Neural bases of personal and extrapersonal neglect in humans

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Human awareness of left space may be disrupted by cerebral lesions to the right hemisphere (hemispatial neglect). Current knowledge on the anatomical bases of this complex syndrome is based on the results of group studies that investigated primarily the best known aspect of the syndrome, which is visual neglect for near extrapersonal (or peripersonal) space. However, another component–neglect for personal space–is more often associated with, than double-dissociated from, extrapersonal neglect, especially, in chronic patients. The present investigation aimed at exploring the anatomical substrate of both extrapersonal and personal neglect by using different advanced methodological approaches to lesion–function correlation. Fifty-two right ischaemic patients were submitted to neuropsychological assessment and in-depth MRI evaluation. The borders of each patient’s lesion were delimited onto its own high-resolution anatomical image and then submitted to an automated spatial normalization algorithm. Besides conventional lesion density plots and subtraction analysis, region-based statistical analyses were performed on percentage values of the lesioned tissue also using a new parcellation of the white matter (WM). Data were finally submitted to voxelwise statistical analysis also using a recently proposed method (voxel-based lesion–symptom mapping). Results converged in showing that awareness of extrapersonal space is based on the integrity of a circuit of right frontal (ventral premotor cortex and middle frontal gyrus) and superior temporal regions, whereas awareness of personal space is rooted in right inferior parietal regions (supramarginal gyrus, post-central gyrus and especially the WM medial to them). Common but less crucial regions for both neglect sub-types were located in the temporo-peri-Sylvian cortex. We suggest that extrapersonal space awareness critically involves a ventral circuit recently described for the exogenous allocation and reorienting of attention in space. Disruption of personal space awareness, instead, seems to be due to a functional disconnection between regions important for coding proprioceptive and somatosensory inputs, and regions coding more abstract egocentric representations of the body in space. In conclusion, present data strongly support a segregation of personal and extrapersonal spatial awareness in humans, both from a functional and an anatomical point of view.

Keywords: hemispatial neglect; personal; extrapersonal; frontal; parietal

Abbreviations: CR = corona radiata; FEF = frontal eye field; IPL = inferior parietal lobule; MFG = middle frontal gyrus; SMG = supramarginal gyrus; VLSM = voxel-based lesion–symptom mapping; WM = white matter


Introduction

Spatial awareness has been a topic of great interest for many decades, and hemispatial neglect is the neuropsychological syndrome which best represents the breakdown of such a crucial function in everyday life. Patients with hemispatial neglect, in fact, fail to orient to and explore the portion of space contralateral to their cerebral lesion, even in the
absence of primary sensory or motor deficits (Vallar, 1998). Therefore, studying the neuroanatomic bases of neglect represents an excellent opportunity to learn more about the neural bases of spatial cognition in humans.

Monkey models of spatial cognition (Colby, 1998; Rizzolatti et al., 2000) show that the space around us is a multifactorial construct of our brain and that distinct areas are responsible for coding space outside reaching distance (far extrapersonal space), space within reaching distance (near extrapersonal or peripersonal space), and space of the body surface (personal or bodily space). In a similar fashion, dissociations between neglect for far and near extrapersonal space (Halligan and Marshall, 1991; Vuilleumier et al., 1998), as well as for extrapersonal and personal space (Bisiach et al., 1986a; Guariglia and Antonucci, 1992; Peron and Pinna, 1997; Marangolo et al., 2003), have been described. Together with many other behavioural dissociations (Halligan and Marshall, 1994), they support the view of neglect as a complex syndrome (Vallar et al., 2003).

However, current knowledge about the anatomical bases of spatial neglect is based on the results of group studies that investigated primarily the best known aspect of the syndrome, which is visual extrapersonal neglect. The traditional view of a particularly relevant role of the right inferior parietal lobule (IPL) at the temporoparietal junction (Heilman et al., 1983; Vallar and Perani, 1986; Vallar, 2001; Halligan et al., 2003; Mort et al., 2003) has been undermined by two recent reports stressing the role of the right superior temporal cortex (Karnath et al., 2001, 2004). The lack of agreement may be due to differences in the behavioural testing procedures (Binder et al., 1992; Ellison et al., 2004; Rorden et al., 2006), but also to different proportions of patients who, in addition to extrapersonal neglect, may have been affected by other less-investigated components of the syndrome. In particular, these previous studies did not report data on personal neglect, which is more often associated with, than double-dissociated from, extrapersonal neglect, especially, in chronic patients (Beschin and Robertson, 1997; Maguire and Ogden, 2002).

The aim of the present study is to contrast, for the first time in humans, the neural bases of the personal versus the extrapersonal components of spatial neglect in a large group of right brain-damaged patients. To achieve this aim, a robust methodological accuracy is required, because the critical disputed regions such as inferior parietal and superior temporal cortex are close to each other, and because the inter-subject anatomical variability is extremely high.

