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The attention network of the human brain: Relating structural damage associated with spatial neglect to functional imaging correlates of spatial attention

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ABSTRACT

Functional imaging studies of spatial attention regularly report activation of the intraparietal sulcus (IPS) and dorsal premotor cortex including the frontal eye fields (FEF) in tasks requiring overt or covert shifting of attention. In contrast, lesion-overlap studies of patients with spatial neglect – a syndrome characterized by severe impairments of spatial attention – show that the critical damage concerns more ventral regions, comprising the inferior parietal lobule, the temporal–parietal junction (TPJ), and the superior temporal gyrus. We performed voxel-based lesion-symptom mapping of 29 right-hemisphere stroke patients, using several performance indices derived from a cueing task as measures of spatial attention. In contrast to previous studies, we focused our analyses on eight regions of interest defined according to results of previous functional imaging studies. A direct comparison of neglect with control patients revealed that neglect was associated with damage to the TPJ, the middle frontal gyrus, and the posterior IPS. The latter region was also a significant predictor of the degree of contralesional slowing of target detection and the extent to which ipsilesional distracters captured attention of neglect patients. Finally, damage to the FEF and posterior IPS was negatively correlated with the tendency of neglect patients to orient attention toward behaviourally relevant distracters. These findings support the results of functional imaging studies of spatial attention and provide evidence for a network account of neglect, according to which attentional selection of relevant environmental stimuli and the reorienting of attention result from dynamic interactions between the IPS, the dorsal premotor cortex, and the TPJ.

1. Introduction

Functional neuroimaging studies of spatial attention consistently report activations of several regions located in the parietal and frontal association cortex when participants are engaged in tasks probing spatial attention. The prototypical paradigm used to examine regions involved in the shifting of attention is the spatial cueing task (Eriksen & Hoffman, 1972; Posner, 1980): participants are required to detect or discriminate a stimulus presented left or right of fixation following a brief cue that summons attention to the left or right hemifield. At the behavioural level, this task reveals that detection of the target is faster when the cue indicates its correct position (valid cue) than when it orients attention to the hemifield opposite the target (invalid cue, Posner, 1980; Posner & Petersen, 1990). At the anatomical level, this pattern results in strong activation increases in dorsal fronto-parietal cortex including the intraparietal sulcus (IPS) and the frontal eye fields (FEF), a cortical area with a decisive role in saccade programming (Bruce & Goldberg, 1985; Paus, 1996; Pierrot-Deseilligny, Ploner, Müri, Gaymard, & Rivaud-Péchaux, 2002). The IPS and FEF exhibit strong activity related to the cue – independently of whether subjects move their attention covertly or by shifting their gaze – though both regions also show target-evoked activity (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Hopfinger, Buonocure, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Mort et al., 2003b; Perry & Zeki, 2000; Yantis et al., 2002). In contrast to these dorsal regions the activation of more ventral areas – the inferior parietal lobule (IPL), the temporal–parietal junction (TPJ), and the lateral prefrontal cortex – is more variable, as suggested by the failure of some studies to observe significant activity (Corbetta

Abbreviations: ANOVA, analysis of variance; BOLD, blood–oxygen level dependent; FEF, frontal eye field; fMRI, functional magnetic resonance imaging; IPL, inferior parietal lobule; IPS, intraparietal sulcus; TPJ, temporal–parietal junction; MFG, middle frontal gyrus; ROI, region of interest; VLSM, voxel-based lesion-symptom mapping; VOI, volume of interest.

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et al., 1998; Gitelman et al., 1999). However, studies attempting to distinguish activity related to the cue from activity evoked by the target reported that TPJ activity is mainly associated with the target (Corbetta et al., 2000; Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005). In addition, while the IPS and FEF increase their activity whether subjects shift attention voluntarily or reflexively, the TPJ only becomes active when a stimulus of high behavioural relevance (e.g. a distracter that possesses some target-defining properties) appears at an unexpected position (Corbetta et al., 2000; Indovina & Macaluso, 2007; Natale, Marzi, & Macaluso, 2010).

Compared to these findings, lesion studies of spatial neglect show a different picture. Patients with left neglect exhibit striking deficits of spatial attention: they may fail to find an object left of their body, particularly when it is presented together with other, distracting objects on their right; they may bump into objects on their left, or fail to react to a person addressing them from their left side (Halligan, Fink, Marshall, & Vallar, 2003; Kerkhoff, 2001; Milner & McIntosh, 2005). Neglect patients also show a supramodal deficit of attentional disengagement from ipsilesional cues (Bartolomeo, Siéroff, Decaix, & Chokron, 2001; Golay, Hauert, Greber, Schnider, & Ptak, 2005; Posner, Walker, Friedrich, & Rafal, 1987). Several lesion studies have attempted to specify the region critical for spatial neglect by analysing the maximal overlap of multiple lesions or by comparing patients with neglect to right-hemisphere damaged patients without neglect. These studies identified the inferior parietal lobule (Golay, Schnider, & Ptak, 2008; Mort et al., 2003a; Vallar & Perani, 1986), the white matter beneath the central sulcus (Doricchi & Tomaiuolo, 2003), and the superior temporal gyrus (Karnath, Fruhmann Berger, Küker, & Rorden, 2004) as the brain regions whose damage is most predictive of spatial neglect. Importantly, none of the studies that used a lesion-averaging approach reported an association of spatial neglect with damage to the IPS or FEF. Thus, whereas functional imaging studies of spatial attention regularly report activation of a dorsal fronto-parietal network, lesion studies frequently report damage to more ventral regions and fail to present evidence that would support involvement of the dorsal network.

