The Anatomy of Spatial Neglect based on Voxelwise Statistical Analysis: A Study of 140 Patients

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A major challenge for any anatomical study of spatial neglect in neurological patients is that human lesions vary tremendously in extent and location between individuals. Approaches to this problem used in previous studies were to focus on subgroups of patients that are more homogeneous either with respect to the branch territory affected by the stroke or with respect to existing additional neurological symptoms (e.g. additional visual field defects). It could be argued that such strategies might bias the conclusions on the critical substrate associated with spatial neglect. The present study thus addressed the high variability inherent in naturally occurring lesions by using an unselected, but very large sample size and by comparing a neglect group with a non-neglect group using voxelwise statistical testing. We investigated an unselected 7 year sample of 140 consecutively admitted patients with right hemisphere strokes. Seventy-eight had spatial neglect, 62 did not show the disorder. The incidence of visual field defects was comparable in both groups. For assessing lesion location, in a first step, we used conventional lesion density plots together with subtraction analysis. Moreover, due to the large size of the sample voxelwise statistical testing was possible to objectively estimate which brain regions are more frequently compromised in neglect patients relative to patients without neglect. The results demonstrate that the right superior temporal cortex, the insula and subcortically putamen and caudate nucleus are the neural structures damaged significantly more often in patients with spatial neglect.

Keywords: attention, brain-damage, human, orientation, parietal lobe, space, temporal lobe

Introduction

Spatial neglect is a common and debilitating consequence of unilateral right-hemisphere brain damage. Patients with neglect fail to respond or orient to stimuli appearing in contralesional space. Neglect can lead to profound deficits in everyday behavior (e.g. eating, reading, navigating and grooming) and has also been shown to be predictive of a poor prognosis (Karnath and Zihl, 2003). Understanding the anatomical substrate of this deficit is therefore not only of theoretical but also of great clinical importance.

Heilman *et al.* (1983) conducted the first study designed to identify the cortical correlate of spatial neglect using modern imaging techniques. They analyzed the computerized tomography (CT) scans of 10 patients with spatial neglect and revealed an overlap of lesion location in the inferior parietal lobule and the temporo-parietal-occipital (TPO) junction. Three years later, Vallar and Perani (1986) also analyzed CT scans of right hemispheric stroke patients with spatial neglect. Sixteen neglect patients showed an overlap area involving perisylvian regions. In six patients, the brain lesions centered on the parieto-occipital junction and in eight patients the overlap was found on the supramarginal gyrus of the inferior parietal lobule. Subsequent studies have largely confirmed these early findings, but have found additional pathology leading to spatial neglect (Perenin, 1997; Samuelsson *et al.*, 1997; Leibovitch *et al.*, 1998, 1999).

These early anatomical studies combined lesions from neglect patients regardless of their other symptoms. One potential confound was the inclusion of neglect patients with primary visual field defects (VFDs). Although field cuts and hemispatial neglect co-occur, VFDs obviously represent a separate disorder and cannot be regarded as an integral part of the neglect syndrome. If VFDs have masqueraded as neglect in studies of neglect anatomy it is possible that the cortical regions previously thought to be the crucial locus for neglect are instead significantly associated with the VFDs. Therefore it is possible that studies that include a considerable number of patients with clear field cuts may necessarily be biased toward identifying posterior regions (near the primary visual cortex and underlying optic radiation).

Karnath *et al.* (2001) examined the cortical overlap in patients with middle cerebral artery infarcts who had 'pure' visual field defects, i.e. who had field cuts but no symptoms of neglect. Not surprisingly, these patients showed damage to the subcortical optic radiation. However, it was also found that these lesions typically extended to cortical areas in the inferior parietal lobule and the TPO junction (as these cortical regions lie above the subcortical optic radiation). Therefore, the regions classically associated with neglect have also been implicated with visual field defects. This finding lends support to the notion that previous studies might have confused the anatomical effects of visual field defects with spatial neglect.

To test this possibility directly, in a recent study we intentionally excluded patients with visual field cuts, aiming to isolate the anatomical regions involved with the core deficit of spatial neglect (Karnath *et al.*, 2001). Unlike previous studies, we observed that the centre of lesion overlap covered the right superior temporal gyrus (Brodmann areas 22 and 42) suggesting that the superior temporal cortex rather than the inferior parietal lobule is the critical substrate for spatial neglect in humans. This conclusion is fundamentally different from the conclusions of previous studies and offers a new perspective regarding the function of intact superior temporal cortex.

However, it has been suggested that exclusion of patients with primary visual field defects may be a problematic experimental strategy that may lead to an inadvertent selection bias in favour of patients with more anterior damage (Husain and Rorden, 2003). To address this criticism, the present study followed an alternative strategy for lesion analysis based on an

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unselected patient sample. This method compares a group of consecutively admitted neglect patients (some who also exhibit VFDs) with a control group of brain damaged patients who have a similar incidence of VFDs.