To date, lesion information is mainly derived from low spatial resolution imaging techniques (e.g. CT scan) and referred to templates with low spatial resolution (slices >3 mm). Simple overlaps and subtractions of lesions have been more frequent than quantitative statistical analysis, and almost every study acknowledged the possible bias coming from the very different sizes of the lesions of patients with and without hemineglect. Furthermore, time since stroke often differs among studies, making it more difficult to compare and generalize the obtained results. To overcome these problems, previous studies focused on homogeneous subgroups of patients, either with respect to whether lesions fell in the territory of the middle or posterior cerebral artery (Mort et al., 2003) or with respect to additional neurological symptoms, such as visual field defects (Karnath et al., 2001; Doricchi and Tomaiuolo, 2003). A recent report, instead, studied an unselected but very large sample of patients with and without neglect and compared their lesions through voxelwise statistical testing (Karnath et al., 2004). In all cases, however, only visual extrapersonal neglect was tested.

Here we used classical and more recent methodological approaches to lesion–function correlation to study the anatomical substrate of both extrapersonal and personal neglect. First, we delimited the borders of each patient’s lesion onto its own high-resolution anatomical image rather than onto slices of a template as in previous studies (Vallar and Perani, 1986; Karnath et al., 2001, 2004; Maguire and Ogden, 2002; Doricchi and Tomaiuolo, 2003) and applied an automated spatial normalization algorithm to lesions, so as to have them all in common Talairach coordinates (Talairach and Tournoux, 1988; see also Mort et al., 2003, for the same approach). Then, besides conventional lesion density plots and subtraction analysis, we performed region-based statistical analyses on percentage values of lesioned tissue. We also used a new parcellation of the white matter (WM), the importance of which has been recently emphasized for the genesis of visual extrapersonal neglect (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005). Moreover, we submitted our data to voxelwise statistical analysis using a recently proposed method (voxel-based lesion-symptom mapping, or VLSM) (Bates et al., 2003). The latter has already been successfully applied to the study of linguistic processing (Dronkers et al., 2004) and biological motion perception (Saygin et al., 2004) in left-brain damaged patients. VLSM analyses continuous behavioural and lesion information without classifying the patients, thus allowing to co-vary out some effects of no interest, such as the lesion size, the time since stroke and, crucially, the effect of one neglect component on the other.

Material and methods

Patients

All patients consecutively admitted to the Neuropsychology Unit of the Santa Lucia Foundation over a 3-year period (from 2001 to 2004) with a diagnosis of right cerebral stroke were potential participants in the study. Only subjects who were able to understand the test requirements were assessed. Of the 160 right-brain damaged patients initially enrolled, 72 were excluded for medical problems that did not permit MRI acquisition. The remaining patients were submitted to neuropsychological and MRI examinations. Then, 36 patients were excluded from the study for several reasons, such as a non-vascular aetiology, a diagnosis of bilateral lesion, lesions restricted to the pons and excessive motion artefact on MRI. Therefore, 52 patients constituted the final sample. Aetiology was haemorrhagic in 13% of patients, and ischaemic in the rest, that, in most
cases, involved the territories of the middle cerebral artery (MCA). The three groups of neglect patients (only extrapersonal, only personal, both extrapersonal and personal) and the control group were comparable for age and days since stroke ($P > 0.05$).

The protocol was approved by the local ethical committee, and written informed consent was obtained from each participant before starting the study.

### Neuropsychological examination

We assessed the presence of extrapersonal neglect by means of a standard neuropsychological battery (Pizzamiglio et al., 1989) comprising four tests: (i) line cancellation; (ii) letter cancellation; (iii) Wundt–Jastrow area illusion test; (iv) sentence reading test. We considered the patients who scored below the cut-off on at least two of these tests to have an extrapersonal deficit. The cut-off was as follows: (i) $>2$ omissions on the left side; (ii) a difference $>4$ between omissions on the left and on the right side; (iii) a difference $>2$ between unexpected responses (i.e. responses in the direction opposite to the illusory effect in normals) given for left oriented minus right oriented stimuli; (iv) one or more sentences incompletely read on the left side. This battery has been widely used in 15 years in clinical practice and has the advantage that it assesses different aspects of extrapersonal space awareness. It does not include the line bisection task which, in our opinion, is a very good test for research purposes but not for diagnostic purposes. This is because elderly healthy subjects may show a deviation up to 3% to the right of the true midline (Halligan et al., 1990), the performance does not correlate with the neglect observed in everyday life (Ferber and Karnath, 2001) and it is not rare that subjects showing neglect in other tests of visual neglect do not have a rightward bias in line bisection (e.g. Mort et al., 2003). Although the battery does not include the line bisection test, it does include a perceptual test (the Wundt–Jastrow area illusion test) the results of which have been shown to cluster with line bisection results in neglect patients (Pizzamiglio et al., 1992).

Personal neglect was assessed by a standardized and widely-used test (Zoccolotti and Judica, 1991; Zoccolotti et al., 1992; Pizzamiglio et al., 1992) requiring the use of three objects (eyeglasses, a razor or powder and a comb) in the body space. For each object, the clinical neuropsychologist assigned a score from 0 to 3 on the basis of the asymmetry in performance of the patient in the left and right space ($0 = no asymmetry, 3 = maximal asymmetry$). The final score consisted in the sum of the three distinct evaluations obtained in the three subscales, with the cut-off being 2 (0–1 = absence of personal neglect, 2–9 = personal neglect from minor to severe). Therefore, both the extrapersonal and the personal evaluation required patients to act towards the contralesional space. By means of a standardized neurological examination, we also assessed the presence of motor and somatosensory deficits on the contralesional side as well as the presence of visual and tactile extinction. Visual field defects were assessed through Goldman perimetry.

