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Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping

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Spatial neglect is a perplexing neuropsychological syndrome, in which patients fail to detect (and/or respond to) stimuli located contralaterally to their (most often right) hemispheric lesion. Neglect is characterized by a wide heterogeneity, and a role for multiple components has been suggested, but the exact nature of the critical components remains unclear. Moreover, many different lesion sites have been reported, leading to enduring controversies about the relative contribution of different cortical and/or subcortical brain regions. Here we report a systematic anatomo-functional study of 80 patients with a focal right hemisphere stroke, who were examined by a series of neuropsychological tests assessing different clinical manifestations of neglect. We first performed a statistical factorial analysis of their behavioural performance across all tests, in order to break down neglect symptoms into coherent profiles of co-varying deficits. We then examined the neural correlates of these distinct neglect profiles using a statistical voxel-based lesion-symptom mapping method that correlated the anatomical extent of brain damage with the relative severity of deficits along the different profiles in each patient. Our factorial analysis revealed three main factors explaining 82% of the total variance across all neglect tests, which suggested distinct components related to perceptive/visuo-spatial, exploratory/visuo-motor, and allocentric/object-centred aspects of spatial neglect. Our anatomical voxel-based lesion-symptom mapping analysis pointed to specific neural correlates for each of these components, including the right inferior parietal lobule for the perceptive/visuo-spatial component, the right dorsolateral prefrontal cortex for the exploratory/visuo-motor component, and deep temporal lobe regions for the allocentric/object-centred component. By contrast, standard anatomical overlap analysis indicated that subcortical damage to paraventricular white matter tracts was associated with severe neglect encompassing several tests. Taken together, our results provide new support to the view that the clinical manifestations of hemispatial neglect might reflect a combination of distinct components affecting different domains of spatial cognition, and that intra-hemispheric disconnection due to white matter lesions might produce severe neglect by impacting on more than one functional domain.

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Introduction

Spatial hemineglect is a common and striking neuropsychological syndrome, in which patients fail to detect (and respond to) stimuli located contralaterally to a focal hemispheric lesion, even in the absence of primary sensory or motor deficits (Vallar, 1998; Mesulam, 1999). Hemineglect entails severe deficits in spatial awareness and behaviour that correlate with poor prognosis for long-term recovery (Hier *et al*., 1983). A better knowledge of the neural mechanisms underlying this complex syndrome is not only crucial to understand spatial cognition in humans better, but also to improve rehabilitation strategies.

However, hemineglect is characterized by a large heterogeneity in both clinical manifestations and neuroanatomical correlates, leading to several ongoing controversies. Many dissociations have been described between different aspects of neglect (Halligan *et al.*, 2003); and in clinical practice, many patients may show neglect in a given test but not in another. Hence, the neuropsychological diagnosis of neglect usually relies on batteries that include several different tests (e.g. cancellation, line bisection, drawing, reading, writing, etc.) rather than on a single measure, in keeping with the idea that it is a multi-componential syndrome (Driver *et al.*, 2004; Vuilleumier *et al.*, 2007). This complexity also accords with the multiple lesion sites associated with neglect (Mesulam, 1999). Nevertheless, most studies investigating the neuroanatomical substrates of neglect still tend to consider neglect as a unitary deficit, often diagnosed by averaging performance across different tests (Karnath *et al.*, 2001; Mort *et al.*, 2003), which might possibly account for different findings obtained in different populations of patients. In the present study, we sought (i) to identify distinct functional components underlying neglect symptoms across a range of clinical tests in a large patient group, using an objective statistical approach; and (ii) to determine whether these components might correspond to distinct neural substrates by using voxel-based lesion mapping.

Clinical dissociations within the neglect syndrome

Behavioural dissociations between neglect symptoms may concern many different domains, including sensory modality, reference frame, spatial scale, or motor effectors (among others), but few studies have suggested specific brain correlates for these dissociations (Hillis *et al.*, 2005; Committeri *et al*., 2007). Our study examined only some of these various dimensions, therefore we will not provide an exhaustive review here (see Kerkhoff, 2001). One of the most classic distinctions is between "egocentric" versus "allocentric" neglect, whereby patients miss stimuli located on the contralesional (left) side of their spatial environment versus the left part of each stimulus regardless of its location in space, respectively. Although both egocentric and allocentric neglect can affect performance on cancellation tasks by producing omissions on the left side of the page (Hillis *et al.*, 2005), these two components can be distinguished by some tests, such as Ota's search task (Ota *et al*., 2001) or compound-word reading. In a recent study of acute stroke patients (Hillis *et al.*, 2005), egocentric and allocentric neglect were associated with distinct sites of hypoperfusion in parietal (right angular gyrus) and temporal regions (right superior temporal gyrus), respectively.

Other dissociations have been described between different sectors of space such as around the body surface (personal space), within reaching distance (near extrapersonal space), or outside reaching distance (Halligan and Marshall, 1991; Vuilleumier *et al.*, 1998). Most often, however, personal and extrapersonal neglect are associated rather than dissociated, although a recent study (Committeri *et al.*, 2006) suggested that deficits for extrapersonal space might correlate with lesions in a right frontal and superior temporal network, whereas deficits for personal space might relate to the right inferior parietal lobe. Finally, several authors proposed to distinguish between perceptual and motor components of neglect (Bisiach *et al.*, 1990), possibly associated with different lesions in parietal and frontal areas, respectively. However, other studies have cast doubt on this distinction by showing that patients with parietal lesions may also exhibit motor neglect unexplained by perceptual deficits (Mattingley *et al*., 1998).

Anatomy of hemispatial neglect

In parallel to these multiple behavioural facets, many different brain regions are known to be implicated in the neglect syndrome. At the cortical level, critical lesions have been reported in the temporo-parietal junction (Heilman *et al.*, 1983; Vallar and Perani, 1986), posterior parietal cortex (Mesulam, 1999; Azouvi *et al.*, 2002), angular gyrus (Mort *et al.*, 2003; Hillis *et al.*, 2005), supramarginal gyrus (Doricchi and Tomaiuolo, 2003; Buxbaum *et al*., 2004), superior temporal gyrus (Karnath *et al.*, 2001, 2003, 2004; Ringman *et al.*, 2004), insula (Karnath *et al.*, 2004), as well as dorsolateral and inferior fontal corticies (Heilman and Valenstein, 1972; Husain and Kennard, 1997; Ringman *et al.*, 2004). At the subcortical level, damage to the thalamus (Watson and Heilman, 1979; Cambier *et al.*, 1980; Ringman *et al.*, 2004) and basal ganglia (Vallar and Perani, 1986; Ferro *et al.*, 1987; Karnath *et al.*, 2004; Ringman *et al.*, 2004) may also produce neglect. Finally, lesions in the subcortical white matter around the frontal, temporal, and parietal lobes have also been described (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten *et al.*, 2005; Bird *et al.*, 2006; He *et al.*, 2007; Shinoura *et al.*, 2009), suggesting that some disconnection between cortical and/or subcortical areas might be responsible for neglect (Gaffan and Hornak, 1997).

Hence, several controversies remain concerning the role of these different brain structures (Milner and McIntosch, 2005). In particular, whilst several studies suggest that damage to the right inferior parietal lobe might be critical (Vallar and Perani, 1986; Azouvi *et al.*, 2002; Mort *et al.*, 2003; Hillis *et al.*, 2005), other

recent studies in large samples of patients found that the superior temporal cortex was the most common site of injury (Karnath *et al.*, 2001, 2004; Ringman *et al.*, 2004). Most of these lesion mapping studies examined anatomical damage by computing the maximal overlap of lesions in patients with neglect relative to those without neglect (Doricchi and Tomaiuolo, 2003), or by subtracting lesion extent in patients without neglect from those with neglect (Karnath *et al.*, 2001; Mort *et al.*, 2003). However, these anatomical studies brought conflicting results, which might reflect limitations inherent to comparing different patients with heterogeneous deficits.