A major challenge for any anatomical study of spatial neglect in neurological patients is that human lesions vary tremendously in extent and location between individuals. This high variability will reduce the power of any analysis. One approach to this problem is to focus exclusively on patients with small lesions, but this approach leads to a series of problems. First, such a selection reduces the number of patients – which itself reduces statistical power. Secondly, it biases the conclusions towards identifying smaller brain systems. Suppose that damage to either a large, or a small area of the brain leads to neglect. Either area may be just as important to the genesis of neglect, but selecting patients with small lesions could lead to the conclusion that only the smaller area was involved. Moreover, there is the problem that many patients exist who also have small lesions at exactly the same location but do not show spatial neglect. Therefore, imposing such selection criteria (e.g. only including patients with small lesions) has intrinsic dangers. In the present study, we thus address the high variability inherent in naturally occurring lesions by using an unselected, but very large sample size and by comparing a neglect group with a non-neglect group using voxelwise statistical testing.

The study was based on an unselected sample of 140 stroke patients (with or without visual field defects) consecutively admitted to the Neurology Department in Tübingen within a period of 7 years. Of this group, 78 exhibited spatial neglect. Anatomical studies that simply superimpose lesions from neglect patients, may reflect vulnerability of certain regions to injury (e.g. due to the vasculature of these regions) rather than any direct involvement with spatial neglect. Thus, it is necessary to contrast directly the lesion sites of these patients with those of right-brain-damaged control patients who do not exhibit neglect but are comparable with respect to relevant other variables, e.g. the incidence of VFDs.

Subtraction plots directly contrast neglect patients (a lesion overlay with positive values) with a control group (a lesion overlay with negative values). The resulting subtraction image only highlights regions that are both frequently damaged in neglect patients as well as being typically spared in control patients. Subtraction analysis thus is an essential tool for exploring the critical structures associated with a cognitive function. However, even this technique does not attempt to statistically assess the significance of damage to different regions of the brain. The present study thus uses voxelwise statistical testing to examine the neural correlate of spatial neglect. Voxelwise statistical analysis objectively estimates which brain regions indeed are more frequently compromised in neglect patients relative to patients without neglect.

Subjects and Methods

We investigated all stroke patients with circumscribed right-hemisphere lesions consecutively admitted from a well-defined recruitment area belonging to the University of Tübingen over a period of 7 years. The lesions were demonstrated by magnetic resonance imaging (MRI) or by computed tomography (CT). Patients with diffuse or bilateral brain lesions, patients with tumors, as well as patients in whom MRI or CT scans revealed no obvious lesion were excluded. Also excluded were patients with subcortical lesions confined to the basal ganglia or confined to the thalamus [these patients have been described separately (Karnath *et al.*, 2002)].

We obtained a group of 140 patients. Following a standardized testing for spatial neglect (see below), this group was divided into a group of 78 patients with neglect and 62 control patients without neglect [including the 25 patients with and without neglect of our previous study (Karnath *et al.*, 2001) who were admitted in the same 7 year period]. The neglect group and the control group were comparable with respect to age ($z = -0.48$, $P = 0.629$) and the frequency of additional visual field defects ($\chi^2 = 0.67$, $P = 0.414$) while the frequency of contralateral motor and somatosensory deficits as well as lesion volume did differ between the two groups (Table 1). All patients gave their informed consent to participate in the study which has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Clinical Investigation

Spatial neglect was diagnosed when the patients showed the typical clinical behavior such as orienting towards the ipsilesional side when addressed from the front or the left and/or ignoring of contralesionally located people or objects. In addition, all patients were further assessed with the following four clinical tests: the 'letter cancellation' task, the 'bells test', the 'baking tray task' and a copying task. Neglect patients had to fulfill the criterion for spatial neglect in at least two of these four clinical tests.

The Letter Cancellation Task (Weintraub and Mesulam, 1985)

Sixty target letters 'A' are distributed amid distractors on a horizontally oriented 21 × 29.7 cm sheet of paper, 30 on the right half of the page and 30 on the left half of the page. Patients were asked to cancel all of the targets. The number of targets found was reported for the left and right sides of the page. Patients were classified as suffering from spatial neglect when they omitted at least five left-sided targets.

The Bells Test (Gauthier et al., 1989)

This consists of seven columns each containing five targets (bells) and 40 distractors. Three of the seven columns (=15 targets) are on the left side of a horizontally oriented 21 × 29.7 cm sheet of paper, one is in the middle and three are on the right (=15 targets). Again, patients are asked to cancel all of the targets and the number of targets found was reported. More than five left-sided target omissions was taken to indicate neglect.

The Baking Tray Task (Tham and Tegnér, 1996)

Patients had to place 16 identical items as evenly as possible on a blank test sheet (21 × 29.7 cm). The number of items distributed within each half sheet is reported, with the ideal score being eight. As suggested by the authors (Tham and Tegnér, 1996), any distribution that was more skewed than seven items in the left half and nine on the right was considered a sign of neglect.

Copying Task

Patients were asked to copy a complex multi-object scene consisting of four figures (a fence, a car, a house and a tree), two in each half of a horizontally oriented 21 × 29.7 cm sheet of paper. Omission of at least one of the left-sided features of each figure was scored as one and omission of each whole figure was scored as two. One additional point was given when left-sided figures were drawn on the right side. The maximum score was eight. A score higher than one (i.e. >12.5% omissions) was taken to indicate neglect.

Visual field and somatosensory defects were assessed using standardized neurological examination. The degree of paresis of the upper and lower limbs was scored with the usual clinical ordinal scale, where '0' stands for no trace of movement and '5' for normal movement.