### MRI scanning

Given that the vascular lesion is constituted by necrotic and gliotic parts, it is particularly critical to identify them and to distinguish these two components from the normal tissue. Not all the MRI sequences show equal sensitivity in the definition of a vascular lesion. For example, $T_1$-weighted images are particularly sensitive in delineating the necrotic part (appearing hypointense due to the presence of internal CSF). However, on a $T_1$-weighted image the gliotic part would appear not well separated from the normal tissue (often appearing hypointense in respect to the normal tissue). Conversely, $T_2$-weighted images are more capable in revealing gliotic parts (appearing slightly hyperintense due to the presence of gliosis). Among the $T_2$-weighted images, the fluid attenuated inversion recovery (FLAIR) is particularly useful to differentiate the gliosis from the necrotic parts (that appear hypointense for the attenuation of the CSF). The combination of different MR parameters, mainly $T_1$ and $T_2$ relaxation times, may thus provide not only sensitivity, but tissue specificity, allowing the complete and accurate characterization of pathological tissue in vivo (e.g. Damadian, 1971).

For these reasons, and differently from most previous studies, an in-depth MRI evaluation was carried out for all patients. For each subject, we acquired four different anatomical sequences: (i) a $T_2$-weighted turbo spin echo image ($TR = 3800\text{ ms}, TE = 90\text{ ms}, FoV = 173 \times 230\text{ mm}^2$); (ii) a proton density image ($TR = 3800\text{ ms}, TE = 20\text{ ms}, FoV = 173 \times 230\text{ mm}^2$); (iii) a FLAIR image ($TR = 9999\text{ ms}, TE = 105\text{ ms}, FoV = 188 \times 250\text{ mm}^2$); (iv) a dedicated high-resolution ($1 \times 1 \text{ mm}^3$) $T_1$-weighted image of the whole brain, using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence ($TR = 11.4\text{ ms}, TE = 4.4\text{ ms}, FoV = 256 \times 256\text{ mm}^2$, flip angle = $10^\circ$, $1 \times 1\text{ mm}^2$ in-plane resolution, 220 contiguous $1\text{ mm}$ coronal slices).

### Lesion analysis

We manually drew the lesions onto the digital MPRAGE images, slice-by-slice (i.e. with a resolution of 1 mm), using the MRICro software (Rorden and Brett, 2000). The visual co-inspection of the other acquired clinical images allowed us to obtain a detailed lesion image, corroborated by two clinical neuroradiologists (U.S. and A.C.S.) who were blind to the patients’ behavioural deficits. Normalization of each patient’s MRI to a common spatial framework was performed using the SPM99 software (Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab (The MathWorks Inc., Natick, MA, USA), through an automatic non-linear stereotaxic normalization procedure (Friston et al., 1995), and restricting the estimation of the normalization parameters to the healthy tissue (Brett et al., 2001). When distorted, the lateral ventricles were also excluded from the computation.

### Lesion density plots and subtractions

In-house software (written in Matlab) was used to calculate voxel-based lesion density plots of patients with extrapersonal neglect and with personal neglect. However, simply overlapping lesions from patients who show a specific deficit hides a potential confound, i.e. the possible highlighting of regions more susceptible to damage and not necessarily crucial for the function. Instead, voxel-by-voxel comparisons or subtractions between superimposed lesions of patients with and without extrapersonal neglect, and between patients with and without personal neglect, allow cancelling out of regions more susceptible to damage, because they will occur with similar frequency in both groups. Lesion subtractions were calculated on relative frequencies, given the difference in sample size between the patient groups.

### Automated anatomical labelling and region-based statistical analysis

Lesion images, once in standard space, were submitted to an automated anatomical labelling procedure using in-house software
BrainShow), written in Matlab. This procedure was based on a macroscopic anatomical parcellation of the MNI single-subject brain (Tzourio-Mazoyer et al., 2002), which includes all main gyri of the cerebral cortex, but not the deep WM. This parcellation was further refined by splitting the largest gyri into smaller sub-regions: e.g. the precentral gyrus was split into an inferior and a superior portion, the superior temporal gyrus (STG) into a posterior, a middle and an anterior portion, and so on. Importantly, we also added a parcellation of the deep WM bundles (Fig. 1), comprising the centrum semiovale ($z > 30$), the supralenticular ($0 < z < 30$) and sublenticular ($z < 0$) corona radiata (CR), the external capsula (EC, $-8 < z < 12$), and the internal capsula (IC, $-8 < z < 12$). The first patients acquired were used to make a blind check of the congruence between the automated method and a clinical neuroradiological description. Given its high consistency, we adopted the automated labelling for all patients.