Firstly, to prove that a cerebral area is critical to a deficit would require showing not only that damage to this area produces the deficit, but also that preservation of this area does not produce such deficit, a prediction not systematically tested in overlap studies of neglect (Rorden and Karnath, 2004). Secondly, discrepancies between studies might reflect differences in diagnostic criteria and/or clinical tests used. For instance, neglect was defined by tests including line bisection in some studies [for example, Mort *et al*. (2003) reported a crucial role for parietal areas], but without line bisection in other studies [Karnath *et al*. (2001) reported a key role for temporal areas]. There is no single or perfect test to assess neglect, as there might be distinct subtypes or different cognitive components within this syndrome, therefore it is unlikely that damage to a unique area could explain all of its clinical manifestations. Another major problem of previous anatomical studies is that neglect has typically been diagnosed as a unitary entity, e.g. when deficits were found 'in at least one (or two) tests' out of a battery (Karnath *et al.*, 2001, 2004; Mort *et al.*, 2003), or when a total score averaged from multiple tests surpassed a predefined threshold (Ogden, 1985). Thus, in such studies, different patients could be included in the same "neglect group" (because of their similar total score) even though they showed deficits in different tests. Yet, it is known that the severity of neglect may show a relatively poor correlation between different tests (Hier *et al.*, 1983; Agrell *et al.*, 1997, Buxbaum *et al.*, 2004). Finally, measures of lesion overlap across patients may be insufficient to identify reliable brain–behaviour relationships when multiple lesion sites are potentially implicated in the same function (Godefroy *et al.*, 1998) – as it is in fact observed in neglect. For instance, if a deficit can result from damage to either region A or region B, but such damage always extends to a third neighbouring region C between A and B (due to anatomical or vascular factors), it is possible that the greatest overlap across the whole group of patients would be placed in C (rather than A or B).

In our study, we therefore adopted a different approach. First, we used a comprehensive battery of several standard tests to assess neglect symptoms in a large population of right brain-damaged patients and probed for the existence of distinct functional components underlying these symptoms, by applying a factorial statistical analysis to results from all tests. We then investigated the neural correlates of each component separately, by using a quantitative statistical mapping analysis of brain damage in each patient. Our voxel-based lesion-symptom mapping (VLSM) approach allowed a correlation of lesions on a voxel-by-voxel basis with continuous behavioural measures, rather than based on dichotomous group classification (Bates *et al.*, 2003). We reasoned that, while each individual test may not measure a single cognitive component of hemispatial neglect, some aspects of the syndrome might be reflected by performance on a few tests and not on others. Thus, a factorial analysis based on the pattern of results from several tests should uncover the major functional dimensions of neglect behaviour, which should in turn help determine distinct anatomical correlates corresponding to the cognitive processes associated with each dimension. This approach might reconcile discrepancies between previous anatomical studies, and clarify the critical nodes within large-scale brain networks that underlie neglect syndrome and spatial cognition in humans.

Methods

Patients

We recruited 80 patients (47 males) with a first right hemisphere stroke (four left-handed), who were consecutively admitted to the Neurology Department of Geneva University Hospital during a 2-year-period. No previous cerebral damage was reported in their medical history. Their mean age was 67 years (SD 14.6; range 22–89 years) and the mean time of testing since stroke onset was 14.8 days (SD 6.9; range 6–23 days). Thus, neglect was assessed in the acute and subacute stages, when deficits are most pronounced. According to neuropsychological testing (see below), 16 patients showed severe neglect (i.e. deficits on at least four of all tests administered) and 25 patients showed no sign of neglect (i.e. no deficit in any of the tests). The remaining patients ($n = 39$) showed different degrees of neglect severity on the different tests.

Neuropsychological assessment

Neglect was assessed in each patient using a systematic battery of standard paper-and-pencil tests that could be easily administered in a clinical setting. Our battery focussed on classic tests assessing extrapersonal neglect in near space, which have been widely employed in clinical practice and previous studies (Ogden, 1985; Vallar and Perani, 1986; Karnath *et al.*, 2001, 2004; Mort *et al.*, 2003). However, we took care of selecting tests that tap into a range of different domains, including perceptual, attentional, and visuo-motor activity (Azouvi *et al*., 2002), as well as both space-based and object-based processing (Hillis *et al.*, 2005). These tests included the following:

(i) Bells cancellation (Gauthier *et al.*, 1989): patients were asked to mark all bells disseminated among distractors (i.e. other symbols), on an A4 sheet of paper presented horizontally. The main score was the difference between omissions on the left side relative to the right side of space (see below).

(ii) Copy of a landscape (Gainotti and Tiacci, 1970): patients were asked to copy a drawing made of five elements (two trees, a fence, a house, a pine-tree) arranged horizontally on an A4 sheet of paper. The score consisted of the number of items omitted and ranged from zero (no omission) to five (all items omitted). We did not separate object-based from space-based errors, because the first were difficult to distinguish reliably from constructive apraxia.

(iii) Line bisection (Schenkenberg *et al.*, 1980): patients were asked to mark the middle of five 20 cm horizontal lines, presented

Table 1 Neglect scores derived from neuropsychological tests and range of performance observed in the 80 patients with right hemisphere damage

Tests	Scores	Range
Bells cancellation	Omissions (left) – omissions (right)	From −2 to 13
Drawing copy	Number of items (drawings) omitted	From 0 to 5
Line bisection	Leftward deviation from the true centre (in mm)	From −10 to 77
Text reading	Omissions (left) – omissions (right)	From 0 to 36
Compound-word reading	Egocentric errors (left) – egocentric errors (right) Allocentric error (left) – allocentric errors (right)	From −1 to 13 From −5 to 4
Ota search task	Egocentric errors (left) – egocentric errors (right) Allocentric errors (left) – allocentric errors (right)	From −2 to 19 From −1 to 9

individually on an A4 sheet of paper. The score was the magnitude of rightward deviation from the true centre (in millimetres), and results for the five lines were averaged.

(iv) Text reading: patients were asked to read aloud a paragraph composed of eight lines presented on an A4 sheet of paper, commonly used in our clinical neuropsychology unit (Mayer *et al*., 1999). The score consisted of the number of words omitted on the left side.

(v) Reading of compound-words: patients were asked to read aloud 23 single words that were compound names (i.e. *"tiroir-caisse"*), all dispersed pseudo-randomly on an A4 sheet of paper. Two scores were obtained to reflect egocentric neglect (omissions of words on the left side of the sheet) and allocentric neglect (omission of the left part of word regardless of their position on the sheet).

(vi) Ota search task (Ota *et al.*, 2001): patients were asked to mark all circles with a gap (on the circle's left or right side) among other circles without gap. Two scores were obtained to reflect egocentric neglect (omissions of targets on the left side of the sheet) and allocentric neglect (omission of targets with a gap on their left).

Other symptoms often associated with neglect (such as extinction or anosognosia) were assessed using the procedure described by Bisiach *et al.* (1986). Additional tests were also given to examine mental imagery, motor biases, or memory in a few patients. Due to clinical contingencies, some of these tests could not be administered in all cases during the acute hospitalization phase, and will therefore not be reported here.

The tests above were used to compute eight different scores in each individual patient. Three tasks yielded a single score of left inattention defined by the number of omissions on the left side relative to the right side of space (bells cancellation, text reading, landscape copy). This comparison might underestimate neglect when patients with severe deficits do not cross the midline and make many right-sided omissions (Chatterjee *et al.*, 1999); therefore, we used a modified measure of spatial asymmetry by computing the sum of omissions on the leftmost and central thirds of the sheet minus the number of omissions on the right third of the sheet (10 in each sector). Although slightly different methods have also been proposed to control for this problem (Bartolomeo *et al.*, 1994), we could verify that this measure captured both the asymmetry and severity of inattention when inspecting individual data from our patients. Line bisection errors were quantified by the amount of leftward deviation from the true centre. Two tasks (word reading and Ota cancellation) provided two different measures each, assessing space-based and object-based neglect, respectively. Table 1 describes the range of performance observed on each test across the 80 patients and the scores used in our subsequent statistical analysis.

Table 2 Principal components obtained by factor analysis and corresponding amount of variance explained, eigenvalues, and factor loadings for the eight test scores

	Comp. 1	Comp. 2	Comp. 3
Variance explained	49.3%	22.4%	10.4%
Eigenvalues	3.943	1.796	0.831
Text reading	0.87	0.26	0.08
Line bisection	0.86	0.03	0.05
Compound-word reading (egocentric errors)	0.82	0.24	0.15
Drawing copy	0.48	0.06	0.41
Ota search task (allocentric errors)	0.20	0.91	0.04
Compound-word reading (allocentric errors)	0.22	0.89	0.10
Ota search task (egocentric errors)	0.32	0.24	0.79
Bells cancellation	0.21	0.02	0.95

For compound-word reading and Ota task, *'egocentric errors'* refer to omissions of targets in left space, and *'allocentric errors'* refer to transformations of the left side of targets independently of their spatial location.

