DOI: 10.1093/brain/awg200 Advanced Access publication June 23, 2003 *Brain* (2003), **126,** 1986–1997

# The anatomy of visual neglect

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## Summary

**The brain regions that are critically associated with visual neglect have become intensely disputed. In particular, one study of middle cerebral artery (MCA) stroke patients has claimed that the key brain region associated with neglect is the mid portion of the superior temporal gyrus (STG), on the lateral surface of the right hemisphere, rather than the posterior parietal lobe. Such a result has wide-ranging implications for both our understanding of the normal function these cortical areas and the potential mechanisms underlying neglect. Here, we use novel high resolution MRI protocols to map the lesions of 35 right-hemisphere patients who had suffered either MCA or posterior cerebral artery (PCA) territory stroke. For patients with MCA territory strokes, the critical area involved in all neglect patients was the angular gyrus of the inferior parietal lobe (IPL). Although the STG was damaged in half of our MCA neglect patients, it was spared in the rest. For PCA territory strokes, all patients with neglect had lesions involving the parahippocampal region, on the medial surface of the temporal lobe. PCA patients without neglect did not have damage to this area. We conclude that damage to two posterior regions, one in the IPL and the other in the medial temporal lobe, is associated with neglect. Although some neglect patients do have damage to the STG, our findings challenge the recent influential proposal that lesions of this area are critically associated with neglect. Instead, our results implicate the angular gyrus and parahippocampal region in this role.**

**Keywords**: neglect; parietal; temporal; angular gyrus; parahippocampal region

**Abbreviations**: ANG = angular gyrus; IFG = inferior frontal gyrus; IPL = inferior parietal lobe; IPS = intraparietal sulcus; LF = lateral fissure; MCA = middle cerebral artery; MFG = middle frontal gyrus; MNI = Montreal Neurological Institute; PCA = posterior cerebral artery; ROI = region of interest; SMG = supramarginal gyrus; SPL = superior parietal lobe; STG = superior temporal gyrus; STS = superior temporal sulcus; TPJ = temporoparietal junction

## Introduction

The search for those brain areas that, when damaged, are capable of producing visual neglect has become the subject of intense debate (Karnath and Himmelbach, 2002; Marshall *et al*., 2002). Until recently, in case series of unselected middle cerebral artery (MCA) patients who typically have large strokes, the most consistent observation has been that the brain area most commonly associated with neglect is the right posterior parietal lobe, particularly the region around the temporoparietal junction (TPJ) (Heilman *et al*., 1983; Vallar and Perani, 1986; Leibovitch *et al*., 1998; Vallar, 2001). Neglect has also been observed following more focal strokes of the right inferior frontal lobe (Husain and Kennard, 1996) and subcortical structures such as the thalamus (Cambier *et al*., 1980) and basal ganglia (Damasio *et al*., 1980; Karnath *et al*., 2002), although accompanying hypoperfusion of overlying cortex may be an important determinant of neglect in subcortical cases (Vallar *et al*., 1988; Hillis *et al*., 2002).

In addition to these locations—all within the territory perfused by the MCA—there have been reports of neglect following strokes in the territory of the posterior cerebral artery (PCA), but the exact medial occipito-temporal regions critical for neglect have not been defined (Doricchi and Angelelli, 1999; Cals *et al*., 2002). Vallar and Perani (1986) noted that the syndrome was usually absent when infarction was limited to the occipital lobe, as has a more recent study which reported that neglect occurred in nine out of 53 patients with isolated superficial right PCA strokes (Cals *et al*., 2002). This study also observed that neglect was more frequent in patients with occipital infarcts that extended more anteriorly, although lesions were not plotted. In another study, lesion

reconstructions demonstrated medial temporal lobe involvement, but the plots also included posterior MCA territory strokes (Doricchi and Angelelli, 1999). Moreover, there was no lesion contrast made with PCA controls without neglect, so it is not possible to distinguish between the PCA territory regions specifically involved with neglect and those regions that are typically damaged following PCA lesions.

Almost all previous anatomical series of neglect have used CT imaging (but see Maguire and Ogden, 2002). Although the best in-plane resolution of most CT scans is very good (0.3–0.5 mm), the slice thickness (or *z*-plane resolution) is much larger, typically 8–10 mm. This is one important limiting factor for lesion reconstruction using this imaging modality. Thus, in the published literature, reconstructions from CT are relatively coarse, typically showing 10 or often fewer slices (e.g. Husain *et al*., 1997). Moreover, if scans are acquired for clinical purposes and do not follow a strict research protocol (as used, for example, by Friedrich *et al*., 1998), the orientation of these slices will vary slightly across patients. Thus they may not match exactly the templates onto which the lesions will be placed, even if several different templates are used. Finally, standard practice is to draw the lesions by hand onto templates. Although some investigators develop great expertise in this, lesion reconstruction in this manner is observer dependent. All these factors limit the spatial accuracy of standard CT-acquired reconstructions.

A recent study of MCA patients, in which MRI was available for many of the participants, came to a radically different conclusion from previous investigations, implicating a region along the right mid superior temporal gyrus (STG) as the critical zone associated with neglect (Karnath *et al*., 2001). Note that this region of the STG is not the posterior portion that has sometimes been taken to be part of the TPJ. If this new result is correct, it would have potentially far-reaching consequences for our understanding of the mechanisms underlying neglect, as well as of the normal functions of both the posterior parietal lobe (the region previously implicated in neglect) and the STG in healthy individuals (Karnath, 2001). However, the study had several important drawbacks.

