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The anatomy underlying acute versus chronic spatial neglect: a longitudinal study

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Our aim was to examine how brain imaging in the initial phase of a stroke could predict both acute/subacute as well as chronic spatial neglect. We present the first voxel-wise longitudinal lesion-behaviour mapping study, examining acute/subacute as well as chronic performance in the same individuals. Acute brain imaging (acquired on average 6.2 days post-injury) was used to evaluate neglect symptoms at the initial (mean 12.4 days post-stroke) and the chronic (mean 491 days) phase of the stroke. Chronic neglect was found in about one-third of the patients with acute neglect. Analysis suggests that lesion of the superior and middle temporal gyri predict both acute/subacute as well as chronic neglect. At the subcortical level, the basal ganglia as well as the inferior occipitofrontal fasciculus/extreme capsule appear to play a significant role for both acute/subacute as well as chronic neglect. Beyond, the uncinate fasciculus was critically related to the emergence of chronic spatial neglect. We infer that individuals who experience spatial neglect in the initial phase of the stroke yet do not have injury to these cortical and subcortical structures are likely to recover, and thus have a favourable prognosis.

Keywords: spatial neglect; anatomy; prognosis; chronic; acute; recovery; plasticity; stroke; human
Abbreviation: AC-PC = anterior commissure-posterior commissure; VLBM = voxel-wise lesion-behaviour mapping

Introduction

Individuals with acute right hemisphere stroke often exhibit spatial neglect. While many patients recover rapidly, others remain impaired. The factors influencing this recovery remain controversial. Our aim was to determine whether acute brain imaging could differentiate between acute and chronic neglect. To achieve this, we conducted the first voxel-wise longitudinal study of neglect anatomy, examining acute and chronic performance in the same individuals.

Recovery rates from acute neglect have been reported from 60 to 90% within 3–12 months of injury. Factors that have been suggested as predictors for recovery include patients' age, severity of neglect, absence of visual field defects, lesion location or size and premorbid atrophy (Campbell and Oxbury, 1976; Colombo *et al*., 1982; Hier *et al*., 1983; Levine *et al*., 1986; Stone *et al*.,

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1992; Black *et al*., 1995; Samuelsson *et al*., 1997; Cassidy *et al*., 1998, 1999; Jehkonen *et al*., 2000, 2007; Farné *et al*., 2004). Unfortunately, due to the heterogeneous and even contradictory results, it remains difficult to draw firm conclusions about the impact of these factors.

The present study focuses on lesion location as a factor for predicting recovery from spatial neglect. However, even on this topic, previous research remains contradictory. For example, Hier *et al*. (1983) reported that neglect due to haemorrhages and small lesions involving $<6\%$ of the right hemisphere recover more quickly than neglect after infarcts or big lesions. Further, they found that damage to the right frontal or temporal lobes was negatively associated with the recovery of spatial neglect, while the involvement of any other cortical or subcortical region had no impact. In contrast, Levine *et al*. (1986) argued that lesion location had no effect on the time course of spatial neglect. According to their findings, the initial severity of neglect behaviour seemed to be the critical factor.

In a more recent study, Samuelsson *et al*. (1997) conducted a detailed lesion analysis of patients with chronic neglect by dividing the right hemisphere into discrete substructures. They determined the frequency of involvement of these structures by inspecting the CT scans of those patients who showed neglect 6–7 months post-stroke. The authors found that involvement of the subcortical central white matter below the collateral trigone in the temporal lobe had a high incidence of chronic neglect. Maguire and Ogden (2002) used a similar strategy for analysing the MRI scans of nine stroke patients with persistent spatial neglect at 3–22 months post-stroke. In all patients, they found large lesions affecting part of at least three cortical lobes and the basal ganglia. In eight patients the lesion extended into the posterior frontal lobe and/or the superior dorsolateral prefrontal cortex. Seven patients showed damage to the anterior and medial temporal lobe; and in seven patients the parietal lobe was involved. By using the Damasio and Damasio (1989) brain templates, Farné *et al*. (2004) compared the lesions of neglect patients with improvement in a cancellation test to those without improvement. Unfortunately, the vast majority of their sample could only be followed over a 2-week period within the acute phase of the stroke. For those patients who showed no improvement in this short period, they found frontal and parietal areas involved.