A factorial analysis was then performed on the eight test scores from all patients, using a standard procedure with varimax rotation and Kaiser normalization in the Statistical Package for the Social Sciences 15.0 (SPSS Inc., Chicago, Illinois, USA). We selected the most significant factors on the basis of the amount of variance explained for components with eigenvalues above 0.8 (Table 2). Then, we extracted the relative contribution (loading) of each test score to these factors, as well as the relative magnitude of each factor for each individual patient. The latter values were then used for the VLSM.

Brain imaging and lesion analysis

Each patient underwent a standard clinical radiological assessment including MRI and/or CT scans of the brain, according to standard stroke protocols at the Radiology Department of Geneva University Hospital. Brain MRI scans included T_1, T_2, fluid attenuated inversion recovery, and diffusion images obtained with standard parameters on a 1.5 T Philips Intera scanner. Lesion extent was determined for each

patient by selecting brain scans that showed the greatest extent of damage and drawing the lesion borders directly onto the original 3D images, using the MRIcro software (Rorden and Brett, 2000) available on-line (http://www.sph.sc.edu/comd/rorden/mricro.html). Five patients could not undergo MRI and had only a brain CT scan available. Their lesions were delineated using a similar procedure, first drawn from the CT image and then transposed to the standard MRI template of MRIcro. All lesion maps were double-checked by a neurologist (PV) and a clinical neuropsychologist (VV) trained to read brain scans. The 3D brain scan and lesion volume were then normalized to a standard brain template using a combination of MRIcro (http://www.mricro.com/lesionmask.zip) and Statistical Parametric Mapping-2 (http://www.fil.ion.ucl.ac.uk/spm) running under Matlab (http://www.mathworks.com). The normalized lesion images were used as a region of interest for subsequent analysis in MRIcro (to compute group overlap and group comparisons), as well as for voxel-based statistical analysis using the VLSM software (http://crl.ucsd.edu/vlsm).

Three complementary types of analysis were conducted on the lesions of our patients (see below). First, we examined the overlap of the normalized lesion regions of interest for specific subgroups of patients (e.g. those with or without neglect). Second, we performed statistical comparisons between groups of patients using voxel-by-voxel *t*-tests on lesion extent in normalized brain coordinates. Similar overlap and paired comparison approaches have been widely used in recent studies of neglect (Karnath *et al.*, 2001, 2003, 2004; Mort *et al.*, 2003), but can be criticized (Committeri *et al.*, 2006) because they classify patients based on their qualitative performance across one or several tests (i.e. passed or failed) without taking in account the quantitative performance (i.e. the exact score of each patient in individual tests). Although this overlap analysis might be seen as inferior compared to the (subsequent) VLSM analysis, it is reported to allow comparison with the latter and with traditional studies. Therefore, in the present study, our third and main analysis used VLSM to obtain a finer (and more quantitative) analysis of behavioural performance across different tests, allowing us to map the functional components identified by our prior factorial analysis. VLSM is a voxel-based statistical method that allows a correlation between continuous behavioural measures and lesion on a voxel-by-voxel basis, similar to voxel-based morphometry (Bates *et al.*, 2003). Here, we performed a parametric mapping analysis of individual lesion regions of interest weighted by the component scores obtained from the factorial analysis for each individual patient, in order to determine brain areas whose damage had the greatest impact on each of the identified factors. All reported peaks were significant at $P<0.001$ uncorrected at the singe voxel level (minimizing for false positives) and survived Bonferroni correction cutoffs at $P<0.05$ for multiple comparisons (Bates *et al.*, 2003; Committeri *et al.*, 2006). For illustration purpose, statistical maps of lesion distribution are displayed at uncorrected thresholds (except for Fig. 5). The same VLSM methodology has been applied in previous studies on language (Baldo *et al.*, 2006), motion perception (Saygin *et al.*, 2004), or dissociations between personal and extrapersonal neglect (Committeri *et al.*, 2006). However, our study is the first to apply this method to components estimated by an independent, data-driven factorial analysis.

Results

Factorial analysis

The results of our factorial analysis on neglect test scores from all 80 patients extracted three significant factors that explained 82.1% of the total variance observed. In other words, factorial analysis indicated that three basic components could account for a substantial part of the performance of patients across all neglect tests.

Table 2 summarizes the factor loadings of each test score for these three principal components, and Fig. 1 plots the relative importance of factor loadings across tests. As can be seen, different clusters of tests could be distinguished as a function of their

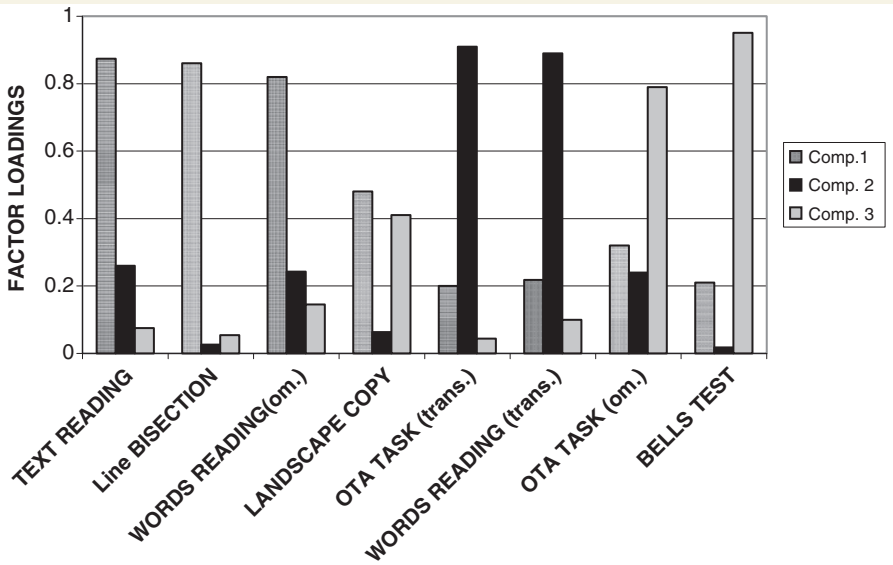

Figure 1 Illustration of the relative loading of each clinical test for the three main components identified in the factorial analysis (for words reading and Ota task, *'om.'* refers to omissions of targets in left space, and *'trans.'* refers to transformations of the left side of targets independently of their spatial location).

loading on a specific factor. The first factor regrouped performance on text reading and left-sided omissions in word reading, together with deviation on line bisection. The second factor regrouped the two scores reflecting object-based neglect, i.e. transformations of the initial left-part of words in the compound-word reading task, plus omissions of targets defined by a gap on their left-side in Ota search task. Finally, the third factor regrouped the number of misses in left space for the two cancellation tests (Bells and Ota search task). In addition, performance on the drawing task (landscape copy) showed loading values that were almost equally distributed between factors 1 and 3. This pattern might be consistent with a perceptive visuo-spatial component associated with factor 1 and a more exploratory visuo-spatial component associated with factor 3, which could both contribute to neglect on the drawing task.

Although our factorial analysis was performed using an orthogonal (*varimax*) rotation to obtain independent factors, the factorial scores obtained for each patient were nevertheless positively correlated. This is relatively unsurprising given that we compared a large group of patients with and without neglect signs, such that there is a general correlation between absolute score values from the factorial analysis due to non-specific lesion severity effects. Furthermore, we note that the correlation was higher between factors 1 and 3 (0.71), that both reflected egocentric aspects of neglect (i.e. egocentric), than between factors 1 and 2 (0.46) or 2 and 3 (0.48) that reflected different aspects of egocentric and allocentric neglect.

In any case, it would be problematic to use the raw factorial scores themselves to conduct a VLSM analysis of brain lesions since their correlation would be likely to yield similar anatomical correlates. We therefore computed a composite index for each neglect component identified by the previous factorial analysis, based on individual results in all those tests that showed reliable loading values ($\geqslant 0.4$) on a particular component. The behavioural performance of each patient in each test was first normalized to a *z*-score value (to be comparable across tasks), and these values were then grouped together into a specific composite index according to their dominant factor loadings. The drawing task showed factor loadings equally distributed between factors 1 and 3, therefore we attributed half of the performance scores on this test to each of these two factors. Thus, the composite index for factor 1 was calculated by summing the *z*-scores obtained on text reading, words reading (omissions), line bisection, plus half of the *z*-score on the drawing task. The composite index for factor 2 was the sum of left-sided transformations in the compound-word reading task, plus omissions of the left-gap targets in Ota search task. Finally, the composite index for factor 3 combined the number of targets missed in left space during Ota search task and bells cancellation, plus half of the *z*-score on the drawing task. To illustrate this procedure, in a given patient, the composite index for the first factor was: (*z*-score for the omissions on text reading) + (*z*-score for omissions on word reading) + (*z*-score for deviation in line bisection) + 0.5 × (*z*-score for performance on the drawing task). Although this procedure cannot entirely abolish the positive relation between factors, the correlations between our three composite indices were strongly reduced (0.58 between indices 1 and 3, 0.24 between indices 1 and 2, and 0.25 between indices 2 and 3). These composite indices were subsequently used in our VLSM lesion analysis.