First, although MRI scans were available for many of the patients, the imaging was all acquired for clinical purposes, so there were relatively few axial slices. In this respect, these image acquisitions do not improve greatly on standard CT studies. Secondly, some patients actually had only CT scanning, and CT scans are acquired in orientations very different from MRIs. Thus, there would not only have been variability among patients scanned using one particular modality (CT or MRI), but there would also have been big differences between the orientations of templates used to plot images acquired by CT and MRI. Thirdly, for all patients in this study, lesions were demarcated by hand onto only one template set, consisting of eight MRI axial slices in the published data set, so lesions originally acquired either for CT or MRI would have to be mapped by the investigators into what was considered the appropriate location on a single standard MRI template. Fourthly, for the primary analysis, neglect patients with visual field defects were excluded because the investigators felt it was important to assess the lesions of only patients with 'pure' spatial neglect. However, this biases the lesion analysis. Specifically, this policy is likely to lead to exclusion of patients with more posterior lesion sites and the inclusion of patients with more anterior damage. Furthermore, taken to its logical conclusion, one might argue that if the aim was to study only 'pure' neglect patients, then individuals with hemiparesis or somatosensory loss should also have been excluded. Because stroke patients with only neglect (and no other neurological or neuropsychological dysfunction) are extremely rare, it is preferable not to exclude any particular subgroup and study instead all patients with neglect, comparing them with all patients without neglect. Finally, it is important to note that the area of maximum lesion overlap in the study of Karnath *et al*. (2001) did not encompass all neglect patients; rather a maximum of about half the sample overlapped any particular voxel within the STG (see their Fig. 1b, including the key for degree of lesion overlap).

Here, we attempt to overcome previous limitations by prospectively MRI scanning all neglect patients, with either MCA or PCA territory stroke, at high isotropic spatial resolution (1 mm × 1 mm × 1 mm), and comparing their lesions with MCA and PCA control patients without neglect. Our method does not rely on transfer of lesions to a few standard template slices; we acquire 256 slices so that the *z*-plane resolution is ~20 times that of standard CT scans. Lesions are demarcated on every 1 mm axial slice of each brain image and then normalized to a common spatial framework to allow comparison across groups. Normalization is an automated process that adjusts the size and shape of each individual's scan, and avoids the requirement of the individual investigators making (observer-dependent) decisions based on a limited number of slices. Furthermore, normalization allows us to compare lesion data directly with functional imaging data in normal individuals, so that one can make predictions about the types of function that are normally carried out by the brain regions that are lost in neglect. Finally, to check on the validity of our conclusions and to make sure that normalization does not distort the result in some way, we also inspected lesion locations within individual brains using a painstaking procedure to study lesion involvement of segmented defined regions of interest (ROIs). These new methods allow us to define with precision, and confidence, the posterior structures that are associated with neglect.

However, because neglect is a heterogeneous condition (Heilman *et al*., 1993; Halligan and Marshall, 1994; Bisiach and Vallar, 2000), it might be argued that such a search for critical regions associated with the condition is a fruitless enterprise. We would argue that it remains extremely worthwhile attempting to determine, with high spatial accuracy, whether there are common brain regions that are involved in neglect patients. Although we strongly favour the

**Table 1** *Neglect patient details*

| Patient | M/F | Age (years) | Mesulam score (/60) | Line bisection (% deviation) | Field defect | Lesion volume ($cm^3$) |
|---|---|---|---|---|---|---|
| M1 | M | 66 | 31 | 11.8 | + | 44 |
| M2 | M | 87 | 34 | 18.3 | + | 30 |
| M3 | M | 64 | 6 | NA | – | 64 |
| M4 | M | 68 | 17 | 13.9 | – | 27 |
| M5 | M | 70 | 57 | 8.5 | – | 160 |
| M6 | M | 51 | 31 | –4.6 | – | 58 |
| M7 | F | 29 | 55 | 6.3 | – | 10 |
| M8 | F | 81 | 6 | 19.4 | – | 13 |
| M9 | M | 54 | 5 | 6.1 | – | 2 |
| M10 | M | 55 | 48 | 20.0 | – | 242 |
| M11 | F | 75 | 4 | –0.7 | – | 68 |
| M12 | M | 83 | 55 | 5.0 | – | 54 |
| M13 | F | 35 | 34 | 0.0 | – | 32 |
| M14 | M | 63 | 55 | 1.8 | – | 20 |
| P1 | M | 76 | 41 | –0.2 | + | 109 |
| P2 | M | 68 | 36 | 16.5 | + | 61 |
| P3 | M | 68 | 17 | 48.2 | + | 111 |
| P4 | F | 77 | 54 | 8.3 | + | 214 |
| P5 | M | 63 | 24 | 6.7 | + | 22 |

MCA patients are labelled M1–14 and PCA patients are designated P1–5. Details are given of neglect indices, the presence of a contralateral visual field defect and lesion volume (measured precisely as the number of 1 $mm^3$ voxels contained within each patient's lesion ROI).

view that neglect may result from different combinations of component deficit in different patients (e.g. Husain and Rorden, 2003), finding critical common regions across patients would suggest there may be core deficits that are common to many patients with neglect. Here, we use our new methods to determine whether there are such key common structures involved in a group of MCA or PCA territory stroke patients with visual neglect.

## Methods

### *Patients and MRI scanning*

Thirty-five patients presenting with acute uncomplicated right cerebral hemisphere stroke participated in this study. Twenty-four individuals had lesions in the territory of the right MCA and 11 in the territory of the right PCA. Written, informed consent was obtained according to the Declaration of Helsinki, and the study was approved by the Charing Cross Hospital and Hospital for Neurology and Neurosurgery ethics committees.