Only a few studies of post-acute neglect have been conducted using modern voxel-wise lesion analysis approaches. These techniques contrast brain injury from patients with symptoms to those without symptoms, and have two primary benefits (*cf*. Rorden and Karnath, 2004). First, independent statistics are computed for each voxel of the brain allowing us to detect new functional modules (whereas traditional methods pool data across predefined regions of interest whose boundary is often not directly related to the behaviour of interest). Second, these methods specifically identify regions that are injured in those with impairment yet spared in those without impairment. This aspect allows us to decouple regions that are specific to an impairment from regions that simply have a high incidence of injury. Mort *et al*. (2003) and Golay *et al*. (2008) investigated patients showing spatial neglect on average 64 days post-stroke, and Commiteri *et al*. (2007) ~128 days post-stroke. The studies found damage of the superior and middle temporal cortices (Commiteri *et al*., 2007; Golay *et al*., 2008), insula (Commiteri *et al*., 2007; Golay *et al*., 2008), inferior and middle frontal cortices (Commiteri *et al*., 2007), as well as the inferior parietal cortex (Mort *et al*., 2003; Golay *et al*., 2008) to be associated with post-acute neglect. However, since these experiments did not record the patients' behaviour in the acute phase of the stroke, it is possible that a certain percentage of the 'non-neglecting' patients included may have suffered from spatial neglect in the acute phase, but had already recovered by the time of the experimental investigation. If so, lesion analysis of such a sample of post-acute data would treat such recovered neglect subjects as patients contributing a lesion pattern 'not related to spatial neglect'. However, obviously this is not the case. Therefore, by only examining chronic performance, one cannot determine which factors help predict chronic versus acute deficits. This feature highlights the key benefit of a longitudinal study, where data for both an individual's initial as well as chronic state are available. Information from a longitudinal study is also useful for clinical practice; given that an acute patient exhibits a deficit, what is the anatomy that can assist in deriving a prognosis?.

Thus, our objective was to conduct a longitudinal study, where we examined neglect severity at both the acute and chronic phase of the stroke, and examined whether acute scans could predict neglect recovery. In addition, our anatomical analysis employed a recently developed continuous measure of neglect severity (Rorden and Karnath, 2010) that should provide a more sensitive analysis of this disorder than the binary cut-offs used in previous studies.

Materials and methods

Subjects

Neurological patients consecutively admitted to the Centre of Neurology at Tübingen University were screened for an acute right-hemisphere stroke. Patients with a left-sided stroke, patients with diffuse or bilateral brain lesions, patients with tumours, as well as patients in whom MRI or CT scans revealed no obvious lesions were not included in the present study. Sixty-six patients were recruited. The subjects gave their informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The initial behavioural testing (see below) of the 66 patients was carried out in the acute/subacute phase of the stroke. We then attempted to re-examine these individuals at least 1 year after their initial injury. Follow-up data were not available for 12 patients, and they were excluded from the subsequent analysis. Reasons for exclusion were as follows: seven patients had died, one patient had a second stroke in the intermediate period, three patients did not consent to follow-up testing and one patient had moved far beyond the catchment area. The second behavioural testing during the chronic phase of the remaining 54 patients was conducted on average 490.8 days [standard deviation (SD) 218.3] post-stroke. The initial testing in the acute/subacute phase of the stroke of these subjects took place on average 12.4 days (SD 24.7) post-stroke. Table 1 gives an overview of the demographic and clinical data of the 54 patients; Fig. 1 demonstrates a simple overlap of their brain lesions.

Table 1 Demographic and clinical data of all 54 right brain damaged stroke patients

	Spatial neglect		No neglect
	Recovered	Chronic	
Number	16	8	30
Sex (M/F)	6/10	2/6	17/13
Age (years)	63.1 (13.4)	68.4 (7.9)	61.8 (15.9)
Aetiology	14 infarct, 2 haemorrhage	8 infarct	25 infarct, 5 haemorrhage
Visual field defects (% present)	13	50	17
Hemiparesis (% present)	94	100	67
Arm	2.3 (2.0)	1.9 (1.4)	4.0 (1.0)
Leg	2.7 (1.9)	2.1 (1.8)	4.4 (0.8)
Spatial neglect			
Letter cancellation			
Initial phase (CoC)	0.54 (0.29)	0.73 (0.11)	<0.01 (0.01)
Chronic phase (CoC)	0.01 (0.02)	0.36 (0.33)	
Bells test			
Initial phase (CoC)	0.53 (0.33)	0.79 (0.11)	<0.01 (0.03)
Chronic phase (CoC)	<0.01 (0.03)	0.31 (0.30)	
Copying			
Initial phase (% correct)	54 (28)	41 (22)	97 (5)
Chronic phase (% correct)	98 (5)	25 (25)	
Eye-in-head position (°)	5.0 (10.6)	8.1 (7.1)	−2.5 (10.6)

Data are presented as mean (SD).
CoC = Centre of Cancellation. (Rorden and Karnath, 2010).