Lesion overlap analysis

The overall distribution of right hemisphere damage among all patients is shown in Fig. 2A. To determine the anatomical correlates of hemispatial neglect, we first computed the overlap of lesion regions of interest in MRIcro for patients with or without neglect. Two subgroups of patients were created by separating those who exhibited consistent neglect (deficits in at least four of the clinical tests used; $n = 16$) and those who had no sign of neglect in any of these tests ($n = 25$). The 39 patients with intermediate performance (neglect in <4 tests) were not included in this overlap analysis. Figure 2B shows that the maximal lesion overlap in the neglect group falls in the subcortical white matter next to the lateral ventricle and above the insula [Montreal Neurological Institute (MNI) coordinates: 29, −20, 20]. No consistent lesion pattern was found in the group without neglect (Fig. 2C).

However, a potential problem with this traditional overlap method is that the lesion maxima could reflect the centre of mass of the distribution of large strokes within the right hemisphere, instead of truly specific correlates of neglect. Indeed, lesion overlap across the whole group of 80 patients also highlighted a frequent damage in similar subcortical white matter regions (Fig. 2A).

We therefore performed a direct statistical comparison between lesions in the patient group with consistent neglect across all tests ($n = 16$) and lesions in the patient group with a clear absence of neglect ($n = 25$), using voxel-by-voxel chi-square statistics (Rorden and Karnath, 2004). Figure 3 shows the result of this analysis, with yellow regions indicating the significant ($P < 0.001$) difference between neglect and control patients. Compared to the controls, neglect patients showed a much more frequent involvement of the subcortical white matter that extended from the posterior paraventricular regions in the depth of the parietal lobe (peak MNI coordinates: 29, −29, 18) towards more anterior regions in the frontal lobe (peak MNI coordinates: 20, −2, 30), above the insula and basal ganglia. This subcortical region overlaps with the parieto-frontal fibre-tracts (superior occipito-frontal fasciculus and superior longitudinal fasciculus), as identified by diffusion tensor imaging studies of the healthy human brain (Catani *et al.*, 2002), and agrees with other recent anatomical studies of neglect (Bartolomeo *et al.*, 2007).

However, another potential limitation of this standard mapping approach is that a multi-component and multi-focal disorder might be improperly localized to a third, marginal area located between two other critical sites that are separated by some distance, each of which could be damaged in a portion of the patients only (Godefroy *et al.*, 1998). To examine this question, we further split our patients into subgroups who had mainly anterior lesions (i.e. largest extent in front of sensorimotor cortices) or mainly posterior lesions (i.e. largest extent behind sensorimotor cortices), and again compared those with neglect ($n = 8$ and 6, respectively) and those without neglect ($n = 5$ and 7, respectively) across all clinical tests. (An intermediate group of 16 patients with large or

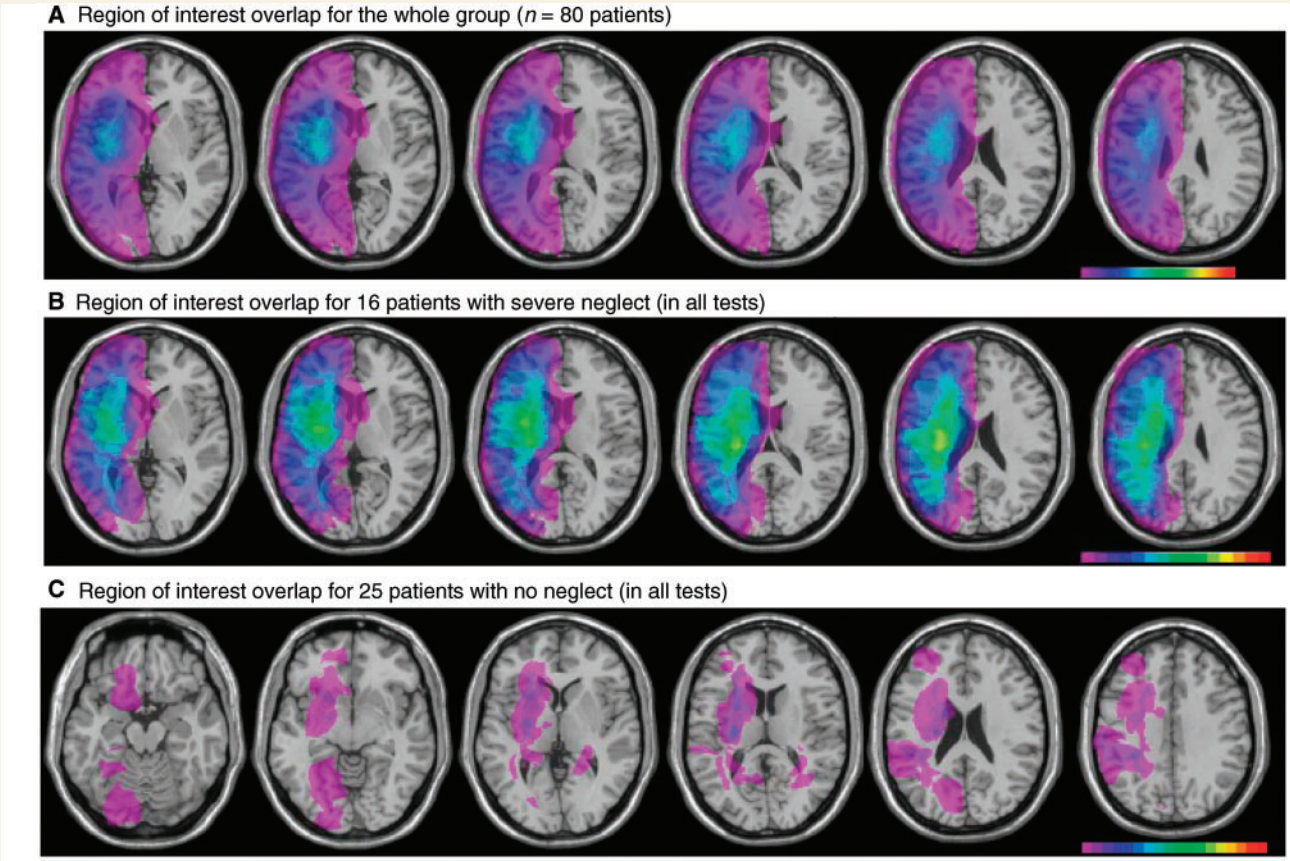

Figure 2 Overlap of the brain lesions for (**A**) all 80 patients included in our study, (**B**) a subgroup of 16 patients showing consistent neglect in all clinical tests, and (**C**) a subgroup of 25 patients showing no neglect in any of the clinical test. The colour range indicates the proportion of overlap between different patients, from violet (⩽6% overlap) to red (100% overlap). Note that the maxima of damage to posterior white matter for patients with severe neglect corresponded to 13 out of 16 cases (yellow, 80% overlap). Brain slices displayed from *z*-coordinates +3 to +27 (**A** and **B**) and −17 to +33 (**C**) in MNI space.

central hemispheric lesions had to be excluded from this subsidiary analysis.) These new comparisons confirmed a maximal overlap in the subcortical paraventricular white matter for neglect patients with anterior lesions (Fig. 4A), but now highlighted a more posterior maximum in parietal lobe for neglect patients with posterior lesions (Fig. 4B).