The output of the automated parcellation procedure was, for each patient, the total volume of the lesion (cm$^3$) and the percentage of each brain region which resulted as damaged (area percent). Both measures first entered descriptive statistics and then a series of ANOVAs with extrapersonal and personal neglect (present/absent) as factors. Area percent data were submitted to a logarithmic transformation before entering the statistical analysis. The number of comparisons (i.e. of analysed areas) set the statistical threshold for significance at $P < 0.002$ (Bonferroni correction for multiple comparisons). They included all the regions that, to date, have been shown to contribute in some way to neglect syndrome, as well as other main parietal, frontal and temporal gyri, and the above-described WM bundles.

**Voxel-based lesion–symptom mapping**

Normalized lesion images were re-sampled at $4 \times 4 \times 4$ mm$^3$ and then entered the VLSM analysis (Bates et al., 2003) together with two summary behavioural scores: (i) a mean percentage value of severity of extrapersonal neglect; and (ii) a mean percentage value of severity of personal neglect. Both scores were obtained by averaging the percent number of correct responses in all tests administered. VLSM analysis was also conducted on standardised measures, obtained by transforming the original behavioural scores into $t$-scores (on the basis of a greater sample of unselected right brain-damaged patients who have been studied at the Neuropsychology Unit over the past years). Statistical parametric maps of the $t$ statistics were computed for extrapersonal and personal space awareness by comparing, through two-sample $t$-tests, at each voxel, behavioural scores of patients having versus not having a lesion in that voxel. Multiple comparisons were controlled using both the expected proportion of false positives (FDR correction), and a Bonferroni correction. Several ANCOVAs were then performed to factor out the effect of different covariates of no interest, such as the time since stroke, the lesion size and each neglect subtype relative to the other.

**Visualization of results**

Visualization of all lesion analyses was achieved by using BrainShow, which allows superimposing regions of interest (ROIs) and statistical maps over brain slices of the single-subject MNI brain.

**Results**

Out of 88 patients submitted to both neuropsychological and MRI examinations, 52 constituted the final sample, after the application of a series of exclusion criteria (see Material and methods). Demographic and clinical data are shown in Table 1. 22 patients (42%) showed both extrapersonal and personal neglect (EP group), 6 (12%) only extrapersonal neglect (E group), 8 (15%) only personal neglect (P group) and 16 (31%) did not show any sign of hemispatial neglect (control or C group). All the patients with extrapersonal neglect scored below the cut-off at the letter cancellation test: 25 of them (89%) scored below the cut-off also in the Wundt–Jastrow area illusion test, 18 (64%) also in the sentence reading test and 7 (25%) also in the Albert cancellation test.

The scores obtained for the two forms of neglect were significantly correlated ($r = 0.55$, $P = 0.001$). Some patients with extrapersonal neglect showed visual field defects (32%),

![Fig. 1 WM parcellation. Sagittal views of the MNI-MRI single-subject brain: In red is the centrum semiovale, in blue the supralenticular CR, in yellow the sublenticular CR, in pink the internal capsula, and in green the external capsula.](image-url)
Table 1  Demographic and clinical data of the sample

<table>
<thead>
<tr>
<th></th>
<th>Both extrapersonal and personal neglect (EP) (n = 22)</th>
<th>Only extrapersonal neglect (E) (n = 6)</th>
<th>Only personal neglect (P) (n = 8)</th>
<th>Neither extrapersonal nor personal neglect (C) (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years [mean (SD) (range)]</td>
<td>61 (10) (30–73)</td>
<td>67 (6) (61–75)</td>
<td>68 (5) (60–72)</td>
<td>55 (13) (39–74)</td>
</tr>
<tr>
<td>Sex</td>
<td>8 f, 14 m</td>
<td>2 f, 4 m</td>
<td>2 f, 6 m</td>
<td>4 f, 12 m</td>
</tr>
<tr>
<td>Aetiology</td>
<td>4 Haem, 18 Inf</td>
<td>2 Haem, 4 Inf</td>
<td>8 Inf</td>
<td>1 Haem, 15 Inf</td>
</tr>
<tr>
<td>Days since stroke [mean (SD) (range)]</td>
<td>104 (150) (20–690)</td>
<td>122 (130) (20–360)</td>
<td>137 (215) (30–660)</td>
<td>160 (158) (20–420)</td>
</tr>
<tr>
<td>Extinction</td>
<td>5VT, 4T, 1V, 5*</td>
<td>2VT, 1T, 1*</td>
<td>2T</td>
<td>2VT, 1T, 1*</td>
</tr>
<tr>
<td>Visual field</td>
<td>8H+, 3*</td>
<td>1H+, 1*</td>
<td>Intact</td>
<td>Intact</td>
</tr>
<tr>
<td>Lesion volume [cm³]</td>
<td>166</td>
<td>87</td>
<td>86</td>
<td>41</td>
</tr>
<tr>
<td>Letter cancellation (mean/max)</td>
<td>32/53 [(20) (2–53)]</td>
<td>29/53 [(15) (6–47)]</td>
<td>3/53 [(3) (0–7)]</td>
<td>1/53 [(2) (0–1)]</td>
</tr>
<tr>
<td>[left omissions (SD) (range)]</td>
<td>2/11 [(4) (0–11)]</td>
<td>0/11 [(0) (0–1)]</td>
<td>0/11 [(1) (0–3)]</td>
<td>0/11 [(0) (0–1)]</td>
</tr>
<tr>
<td>Line cancellation (mean/max)</td>
<td>10/20 [(8) (0–20)]</td>
<td>6/20 [(4) (0–12)]</td>
<td>1/20 [(3) (0–8)]</td>
<td>0/20 [(0)]</td>
</tr>
<tr>
<td>[left omissions (SD) (range)]</td>
<td>2/6 (2) (0–6)</td>
<td>2/6 (2) (0–5)</td>
<td>0/6 (0)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Wundt–Jastrow (mean/max)</td>
<td>4/9 (2) (2–9)</td>
<td>1/9 (1) (0–1)</td>
<td>3/9 (2) (2–6)</td>
<td>0/9 (0)</td>
</tr>
<tr>
<td>[left omissions (SD) (range)]</td>
<td>5.89, 30</td>
<td>5.99, 1,48</td>
<td>5.89, 1,48</td>
<td>5.89, 1,48</td>
</tr>
<tr>
<td>Personal neglect (severity)</td>
<td>4/9 (2) (2–9)</td>
<td>1/9 (1) (0–1)</td>
<td>3/9 (2) (2–6)</td>
<td>0/9 (0)</td>
</tr>
<tr>
<td>[mean/max (SD) (range)]</td>
<td>45%</td>
<td>45%</td>
<td>45%</td>
<td>45%</td>
</tr>
</tbody>
</table>
| Max                  | maximum number of possible omissions, errors or deficit, Haem = haemorrhage, Inf = infarct, V = visual extinction, T = tactile extinction, VT = visual–tactile extinction, H+ = left hemianopia, * = missing data.