Lesion Analysis

Using two standard protocols, MRI was carried out in 68 of the stroke patients and CT imaging in 72 patients. Under both protocols the initial scanning optionally was repeated during the following days until a firm diagnosis could be made and the infarcted area became clearly demarcated. The final scans were used for the present study.

Table 1
Demographic and clinical data of the right brain damaged patients with and without spatial neglect

			Spatial neglect	Controls
Number			78	62
Sex			43 Females, 35 males	23 Females, 39 males
Age (years)		Median (range)	67 (29–88)	65 (32–80)
Etiology			65 Infarct	49 Infarct
			13 Hemorrhage	13 Hemorrhage
Time since lesion — clinical examination (d)		Median (range)	8 (1–89)	4 (1–58)
Lesion volume (% of right hemisphere)		Mean (SD)	15.0 (9.7)	4.6 (5.2)
Paresis of contralesional side		% present	87	45
Somatosensory deficit of contralesional side (touch)		% present	56	33
Visual field deficit		% present	23	29
Neglect		% Present	100	0
Letter cancellation	Left	Median (range)	0 (0–26)	29 (16–30)
	Right	Median (range)	18 (1–30)	29 (17–30)
Bells test	Left	Median (range)	0 (0–15)	14 (8–15)
	Right	Median (range)	8 (1–15)	15 (7–15)
Baking tray task	Left	Median (range)	3 (0–12)	8 (6–10)
	Right	Median (range)	13 (4–16)	8 (6–10)
Copying (% omitted)		Median (range)	56 (0–100)	0 (0–50)

To fit approximately the canonical AC–PC orientation of the MR scans, the CT imaging protocol used the line drawn between the occiput and the lower margin of the orbita to orient the scans in each individual.

In those patients who underwent the MR imaging protocol, we used diffusion-weighted (DWI) imaging within the first 48 h post stroke and T_2-weighted fluid-attenuated inversion-recovery (FLAIR) sequences when imaging was conducted 48 h or later after the stroke. While FLAIR images provide high sensitivity for acute cerebral infarcts, DWI has proved to be particularly sensitive for the detection of hyperacute infarcts and shows high accuracy in predicting final infarct size (Brant-Zawadzki *et al.*, 1996; Noguchi *et al.*, 1997; Ricci *et al.*, 1999; Schaefer *et al.*, 2002). The mean time between lesion and the MRI used for the present study was 5.0 days (SD 5.4). In those subjects who underwent the CT imaging protocol, the mean time since lesion and the CT used for the present study was 6.7 days (SD = 8.4).

All lesions were mapped using the free MRIcro (www.mricro.com) software distribution (Rorden and Brett, 2000) and were drawn manually (while being blind for the diagnosis of spatial neglect) on slices of a T_1-weighted template MRI scan from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view). This template is approximately oriented to match Talairach space (Talairach and Tournoux, 1988) and is distributed with MRIcro. Lesions were mapped onto the slices that correspond to *Z*-coordinates −40, −32, −24, −16, −8, 0, 8, 16, 24, 32, 40 and 50 mm in Talairach space by using the identical or the closest matching transversal slices of each individual.

Since the two patient groups differed in sample size, we used proportional values for the MRIcro subtraction analysis. We modified MRIcro to allow voxelwise statistical analysis. Voxelwise statistical analysis of neurological lesions has previously been applied to continuous measures of language deficits (Bates *et al.*, 2003). Here we introduce this technique to examine a discrete variable. The idea of a voxelwise test is to compute an independent statistical test (here a χ^2 test) between two groups of subjects for each and every voxel of the brain. To prevent a rise in the probability of familywise error, we computed a Bonferroni correction.

It must be noted that a certain amount of caution should be used when making an inference based on a statistical map based on neurological lesions. From many previous observations we can predict a priori that an unselected sample of neglect patients will have more extensive lesions than control patients. This logically follows from the fact that larger lesions have a higher probability of including a region involved with a task than a small lesion. One could attempt to eliminate this difference by matching lesion volume between groups (excluding neglect patients with large lesions and control patients with small lesions), but this would reduce substantially the sample size (reducing statistical power) and, more critically, such measures would make the sample less representative of the general populations. Logistic regression offers an alternative approach to account for the differences in lesion volume between the two patient populations. We modified MRIcro to compute logistic regression using a Newton's method iteratively to minimize the log likelihood function (Hosmer and Lemeshow, 1989). This approach allows us to identify regions that have predictive value even after overall lesion volume is taken into account. By covarying out lesion volume, we can control for differences in lesion size between the two groups. The disadvantage of this method is that it only has low statistical power when the anatomical structures relevant for spatial neglect correlate with large lesions (due to the anatomy of the middle cerebral artery). The causal relationship between damage to these regions and lesion volume means that logistic regression may not be able to detect a correlation between neglect and damage to these regions after lesion volume has been covaried out. Reflecting the lower statistical power of this test, here we present statistically significant results which are uncorrected for multiple comparisons.

