 2005, Bouret & Sara 2005, Corbetta et al. 2008).

The similar right hemisphere specializations in animals and humans may reflect convergent evolution rather than homology, but raise the possibility that the lateralization underlying human neglect is of longstanding origin.
in frontal, parietal, and temporal cortex that show right hemisphere dominance in direct interhemispheric voxelwise comparisons (Stevens et al. 2005). Similar, although not identical, right hemisphere regions are activated by novel stimuli that are task irrelevant (Stevens et al. 2005).

Right hemisphere dominance during target detection is observed in regions that are frequently associated with neglect (IPL, STG, IFG) and for visual targets in both left and right hemifield (Shulman et al. 2010), consistent with the nonspatial deficit in neglect (Figure 6b). Unlike the simple detection tasks studied in neglect patients, however, the above paradigms presented both targets and nontargets, and the frequency of targets was relatively low.

**Arousal and vigilance.** Neuroimaging studies of arousal and vigilance using simpler auditory and visual detection paradigms, more similar to those adopted in neglect subjects, have qualitatively reported right hemisphere dominance (direct interhemispheric comparisons were not conducted), usually in lateral prefrontal, insula/frontal operculum, and TPJ regions (Coull et al. 1998; Foucher et al. 2004; Pardo et al. 1991; Paus et al. 1997; Sturm et al. 1999, 2004). Figure 6c shows that arousal-related activations are recorded more frequently in ventral cortex of the right than left hemisphere, and are not frequently reported in dorsal frontoparietal cortex, indicating a much stronger overlap with ventral than dorsal attention networks. Importantly, arousal-related activations overlap more the ventral than dorsal attention network.

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**Ventral attention network:** regions centered around TPJ and ventral frontoparietal cortex, involved in reorienting to salient stimuli outside the focus of attention.
activations in the TPJ and insula/frontal operculum overlap with regions that are damaged in spatial neglect, and recruited during reorienting and target detection, although prefrontal activations are localized more anteriorly.

Summary

The widespread view that attention in healthy adults is right hemisphere dominant is more consistent with the evidence for right lateralization in ventral frontoparietal cortex of reorienting, detection, and arousal than the more modest evidence for right lateralization in dorsal frontoparietal cortex of the mechanisms controlling spatial attention. The main conclusion is that the right hemisphere ventral regions (IPL, STG, IFG/insula) associated with neglect underlie the above nonspatial functions impaired in patients.

VENTRAL AND DORSAL ATTENTION NETWORKS AND SPATIAL NEGLECT

What remains to be considered is how damage to these ventral regions produces the documented abnormalities in the dorsal attention network that likely underlie the egocentric spatial bias. We next consider behavioral evidence for interactions between nonspatial and spatial functions that map to ventral and dorsal regions, and physiological studies that have attempted to identify the specific pathways that might mediate these interactions. Finally, we present a novel physiological model of spatial neglect based on the structural-physiological interaction of ventral and dorsal attention networks.

Interactions Between Ventral and Dorsal Mechanisms

Recent behavioral evidence in healthy adults indicates that arousal, a right lateralized, nonspatial function impaired in neglect patients, interacts with spatial attention, the primary spatial function impaired in neglect patients. Healthy adults show a slight tendency to attend to the left side of an object (Nicholls et al. 1999), but this bias is reduced or shifted to the right under conditions of low arousal (Bellgrove et al. 2004, Manly et al. 2005, Matthias et al. 2009). The specific form of the interaction between arousal and spatial attention predicts that increases in arousal should bias attention to the left visual field, ameliorating left-field neglect.

Robertson and colleagues observed this result in two important studies. Increases in either phasic (Robertson et al. 1998) or sustained arousal (Robertson et al. 1995) decreased neglect of the contralesional field, consistent with a direct effect of the activation of ventral right hemisphere mechanisms on the dorsal attention network. Biases in spatial attention have also been observed immediately following target detection, another right lateralized, nonspatial function damaged in neglect patients (Perez et al. 2009). Perez and colleagues suggest that conditions that reduce processing capacity, such as the attentional blink and low arousal, bias spatial attention to the right.

There is currently only limited evidence of the anatomy and physiology underlying the interactions between nonspatial and spatial mechanisms observed in behavioral studies of healthy adults, and the effects of ventral lesions on dorsal physiology observed in neglect patients. Both may involve similar pathways. Studies in healthy adults have suggested possible linkages between ventral and dorsal regions that run through lateral frontal cortex. A region near IFJ, for example, that shows resting-state connectivity with both dorsal and ventral networks (Figure 2b) (He et al. 2007) and shares task-evoked properties with each network (Asplund et al. 2010) may act as a pivot point. Ventral frontal lesions that include IFJ produce greater deficits in spatial attention than temporoparietal lesions (Figure 5a) (Rengachary et al. 2011).