A tempting solution to this paradox is to ascribe such discrepancies to the methodological limits of functional imaging and lesion studies. For example, activation of the dorsal fronto-parietal network might be considered as epiphenomenal and thus not necessary for spatial attention. However, this explanation fails to consider two important findings: First, neurons in the posterior parietal cortex (Bisley & Goldberg, 2003; Bushnell, Goldberg, & Robinson, 1981; Cohen, Cohen, & Gifford, 2004; Constantinidis & Steinmetz, 2001; Gottlieb, Kusunoki, & Goldberg, 1998) and the FEF (Bichot & Schall, 1999; Fecteau & Munoz, 2006; Thompson, Hanes, Bichot, & Schall, 1996) are critically involved in biasing attention in favour of particular stimuli or locations in space. Second, though structurally intact, the dorsal fronto-parietal network is nevertheless functionally impaired in the acute phase of neglect (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005), and damage or functional inhibition of the main fibre tract interconnecting the intact IPS and FEF results in signs of neglect (Shinoura et al., 2009; Thiebaut de Schotten et al., 2005).

Here, we explore the possibility that the dorsal regions apparently lying outside the typical lesion area of neglect patients are not systematically damaged and thus escape the lesion averaging approach. Indeed, previous lesion studies were mostly interested in the 'critical' damage predicting spatial neglect relative to control patients, and thus may have failed to highlight rarely damaged, yet important regions lying in the dorsal network. Neglect is a heterogeneous disorder, and may affect attentional, intentional, or representational processes to different degrees, as a function of the extent to which damage extends into parietal (Binder, Marshall, Lazar, Benhamin, & Mohr, 1992; Golay et al., 2008), temporal (Hillis et al., 2005; Ptak & Valenza, 2005), or prefrontal cortex (Husain & Kennard, 1997; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). If regions such as the FEF, prefrontal cortex, or cortex around the IPS are only involved in a relatively small number of neglect patients (or subgroups characterized by specific patterns of impairment) this comparison will fail to confirm their importance.

This problem has much to do with statistical power. Voxel-based lesion-symptom mapping (VLSM) analyses examine the implication of anatomical regions in the manifestation of a behavioural symptom by performing a statistical test on each damaged voxel (Bates et al., 2003; Kimberg, Coslett, & Schwartz, 2007; Rorden, Karnath, & Bonilha, 2007). Given that across several patients many thousands of voxels may be damaged this procedure amounts to a vast number of statistical tests being performed. Consequently, in order to decrease the risk of alpha (false positive) error it is important to perform adequate corrections of the level of statistical significance. However, given the high number of statistical comparisons the correction of the alpha-level often leads to the statistical analysis being overly conservative, seriously limiting the number of significant results. In order to reduce the number of statistical tests to be performed, functional neuroimaging studies often confine statistical analysis to specific regions of interest (ROI). The methodological rationale of this approach relies on the assumption that the choice of ROIs is independent of the statistical significance observed in the examined data set: independence would be violated if only regions that provide the most significant results in a preliminary analysis were selected as ROIs for further statistical treatment (Vul, Harris, Winkielman, & Pashler, 2009).

The aim of this study was to verify the hypothesis that the lesion-overlap method underestimates the contribution of key regions of the fronto-parietal attention network to spatial attention deficits in neglect. We therefore used the ROI approach to analyse a data set comprising 20 neglect patients whose maximal overlap of lesions is localized in the right inferior parietal lobule (Ptak & Schnider, 2010). We avoided the independence error by selecting ROIs based on regions identified by previous functional imaging studies of spatial attention. In addition, we tested whether damage to specific ROIs is predictive of performance in parameters of attentional orienting derived from a spatial cueing task.

2. Materials and methods

2.1. Participants

Twenty patients with left spatial neglect (13 females), 10 right-hemisphere (RH) damaged control patients without neglect (4 females), and 10 healthy controls (6 females) were involved in this study. Since the focus of the study was on impairments of attentional orienting that characterize neglect, we did not seek to equalize group sizes. Approval was obtained from the ethical committee of the University Hospitals Geneva, and all participants gave written consent. Patients were examined within a week while hospitalized for neurorehabilitation following a first-ever ischemic or haemorrhagic stroke.

Table 1 shows demographic data and the results of clinical testing of neglect and control patients. All patients had preserved visual fields for the central $\sim 20^{\circ}$ as assessed with computerized perimetry testing and/or clinical confrontation. All neglect patients manifested behavioural signs of left unawareness (e.g. failure to notice objects or persons placed on their left, difficulties with dressing or grooming) and lateralized failures in the following neglect tests: 'Bells' cancellation (Gauthier, Dehaut, & Joanette, 1989), cancellation of inverted among upright Ts, line bisection (Schenkenberg, Bradford, & Ajax, 1980), sentence copying (Wilson, Cockburn, & Halligan, 1987), and copying a landscape. The three groups had similar age (ANOVA: $F_{2,37} = .13$), and the elapsed time between lesion onset and testing was comparable between the two patient groups (T-test: $t_{28} = .88$). The neglect group scored significantly worse compared to RH-controls on 'Bells' cancellation (Mann–Whitney $z = 3.67$, $p < .001$), 'T' cancellation ($z = 4.41$, $p < .0001$), line bisection ($z = 2.46$, $p < .05$), sentence copying ($z = 2.30$, $p < .05$) and the landscape-copying test ($z = 3.42$, $p < .001$).