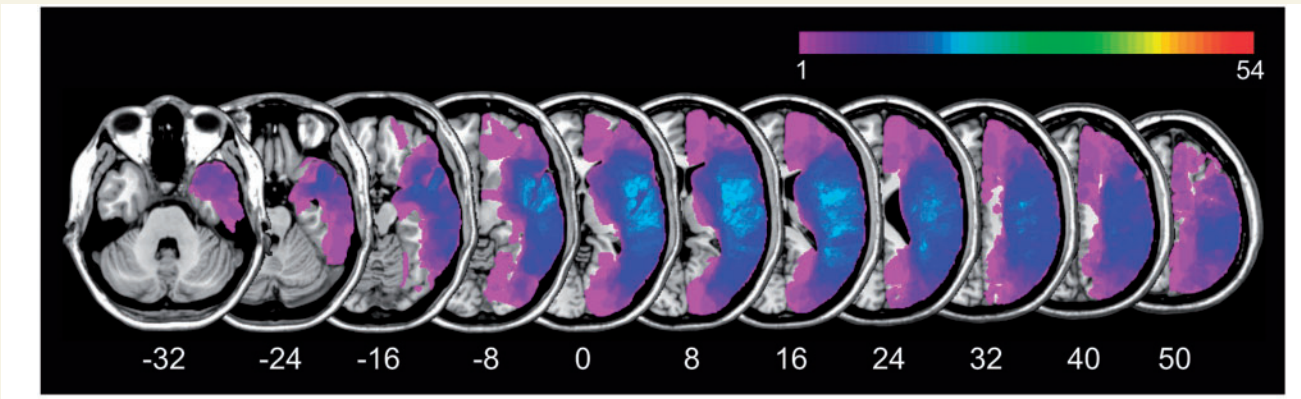

Figure 1 Simple overlap of all 54 stroke patients with right-hemisphere brain lesions.

Clinical investigation and data analysis

The following clinical tests were applied: Letter Cancellation Task (Weintraub and Mesulam, 1985), Bells Test (Gauthier *et al*, 1989) and a Copying Task (Johannsen and Karnath, 2004). All three tests were presented on a horizontally oriented 21 × 29.7 cm sheet of paper. In the Letter Cancellation Task, 60 target letters 'A' are distributed amid distracters. Patients were asked to cancel all of the targets. The Bells Test requires identifying 35 bell symbols distributed on a field of other symbols. In the 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 the test sheet. Omission of at least one of the contralateral features of each figure was scored as 1, and omission of each whole figure was scored as 2. One additional point was given when contralaterally located figures were drawn on the ipsilesional side of the paper sheet. The maximum score was 8.

For the Letter Cancellation Task and the Bells Test, we calculated the Centre of Cancellation using the procedure and software by Rorden and Karnath (2010; www.mricro.com/cancel/). This value indicates the centre of mass for all the detected items, such that identifying all the targets would generate a score of zero, whereas identifying only the rightmost item would provide a score of one. This measure is sensitive to both the number of omissions and the location of these omissions. Centre of Cancellation scores >0.09 in the Letter Cancellation Task and the Bells Test were taken to indicate neglect behaviour (*cf*. Rorden and Karnath, 2010). In the Copying Task, a score >1 (i.e. >12.5% omissions) indicated neglect (*cf*. Johannsen and Karnath, 2004). For a firm diagnosis of spatial

neglect in the acute/subacute stage of the stroke, i.e. when the pathological behaviour is most extreme, the patients had to fulfil the above criteria in at least two of the three tests. At the time of the second (chronic) examination, patients were classified as showing chronic neglect when they fulfilled the above criteria in at least one of the three tests.

To investigate whether the clinical neglect tests used in the present study measure spatial neglect in the chronic phase in a sufficient and sensitive manner, we conducted a receiver operating characteristic analysis (Swets, 1996). A receiver operating characteristic analysis rates the accuracy of different instruments by combining sensitivity and specificity into a single value. In this kind of analysis, the area under the curve is the direct measure of the diagnostic power of a test. A 'perfect' test that classifies all patients with and without neglect correctly is indicated by an area under the curve value of 1, while a value of 0.5 reveals that a test operates at chance level. For the three clinical tests admitted in the chronic phase we revealed the following area under the curve values: 0.914 (Letter Cancellation Test), 0.938 (Bells Test), 0.938 (Copying Task). The data indicate that the clinical neglect tests reached a sufficient level of accuracy and sensitivity in the chronic phase of the stroke.

For our voxel-wise anatomical analysis (see below), neglect severity was determined as a continuous variable by averaging the *z*-transformed Centre of Cancellation scores from the Letter Cancellation Task and the Bells Test, as well as the *z*-score for the performance in the Copying Task, separately for the initial and the chronic phase of the stroke. An additional receiver operating characteristic analysis for this variable revealed an area under the curve value of 1.

Visual field defects were examined by the common neurological confrontation technique. The degree of limb paresis was scored with the Medical Research Council scale, where '0' indicates no trace of movement and '5' represents normal movement.

Further, we measured the patients' eye-in-head position on the initial clinical scans taken at admission, applying the procedure described by Becker and Karnath (2010).

Imaging and lesion analysis

All patients had circumscribed right-hemisphere brain lesions due to ischaemic stroke or haemorrhage demonstrated by MRI ($n = 31$) or by spiral computed tomography ($n = 23$). In the subjects who underwent MRI scanning at admission, we used diffusion-weighted 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 stroke onset. To approximately fit the canonical AC–PC orientation of the MRI scans, the spiral CT imaging protocol used the line drawn between the occiput and the lower margin of the orbita to orient the scans in each individual. Under both protocols, the initial scanning was optionally 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. The mean time between stroke and imaging was 6.2 days (SD 17.5).