The presence of left visual neglect was based on clinical assessment, including performance on the Mesulam shape cancellation task (Mesulam, 1985) and line bisection (Halligan *et al*., 1990). Several patients showed no significant rightward deviation on line bisection (elderly healthy individuals may show a deviation of up to 3% to the right of the true midline; Halligan *et al*., 1990), but they showed left visual neglect on the Mesulam cancellation task. This type of dissociation has been noted previously (Binder *et al*., 1992) and it has been suggested that dense cancellation tests may be more sensitive measures of neglect (Ferber and Karnath, 2001). Fourteen of the 24 MCA patients and five of the 11 PCA patients were found to have visual neglect on either or both the cancellation and line bisection tests (see Table 1). These patients also showed evidence of neglect in their everyday behaviour. There was no significant difference in the severity of neglect between the MCA and PCA neglect patients, as assessed on the Mesulam cancellation test (Mesulam, 1985) or line bisection (Halligan *et al*., 1990). The rest of the patients (10 MCA and six PCA individuals) did not demonstrate visual neglect on clinical assessment (including cancellation and line bisection) or in everyday life.

Visual fields were recorded by the standard clinical method of confrontation. In our experience, this is superior to automated perimetry which frequently confuses neglect for absolute visual field loss (Muller-Oehring *et al*., 2002). All PCA patients had a left homonymous hemianopia; only two of the MCA neglect patients had left visual field defects.

Each patient underwent a dedicated high resolution structural MRI scan which comprised one 256 slice $T_1$-weighted acquisition (MPRAGE: repetition time, TR 9.7 ms; echo time, TE 4 ms; flip angle 12°; acquisition time, TA 12 min) performed in the coronal plane, on a 1.5 T MRI scanner (Siemen's Vision, Munich, Germany). Within- and between-slice resolution was 1 mm, giving an isotropic voxel dimension of 1 $mm^3$. MRI scanning was not performed immediately at the time of stroke because these images were acquired for research, rather than clinical, purposes. In the MCA neglect group, the median time between stroke and

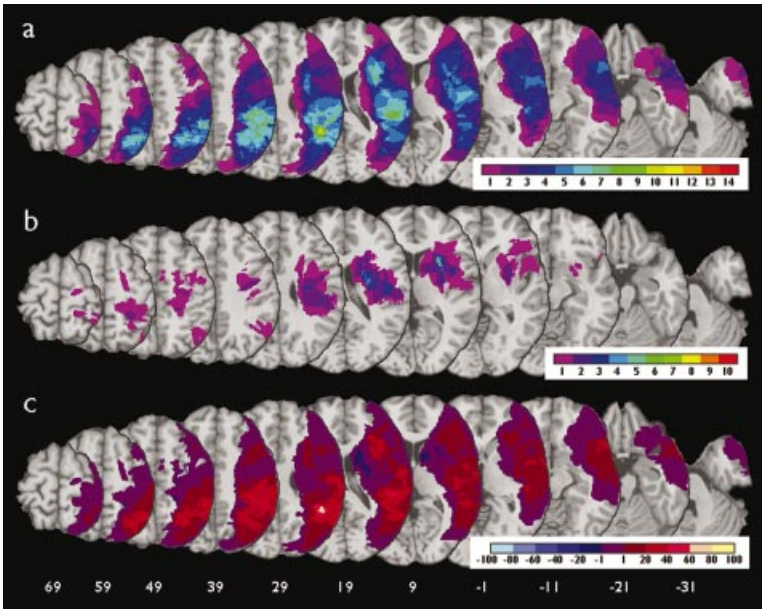


**Fig. 1** MCA patients. (**A**) Neglect patients. Overlap map showing the degree of involvement of each voxel in the lesions of the MCA neglect patient group ($n$ = 14), normalized to the smoothed MNI template. The map is presented as 2D axial renderings on the MNI 'representative' brain, in 10 mm ascending steps. The range of the colour scale derives from the absolute number of patient brains in each group. The $z$ position of each axial slice is presented at the foot of the figure in units of cm above the AC–PC plane. (**B**) Non-neglect patients. Overlap map for the MCA patients without neglect ($n$ = 10). (**C**). Neglect versus non-neglect patients. Contrast map showing the relative involvement (bins of 20%) of each voxel in the lesions of the neglect patient group compared with the non-neglect patient group. The colour scale covers a range of voxel involvement in the two lesion groups, from involvement in the neglect group only (light yellow) to involvement in the non-neglect group only (light blue).

scan was 63 days, with the shortest interval being 35 days; for the PCA neglect group, one patient had to be scanned relatively early at 9 days, but the median time was 140 days.

## *Lesion mapping*

The extent and location of lesions were defined and visualized using the free MRIcro software package (Rorden and Brett, 2000; www.mricro.com). For each patient, the area of damage was determined by detailed visual inspection of the digital brain image, for every single slice, by author D.M. and separately corroborated by M.H., both clinical neurologists. This was best performed viewing the axial views, but also corroborating the extent of parenchymal involvement by co-inspection of the coronal view (image 'yoking'). The boundary of the lesion was delineated directly on the digital image as a 2D ROI at the level of individual voxels, traced by hand on each 1 mm axial image slice, using a graphics tablet (WACOM Intuos A6, Vancouver, Washington, USA). Note that although this process is dependent upon visual inspection, the lesion was not transferred to a template as is standard procedure, but mapped directly on the image. Combining all slices produced a 3D lesion ROI for each patient.

## *Spatial normalization and group contrasts*

Normalization of each MRI, including the 3D lesion ROI, to the smoothed $T_1$ template was performed with SPM99 (www.fil.ion.ucl.ac.uk/spm). The 3D lesion ROI was used as a mask for the lesion during determination of alignment parameters, to minimize the contribution of the abnormal brain to this process (Brett *et al*., 2001). Simple voxel-based comparisons establishing the anatomical subregions of maximal lesion overlap in the MCA and PCA neglect groups (and compared with their respective controls) were made within MRIcro software.