Furthermore, the overlap results in Fig. 2B indicated that the cumulative maxima of lesions affecting the deep fronto-parietal white matter tracts (yellow colour) concerned only 13 out of the 16 patients with severe neglect, meaning that at least 3 patients showed severe neglect with a different lesion site. Inspection of individual cases revealed that among these 3 patients, one had damage in the medial temporal lobe with an extension to the thalamus, one had damage in occipital and posterior superior parietal lobes (including some parietal subcortical white matter), and one had damage in the dorsolateral frontal lobe (including some frontal subcortical white matter). In addition, note that this approach also disregarded data from 39 other patients, an even larger group who showed neglect in some tests but not others, as typically observed in clinical practice. The next VLSM analysis allowed us to circumvent these problems by performing a voxel-by-voxel regression on continuous measures that were derived from the behavioural performance of all 80 patients, and regrouped into the independent components identified by factorial analysis.

VLSM analysis

Our VLSM analysis tested for the anatomical correlates of each factor obtained by our prior factorial analysis. We entered the composite indices calculated for each factor (as described above) in a voxel-by-voxel statistical *t*-test assessing the effect of damage to each voxel on performance scores, following the procedure used in previous studies (Dronckers *et al.*, 2004; Baldo *et al.*, 2006; Committeri *et al.*, 2007). This procedure could thus take into account the severity of deficits (or the lack thereof) for each neglect component in each individual patient across the whole sample.

Mapping of component 1 (perceptive/visuo-spatial egocentric neglect) revealed a significant involvement of posterior brain regions (Fig. 5A), namely in the right inferior parietal lobe (peak MNI coordinates: 33, −47, 37) near the supramarginal gyrus (Brodmann area 40), with an extension into the adjacent white matter (peak MNI coordinates: 28, −60, 28). In sharp

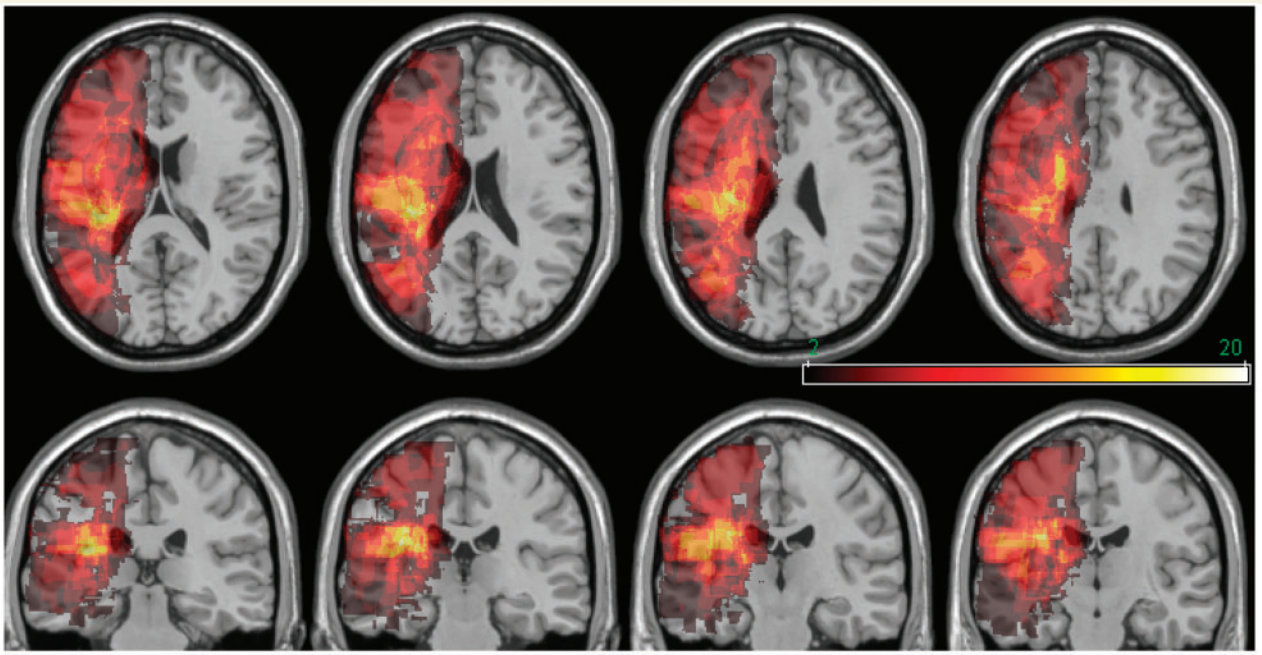

Figure 3 Anatomical correlates of severe hemispatial neglect, obtained by a voxelwise comparison of lesions in patients with severe neglect ($n = 16$) versus patients with no neglect ($n = 25$). The colour range indicates chi-square values from black (non-significant) to white (maximum significance), with orange to yellow ($\chi^2 > 10.8$) corresponding to a statistical threshold of $P < 0.001$ at the voxel level, and yellow to white ($\chi^2 \geqslant 16.5$) corresponding to the Bonferroni-corrected cutoff for multiple comparisons. Brain slices displayed from *z*-coordinates +18 to +30 (upper row) and *y*-coordinates −28 to 16 (lower row) in MNI space.

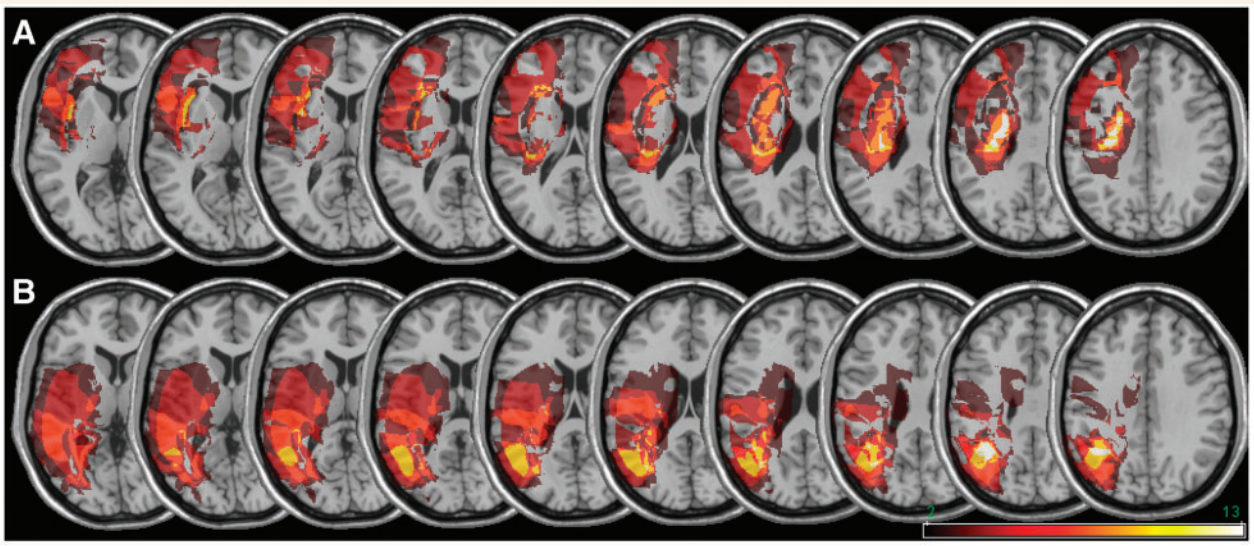

Figure 4 Anatomical correlates of neglect in patients with (**A**) anterior and (**B**) posterior brain lesions, by voxelwise comparison between those with severe neglect and those without neglect in each group. The colour range indicates chi-square values from black (non significant) to white (maximum significance), with orange to yellow ($\chi^2 > 6.64$) corresponding to a statistical threshold of $P < 0.01$ uncorrected at the voxel level, and yellow to white ($\chi^2 \geqslant 12.11$) corresponding to Bonferroni correction for the volume of lesioned voxels. Brain slices displayed from z-coordinates +6 to +33 (**A** and **B**).

contrast, the correlates of component 3 (exploratory/visuo-motor egocentric neglect) showed a predominant involvement of anterior brain regions (Fig. 5C), including peaks in the right inferior frontal gyrus (Brodmann area 45, MNI coordinates: 49, 29, 15) and more anterior dorsolateral prefrontal cortex (Brodmann area 46/Brodmann area 10, MNI coordinates: 38, 49, 8), as well as a distinct peak in the posterior part of the middle frontal gyrus (Brodmann area 6, MNI coordinates: 52, 2, 33), and some portion