and visual or visual–tactile extinction (28%). The two associated symptoms were never observed for patients with pure personal neglect.

Density plots and lesion subtractions
To be in line with previous studies, the first operation we performed on lesion data was a simple lesion overlap (or density plot) of all patients showing either extrapersonal or personal neglect. Due to the large number of patients with both kind of neglect in our sample, and also to the intrinsic methodological limitations of lesion overlapping procedures, lesion density plots were not very informative. Both density plots, in fact, revealed a large region of overlap spanning the basal ganglia, the insula and the perisylvian cortices with the surrounding WM (data not shown).

The direct lesion comparisons or subtractions between patients with and without each form of neglect, instead, revealed a clearer pattern of involved regions (Fig. 2). Top row shows the subtraction between all patients with (n = 28) and without (n = 24) extrapersonal neglect [(EP+E) − (P+C)]: orange and red zones in the figure (overlay >45%) are clearly centred in the inferior precentral and in the perisylvian cortex, the latter including the STG and the parietal operculum; moving medially, we find the posterior insula with the WM immediately dorsal (suprarectal cortical and centrum semiovale) and ventral (subrectal cortical). The direct lesion comparison between all patients with (n = 30) and without (n = 22) personal neglect [(EP+P) − (E+C)]: yielded a partially different pattern (Fig. 2, second row). Orange and red zones of greater percentage values, while still centred on perisylvian regions, now spare the inferior precentral cortex and extend dorsally in the inferior parietal lobe to include the supramarginal gyrus (SMG) and the parietal WM medial to it. We conducted also more restrictive subtractions between the groups of pure patients (suffering from either personal or extrapersonal neglect only) and the control group without any form of neglect. Notwithstanding the smaller number of subjects in both pure groups, the two subtractions revealed a similar pattern of results to that described above (see Fig. 2, third row for P−C; see Fig. 2, bottom row for E−C).

Region-based statistical analysis
After lesion subtractions, which do not provide statistical significance for the observed differences, we performed region-based statistical analysis on the outputs of an automated parcellation procedure (see Material and methods). First, a 2 × 2 ANOVA, with extrapersonal and personal neglect (present/absent) as factors, was performed on the lesion volume. We detected a main effect of both neglect types (extrapersonal: $F_{1,48} = 5.99, P < 0.05$; personal: $F_{1,48} = 5.89, P < 0.05$) and the absence of a significant interaction, thus suggesting additivity for the two deficits. As shown in the graph, in fact, patients with pure extrapersonal or personal neglect have practically the same amount of lesioned tissue (87 versus 86 cm³), while patients having both extrapersonal and personal neglect have a mean lesion size that almost corresponds to the sum of the two (166 cm³). Patients without any form of neglect, instead, have a much smaller (41 cm³) mean lesion size.