Putative ventral-dorsal linkages have also been evaluated by measuring the relationship between ventral to pivot-region functional connectivity and connectivity within the dorsal network. Impaired functional connectivity
between STG/TPJ and MFG, for example, is correlated with impaired interhemispheric connectivity between left and right posterior IPS/SPL, which in turn relates to the magnitude of the spatial deficit (He et al. 2007). The same study also assessed structural damage to a white matter tract that putatively connected ventral/pivot regions to the dorsal network, and observed the resulting effects on dorsal network connectivity and spatial behavioral biases. Neglect patients who suffered damage to the superior longitudinal fasciculus showed reduced interhemispheric functional connectivity in posterior parietal cortex and more severe spatial neglect. This may explain why patients with more severe neglect have more involvement of the white matter tracts connecting parietal, temporal, and frontal regions (Gaffan & Hornak 1997, Karnath et al. 2011, Verdon et al. 2010) (Figure 2c).

Consistent with this latter result, stimulating a white matter tract that connects right frontal and parietal cortex produced rightward deviations in bisection performance (Thiebaut de Schotten et al. 2005). Finally, the neural mechanisms behind ventral-dorsal interactions are unknown but may depend on synchronization of neural activity in ventral and dorsal regions that is time-locked to behaviorally relevant events (Daitch et al. 2010).

These results are provisional and exploratory but suggest that in neglect patients, both the severity of spatial biases and the interhemispheric functional connectivity of dorsal regions are related to the functional connectivity or integrity of ventral/pivot regions and to the integrity of white matter tracts that likely connect ventral and dorsal regions.

A Physiological Framework for Understanding Spatial Neglect

Our review suggests the following account of spatial neglect, as observed in L.J.’s case report. L.J.’s reduced vigilance and slowness in responding to targets, even in his right visual field, reflected impairments in arousal, reorienting, and the detection of novel and behaviorally important stimuli. These nonspatial processes are directly damaged by stroke and other focal brain injuries in neglect patients (in L.J. a ventral frontal stroke involving the anterior insula), and correspondingly, all involve in healthy adults right hemisphere ventral regions that are commonly associated with neglect, including superior temporal cortex, TPJ, IPL, and VFC/insula. These nonspatial mechanisms directly interact with spatial attention mechanisms, providing a link between damage to ventral regions and the abnormal physiology of dorsal regions. Damage to right hemisphere ventral regions, which impairs arousal, reorienting, and detection, hypoactivates the right hemisphere, reducing interactions between the ventral and dorsal attention networks and between regions of the ipsilesional (right) dorsal network. The result is unbalanced interhemispheric physiological activity in the dorsal network, both at rest and during a task, in a direction that favors the left hemisphere. As the locus of attention is coded by mechanisms that take into account activity from both sides of the brain, this imbalance drives spatial attention and eye movements to the right visual field (Figure 7a and 7b). This spatial bias explains L.J.’s tendency to look at and explore first the right visual field, and his inability to detect stimuli in the left visual field.

The right hemisphere dominance of neglect follows from the specific biases produced by right lateralized nonspatial mechanisms on the direction of spatial attention, reflecting the interhemispheric balance of activity in the dorsal network. Right hemisphere lesions may also impair mechanisms that do not directly affect the interhemispheric balance of activity within the dorsal attention network, but increase the behavioral effects produced by the extant stroke-induced imbalance. Full-field deficits in VSTM, trans-saccadic memory, and global perception may act in this fashion (Husain et al. 2001, Robertson & Rafal 2000). Finally, while physiological evidence that the right but not left hemisphere directs spatial attention to both visual fields has not been reported in the majority of studies, the predicted
Pathophysiology of spatial neglect. (a) In the healthy brain, activity during visual search is symmetric, and interhemispheric interactions between left and right dorsal attention and visual occipital areas are balanced. Each side of the dorsal attention network directs shifts of attention and eye movements contralaterally, and the locus of spatial attention is coded by a differencing mechanism that takes into account activity from both hemispheres, as described in Figure 3d and by Sylvester et al. (2007). Balanced interhemispheric activity results in a normal eye movement search pattern, shifts of attention, and coding of stimulus saliency. The ventral network is lateralized to the right hemisphere due to a slight asymmetric (right > left) arousal input from the brainstem locus coeruleus/norepinephrine (LC/NE) system, and interacts with the dorsal network (right > left). Accordingly, decreases in arousal shifts spatial attention rightward because of greater left than right activity in the dorsal attention network, while under normal conditions spatial attention shows a slight leftward bias due to slightly greater right than left dorsal activity. (b) In a patient with a ventral stroke, direct damage of ventral regions causes a reduction of arousal, target detection, and reorienting that leads to a bilateral visual field impairment. Abnormal ventral-to-dorsal interactions cause an interhemispheric imbalance in the dorsal attention network and visual cortex, leading to tonic and task-dependent rightward spatial biases in attention, eye movements, and stimulus saliency.
responses are sometimes observed (Sheremata et al. 2010), suggesting that hemispheric asymmetries in dorsal attentional mechanisms may contribute to the laterality of neglect even if they do not account for its ventral anatomy.