Results

Figure 1*a* illustrates a conventional lesion density plot for each group of patients. The number of overlapping lesions are color coded with increasing frequencies from violet (n = 1) to red (n = 78) in the group of neglect patients and from violet (n = 1) to red (n = 62) in the control group. To identify the cortical structures that are commonly damaged in patients with spatial

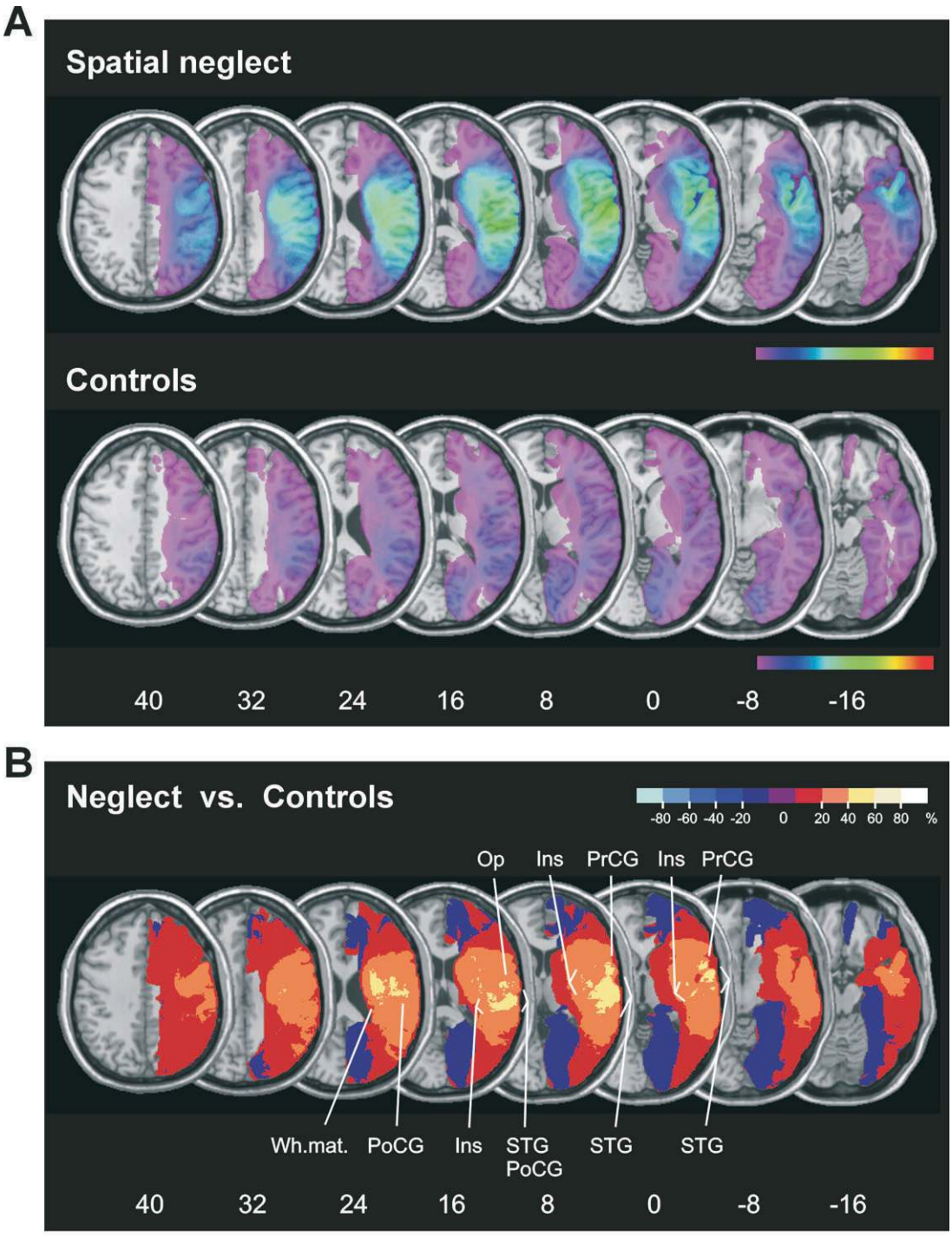

Figure 1. (*A*) Overlay lesion plots of the patients with spatial neglect ($n = 78$) and of the patients with right brain damage without spatial neglect (controls; $n = 62$). The number of overlapping lesions is illustrated by different colors coding increasing frequencies from violet ($n = 1$) to red ($n = 78$, spatial neglect; $n = 62$, controls). Talairach *z*-coordinates (Talairach and Tournoux, 1988) of each transverse section are given. (*B*) Overlay plot of the subtracted superimposed lesions of the patients with spatial neglect minus the control group. The percentage of overlapping lesions of the neglect patients after subtraction of controls is illustrated by five different colors coding increasing frequencies from dark red (difference = 1–20%) to white-yellow (difference = 81–100%). Each color represents 20% increments. The center of overlap represents regions that are damaged at least 40% more frequently in neglect patients than in controls. The different colors from dark blue (difference = –1 to –20%) to light blue (difference = –81 to –100%) indicate regions damaged more frequently in control patients than in neglect patients. Purple (middle of the color bar) designates regions where there is an identical percent of lesions in the neglect and the control groups (=0%). STG, superior temporal gyrus; Ins, insula; Op, operculum; PrCG, precentral gyrus; PoCG, postcentral gyrus; Wh.mat., white matter.

neglect but are typically spared in patients without neglect, we subtracted the superimposed lesions of the control group from the overlap image of the neglect group revealing a percentage overlay plot (Fig. 1*b*). Note that this subtraction technique codes the relative incidence of damage specific to neglect. The power of this technique is that common lesions that are damaged with equal incidence in both groups (presumably due to the vulnerability of this region) are not highlighted.