Lesion location was evaluated using MRIcron software (Rorden *et al*., 2007; www.mricro.com). In those patients with spiral CT scanning at admission, lesions were drawn directly on the slices of a normalized T_1-weighted template MRI scan from the Montreal Neurological Institute with a 1×1 mm in-plane resolution, distributed with the MRIcron toolset. Lesions were mapped by one experimenter (blind for the diagnosis of spatial neglect) onto the slices that correspond to MNI *z*-coordinates −40, −32, −24, −16, −8, 0, 8, 16, 24, 32, 40 and 50 mm by using the identical or closest matching axial slices of each individual. In contrast, for those individuals with an MRI scan, the experimenter delineated the boundary of the lesion directly on the image for every single transverse slice using MRIcron software. Both the MRI scan and the lesion shape were then mapped into stereotaxic space using the normalization algorithm provided by SPM5 (http://fil.ion.ucl.ac.uk/spm/). Automated normalization techniques can fail to accurately warp scans from individuals with brain injury, as the damaged region has different signal intensity relative to the corresponding location in the template image (which is derived from neurologically healthy individuals). To address this, we used cost-function masking when calculating transformation parameters (Brett *et al*., 2001). The MRI images were resliced to match the template image used for CT. Only the slices mapped for the CT scans were used for the subsequent statistical analysis, regardless of image modality.

For the continuous variable 'neglect severity' (see above) we employed statistical voxel-wise lesion-behaviour mapping (VLBM) analyses, using the *t*-test statistic (Bates *et al*., 2003) implemented in the MRIcron software package (Rorden *et al*., 2007). The parametric *t*-test was performed on *z*-transformed behavioural data that helps normalize the data. We controlled for multiple comparisons by using the false discovery rate correction. All results presented here survived a 1% false discovery rate cut-off threshold. To evaluate the resulting statistical maps with respect to cortical and subcortical grey matter structures, we overlaid the maps on the Automated Anatomical Labelling atlas (Tzurio-Mazoyer *et al*., 2002) distributed with MRIcron. In order to identify the white matter fibre tracts affected by the lesion, we overlaid the resulting statistical maps with the white matter fibre tract templates from the Jülich probabilistic cytoarchitectonic atlas (Bürgel *et al*., 2006). This atlas is in the same space as the Montreal Neurological Institute reference brain, with each atlas template illustrating the relative frequency with which a certain fibre tract of 10 normal human post-mortem brains was histologically observed. For our analysis, we used any voxel that was part of a fibre tract in at least one individual brain. The number of overlapping voxels was determined by using the MRIcron software package. It should be noted that both the Automated Anatomical Labelling and Jülich atlases are probabilistic. These maps thus allow familiar terms to be applied in a manner that can be replicated in future studies and should be relatively robust when applied to a group of individuals.

Results

Clinical differences between chronic and recovered neglect

Of the 24 individuals who exhibited spatial neglect at the initial phase, a total of eight (33.3%) persisted in exhibiting deficits in at least one of the behavioural tests when re-examined during the chronic stage (mean = 490.8 days post-injury, SD 218.3). Even with a more conservative criterion, requiring a positive result in at least two of the four neglect tests, seven (29.2%) of the patients were classified as showing spatial neglect. While overt neglect symptoms had disappeared in the recovered neglect patients (0.01% of the neglect severity measured in the initial phase of this group), they were still salient more than a year post-stroke in the patients with chronic neglect (during the chronic

phase this group exhibited 45% of the neglect severity measured in the initial phase).

In the eight patients with chronic neglect and the 16 patients who had recovered from neglect, we analysed the following factors: age, lesion volume, severity of neglect, presence of visual field defects, strength of contralateral hemiparesis and spontaneous eye-in-head deviation. We found no significant difference in age [$t(22) = 1.03$, $P = 0.31$], lesion volume [$t(22) < 1$, $P = 0.97$], eye-in-head deviation [$t(17) < 1$, $P = 0.56$] or in the presence ($\chi^2 = 0.52$, $P = 0.47$) or the severity of contralateral hemiparesis (arm: U = 49, $P = 0.35$; leg: U = 34, $P = 0.06$) between the two neglect groups. Instead, neglect severity in the initial phase was a strong predictor for chronic neglect severity [$t(21) = 2.29$, $P = 0.03$]; patients who persisted with chronic neglect had significantly higher acute neglect severity scores than those who recovered. Also there was a statistical difference between the two groups for the presence of visual field defects ($\chi^2 = 4.0$, $P = 0.05$); patients with chronic neglect showed a higher percentage compared with those who recovered.

Anatomical differences between chronic and recovered neglect

To identify the cortical structures typically involved in patients with acute/subacute spatial neglect, we analysed the entire sample of 54 patients with right hemisphere damage based on their continuous neglect severity scores measured in the initial phase of the stroke. Figure 2A illustrates the VLBM results. The largest parts of the statistically significant lesion map affected the superior temporal gyrus (21% of the voxels of the statistical map that survived thresholding) and the middle temporal gyrus (16%). Beyond, the inferior parietal lobule (8%), insula (5%), inferior frontal gyrus (4%) and the rolandic operculum (5%) were involved. The lesion map further affected the inferior temporal