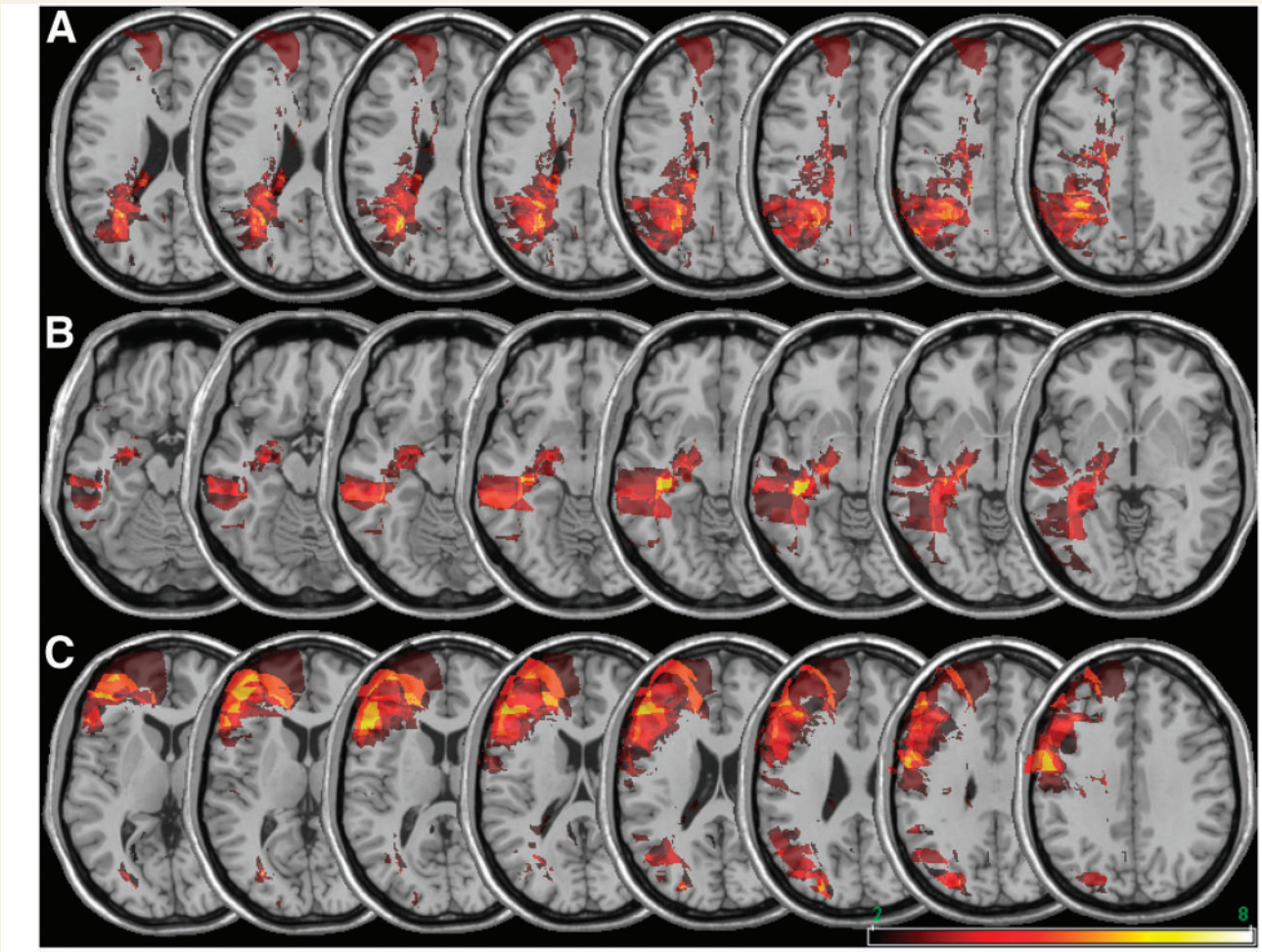

Figure 5 Anatomical correlates of the three neglect components identified by the factorial analysis and submitted to VLSM analysis. (**A**) Lesions in inferior parietal lobe correlated with the severity of deficits linked to the component 1, including deviation on line bisection, omission of words during reading, and to a lesser degree, omission of items in drawing. (**B**) Lesions in temporal lobe correlated with the severity of deficits in component 2, including transformation for the left-side of words during reading and for the left-side of targets in Ota search task. (**C**) Lesions in inferior and middle frontal lobe correlated with deficits in component 3, including omission of targets in bells cancellation and Ota search task, and to a lesser degree, omission of items in drawing. The colour range indicates *t*-test values from VLSM analysis, from black (non-significant) to white (maximum significance). Only voxels significant at $P<0.05$ (false discovery rate corrected) are shown colour-coded, with orange to white colours (t values $\geqslant 4.29$) corresponding to the Bonferroni correction cutoff for multiple comparisons. Brain slices displayed from z-coordinates +23 to +37 (**A** and **B**) and +6 to +33 (**C**).

of the frontal subcortical white matter. Finally, the component 2 (allocentric neglect) showed a specific anatomical pattern involving the temporal lobe, with a peak located near the parahippocampal gyrus (MNI coordinates: 35, −26, −10) but extending throughout the white matter towards the middle temporal gyrus on the lateral surface (Fig. 5B). A more detailed inspection of lesions in individual patients with the most important deficits in this factor indicated that roughly half had lesions in the posterior cerebral artery territory, extending from occipital to medial temporal lobe, while the other half had lesions in the middle cerebral artery territory, extending from more lateral and anterior areas into the deep temporal lobe regions.

In summary, our anatomical mapping data converge with factorial analysis results to suggest that these three components might reflect independent dimensions of impairments underlying neglect symptoms in different clinical tests.

Elementary neurological deficits

As a control analysis (Rorden and Karnath, 2004), we also contrasted the lesion overlap between patients with complete hemianopia and those without (Fig. 6A), and between patients with complete hemiplegia and those without (Fig. 6B). As expected, these comparisons revealed differential damage to the occipital lobe and occipital radiations for hemianopia; and to the motor, premotor, and internal capsule regions for hemiplegia. This auxiliary test indirectly corroborates the validity of our anatomical analyses.

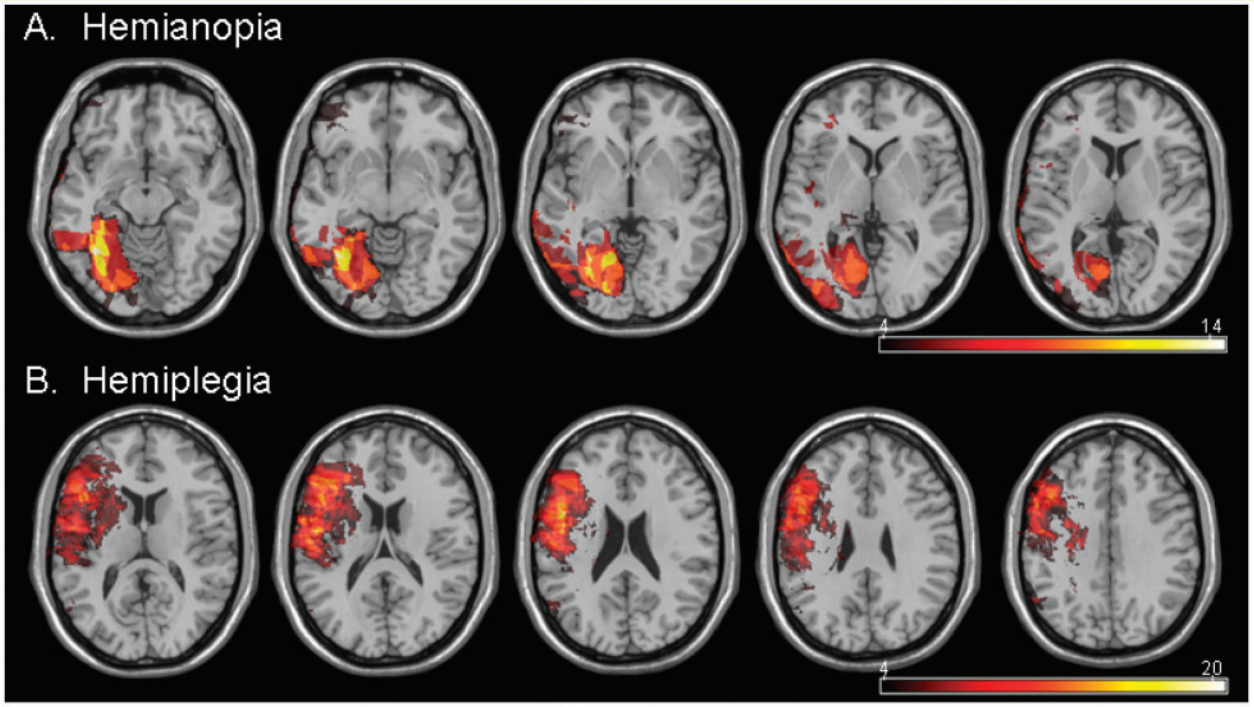

Figure 6 Anatomical correlates of elementary neurological disorders. (**A**) Patients with versus without complete hemianopia, and (B) patients with versus without complete hemiplegia, as determined by clinical examination. The colour range indicates chi-square values from black (non-significant) to white (maximum significance), with orange to yellow ($\chi^2 > 10.8$) corresponding to a statistical threshold of $P < 0.001$ at the voxel level. Brain slices displayed from *z*-coordinates −12 to +8 (**A**) and +13 to +33 (**B**).