The center of overlap was defined as those voxels in the subtracted lesion overlap that were damaged at least 40% more often in neglect patients than control patients. We found the area of greatest lesion overlap in the middle part of the superior temporal gyrus (Fig. 1*b*), from Talairach coordinates (*x*, 64; *y*, –24; *z*, 8) to (*x*, 61; *y*, 2; *z*, 0). The center of overlap extended into the planum temporale, the insula, operculum, and the pre- and postcentral gyri.

A χ^2 analysis was computed for each voxel damaged in at least one patient. This 2×2 test was based on the factors group (neglect versus control) and frequency (number intact, number damaged). In total, 77 312 voxels were tested, yielding a Bonferroni-corrected $P < 0.05$ threshold of 24.37. All statistically significant voxels observed are presented in Figure 2. They were all due to a higher incidence of damage in the neglect group than expected based on the control group. In other words, we did not observe any regions with higher incidence in the control group than in the neglect group. We found the most statistically significant voxel at Talairach coordinates (*x*, 61; *y*, –19; *z*, 8), Brodmann's area 22 of the superior temporal gyrus. Beyond superior temporal gyrus, regions signficantly damaged involved the planum temporale, the insula, pre- and postcentral gyri, and subcortically putamen and caudate nucleus.

The logistic regression used two independent variables: overall lesion volume (a continuous measure) and whether or not the target voxel was damaged in each individual (a binary measure). We then calculated whether these two values were accurate predictors of neglect (the dependent variable, a binary measure). This test was computed independently for each voxel and the resulting statistical map (based on the *Z*-scores for the voxel incidence factor) is plotted in Figure 3. Since this figure is not corrected for multiple comparisons, some caution must be excercised in interpretting these results. Subcortically, damage to the putamen and caudate nucleus correlated with neglect (Fig. 3; slices 0, 8, 16 and 24). Cortically, we found regions of the superior temporal gyrus (Fig. 3; slices 0, 8 and 16) and the posterior junction between superior parietal and occipital cortex (Fig. 3; slices 32, 40 and 50) predicting the presence of neglect. Unsurprisingly, damage to the primary visual cortex predicted an absence of neglect. Less prominently, but potentially more interestingly, there was some suggestion that damage to the inferior parietal lobule including supramarginal gyrus also predicted an absence of neglect (Fig. 3; slices 32 and 40).

Discussion

The present study used voxelwise statistical testing to examine the neural correlate of spatial neglect. The results suggest that damage to the superior temporal cortex is the most frequent cortical correlate of spatial neglect in humans as detected by anatomical MRI and CT scans. This study therefore reaches the same conclusion of a previous study (Karnath *et al.*, 2001) while using a larger and unselected sample of 140 patients, whereas the previous study used a principled selection procedure.

While the superior temporal cortex in the human left hemisphere had long been identified subserving language processes, its function in the human right hemisphere remained uncertain. Evidence for involvement of superior temporal cortex in visuospatial processes corroborating the present findings derives from ablation studies in monkeys. Removal of the anterior part of the superior temporal sulcus (STSa) in monkey leads to an increase in saccade latency for contralesional targets, while saccades directed to targets in the ipsilesional hemifield were not impaired (Ó Scalaidhe *et al.*, 1995). More extensive lesions including not only STSa but also other parts of the superior temporal sulcus [and even of the superior temporal gyrus (STG)] likewise produced defects in the monkeys' visuospatial orienting behaviour. Luh *et al.* (1986) observed reduced orienting to unilaterally presented visual stimuli on the side contralateral to the lesion and Watson *et al.* (1994) reported a variety of further behavioural abnormalities that typically occur with spatial neglect in humans.

Unfortunately, our knowledge about the superior temporal cortex deriving from single-unit recordings still is very limited. While we know a considerable amount about the polysensory character of area STP at the upper bank and fundus of rostral STS, only a small part of the STG surface has been investigated with microelectrodes. These studies, carried out basically in the so-called 'belt' area, focused on the auditory modality (Rauschecker *et al.*, 1995; Tian *et al.*, 2001). Ventral of the