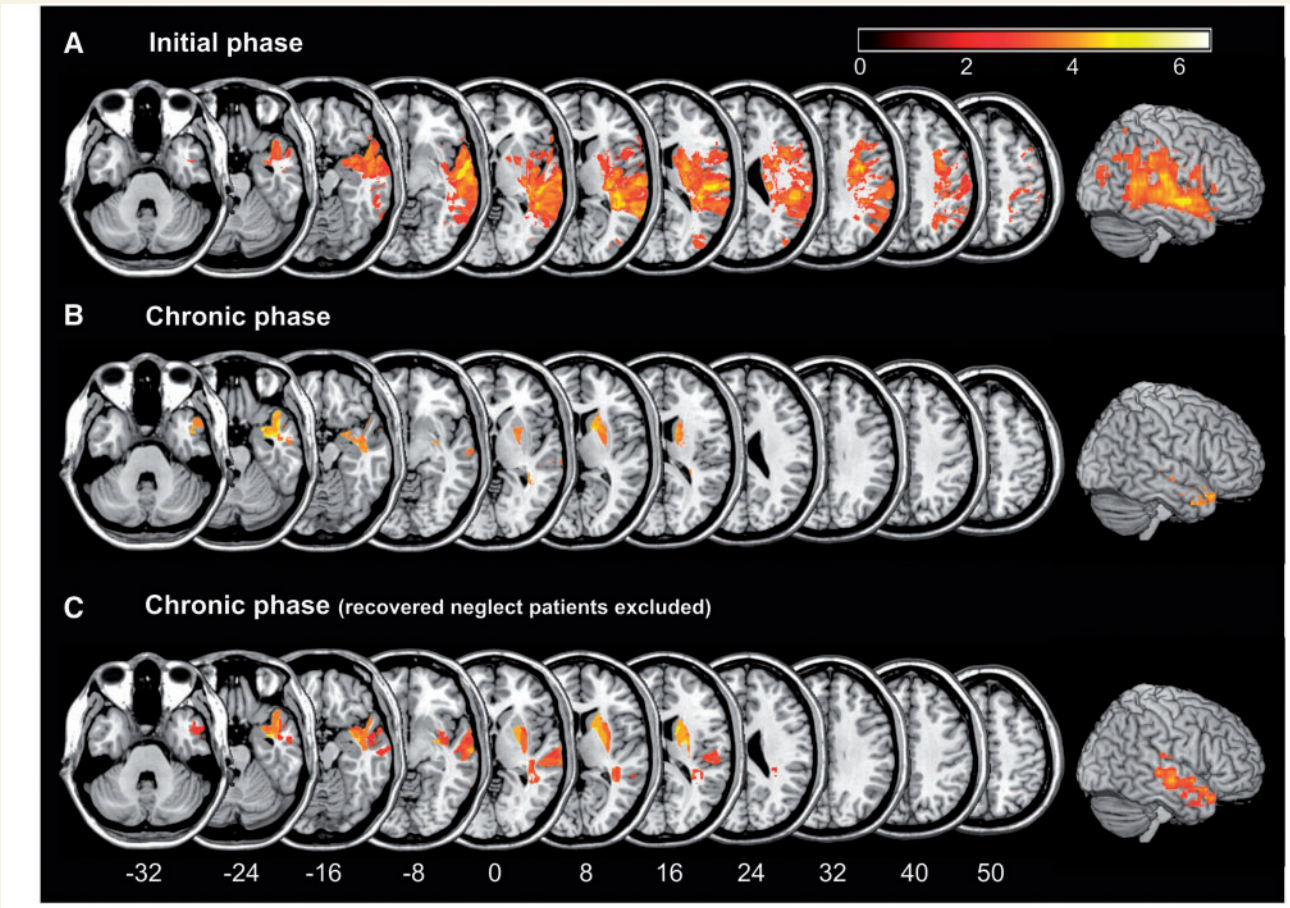

Figure 2 Statistical voxel-wise lesion-behaviour mapping (VLBM) analyses using the *t*-test statistic for the continuous variable 'neglect severity'. Presented are all voxels that survived a 1% false discovery rate cut-off threshold. (**A**) Analysis of all 54 patients with right hemisphere damage based on their neglect severity scores measured in the initial phase of the stroke, on average 12.4 days after stroke onset. Injury to highlighted regions predicts acute/subacute neglect. (**B**) Analysis of all 54 patients with right hemisphere damage based on their neglect severity scores measured in the chronic phase of the stroke, on average 490.8 days after stroke onset. Injury to highlighted regions predicts chronic neglect, regardless of acute behaviour. (**C**) Analysis of the neglect severity scores measured in the chronic phase of the stroke as in (**B**), but now carried out on a subsample ($n = 38$) of the patients with right hemisphere damage. This subsample no longer included those patients that showed spatial neglect in the initial phase of the stroke but had recovered by the time of the second examination. Montreal Neurological Institute coordinates of each transverse section are given.

gyrus (3%), pre- and post-central gyri (1%, 3%), as well as the middle occipital gyrus (1%). At the subcortical level, 4% of the statistical lesion map affected the basal ganglia (putamen, 3%; caudate nucleus, 1%), as well as the following white matter fibre tracts: superior longitudinal fasciculus (3%), superior occipitofrontal fasciculus (2%) and inferior occipitofrontal fasciculus (2%) (Fig. 3). The lesion also comprised the corticospinal tract (10%), the optic radiation (6%), as well as the acoustic radiation (5%).