Then, a series of region-based 2 × 2 ANOVAs were performed on the percentage of lesioned tissue. The interaction between the two neglect factors was very far from significant in all regions, whereas main effects of extrapersonal and personal neglect were significant at the uncorrected level in a series of regions. Frontal and temporal...
regions such as the inferior precentral gyrus \((F_{1,48} = 5.18, P = 0.03)\), the middle frontal gyrus (MFG) \((F_{1,48} = 3.82, P = 0.05)\), the middle STG \((F_{1,48} = 5.94, P = 0.02)\) and, within the WM, the sublenticular CR of the temporal lobe \((F_{1,48} = 5.38, P = 0.02)\), appeared to be more lesioned in patients with than without extrapersonal neglect (Fig. 3, top row). In line with the more caudal and dorsal pattern observed in the lesion subtractions, instead, regions showing greater lesioned tissue for patients with, than without, personal neglect were located in posterior temporal and parietal regions: posterior STG \((F_{1,48} = 7.46, P = 0.008)\), SMG \((F_{1,48} = 5.58, P = 0.02)\), angular gyrus \((F_{1,48} = 4.49, P = 0.04)\), post-central gyrus \((F_{1,48} = 4.34, P = 0.04)\) and, within the WM, parietal SC \((F_{1,48} = 8.21, P = 0.006)\) and supralenticular CR \((F_{1,48} = 4.25, P = 0.04)\) (Fig. 3, bottom row).

**Voxel-based lesion–symptom mapping**

Finally, we submitted our data to the theoretically different approach of VLSM (Bates *et al.*, 2003), which analyses behavioural and lesion information without classifying the patients and using the richness of the continuous behavioural measures. The maps obtained entering mean percentage values of severity and standardized t-scores gave
Fig. 3 Region-based statistical analysis. Bar plots of the percentage of lesioned tissue in several representative regions where the percentage of lesioned tissue was significant for the extrapersonal and not for the personal neglect factor (top row) and vice versa (bottom row). PrecG = precentral gyrus.

Fig. 4 Voxel-based lesion–symptom mapping (VLSM). Representative slices from VLSM maps computed for awareness of extrapersonal (top row) and personal (bottom row) space in right brain-damaged patients. High t-scores (red) indicate that lesions to that voxel affect behaviour in a highly significant manner. Low t-scores (dark blue) indicate regions whose lesions have a relatively little impact on behaviour. All voxels above $t = 1.9$ were significant at $P = 0.05$ (FDR correction), while $t = 4.6$ was the cut-off for Bonferroni correction. PrecG = precentral gyrus.
comparable results. VLSM showed a highly significant impact of frontal and temporal lesions on the awareness of extrapersonal space (Fig. 4, top row; red zones survived also the conservative Bonferroni cut-off of $t > 4.6$). In the frontal lobe, VLSM confirmed the importance of the inferior precentral gyrus ($t = 6.1$, MNI coordinates: 64, 4, 16) and MFG ($t = 5.9$, MNI coordinates: 44, 44, 20), and revealed an interesting involvement of a more superior portion of the precentral gyrus ($t = 4.4$). In the temporal lobe, a relevant role was assigned to the middle portion of both superior ($t = 4.8$, MNI coordinates: 60, −24, 4) and middle ($t = 4.8$, MNI coordinates: 50, −28, −8) temporal gyri, and also to the anterior STG ($t = 5.3$, MNI coordinates: 37, 6, −20).

The mapping of personal neglect symptoms on the lesioned brains through VLSM underlined the involvement of parietal structures (Fig. 4, bottom row). In fact, it showed a highly significant effect (from yellow to red zones, all surviving the Bonferroni cut-off) of the WM bundles at level of the central sulcus and behind, with the maximum $t$-values in the parietal SC ($t = 8.1$, MNI coordinates: 37, −36, 32), the post-central gyrus ($t = 4.7$, MNI coordinates: 40, −19, 39) and the SMG ($t = 4.7$, MNI coordinates: 56, −29, 40). Furthermore, it revealed the involvement of the MFG ($t = 4.8$, MNI coordinates: 35, 13, 38), in a portion more dorsal and posterior to that described for the extrapersonal neglect.

When we co-varied out the effect of personal neglect on extrapersonal neglect, the inferior precentral gyrus, the MFG and the middle STG still showed a significant involvement. Instead, when co-varying out the effect of extrapersonal neglect on personal neglect, we still observed a significant involvement of the WM bundles at the level of the central sulcus and behind (parietal SC) and of the post-central gyrus, but a reduction of SMG significance and a disappearance of MFG involvement. All described regions survived a VLSM analysis conducted by co-varying out the effect of time since stroke. Instead, the effect of lesion size was more critical, because after being co-varied out none of the above-described regions (except for a few voxels in the parietal SC for the personal neglect) survived the statistical correction (see Karnath et al., 2004, for similar results). This may be due to the fact that the analysed voxels are not necessarily independent of one another, given the vascular supply to the brain. Notwithstanding the potential advantages of VLSM over lesion overlapping techniques, this intrinsic limitation must be borne in mind.

In addition, we assessed similarity between the statistical maps for awareness of extrapersonal and personal space by calculating the correlation between $t$-scores on the two measures. We obtained a value of 0.84, which reflects $\sim 70\%$ of overlap in the variance. This suggests that areas associated with one measure of neglect can predict those associated with the other measure quite well. Many voxels, in fact, have a moderate-to-low $t$-score ($t < 4$) in both maps, a score we have not seen survive the Bonferroni correction. They are located in the WM at level of the central sulcus, in the inferior frontal gyrus and mainly in the insular/opercular regions of the temporo-peri-Sylvian cortex. The latter may correspond to a cortical vestibular region (Kahane et al., 2003), which is thought to contribute to the egocentric representation of space by integrating different sensory inputs (Bottini et al., 2001). The remaining voxels have a high $t$-score in one measure but not in the other, are located in the regions described above, and are thus responsible for the picture of a clear dissociation between the VLSM maps of the two measures.