## *ROI analysis on un-normalized brains*

Although normalization may be observer independent, it is important to ensure that analysis of normalized brains concurs with that of the original (un-normalized) brain images. We therefore conducted an independent analysis to document the involvement of specific brain regions in neglect and non-neglect patients. Whereas viewing brain images in the axial plane best suits lesion delineation, regional segregation of the brain MRI is optimally performed in the coronal

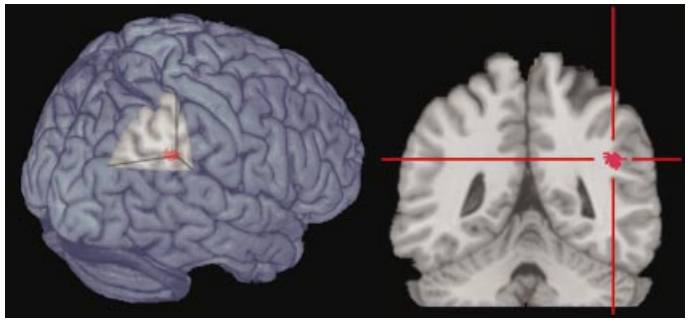

**Fig. 2** MCA patients: subregion of lesion overlap most associated with neglect. (**A**) The region of highest overlap in Fig. 1C is 3D-rendered onto the representative MNI template brain. The coordinates of this subregion [centre (46,–44,29)] lie in white matter just subcortical to the anteroventral part of the angular gyrus of the IPL. (**B**) Coronal view of the same subregion.

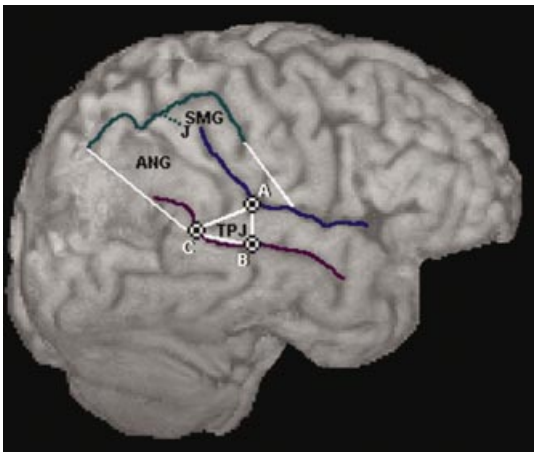


**Fig. 3** Lateral ROIs. Anatomical parcellation of a 3D-rendered patient's brain (for details, see Methods). The limits of the TPJ (temporoparietal junction) are marked by black and white discs. ANG = angular gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus; J = sulcus of Jensen. Bounding sulci are IPS (green), LF (blue) and STS (purple).

plane, based on the landmarks provided by the indenting cortical fissures. This painstaking approach was applied to all patients' lesions.

For the MCA patients, we confined our approach to the three anatomical regions for which there has been considerable recent controversy and which the precise anatomical data of this study could resolve: inferior parietal lobe (IPL), TPJ and STG. First demarcated was the TPJ. Although many authors discuss the TPJ, to the best of our knowledge its boundaries have never been clearly defined (see, for example, Friedrich *et al*., 1998). In this analysis, we attempt to be absolutely clear about what we take to be the TPJ so that there can be no confusion on this issue. Place holders were first marked on the right sagittal view (Fig. 3), defining TPJ as the area enclosed by a triangle linking the following points: A, the origin of the ascending posterior segment of the lateral fissure (LF); B, the point of intersection of a vertical line dropped from point A down to the superior temporal sulcus (STS; orthogonal to the plane of the anterior commissure and posterior commissure); and C, the origin of the ascending posterior segment of STS. Note that the mid portion of the STG is not included within our definition of the TPJ.

The cortical grey matter of the TPJ was then delineated in the coronal plane. The same was performed for the IPL and STG. The IPL was defined as all the parietal lobe bounded above by intraparietal suclus (IPS; from the beginning of the ascending or anterior section, through the horizontal section, and as far posterior as the point at which descending IPS reaches the level of the parieto-occipital sulcus) and, below, by the contiguous demarcation of (i) the caudal portion of the LF; (ii) a line joining points A to C; and (iii) the posterior horizontal segment of STS traced in extension to reach the parieto-occipital sulcus posteriorly. The STG was defined as brain lying rostral to the TPJ, between LF superiorly and STS inferiorly, and extending to the temporal pole.

With the cortical grey matter thus defined for each patient, the 3D lesion ROI could be cleaved objectively into its cortical and subcortical components, as pertaining to the three anatomical ROIs (TPJ, IPL and STG). This focused the analysis on the relative importance of damage to each of these candidate anatomical regions in the production of neglect. Further subdivision of IPL into supramarginal gyrus (SMG) and angular gyrus (ANG), as part of the lesion analysis for each patient, was also based on surface anatomy definitions (Duvernoy, 1999). The SMG is centred on the gyral banks either side of the ascending posterior segment of LF. The ANG is IPL posterior to this, extending backwards to the descending IPS. The point of transition between SMG and ANG is marked superiorly by a small descending ramus off the IPS, called the sulcus intermedius primus of Jensen (Duvernoy, 1999), marked 'J' on Fig. 3. IPL was divided into SMG and ANG by drawing a line from the origin of J to the midpoint between A and C of the TPJ (Fig. 3). If the sulcus of Jensen was not apparent, then the same dividing line was placed to run vertically midway between the ascending posterior segments of LF and STS.