An important future goal is to identify the basis of right hemisphere lateralization of nonspatial mechanisms underlying reorienting, detection, and arousal. Several authors (Corbetta et al. 2008, Posner & Petersen 1990) have argued that this lateralization reflects asymmetries in cortical modulation from the locus coeruleus/norepinephrine (LC/NE) system (Robinson 1985). Lesions to right ventral cortex may damage mechanisms normally receiving strong LC/NE inputs, such as IPL (Morrison & Foote 1986), and cause widespread cortical hypoactivation.

**Problems and Omissions**

While we propose that the dorsal frontoparietal network underlies control of overt and covert spatial orienting, unilateral lesions of IPS and SPL in humans are traditionally associated with optic ataxia, i.e., difficulties in pointing rather than a general egocentric spatial bias. However, carefully placed lesions in monkey dorsal areas (e.g., Lateral Intraparietal area) cause contralateral deficits in visual search and memory-guided saccades (Wardak et al. 2004). Similarly, recent lesion studies in humans involving careful psychophysical testing found that lesions centered in SPL or in the white matter connecting IPS/SPL to FEF (superior longitudinal fasciculus) cause deficits in goal-driven shifts of attention (Shomstein et al. 2010) and abnormal capture by irrelevant distracters (Ptak & Schnider 2010, Shomstein et al. 2010), consistent with the proposed role of the dorsal attention network in directing spatial attention and coding of stimulus saliency.

The more important point, however, is that damage to dorsal regions alone is insufficient to produce the full neglect syndrome. We argue that the full syndrome depends on a combination of bilateral hypoactivation but greater on the right, associated with damage to mechanisms for reorienting, detection, and arousal in ventral frontoparietal regions and a resulting imbalance in the dorsal network, generating an egocentric spatial bias. The latter emphasis on the dysfunction of dorsal frontoparietal cortex is necessarily provisional because it partly reflects the lack of evidence that in the healthy human brain ventral regions control spatial attention and eye movements or contain topographic maps.

An important topic that we have omitted owing to space limitation concerns the role of subcortical nuclei in spatial neglect. Similarly, the current review does not consider how visuospatial deficits interact with body representations, which may underlie some of the striking symptoms shown by neglect patients, such as their denial of symptoms and confabulations about body ownership (e.g., L.J.).

**SUMMARY POINTS**

1. The primary spatial impairment in neglect patients is a failure to attend to the contralateral side of space within a reference frame centered on the observer.
2. This spatial deficit is observed both at rest and during task performance.
3. The spatial deficit reflects tonic and task-evoked interhemispheric imbalances of activity within the dorsal attention network.
4. The dorsal attention network may be physiologically impaired across the wide variety of right hemisphere ventral frontal and temporoparietal lesions that can produce neglect.
5. The right hemisphere dominance of neglect primarily reflects the laterality of nonspatial mechanisms for reorienting, detection, and arousal in right ventral frontoparietal cortex, rather than the laterality of mechanisms for spatial attention within dorsal frontoparietal cortex.

6. The activation of nonspatial mechanisms directly biases spatial attention, corresponding to the interaction of ventral and dorsal frontoparietal regions.

7. Damage to right ventral frontoparietal cortex in neglect patients impairs nonspatial functions, hypoactivates the right hemisphere, and unbalances the activity of the dorsal attention network.

8. Ventral-dorsal interactions link the ventral lesions that cause neglect to the egocentric spatial bias that is the hallmark of the neglect syndrome.

**FUTURE ISSUES**

1. What are the anatomy and physiology of the interaction between dorsal and ventral networks? Are there critical frontal regions and fiber tracts that link the two networks? How is activity in the two networks synchronized?

2. Is the right hemisphere dominance of mechanisms for arousal, reorienting, and detection related to asymmetries in the locus coeruleus/noradrenaline system?

3. Are interhemispheric imbalances in the attention-related activity of dorsal frontoparietal regions present across the wide variety of right hemisphere lesions that can cause neglect?

4. Do the ventral frontoparietal regions associated with neglect contain spatial maps that are involved in controlling attention, either independently or in conjunction with the dorsal network?

5. Under what conditions does the dorsal attention network consistently show hemispheric asymmetries in visual field organization?

6. What nonspatial manipulations bias spatial attention to the right hemifield in healthy adults? Are saliency and eye movement deficits related to arousal deficits?

**DISCLOSURE STATEMENT**

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LITERATURE CITED

Behrmann M, Geng JJ. 2002. What is ‘left’ when all is said and done? Spatial coding and hemispatial coding. See Karnath et al. 2002b, pp. 85–100


Malhotra P, Coulthard EJ, Husain M. 2009. Role of right posterior parietal cortex in maintaining attention to spatial locations over time. Brain 132:645–60


596 Corbetta • Shulman


Rogers LJ, Sink HS. 1988. Transient asymmetry in the projections of the rostral thalamus to the visual hyperstriatum of the chicken, and reversal of its direction by light exposure. Exp. Brain Res. 70:378–84


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