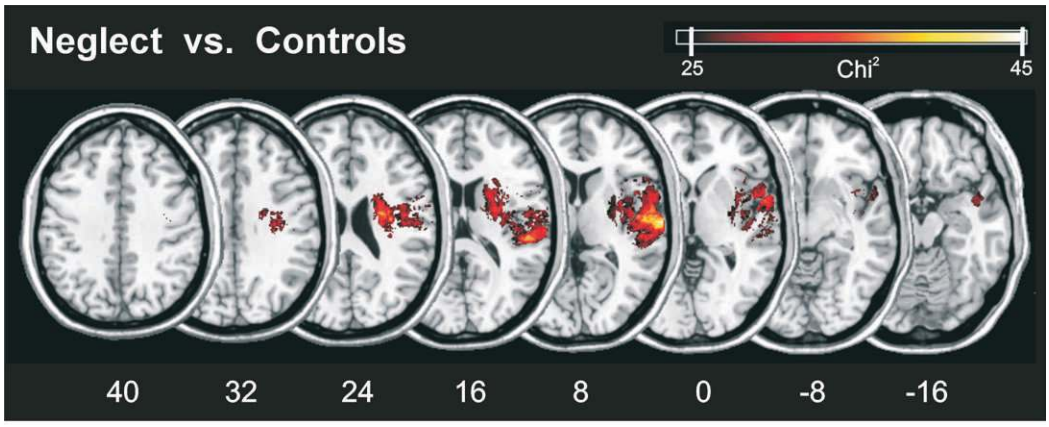

Figure 2. Voxelwise statistical analysis comparing all 78 neglect patients with 62 control patients. Presented are all voxels that were damaged significantly more often in neglect patients than in control patients following a Bonferroni corrected alpha level of $P < 0.05$. The orange-yellow colour gradient corresponds with the χ^2 value. No voxels were found that were significantly more likely to be damaged in control patients than in patients with neglect. Talairach *z*-coordinates (Talairach and Tournoux, 1988) of each transverse section are given.

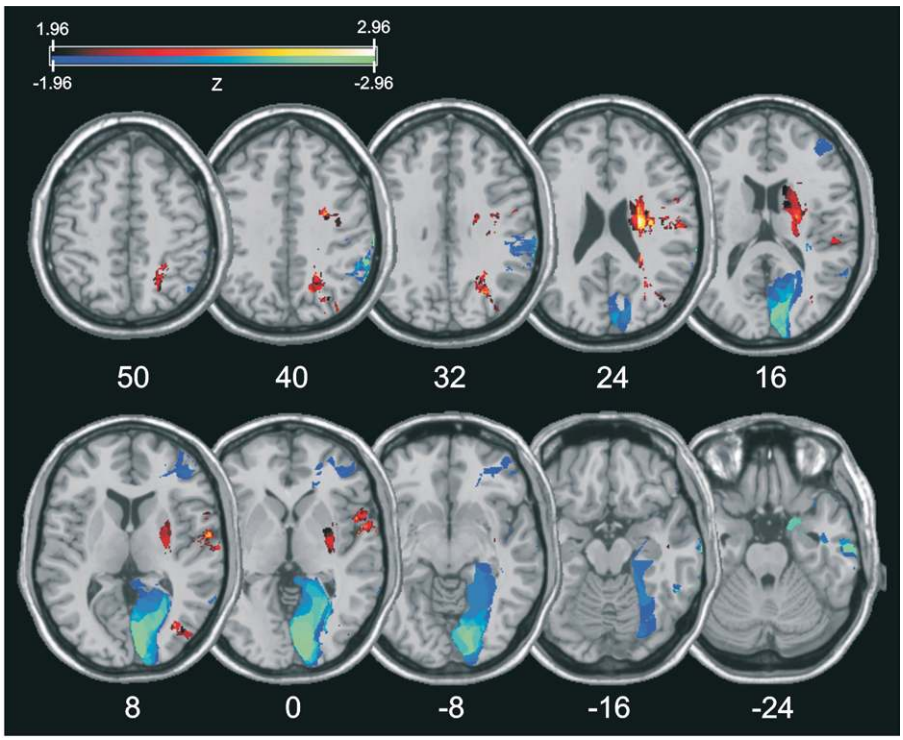

Figure 3. Voxelwise logistic regression. This analysis was computed for all voxels, with overall lesion volume as a covariate. Presented are all voxels that exceed an uncorrected $P < 0.05$. The colours correspond to the *Z*-score, with orange-yellow regions indicating regions that predict the presence of neglect and blue-green regions indicating regions associated with the absence of neglect.

'belt' area, in the so-called 'parabelt' region of the STG, systematic recordings with microelectrodes have not yet been attempted at all.

We know that the superior temporal cortex receives afferent inputs from the inferior temporal cortex as well as from the inferior parietal lobule and intraparietal sulcus, thus representing a site for multimodal sensory convergence (for a recent review, see Karnath, 2001). The properties of STSa neurons show large receptive fields and typically sensitivity to movement, polymodal responsiveness to visual, somatosensory and/or auditory input (Desimone and Gross, 1979; Bruce *et al.*, 1981). Many cells integrate information about the form and motion of objects (Oram and Perrett, 1996) and subpopulations are sensitive to the spatial position of objects (Baker *et al.*, 2000). These findings lend support for the idea that this part of temporal cortex might act as an interface between the dorsal and the ventral streams of visual processing (Karnath, 2001).

The present study also revealed significant damage of the insular cortex in neglect patients. This might be an interesting finding, since this area recently has been identified being involved in integrating vestibular and neck muscle proprioceptive input at the cortical level (Bottini *et al.*, 2001). Disturbed processing of these afferent inputs in building appropriate representations of space has been assumed in spatial neglect, provoked by the observation that asymmetric vestibular and/or neck proprioceptive stimulation improve or even compensate spatial neglect (for a recent review, see Rossetti and Rode, 2002).

At the subcortical level, the present data confirm recent findings showing that the putamen and caudate nucleus are the relevant nuclei within the right basal ganglia associated with spatial neglect (Karnath *et al.*, 2002). There exist close anatomical connections between both subcortical nuclei and superior temporal cortex (Yeterian and Pandya, 1998). The rostral and middle parts of the STG are connected to the rostroventral and caudoventral portions of the putamen, while the caudal portion of the STG projects more dorsally to the caudal putamen. In addition, the rostral and middle parts of the STG are connected with ventral portions of the caudate nucleus, while the caudal portion of the STG projects more dorsally within its head and body (Yeterian and Pandya, 1998). The right putamen, caudate nucleus and STG thus have been suggested to form a coherent cortico-subcortical network representing spatial perception and awareness (Karnath, 2001).