For the PCA patients, the cuneus, lingual and fusiform gyri were defined as in standard practice (Duvernoy, 1999). The

**Table 2** *Involvement of key regions of interest in MCA neglect patients*

| Patient | SPL | IPS | ANG | SMG | TPJ | STG | IFG | MFG |
|---|---|---|---|---|---|---|---|---|
| M1 | + | + | + | – | – | – | – | – |
| M2 | + | + | + | – | +* | +* | – | – |
| M3 | – | + | + | + | + | – | + | – |
| M4 | – | + | + | + | + | + | – | – |
| M5 | – | + | + | + | + | + | + | + |
| M6 | – | – | + | + | + | + | + | – |
| M7 | – | + | + | – | + | – | – | – |
| M8 | – | – | + | – | – | – | + | + |
| M9 | – | – | + | – | – | – | – | – |
| M10 | + | + | + | + | + | + | + | + |
| M11 | – | – | + | + | + | + | + | – |
| M12 | + | + | + | – | + | + | + | – |
| M13 | – | – | +* | + | – | – | + | + |
| M14 | – | + | +* | + | – | – | – | – |
| MC1 | – | – | – | – | – | – | +* | |
| MC2 | – | – | – | +* | – | – | – | – |
| MC3 | – | – | – | – | – | – | + | – |
| MC4 | + | + | – | – | – | – | +* | – |
| MC5 | – | – | – | – | – | – | – | + |
| MC6 | + | + | + | – | – | – | – | – |
| MC7 | – | – | – | – | – | – | – | – |
| MC8 | – | – | – | +* | – | – | + | – |
| MC9 | – | – | – | – | – | – | – | – |
| MC10 | – | – | – | + | – | – | + | + |

Neglect patients are labelled M1–M14, while control non-neglect patients are labelled MC1–MC10. Each patient's lesion was cleaved (Fig. 3) to show the extent of involvement of the superior parietal lobe (SPL), intraparietal sulcus (IPS), angular gyrus (ANG), supramarginal gyrus (SMG), temporoparietal junction (TPJ) and superior temporal gyrus (STG). Involvement by the lesion in each of these areas represents both cortical and subcortical involvement, except where involvement was only subcortical (marked by an asterisk). Note that lesion involvement in the inferior parietal lobe (IPL) has been divided into which of its two component regions (ANG and SMG) was affected. In addition, the involvement of the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) is also reported here.

parahippocampal gyrus and hippocampus were divided in two along the rostro-caudal axis to allow definition of anterior and posterior segments of these regions (Table 3).

## Results

### *Critical subregion for neglect in MCA patients*

Normalization of each patient's lesion into the common MNI (Montreal Neurological Institute) reference space permitted simple, voxelwise, algebraic comparisons to be made within and between patient groups. The first such overlap map identified a subregion of voxels in the IPL, lying just beneath the cortical surface of the rostroventral ANG [centred on Talairach and Tournoux coordinates (46,–44,29), Fig. 1A], as the area most commonly involved in lesions producing neglect in the MCA stroke patients. Ten of the 14 neglect patients' lesions involve this area. The other four patients (cases M7, M8, M13 and M14) had lesions that did not encroach on this area of maximal overlap. Nevertheless, these patients' lesions did involve very nearby regions within the ANG, with cases M7 and M8 having cortical involvement of the ANG (Fig. 3), and cases M13 and M14 having lesions with subcortical involvement of the ANG (see individual brain analysis below and Table 2).

Importantly, the zone of maximal overlap for MCA neglect patients was not involved in the lesion of any of the control MCA stroke patients without neglect (Fig. 1B). Thus this overlap zone appears as the localized brain subregion most associated with neglect in the direct lesion comparison of neglect and non-neglect groups (Fig. 1C). The critical lesion location is demonstrated more clearly in Fig. 2. Note that two of our MCA neglect patients suffered a left visual field defect (one was a quadrantanopia, the other a hemianopia). If these patients' lesions were removed from the analysis, the zone of maximal overlap for neglect patients remained unaltered.

Next, a detailed analysis of the lesion anatomy of each patient in the MCA group was performed by segmenting specific lateral ROIs (see Methods and Fig. 3). A number of posterior areas were involved in lesions within the MCA territory, including superior parietal lobule (SPL), IPS, TPJ, STG and STS, as well as the SMG and ANG of the IPL. However, only the ANG was involved in the lesion of all 14 MCA patients with neglect (Fig. 4; Table 2). Moreover, this posterior part of the IPL was damaged in only one MCA patient without neglect, and this patient's lesion did not encroach upon the critical MCA neglect group subregion. The positive predictive value (Sackett *et al*., 1991) of ANG involvement predicting neglect was therefore 14 out of 15 = 0.93 (because 14 of the 15 patients with ANG lesions had neglect); importantly, the negative predictive value was also high at nine out of nine = 1.0 (because all nine of the nine patients without ANG involvement did not have neglect); giving an overall accuracy of 14 + 9/24 = 0.96 (i.e. sum of all ANG lesioned patients with neglect plus non-neglect patients without ANG involvement divided by total number of patients). The corresponding overall accuracy of STG involvement predicting neglect was 0.71, but note that all the STG neglect patients also had involvement of the ANG (see Table 2). Thus STG involvement was not an independent predictor of neglect.

### *Critical subregion for neglect in PCA patients*

Using the same technique as in MCA patients, the lesions of the PCA patient group were normalized for comparisons in MNI space. The difference in lesion extent between those with neglect and those without is shown in Fig 5. Whereas the control PCA group (who suffered from hemianopia but no neglect) had damage limited to the medial occipital lobe (Fig. 5B), lesions in all PCA patients with neglect extended beyond the medial occipital lobe into the medial temporal lobe (Fig. 5A). The contrast of these groups shows that it was the involvement of inferior medial temporal lobe that was associated with the presence of neglect in PCA patients (Fig. 5C). The subregion most associated with neglect was