Discussion

To our knowledge, this is the first study investigating the neural basis of neglect components by means of a factorial analysis (to identify independent components) coupled with a voxel-by-voxel statistical analysis (i.e. VLSM) of lesions (to uncover distinct cerebral substrates for these components). This approach goes beyond previous studies that either correlated lesions with a single broad category of neglect patients defined by pooling scores from different tests (Karnath *et al.*, 2001; Mort *et al.*, 2003), or focused on a single behavioural test selected out of traditional clinical batteries, such as line bisection (Karnath *et al.*, 2004). Here we could identify three distinct components by using a purely data-driven statistical analysis of performance across several classic tests, which explained a large amount (82.1%) of the variance observed in these tests, and were then mapped onto distinct underlying brain substrates. A first component concerned the more perceptive visuo-spatial aspects of neglect (deviation on line bisection and contralesional word omissions in two reading tasks), whereas another component concerned more exploratory visuo-motor aspects (contralesional misses in different cancellation tasks), and a third component selectively concerned object-based neglect (transformations of the left-side of words during reading and of the left-side of targets during Ota search task). Drawing was found to relate to both the perceptive and exploratory factors. In keeping with these findings, our lesion analysis revealed three distinct sites of brain damage for each of these components, involving the parietal, frontal, and temporal lobes, respectively. In addition, lesions in subcortical white matter correlated with severe neglect on different types of tests, suggesting that an extension to frontal-parietal fibres might exacerbate the disorder. Taken together, our results provide new insights into the possible mechanisms and varieties of spatial neglect following right hemisphere stroke.

Dissecting the cognitive components of spatial neglect by factorial analysis has been attempted by only a few, purely behavioural studies, with mixed results. Furthermore, none examined the corresponding neural correlates. A first study (Kinsella *et al.*, 1993) suggested that two main factors accounted for neglect behaviour across different tests, one related to visual scanning (shape cancellation, circle cancellation, line bisection) and another related to internal space representation (landscape copy, spontaneous drawing, tactile maze), but these two factors accounted only for 50% of the total variance. Likewise, Bartolomeo *et al.* (1998) also used factorial analysis in right brain-damaged patients to distinguish between perceptual and motor performance in visual reaction tasks, and suggested a link between perceptual performance and posterior regions, while motor performance was related to anterior regions. A third study (Azouvi *et al.*, 2002) investigating the sensitivity of clinical tests used in the GEREN battery (Rousseaux *et al.*, 2001) reported that two factors explained 51% of variance, including one factor related to "easy tasks that require little voluntary attentional control and motor activity in left space" (line bisection, clock drawing, embedded

figures), and another factor related to "complex visuo-motor behaviour in left space" (bells cancellation test, drawing, writing). In contrast, another recent study (Maeshima *et al.*, 2001) reported that five factors could explain a greater amount of variance (78%), including visual perception (complex figure copying and colouring), imagery (drawing of clock and man), language skills (reading, figure description, visual counting), visual scanning (line cancellation), and visual judgment (line bisection task); but most of these factors actually derived from a single test, without breaking down performance into more global components. In contrast, other studies found that only one factor was sufficient to account for neglect across a range of tests in a standard battery (e.g. Behavioural Inattention Test, Halligan *et al.*, 1989). Our new results therefore add support to previous work suggesting that neglect might involve a combination of different factors, but provide a more robust delineation of three major plausible factors, which appear to explain a larger amount of variance. Moreover, the factors identified in our study converge with the notion that neglect syndrome may encompass key dimensions related to perceptive and exploratory representations of egocentric space, as well as allocentric object-based representations (Mesulam, 1999; Driver *et al*., 2004), which could be damaged to various degrees in different patients and thus lead to different clinical manifestations.

Parietal lobe and perceptive visuo-spatial components of neglect

The first component identified by our factorial analysis regrouped performance in tasks (reading and bisection) that share a similar requirement for visual scanning in a relatively systematic manner (e.g. from left to right side, back-and-forth). This component might tap into the ability to shift attention to the contralesional side, or to maintain stable representation of locations over time and/or across eye movements. Moreover, a similar factor was proposed by a previous study (Azouvi *et al.*, 2002) where some tests (including line bisection and drawing) were also grouped in a "scanning" dimension, thought to involve 'little attentional control and motor activity'. Importantly, our VLSM analysis revealed that the neural correlates of this component were centred on the right inferior parietal lobule near the supramarginal gyrus (Brodmann area 40), with some extension into posterior white matter.

This finding is consistent with classic accounts of neglect attributing a critical role to right parietal damage but also with the common use of line bisection to assess spatial perception and parietal function in neuropsychology. Many studies reported that neglect is frequently associated with posterior parietal damage (Vallar, 1998; Mesulam, 1999), particularly in the supramarginal (Doricchi and Tomaiuolo, 2003; Buxbaum *et al.*, 2004) or angular gyrus (Mort *et al.*, 2003; Hillis *et al.*, 2005). Given the existence of multiple functional areas within parietal cortex, it is also possible that a "posterior" component of neglect might actually involve several areas, and that damage to only one of them would cause more limited spatial disturbances. However, other studies suggested that neglect might be related to lesions in the middle temporal gyrus instead (Karnath *et al.*, 2001, 2004). These results have been disputed (Mort *et al.*, 2003; Buxbaum *et al.*, 2004), because only half of neglect patients in these studies had temporal lesions. However, Karnath *et al.* (2001, 2004) did not include line bisection among their diagnostic tests, whereas other authors (Mort *et al.*, 2003) who found a predominance of parietal lesions used bisection together with cancellation tasks.

Here, we show that an involvement of the parietal lobe is specifically related to spatial functions recruited by line bisection, whereas lesions in temporal lobe are associated with other dimensions of neglect (see below). These data underscore the importance of the exact neuropsychological factors used to categorize patients for neuroanatomical mapping (Committeri *et al.*, 2007), and the potential problems of using "average" scores conflating different tests to make a diagnosis of "neglect" in different patients (e.g. failures 'in at least 2 out of *n* tests' as in many studies).

In accord with our findings, both lesion studies (Binder *et al.*, 1992; Rorden *et al.*, 2006) and functional imaging in healthy subjects (Fink *et al.*, 2000) showed that line bisection depends on posterior parietal areas. Nevertheless, the exact cognitive processes underlying line bisection and its disturbances in neglect still remain elusive (Bisiach *et al.*, 1998). Although both perceptual and motor aspects are presumably implicated (Bisiach *et al.*, 1990), our findings that a similar parietal component may contribute to neglect in line bisection and reading point to a critical role of spatial representations that are necessary to code for, or shift attention to, contralesional locations even when these can be predicted (unlike during search). These representations of perceptual locations within right parietal structures might not only entail a dynamic remapping across eye and body movements (Pisella and Mattingley, 2004; Vuilleumier *et al.*, 2007), but also subserve the maintenance of previously explored locations in spatial working memory over delays (Husain *et al.*, 2001), two abilities usually impaired in neglect patients and potentially important when localizing each endpoint of a line or when returning to the next line in a text. Alternatively, damage to spatial representations in parietal areas might contribute to relative perceptual weight given to the two halves of visual space (Urbanski and Bartolomeo, 2008), and thus produce contralesional inattention when horizontally elongated objects or lines of text are processed.

It is worth noting that this first component accounted for the largest amount of variance (49%) and showed a secondary site in frontal lobe in addition to the predominant parietal site, suggesting that it could reflect dysfunction in relatively general spatial processes subserved by distributed and tightly interconnected parieto-frontal networks. Thus, while the strong association of this component with parietal areas is consistent with the importance of the latter in egocentric spatial representations, it is also likely that such representations involve cross-talks between anterior and posterior brain regions (Corbetta and Shulman, 2002; He *et al.*, 2007). Moreover, the frontal peak of component 1 was much weaker and did not overlap with the much more extensive frontal peak of component 3, pointing to distinct frontal functions being possibly associated with each of these components.