**Discussion**

To our knowledge, this is the first study to explore the anatomical correlates of spatial neglect for extrapersonal and personal space simultaneously in a large group of patients. Main result can be summarized as a significant dissociation between the neural substrates of the two forms of neglect. The segregation manifests as a clear gradient of regions involved in extrapersonal and personal neglect, with the former more rostral and the latter more caudal. Indeed, the cortical regions detected in all the analyses performed for extrapersonal neglect were found in the frontal lobe (the inferior precentral and MFGs), whereas those detected for personal neglect were found in the parietal lobe (the supramarginal and post-central gyri). The gradient is also evident within the temporal lobe, where the anterior and middle STG were involved only in the genesis of extrapersonal neglect, and the posterior STG only in the genesis of personal neglect (but not consistently among the different analyses). The WM division showed a ventro-dorsal gradient, with the sublenticular CR of the temporal lobe involved in extrapersonal neglect and the suprалenticular CR and centrum semiovale of the parietal lobe involved in personal neglect.

In the present set of data, notwithstanding the significant correlation between the behavioural measures for extrapersonal and personal neglect, the absence of a statistically significant interaction in the region-based analysis suggests that the two deficits are additive and most likely due to lesions of segregated neural substrates. In accordance with this view, a previous study on a large group ($n = 121$) of chronic patients found very low correlation between personal neglect and any other measure of neglect, and also showed the absence of clustering with any of them (Pizzamiglio et al., 1992).

**Personal space awareness**

Introduced by Zingerle in 1913 (see Benke et al., 2004, for an abridged translation of Zingerle’s paper), the label personal neglect refers to lack of exploration of the contralesional part of the body. For instance, patients with personal neglect may appear with their glasses misplaced on the contralateral side of their face or even half-shaved. At neurological examination, they may fail to detect tactile stimuli delivered on the contralesional side of the body, even in absence of primary somatosensory deficits (Bisiach and Vallar, 2000).
Our results are the first to provide group data for the neural substrates of personal neglect in humans. The only previous group study (Bisiach et al., 1986) was conducted on CT scan and could not derive conclusions on the anatomical bases of the deficit because personal neglect was detected on few acute patients, the majority of which showed also extrapersonal neglect.

We found critical regions for personal neglect in the post-central and supramarginal gyri of the parietal lobe, and especially in the WM medial to them. Human SMG corresponds to monkey area PF (or PF 7b), the ablation of which causes sensory/attentional and motor deficits. The monkeys show a preference for the hand ipsilateral to the lesion, respond to tactile stimuli with delay or even neglect them, and also show visual deficits in the ultra-near peri-buccal space. In contrast, they orient towards the contralateral space and explore it [while animals with frontal eye field (FEF) lesions do not] (Rizzolatti et al., 2000). SMG is therefore a good candidate for the neural substrates of personal neglect in humans.

Given the critical role played by the parietal WM, the present data strongly support the hypothesis that the emergence of personal neglect is due to a functional disconnection between regions important for coding proprioceptive and somatosensory inputs, such as the post-central gyrus, and those coding a more abstract egocentric representation of the body in space, such as the SMG (Coslett, 1998; Galati et al., 2001). This account is reminiscent of the second interpretation proposed by Zingerle (1913) in 1913 for its Case III: ‘the patient (…) had somehow lost the representation of this body side, or the correct evaluation of sensations flowing towards it, which are necessary for the spatial perception of the body’ (Benke et al., 2004).

A last note can be devoted to the difference between the present results and those obtained on the neural basis of anosognosia for hemiplegia (Ellis and Small, 1997; Berti et al., 2005; Karnath et al., 2005). Such a difference is in line with the fact that anosognosia for motor and/or sensory impairments on the contralesional body side and neglect are different disorders both from a clinical and a theoretical point of view (Bisiach et al., 1986b). However, this difficult and controversial issue merits further investigations given that personal neglect has been rarely tested in the literature on the neural correlates of anosognosia for hemiplegia (see Pia et al., 2004, for a meta-analysis).

Extrapersonal space awareness

The present data clearly underline the importance of intact frontal regions for a normal awareness of visual extrapersonal space. In particular, data converge in showing as critical areas the ventral premotor cortex in the inferior precentral gyrus (BA6) and the dorsolateral prefrontal cortex (DLPFC) in the anterior and ventral portion of the MFG (BA4/46). Lesion–symptom correlation (VLSM) also suggests the involvement of a small portion of the superior precentral gyrus not far from the human FEF. In primates, frontal neglect regards the extrapersonal space mainly after damage to the FEF, whereas damage to the ventral premotor cortex (inferior area 6) regards more the personal and ultra-near space (Rizzolatti et al., 1983, 2000). In humans, extrapersonal neglect has been observed after lesions to both the ventral and dorsal (including the FEF) premotor cortex and the DLPFC (Heilman and Valenstein, 1972; Husain and Kennard, 1996). This difference suggests a more marked specialization of premotor areas for a particular sector of space in monkeys. We can speculate that this might be due to the greater use of tools in humans and/or to the higher relevance of ultra-near space in monkeys, especially for mouth eating movements.