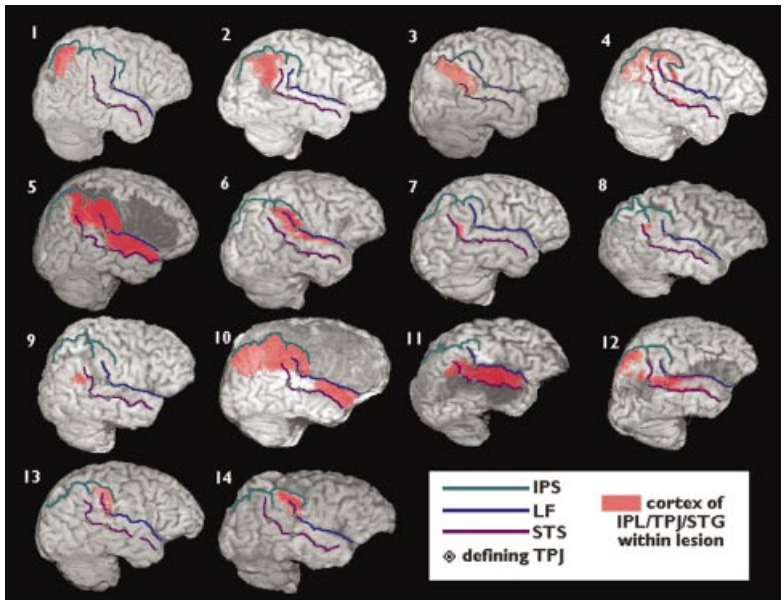


**Fig. 4** MCA patients: individual ROI analysis. Cortex of the IPL/TPJ/STG involved in the lesion (red) of each patient of the MCA neglect patient group ($n$ = 14), 3D surface rendered onto to the native brain of each patient. Note that lesions outside the IPL/TPJ/STG ROIs can be discerned as low signal density in some patients. On each brain, three key sulci are marked: intraparietal sulcus (IPS; green), lateral fissure (LF; blue) and superior temporal sulcus (STS; purple), together with the three points defining the anatomical limits of the TPJ (black and white discs). Native brain extraction ('skull stripping') was performed within MRIcro using the lesion ROI as a mask for the segmentation process.

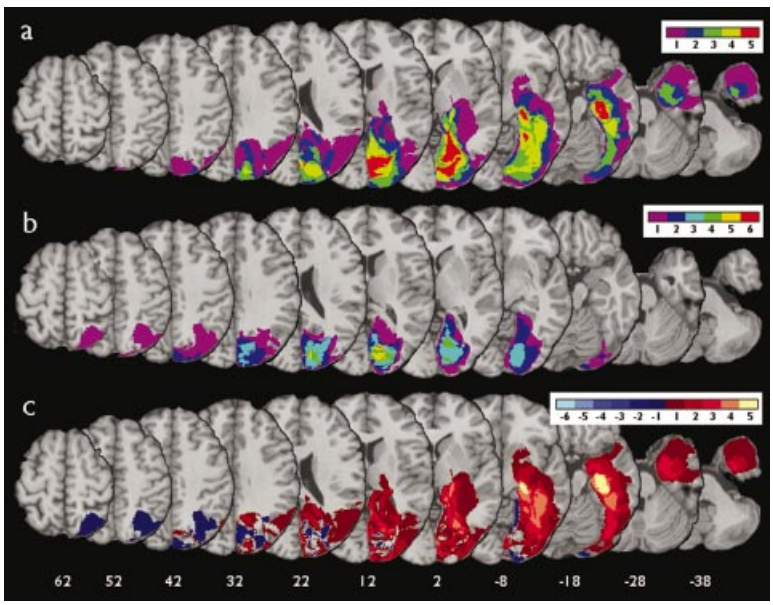


**Fig. 5** PCA patients. (**A**) Neglect patients ($n$ = 5). (**B**) Non-neglect patients ($n$ = 7). (**C**) Neglect versus non-neglect patients. The range of colour scale for the overlap map (**A** and **B**) is determined by patient number, as in Fig. 1. Because the number of PCA patients is smaller than MCA patients, the keys for the contrast map (**C**) represent the absolute number of patients' lesions involved for each voxel, rather than a percentage scale. The $z$ position of axial slices is presented at the foot of the figure. It is known that in the ventral-most slices, there is significant divergence between MNI and Talairach–Tournoux coodinate frames. The largest subregion of highest overlap associated with neglect in PCA patients lies in ventromedial temporal lobe [centre (32,–22,–17) or, if corrected, towards Talairach–Tournoux coordinates (32,–22,–13)].

**Table 3** *Detailed analysis of involvement of medial brain regions in PCA patients*

| Patient | Cuneus | Lingual | Fusiform | Post PHG | Post HC | Ant PHG | Ant HC |
|---|---|---|---|---|---|---|---|
| PN1 | + | + | + | + | + | + | – |
| PN2 | + | + | + | + | – | + | – |
| PN3 | + | + | + | + | + | + | + |
| PN4 | +* | + | – | + | – | + | – |
| PN5 | +* | + | + | + | + | + | – |
| PC1 | + | + | – | – | – | – | – |
| PC2 | +* | – | – | – | – | – | – |
| PC3 | +* | +† | – | – | – | – | – |
| PC4 | + | + | – | – | – | – | – |
| PC5 | + | + | – | – | – | – | – |
| PC6 | + | + | – | – | – | – | – |

Details of anatomical areas identified as being involved in the lesion (un-normalized) in analysis of lesion extent in each PCA patient. Neglect patients are labelled PN and control non-neglect patients are labelled PC. PHG = parahippocamapl gyrus; HC = hippocampus. *Cuneus gyrus involvement only including the dorsal bank of the calcarine fissure. †Lingual gyrus involvement only including the ventral bank of the calcarine fissure

centred on parahippocampal gyrus [corrected Talairach and Tournoux coordinates (32,–22,–13), extending ventrally and medially to (32,–13,–20) and posteriorly and laterally to (32, –31,–10)]. This area was involved in the lesions of all PCA patients with neglect and not encroached upon by any of the lesions of the PCA patients without neglect.

The painstaking analysis of the un-normalized brains also demonstrates that the parahippocampal gyrus is the critical zone associated with neglect in these patients (Table 3). Although the hippocampus was involved in three of the PCA neglect patients, it was spared in the other two. Analysis of un-normalized brains therefore concurs with the analysis of normalized brains implicating the parahippocampal gyrus as the critical medial temporal lesion site associated with neglect.