Temporal lobe and object-based components of neglect

The second component identified by our factorial analysis reflected a purely object-based (allocentric) aspect of neglect, apparent during both word reading and target cancellation – in sharp contrast to the other two components that reflected space-based (egocentric) aspects. This component correlated with a distinctive pattern of damage to the right temporal lobe, consistent with reports of a double dissociation between object-based and space-based neglect in some patients (Hillis *et al.*, 2005). This finding provides new support to previous studies suggesting that the right temporal lobe might be an important site of damage in neglect (Karnath *et al.*, 2001, 2003, 2004; Ringman *et al.*, 2004; Rorden *et al.*, 2006), although the latter studies often used cancellation or line bisection tasks to demonstrate neglect, rather than object-based tasks. Further, a recent study using perfusion MRI reported that allocentric neglect was related to temporal hypoperfusion, whereas egocentric deficits were related to parietal hypoperfusion (Hillis *et al.*, 2005).

The most critical site of temporal damage was difficult to establish with certainty in our study because the main peak was found in the white matter, with an extension towards both the medial and the lateral temporal cortex (Fig. 5C). Moreover, inspection of individual data suggested that this anatomical pattern could result from strokes in either middle or posterior cerebral artery territory (Vuilleumier, 2007). Previous studies have reported neglect after temporal lesions affecting the superior or middle temporal gyrus (Karnath *et al.*, 2001; Buxbaum *et al.*, 2004; Ringman *et al.*, 2004), as well as the parahippocampal gyrus (Maulaz *et al.*, 2005; Bird *et al.*, 2006). In one study (Bird *et al.*, 2006), posterior cerebral artery lesions maximally associated with neglect were also found in the white matter, and suspected to encroach on fibre-tracts running from the parahippocampal gyrus to the angular gyrus (inferior longitudinal fascicle). Another site of disconnection in cases of neglect with more ventral damage might involve the inferior fronto-occipital fasciculus (Urbanski *et al.*, 2008). Both lateral and medial temporal areas have strong reciprocal connections with the parietal cortex (Catani *et al.*, 2002), and both are critically involved in processing object shape and words (Vuilleumier, 2007). Thus, lesions or disconnexions affecting these regions could possibly impair perception or attention for one side of objects and words, without disrupting the representation of large-scale egocentric space.

Frontal lobe and exploratory visuo-motor components of neglect

The third major neglect component found by our analysis primarily reflected misses for targets in left space on cancellation tests (bells and Ota search task), and to a lesser degree omissions in drawing (landscape copy), with anatomical correlates in the dorsolateral prefrontal cortex. This component bears similarities with a factor found by Azouvi *et al*. (2002), which was linked to visuo-motor tests (cancellation, drawing, writing) and imputed to greater demands on exploratory and attentional resources in the left space. Other studies have also reported that neglect on cancellation tests is more severe after anterior or subcortical lesion (Binder *et al.*, 1992); and that frontal damage may cause more severe motor biases in bisection tasks, unlike parietal damage leading to more severe perceptual biases (Bisiach *et al*., 1990).

These results also converge with previous observations suggesting that left spatial neglect after right frontal lobe lesions might be particularly dependent on the presence of distractors, and thus more prominent on cancellation or search tasks (Husain and Kennard, 1997). Similarly, left neglect in drawing tasks may also be aggravated by a capture of attention by elements on the right side of the display (Cristinzio *et al*., 2009). Therefore, deficits in cancellation and drawing tasks associated with a frontal component in our patients might not only reflect an inability to direct attention and motor action in contralesional space, but also greater interference by distracting stimuli. This would accord with a major role of the dorsolateral prefrontal cortex in executive control, allowing efficient selection of target information and suppression of irrelevant distractors during search or perception (Wager and Smith, 2003). Such deficits in executive components of spatial working memory might contribute to the tendency of some patients to explore the same locations repeatedly during cancellation tasks (Husain *et al*., 2001), although working memory deficits in neglect have usually been interpreted as reflecting parietal more than frontal damage (Milner and McIntosh, 2005).

Our VLSM results suggested two distinct peaks of frontal damage, one at the junction between the inferior and middle frontal gyrus, and another at the junction between the posterior middle gyrus and precentral cortex (Fig. 5C, first and last brain sections, respectively). The first area overlapped with a region previously shown to be functionally connected to both dorsal and ventral fronto-parietal networks, and thus suspected to serve as a critical coordination node between brain systems for exogenous and endogenous spatial attention (He *et al*., 2007). The second area overlapped with the frontal-eye-field, which is related to both spatial attention and oculomotor control (Mesulam, 1999; Corbetta and Shulman, 2002), and thought to be critically involved in the visual selection of targets among distractors (Schall, 1999). Both regions are consistently activated in neuroimaging studies of visual search in healthy participants (Anderson *et al*., 2007), together with parietal and visual areas. Hence, damage to these prefrontal areas may contribute to neglect by disrupting mechanisms that guide exploration behaviour and control the allocation of selective attention to task-relevant information.

Fronto-parietal (white matter) pathways

Finally, standard lesion mapping analysis using overlap and group comparison methods showed that severe neglect (affecting performance in all tests used) was associated with white matter damage encroaching on frontal-parietal pathways. This overlap in central, paraventricular white matter was not simply explained by averaging two posterior and anterior lesion groups, because a similar

subcortical maxima was found for a subgroup of patients with anterior lesions (while a posterior subgroup showed predominant overlap in parietal lobe). These results replicate other studies (Samuelsson *et al.*, 1997; Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten *et al.*, 2005; Bartolomeo *et al.*, 2007) that found a high correlation of paraventricular white matter lesions with both acute and chronic neglect after stroke. Consistent with studies in rats (Burcham *et al.*, 1997) and monkeys (Gaffan and Hornak, 1997), these data suggest that a disconnection of parieto-frontal pathways might also contribute to neglect and spatial awareness (Doricchi and Tomaiuolo, 2003; Bartolomeo *et al.*, 2007; He *et al*., 2007; Shinoura *et al.*, 2009). We surmise that an extension of lesions to these subcortical pathways might produce more severe neglect and blur the distinction between separate components, by impacting on additional neural systems through disconnection and remote functional disturbances (He *et al*., 2007; Vuilleumier *et al.*, 2008). This would be consistent with previous proposals that damage to cortical regions may provoke modular deficits, whereas damage to fronto-parietal pathways could disrupt several cortical modules and prevent compensatory changes within distributed brain networks (Doricchi and Tomaiuolo, 2003; Bartolomeo *et al.*, 2007). Hence, full-blown neglect might be considered as the behavioural expression of a combination of component deficits, with various manifestations reflecting the distributed nature of networks subserving attention and awareness (i.e. involving frontal, parietal, and temporal regions) and the multiple sites of lesions.

Conclusion

To summarize, our results add novel support to neuropsychological models of neglect in terms of a disorder affecting a large-scale right hemisphere network (Mesulam, 1999), with distinct components in prefrontal, parietal, temporal, and presumably several other areas; but they also go beyond previous work by combining new anatomical mapping techniques with factorial analysis to delineate the major components responsible for specific neglect manifestations across different tasks. At a theoretical level, our findings may help reconcile previous discrepancies between studies reporting variable cortical or subcortical substrates for neglect symptoms. Here we show that different tests used in different studies might highlight different components, each with a distinctive pattern of brain lesion. Hence, some discrepancies might be due to the fact that previous studies did not distinguish between allocentric and egocentric aspects of neglect, or between exploratory and perceptive aspects, and therefore mixed different groups with a predominance of temporal, frontal, or parietal damage, respectively. Future research should apply a similar approach to investigate the neural substrates of other dimensions of neglect (such as near versus far space, or imaginal versus perceptual space). At a clinical level, our results may suggest new approaches to assess spatial neglect, not only after stroke but also in patients with white matter damage (i.e. multiple sclerosis, brain tumour), using complementary tests that tap into distinct components and distinct neural pathways. Ultimately, a better understanding of neglect components will not only enhance the clinical assessment of this complex syndrome and provide new knowledge on the neural mechanisms of spatial awareness in humans, but also constitute a necessary step to elaborate more efficient rehabilitation in brain-injured patients.

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