It has recently been suggested that the ventral frontal cortex is part of a cortical network responsible for the exogenous ('bottom-up') allocation of attention in space, whose damage would cause hemispatial neglect (Corbetta and Shulman, 2002; Corbetta et al., 2005). In a series of previous neuroimaging studies, the right ventral premotor cortex was also consistently activated by spatial judgements in egocentric coordinates (Galati et al., 2000, 2001; Committeri et al., 2004). Both these functions are disrupted in visual extrapersonal neglect, in agreement with the crucial role of the ventral premotor cortex revealed by the present data.

In addition to the ventral premotor contribution, other cortical regions located in the temporal lobe had a strong impact on the awareness of extrapersonal space: the middle and anterior STG, the superior temporal sulcus (STS), and also the sublenticular WM medial to these regions. In monkeys, lesions to the upper bank of STS, also referred to as superior temporal polysensory (STP) area, are reported to cause a striking inattention (Petrides and Iversen, 1979), probably due to the disruption of neurons with large receptive fields responding to different modalities (Bruce et al., 1981). Our results are in agreement with recent anatomical data on human neglect that revealed an involvement of the deep WM in the temporal lobe (Samuelsson et al., 1997; Leibovitch et al., 1999), of the anterior and medial temporal lobe (Maguire and Ogden, 2002), and of the STG (Karnath et al., 2001, 2004; Corbetta et al., 2005; Thiebaut de Schotten et al., 2005). In the above-cited paper by Corbetta and collaborators (2005), the STG represents a further node of the ventral circuit responsible for the exogenous allocation and reorienting of attention in space. The present data add the important information to these previous studies that the results are really connected to a deficit of visual extrapersonal space and not to other deficits such as heminattention for personal space.

Although the present data support a role for temporal regions, they do not support an essential role for parietal lesions in sub-acute or chronic extrapersonal neglect. None of the above-cited studies that assigned a critical role to IPL (Heilman et al., 1983; Vallar and Perani, 1986;
Mort et al., 2003) or parietal WM (Leibovitch et al., 1998; Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005) reported measures of personal neglect. Thus, it is possible that a substantial proportion of their patients had concomitant personal deficits which biased the results towards regions more dorsal than the STG. Another possibility is that, among our sub-acute patients with pure personal neglect, there were patients who recovered spontaneously from an extrapersonal deficit at the acute stage. If this were true, SMG might be relatively important in the acute phase and less in the sub-acute or chronic phase (as suggested by Egelko et al., 1988, and Samuelsson et al., 1997). However, Karnath and colleagues (2001, 2004) did not find a parietal involvement even in acute patients. Moreover, the unimportant role played by the ‘time since stroke’ variable in the VLSM analysis should caution us against this hypothesis. In any case, a negative result does not permit to draw firm conclusions on the role played by the parietal cortex in the genesis of extrapersonal neglect.

The possible effects of extrapersonal neglect assessment on the involved regions that have been described remains a critical issue in particular because we did not use the line bisection task, recently associated. More posterior lesions at the temporop–occipital junction (Rorden et al., 2006). By possibly excluding patients with deficits on line bisection, there is a likelihood that the lesion analysis has been skewed more anteriorly. However, this possibility is very unlikely because we controlled for the performance of our patients in the line bisection task (obtained for other research purposes) and found that all the patients showing a rightward bias have been classified as having an extrapersonal deficit with the battery, thus they have all been included in the analysis. Moreover, only a part (12/28) of the patients with an extrapersonal deficit as assessed by the battery showed a rightward bias in the line bisection (see Mort et al., 2003, for a similar observation). In any case, further studies are necessary to clarify the issue of line bisection because a rightward bias has been shown also after the stimulation of the middle STG (Thiebaut de Schotten et al., 2005).

Conclusions

In conclusion, the present group study strongly sustains what has so far been suggested by only single subject studies: the neural bases of personal and near extrapersonal (or peripersonal) space awareness in humans are dissociated both from a functional and an anatomical point of view. Extrapersonal space awareness critically involves frontal and temporal regions which are part of a ventral circuit recently described for the exogenous allocation and reorienting of attention in space. Disruption of personal space awareness, instead, is due to parietal lesions and/or functional disconnection between proprioceptive/somatosensory coding and more abstract egocentric representations of the body in space. The research also provides a valuable method for the study of brain-damaged patients with complex neuropsychological syndromes, and future investigation should include functional neuroimaging on the same patients (Corbetta et al., 2005).

Acknowledgements

This work was supported by grants from ‘Fondazione Santa Lucia’ and MIUR. We are grateful to Stephen Wilson for his methodological support with VLSM analysis.

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