Previous studies on neglect anatomy conducted by other groups (Heilman *et al.*, 1983; Vallar and Perani, 1986; Perenin, 1997) typically concluded that the crucial lesion for the generation of neglect lies in the inferior parietal lobule and TPO junction. This contrasts with the present findings that implicate the superior temporal cortex and insula, despite the fact that the inclusion criteria of the present study were similar. Comparable to these previous studies the present, unselected sample included patients both with and without additional visual field defects and patients who suffered from lesions involving cortical structures with or without concomitant subcortical involvement of the basal ganglia or the thalamus. One major difference between the findings of our group and others is that previous studies essentially provided superimposed lesion density plots, the first stage in our analysis. Our second and third steps – that of conducting a subtraction analysis and a voxelwise analysis in a large and unselected sample to statistically identify regions that are

damaged significantly more often in neglect patients than in control patients — was not used.

The results of the first step of our lesion analysis bear direct comparison with the results of previous studies (Heilman *et al.*, 1983; Vallar and Perani, 1986; Perenin, 1997). Figure 1*a* illustrates the superimposed lesion plots for the 78 neglect patients. Although the center of lesion overlap (green area) is found in the superior temporal gyrus, planum temporale and insula, we see — with lower frequency of overlap (turquoise and light blue areas) — involvement of the middle temporal gyrus, the ventral pre- and postcentral gyri, the inferior parietal lobule, the operculum, as well as parts of the frontal and parietal subcortical white matter. However, many of these regions are also commonly compromised in stroke patients who do not show spatial neglect. To identify the areas that are critical for spatial neglect, we thus need to know the distribution of lesion locations in a group of patients with right brain damage but who do not exhibit neglect. Such a comparison with a control group is missing entirely in the studies of Heilman *et al.* (1983) and of Perenin (1997).

Vallar and Perani (1986) focus their interpretation of results (p. 617ff.) on patients who were selected to have posterior lesions (their Fig. 5), which necessarily biases their results to show a posterior focus. In contrast to the present procedure, Vallar and Perani subdivided their entire sample of 34 neglect patients into three subsamples with lesions involving only the anterior parts of the cortex, only the posterior parts and with lesions involving both anterior and posterior parts. While they found only one neglect patient with an anterior (frontal) lesion, superimposed lesion plots were created for the 16 patients with lesions involving both anterior and posterior cortical areas and the 17 patients with posterior lesions. The overlap area in the first group was located on perisylvian regions, while the overlap area in the posterior group centered on the parieto-occipital junction and the supramarginal gyrus. Interestingly, only the anatomical results of the patient group with posterior lesions and the single patient with a frontal lesion were considered in the authors' conclusions (p. 617ff.). The results obtained in the other half of Vallar and Perani's sample, i.e. the 16 patients with lesions clustering on the perisylvian regions, were ignored. It is not surprising that after dividing patients into posterior and anterior groups, the posterior group were most likely to show relatively posterior damage.

One argument that could be leveled against our findings is that they are artifactually caused by the combination of two distinct patient groups — those with 'temporo-parietal–occipital junction neglect' and those with 'inferior frontal neglect' (for such a division, see Mattingley *et al.*, 1998) — within one single sample. According to this explanation, the maximum overlap we observe in the superior temporal cortex represents the combination of these two distinct groups, one with damage in the inferior parietal, the other in the inferior frontal lobe. However, the present study clearly shows that this is not the case. If the sample is large (which is clearly true of the present sample), we would expect two separate foci of lesion overlap to become apparent, one located in the inferior parietal lobe and the other in the inferior frontal lobe. If the concentrically decreasing frequencies of lesion overlap surrounding these two foci is wide and relatively high, one could imagine that we reveal a third, artificial focus located inbetween the two. However, in contrast to this thought experiment, the present study observed no significant between-group differences in the parietal and in the frontal lobes.

In a recent article by Mort *et al.* (2003), the authors criticized that the lesions in the study of Karnath *et al.* (2001) still were demarcated by hand onto standard template images. The same argument could be leveled against the present study. To overcome this limitation Mort *et al.* (2003) used a lesion analysis method that did not rely on the manual transfer of lesions to standard template slices, employing a technique where the location of the lesion is drawn directly onto the patient's own MRI scan with subsequent normalization (Brett *et al.*, 2001). Different from our previous and present findings, Mort *et al.* (2003) came to the conclusion that the most critical brain region associated with neglect in the territory of the middle cerebral artery is the angular gyrus. However, when in a recent study Karnath *et al.* (2004) investigated whether or not the reason for these discrepant findings indeed is due to the different lesion analysis protocols used in both studies, they observed once more that the critical lesion overlap for spatial neglect centered on the STG, the insula and the operculum. This finding obtained from a new sample of neglect patients thus clearly argued against the traditional view that the inferior parietal lobule is the critical substrate for spatial neglect and that the two protocols used for lesion analysis do not explain the discrepant findings of Mort *et al.* (2003) and Karnath *et al.* (2001).