Figure 2B shows brain regions where brain injury (measured acutely) predicts chronic neglect. Like Fig. 2A, this analysis is based on all 54 patients, but examines chronic rather than initial behaviour. At the cortical level, the significant lesion map affected the superior temporal gyrus (15% of the statistical map) and middle temporal gyrus (18%) at their most rostral parts at the temporal pole. At the subcortical level, 30% of the statistical lesion map involved the basal ganglia (putamen, 16%; pallidum, 4%; caudate nucleus, 10%), 7% the amygdala and 1% the hippocampus. In regards to the white matter fibre tracts (Fig. 4A), we found the inferior occipitofrontal fasciculus (6%) and uncinate fasciculus (4%). There was further damage to the optic radiation (11%) and the corticospinal tract (2%).

This latter analysis also included those 16 patients that suffered from spatial neglect in the initial phase of the stroke but had already recovered by the time of the second investigation (1.3 years post-stroke). The statistical map illustrated in Fig. 2B thus treated these cases as subjects contributing a lesion pattern that is 'not related to spatial neglect'. However, obviously this is not the case. Indeed, the lesion pattern of those subjects had evoked spatial neglect in the initial phase of the stroke. Thus, to unambiguously reveal those anatomical structures that are related

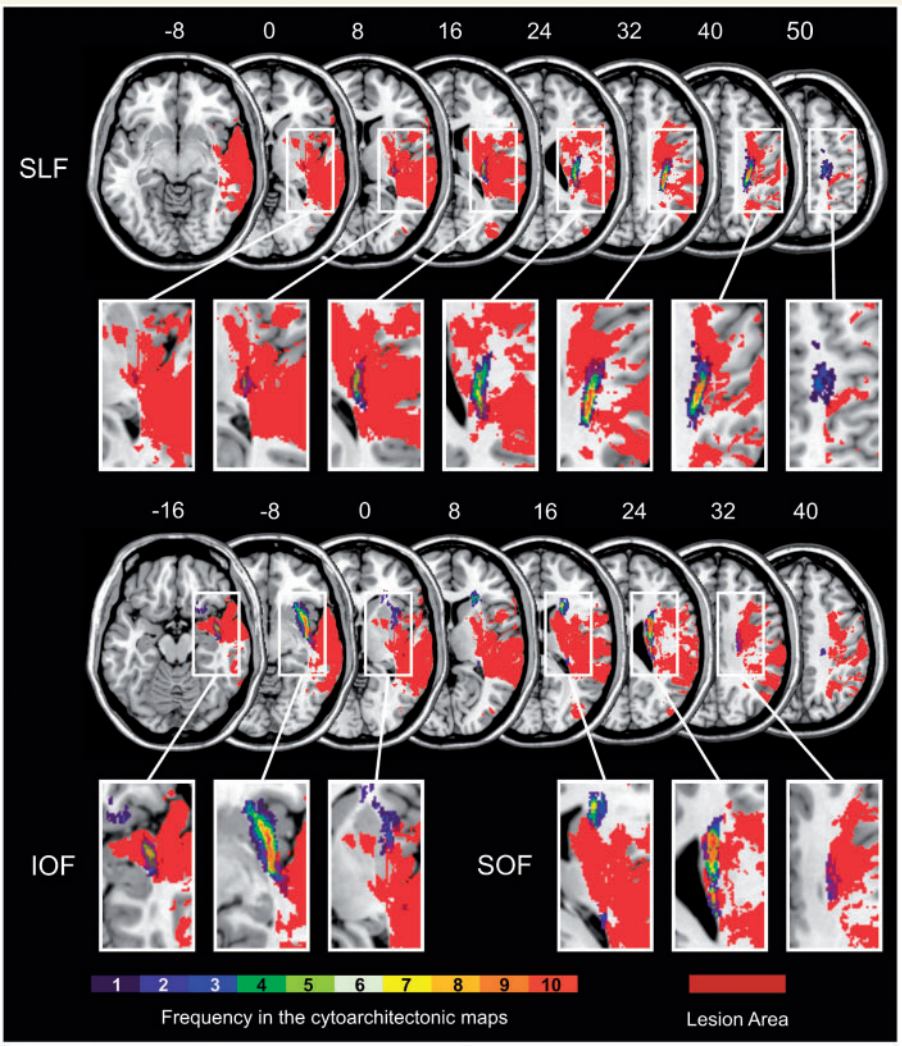

Figure 3 White matter fibre tract analysis in the initial phase of the stroke. Overlap of the statistical lesion map from Fig. 2A (in homogenous orange colour) with the probabilistic, cytoarchitectonic maps of the white matter fibre tracts from the Jülich atlas (right hemisphere only). The colour coding of the atlas from 1 (dark blue, observed in one post-mortem brain) to 10 (red, overlap in all 10 post-mortem brains) represents the absolute frequency for which, in each voxel of the atlas, a respective fibre tract was present. The overlap is illustrated for the superior longitudinal fasciculus (SLF), inferior occipitofrontal fasciculus (IOF) and superior occipitofrontal fasciculus (SOF).