### *Lesion volume*

Although damage to the ANG and parahippocampal gyrus appears to be critically associated with neglect, it is important also to note that lesion volume was significantly larger in the neglect group than in the non-neglect group [Wilcoxon W (74), $P = 0.003$ for MCA comparison; Wilcoxon W (22), $P = 0.01$ for PCA comparison], consistent with both the results of previous studies (Vallar and Perani, 1986; Leibovitch *et al*., 1998) and clinical experience (see also Maguire and Ogden, 2002). It is possible that this may be a confounding factor influencing our conclusions. Alternatively, such a difference may be entirely consistent with the view that although there may be common core deficits across neglect patients, multiple cognitive components need to be damaged for neglect to be apparent (Maguire and Ogden, 2002).

### *Frontal involvement*

In previous studies of selected patients with focal right frontal damage, we have found that lesions predominantly affecting the inferior frontal lobe are associated with neglect (Husain and Kennard, 1996; Husain *et al*., 1997). Eight MCA neglect patients and six MCA non-neglect patients in the present study had lesions which involved the frontal lobe. The subregion of greatest lesion overlap (see Fig. 1A) was centred in white matter subcortical to the inferior frontal gyrus (IFG) at (35,14,20). Its ventral extent begins in the cortex of IFG (41,17,12) and becomes more subcortical as it extends dorsally up to (29,4,28). This subregion was partially or completely involved in the lesions of all eight MCA neglect patients with frontal lobe involvement, but in only four MCA control patients. Direct inspection of individual un-normalized brains revealed that all MCA neglect patients who had frontal lobe involvement had lesions involving the IFG. There was additional involvement of the middle frontal gyrus (MFG) in four of them (see Table 2). Five of the six control MCA patients with frontal involvement also had lesions involving IFG, but, in two of these, the lesion was subcortical only. The remaining MCA control patient had MFG involvement only. Of the 10 MCA neglect patients with lesions which overlapped in the critical subregion identified in IPL, the lesions of six of them also overlapped in the subregion identified in the frontal lobe. Two of the MCA neglect patients whose lesions, though involving the ANG, did not encroach on the critical subregion identified in ANG, did have lesions which included the frontal subregion. Thus, frontal involvement was neither necessary nor sufficient to produce neglect in this group of unselected patients with large lesions.

## Discussion

Using new protocols to map lesion locations with high fidelity, we showed that the most critical brain region associated with neglect in the territory of the MCA is the ANG on the lateral surface of the IPL. On the medial surface of the brain, in the territory perfused by the PCA, the

parahippocampal region was found to be the critical area. Homologues of these two regions in monkey are strongly reciprocally connected and, in addition, the parahippocampal region appears to be an important gateway for information transmitted between the parietal cortex and hippocampus (Ding *et al*., 2000; Clower *et al*., 2001; Burwell and Witter, 2002). Thus, the two regions identified by our methods have a well known, strong neurobiological connection.

A provocative recent study came to a very different conclusion, implicating instead the STG (Karnath *et al*., 2001). Although this region was often involved in our MCA patients with neglect, it was not the critical lesion location associated with neglect, either in the comparison between the neglect versus non-neglect group (Fig. 1) or in the individual analysis of ROIs (Fig. 4; Table 2). Thus our analyses fail to support the hypothesis that the STG is the critical brain region that needs to be damaged to produce neglect. Had this hypothesis been correct, it would have remarkably far-reaching consequences for current models of both IPL and mid STG function (Karnath, 2001), as well as for our understanding of the mechanisms underlying visual neglect. In the event, the methodological advantages of our study bring such a hypothesis into considerable doubt and secure the role of the inferior parietal cortex, and in particular the ANG, in visuospatial awareness.

### *Angular gyrus*

The ANG has been associated with profound deficits of spatial awareness in patients with bilateral lesions (Holmes, 1918; Rafal, 2001) and has also been implicated in maintaining attention to spatial locations in functional imaging studies (Pardo *et al*., 1991; Vandenberghe *et al*., 2001; Husain and Rorden, 2003). In contrast, SPL activity has been linked to spatial shifts of attention (Corbetta *et al*., 1995; Nobre *et al*., 1997; Vandenberghe *et al*., 2001), whilst the TPJ has been implicated in re-orienting spatial attention (Friedrich *et al*., 1998; Corbetta *et al*., 2000) or detection of salient events (Knight *et al*., 1989; Downar *et al*., 2000). Our results, when taken together in the context of the data from functional imaging, suggest the possibility that maintaining attention at spatial locations may be a core feature of many MCA patients with neglect. However, it is likely, even in these patients, that neglect is also influenced by other factors, such as deficits in shifting or re-orienting attention or salience detection, depending upon the extent of lesion involvement of nearby structures such as the SPL or TPJ (Husain and Rorden, 2003).

Note that in the current study, the critical posterior area associated with neglect was not found to be either the SMG or, as we have defined it, the TPJ (for a review see Vallar, 2001). To the best of our knowledge, the TPJ has not been defined clearly in previous anatomical studies of neglect. Regardless of whether other investigators agree partially or completely with our definition, we believe that our exposition has at least the virtue of being clear about the boundaries of the TPJ. We certainly do not include the mid-portion of the STG, the area implicated by Karnath *et al*. (2001), within the area bounded by the TPJ. Our findings would also be consistent with functional imaging (Fink *et al*., 2000, 2001) as well as transcranial magnetic stimulation studies (Fierro *et al*., 2000) in normals that have implicated the right IPL in line bisection.