There is growing evidence that behaviorally and anatomically dissociable patterns of spatial defects can be found. For example, Binder *et al.* (1992) reported that deficits in the line bisection task are associated with more posterior damage than patients who only show neglect as assessed with cancellation tasks. In the present as well as our previous study we did not use the line bisection task, relying instead on a battery of clinical and cancellation tasks to assess neglect. The reason for this decision was an earlier observation that line bisection was normal in 40% of patients with severe, clinically manifest neglect (Ferber and Karnath, 2001). Studies that use patients who show errors in line bisection but have no bias in cancellation and in copying tasks may include a patient group that was excluded from the present study, yielding different anatomical results. In fact, our neglect patients in the previous (Karnath *et al.*, 2001) as well as the present study all had a severe bias in cancellation. Based on the work of Binder *et al.* (1992) one can expect that studies that select patients based on line bisection errors will tend to report more posterior lesions compared to studies where performance on this task is not considered. This conclusion could explain some of the different findings regarding the anatomy of spatial neglect seen in the recent studies by Mort *et al.* (2003) and Karnath *et al.* (2001, 2004).

Other factors might be responsible for the different findings. Such differences include the relatively smaller sample of neglect patients investigated by Mort *et al.* (n = 14; potentially leading to less accurate lesion localization compared to the present sample of n = 78) as well as differences in imaging protocols. For example, unlike Mort and co-workers who used T_1-weighted MRI scans obtained in the post-acute stage ~2 months after the infarct, the present study used T_2-weighted fluid-attenuated inversion-recovery (FLAIR), diffusion-weighted (DWI) imaging, or CT at the time of stroke when the patients showed severe spatial neglect. It is possible that pressure from edema and/or remote dysfunction is more pertinent in the

early days following stroke than 2 months after the infarct. However, we know already from many studies that FLAIR and DWI imaging proved to be particularly sensitive for the detection of acute infarcts and show high accuracy in predicting final infarct size (e.g. Brant-Zawadzki *et al.*, 1996; Noguchi *et al.*, 1997; Ricci *et al.*, 1999; Schaefer *et al.*, 2002). Moreover, although the present scans taken 5 and 6.7 days on average after the stroke might bear uncertainty in some cases with respect to the exact borders of the lesion, pressure from edema, or more pertinent remote dysfunction, this uncertainty does not favor or unfavour any specific anatomical regions. The 'uncertainty' is not direction-specific, i.e. it does not argue for or against involvement of a certain brain area (nor IPL, nor STG, nor any other region under discussion). It just might provoke a higher variability in the data which has to be addressed by using large patient samples and by using statistical procedures to analyse the data. In addition, note that one of our three ways of data analysis revealed some evidence (slices 32, 40 and 50 of Fig. 3) suggesting that posterior damage does correlate with neglect. However, since this figure was not corrected for multiple comparisons (see Subjects and Methods for reasons), some caution must be excercised in interpretting this result.

Potentially, functional neuroimaging and transcranial magnetic stimulation could offer convergent evidence regarding the anatomy of spatial neglect. Both techniques clearly demonstrated that regions near the intraparietal sulcus are involved with tasks that require peripheral spatial perception (Wojciulik and Kanwisher, 1999; Hopfinger *et al.*, 2000; Rushworth *et al.*, 2001; Astafiev *et al.*, 2003). However, this brain region is fairly distant from both the superior temporal cortex and the traditionally assumed location, the temporo-parietal-occipital junction. Hopfinger *et al.* (2000) used fMRI during a cued spatial-attention task to dissociate brain activity related to attentional control from that related to selective processing of target stimuli. Distinct networks were engaged by attention-directing cues versus subsequent targets. Superior frontal, inferior parietal and superior temporal cortex were selectively activated by cues, indicating that these structures are part of a network for voluntary attentional control. Their study thus report evidence for both our present and the conventional claim regarding the anatomical basis of spatial neglect.

To conclude, by using a large and unselected sample of patients together with voxelwise statistical testing, we believe that this study removes a number of confounds that may have biased the findings of previous studies. However, it is also worth noting the limitations of the present study. The anatomical MRI and CT scans used in the present study were scans performed primarily for clinical purposes. Using these imaging data enabled us to study the anatomy of every single patient with right brain damage (showing versus not showing spatial neglect) who was submitted to a neurology department within a 7 year survey. An alternative would have been to study only few, specifically selected patients who agree to return to the hospital considerably after the stroke to gain further images for scientific purposes. Although such images might have offered us a more precise view of the consequences of stroke they would not have represented the true population of right brain damaged stroke patients. Certain types of patients are more likely to return for a scientific investigation, e.g. those with higher mobility and a better outcome after rehabilitation.

Further, anatomical MRI and CT scans – independently of whether they were taken in early or late phases of the stroke – might not necessarily show the full functional extent of a lesion. Areas that appear structurally intact in anatomical scans are not necessarily functioning normally (due to white matter disconnection, limited perfusion, or diaschisis due to distant damage). Therefore, it is theoretically possible that we have not been able to identify the true functional correlate of spatial neglect. This could in principal be investigated with perfusion imaging (Hillis *et al.*, 2002) or fMRI (Vuilleumier *et al.*, 2001) analyses. Future advances in brain imaging might offer further exciting methods for understanding brain function in both stroke patients and healthy humans and might provide a powerful test for the present and previous findings based on anatomical scans.

Notes

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