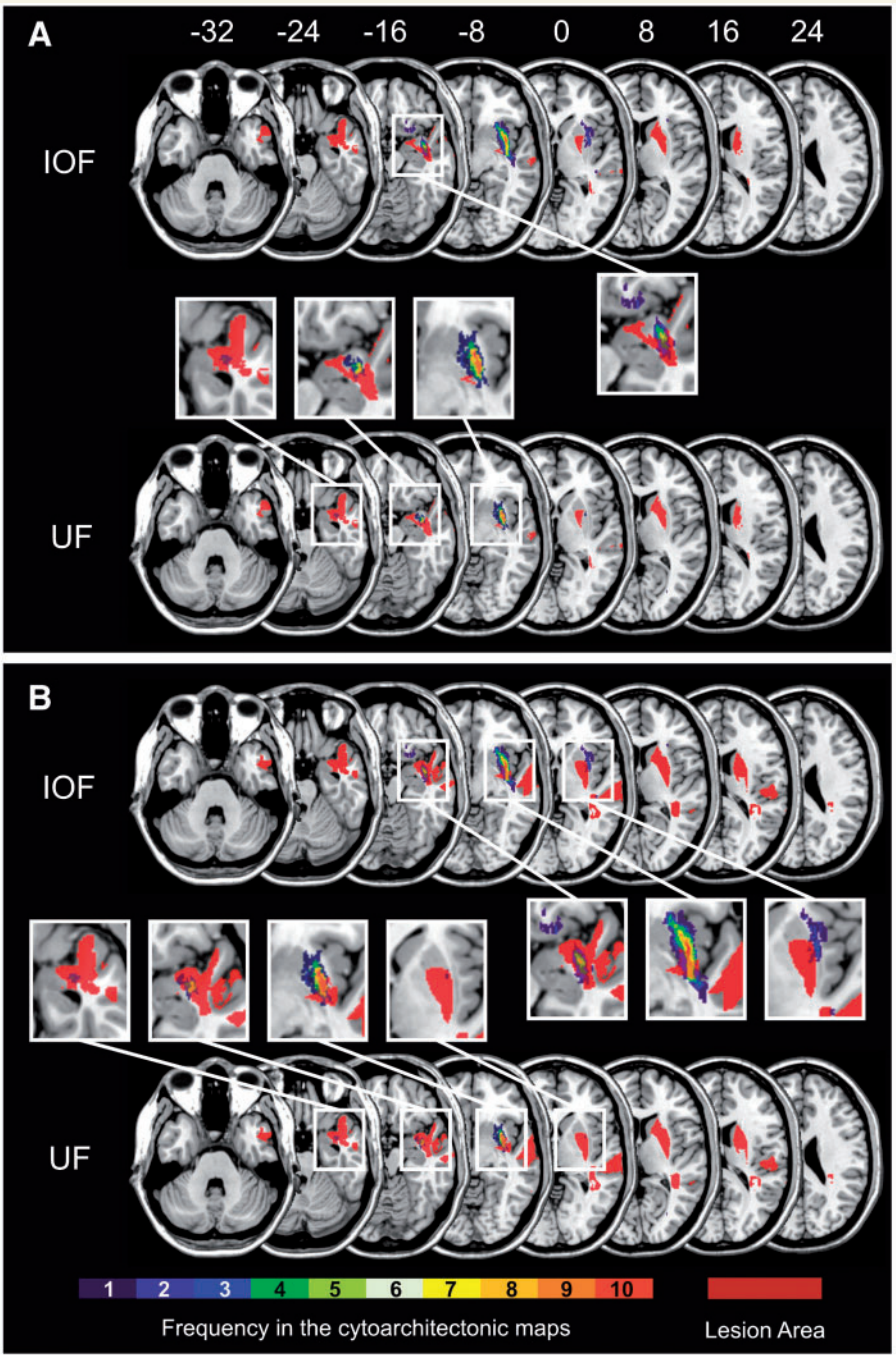

Figure 4 White matter fibre tract analysis in the chronic phase of the stroke. Overlap of the statistical lesion map from Fig. 2B and C (in homogenous orange colour) with the probabilistic, cytoarchitectonic maps of the white matter fibre tracts from the Jülich atlas (right hemisphere only). Data deriving from the analysis of all 54 patients with right hemisphere damage (**A**) and of the subsample of this group that no longer included those patients that showed spatial neglect in the initial phase of the stroke but had recovered by the time of the second examination (**B**). The colour coding of the atlas from 1 (dark blue, observed in one post-mortem brain) to 10 (red, overlap in all 10 post-mortem brains) represents the absolute frequency for which, in each voxel of the atlas, a respective fibre tract was present. The overlap is illustrated for the inferior occipitofrontal fasciculus (IOF) and uncinate fasciculus (UF).

to spatial neglect in the chronic phase of the stroke, we excluded the 16 patients with recovered neglect for an additional VLBM analysis. Figure 2C illustrates the results. The largest parts of the statistically significant lesion map affected the superior temporal gyrus (23%) and middle temporal gyrus (20%). Beyond, the rolandic operculum (2%), the insula (1%) and inferior temporal gyrus (1%) were damaged. At the subcortical level, 22% of the statistical lesion map affected the basal ganglia (putamen, 16%;

pallidum, 2%; caudate nucleus, 4%) and 1% the amygdala. From the white matter fibre tracts (Fig. 4B), we found the inferior occipitofrontal fasciculus (7%) as well as uncinate fasciculus (5%) affected. The lesion area also comprised the optic radiation (13%) and corticospinal tract (4%).