### *Parahippocapmal gyrus*

The critical parahippocampal region observed to be involved in all PCA patients with neglect, but spared in control non-neglect PCA patients, may perhaps be a more surprising finding. However, PCA patients with neglect have been reported previously (Vallar and Perani, 1986; Doricchi and Angelelli, 1999; Cals *et al*., 2002) and, like all our PCA patients, those patients also seem to have suffered from both neglect and hemianopia. One recent study reported that neglect occurred in nine of 53 patients with right isolated superficial PCA strokes (Cals *et al*., 2002). Neglect was usually absent when infarction was limited to the occipital lobe, but was more frequent in patients with occipital infarcts that extended more anteriorly, although lesions were not plotted. In another study, lesions were reconstructed on standard CT templates and these demonstrated medial temporal lobe involvement (Doricchi and Angelelli, 1999). However, the plots also included posterior MCA territory stroke, and there was no lesion contrast made with PCA controls with hemianopia alone. Despite these differences, our results would be consistent with these previous findings and help to confine the critical ROI to the parahippocampal region.

The parahippocamal region is a complex brain area that currently is under intense scrutiny (Witter and Wouterlood, 2002). Highly focal (non-ischaemic) thermo-coagulation lesions of this region in the right hemisphere of humans with epilepsy lead to deficits in spatial memory (Bohbot *et al*., 1998), but neither such small lesions nor larger vascular ones associated with topographical disorientation (Habib and Sirigu, 1987) have been reported classically to produce neglect. However, one recent series of PCA patients with landmark agnosia has reported the occurrence of neglect in some patients (Takahashi and Kawamura, 2002). Functional imaging studies have reported activation of this area in place-encoding (Epstein *et al*., 1999) as well as memory tasks, specifically during retrieval after a delay (Burgess *et al*., 2001; Sakai *et al*., 2002). Anatomical studies in non-human primates have demonstrated a rich connection between parietal cortex and the parahippocampal region, and the latter, in turn, has extensive connections with the hippocampus (Ding *et al*., 2000; Clower *et al*., 2001; Burwell and Witter, 2002). This network of connections is well known to form an important system for spatial navigation and memory (Burgess *et al*., 1999; Maguire, 1999). Our findings also demonstrate its pivotal role in neglect.

Whether there are features that distinguish PCA neglect (involving the parahippocampal region but not the parietal cortex) from MCA neglect (involving the parietal cortex but

not the parahippocampal region) remains to be established. It is possible that the effects of parahippocampal damage are due to remote effects on parietal cortex (diaschisis) rather than to a primary effect of parahippocampal dysfunction. Alternatively, disruption of parieto-temporal white matter tracts may be another possible explanation for neglect following damage to medial temporal lobe (Gaffan and Hornak, 1997).

### *Lesion volume and frontal involvement*

In this study, lesion volume for both MCA and PCA patients was significantly larger in the neglect group than in the non-neglect group, as observed in previous investigations (Vallar and Perani, 1986; Leibovitch *et al*., 1998). Persistent cases of neglect are also associated with large lesions, involving three or more cortical lobes or subcortical regions (Maguire and Ogden, 2002). Although damage to the ANG and the parahippocampal gyrus appeared to be critically associated with neglect in our study, it is possible that lesion volume may be a confounding factor. On the other hand, the difference in lesion volume between neglect and non-neglect patients would be entirely consistent with the view that although there may be common core deficits across neglect patients, multiple cognitive components need to be damaged for the syndrome to be apparent (Maguire and Ogden, 2002). In any case, it is difficult to control for lesion volume in such unselected case series. Moreover, it is also important to note that, at least for the MCA patients, analysis of only neglect patients would not alter the conclusion about the critical lesion location that resulted from the comparison with non-neglect patients (compare Fig. 1A and C).

In previous studies of patients with focal right frontal damage, lesions predominantly affecting the inferior frontal lobe have been observed to be associated with neglect (Husain and Kennard, 1996; Husain *et al*., 1997). In the present study, eight MCA neglect patients had frontal involvement, with lesions of all these patients overlapping in the IFG. However, the same overlap region was also involved in four MCA patients without neglect. Frontal involvement was found to be neither necessary nor sufficient to produce neglect in this series. It is important to appreciate, however, that the current investigation studied a group of unselected patients with large lesions. Thus, many of the neglect patients with inferior frontal damage also had damage to the critical posterior parietal area (the ANG) associated with neglect. The question about the independent frontal contribution to neglect may best be addressed by studying patients with more focal lesions. In unselected patients who have large lesions, parietal damage appears to be the most prominent common factor.

### *Lesion analysis technique*

Finally, although these results are important for understanding the neural substrate associated with visual neglect, it is important also to appreciate that the techniques used in this study represent a significant advance for brain lesion mapping in general, and have wider implications for understanding human brain functions. The methods we employed involve important departures from traditional approaches to lesion mapping in a number of ways. First, high resolution isotropic MRIs were acquired, rather than only a few CT or MR axial slices. Secondly, lesions were demarcated on the digitized acquisitions themselves, rather than transferred onto only a few standard template slices which may not match well the planes of image acquisition. Thirdly, the brains were normalized into a standard space in order to allow comparison between neglect and non-neglect groups. Finally, to check that the validity of any conclusions from the normalized group analysis also held for the individual brains, we went back to the original image acquisitions and analysed segmented ROIs.

These methods provide an important means of improving the spatial accuracy of functional localization using patients with brain lesions. Although functional imaging studies in healthy individuals have made great strides in delineating brain regions active during particular cognitive tasks, they are not capable of demonstrating which parts of the human brain are absolutely necessary for a particular function. Lesion studies remain the best means of doing this. However, although lesion localization using CT has been critical in advancing our knowledge about the functions of brain regions, it is limited in its spatial accuracy. We would contend that the MRI protocols outlined in the current study provide a significant advance in testing, with high precision, hypotheses about brain function that have been generated by other investigative techniques such as functional imaging. Moreover, they allow direct comparison, within the same coordinate system, of functional imaging data from healthy individuals and lesion data from selected patient groups.

## Acknowledgements

We wish to thank the patients who participated in this study. This research was funded by Wellcome Trust grants to M.H. and C.K.

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*Received February 14, 2003.*
*Revised April 9, 2003. Accepted April 14, 2003*