Discussion

The present study examined how brain imaging in the initial phase of the stroke could predict both acute/subacute as well as chronic (mean 1.3 years post-stroke) spatial neglect. Even after such a long period, i.e. when spontaneous improvement of the disorder is highly unlikely, chronic neglect is a relatively frequent phenomenon, present in about one-third of the patients with initial neglect. This is in line with previous studies showing that 3–6 months after the stroke spatial neglect has recovered in only two-thirds of the patients (Campbell and Oxbury, 1976; Colombo *et al*., 1982; Black *et al*., 1995; Samuelsson *et al*., 1997; Cassidy *et al*., 1998). Contrary to previous results (Hier *et al*., 1983; Levine *et al*., 1986) we did not find a significant difference in age or in lesion volume between patients with chronic and with recovered neglect. However, we observed that initial neglect severity was significantly higher in those patients who persisted with chronic neglect than in those who recovered. This finding is in line with previous studies reporting that the recovery from neglect is determined by the initial severity of the disorder (Colombo *et al*. 1982; Stone *et al*., 1992; Black *et al*., 1995; Jehkonen *et al*., 2007).

Our study used a statistical VLBM approach based on a continuous neglect severity measure to analyse the anatomy of spatial neglect. This was aided by the recent development of the Centre of Cancellation measure for neglect severity (Rorden and Karnath, 2010), which provides a robust continuous measure from the popular paper-and-pencil cancellation tasks. In the acute/subacute phase of the stroke, the largest parts of the statistically significant lesion map affected the superior and middle temporal gyri. Beyond, the inferior parietal lobule, insula, inferior frontal gyrus and the rolandic operculum were involved. At the subcortical level, we found the basal ganglia as well as the white matter fibre tracts superior longitudinal fasciculus, superior occipitofrontal fasciculus and inferior occipitofrontal fasciculus affected. The results thus confirm previous findings in acute neglect patients based on a binary classifier that identified the presence or absence of spatial neglect (Karnath *et al*., 2001, 2004, 2009).

Taken together, the two anatomical analyses based on the neglect severity scores measured in the chronic phase of the stroke (Fig. 2B and C) revealed that cortical damage of particularly the superior and middle temporal gyri as well as subcortical injury of the basal ganglia (especially putamen) and the white matter fibre tracts inferior occipitofrontal fasciculus and uncinate fasciculus are critically related to the emergence of chronic spatial neglect. These findings accord with a previous voxel-wise analysis of a continuous measure of neglect in a post-acute patient sample (Committeri *et al*., 2007).

The comparison of our anatomical findings demonstrates that the superior and middle temporal gyri not only appear to be important cortical structures when patients show spatial neglect in the initial phase of a stroke, but also seem to be critical for predicting the chronic disorder. At the subcortical level, the basal ganglia as well as the inferior occipitofrontal fasciculus likewise appear to play significant roles for both acute/subacute as well as chronic neglect.

While the initial, as well as the chronic phase of the stroke the superior and middle temporal gyri sustained the highest per cent damage among the other structures identified, it should be noted that this measure does not necessarily reflect the functional impact of an injury. For example, consider a long white matter fibre tract where a small injury disconnects distant regions. In this situation, proportionally small injuries can have marked impact on the proper functioning of the network. Recent work has highlighted the role of white matter injuries in spatial neglect (Karnath *et al*., 2009; Verdon *et al*., 2010).

Findings from corticospinal tract tracing, myelin staining and diffusion-based imaging techniques suggest a dense perisylvian network interconnecting the cortical areas superior/middle temporal gyri, inferior parietal lobule and inferior frontal gyrus (as reviewed in Karnath, 2009). White matter fibre tracts link the inferior parietal lobule with the ventrolateral frontal cortex, ventrolateral frontal cortex with superior/middle temporal cortices, and superior/middle temporal cortices with the inferior parietal lobule. In this network, the superior longitudinal fasciculus is the major, dorsally located fibre pathway linking parietal and frontal cortices. It is subdivided into three separable components. The superior longitudinal fasciculus II links the inferior parietal lobule and intraparietal sulcus with the posterior and caudal prefrontal cortices, while the superior longitudinal fasciculus III connects the rostral inferior parietal lobule with the ventral part of premotor and prefrontal cortices. In contrast, the inferior occipitofrontal fasciculus is part of the ventral aspects of the perisylvian network. Although there is no common agreement yet, it seems as if the inferior occipitofrontal fasciculus corresponds with the bundle termed 'extreme capsule' by other authors (review in Karnath, 2009). This structure is situated between the claustrum and the insular cortex interconnecting the inferior frontal and orbitofrontal gyri with the mid-portion of the superior temporal region. It further continues caudally toward the occipital cortex and toward the inferior parietal lobule. The uncinate fasciculus is also part of the ventral aspects of the perisylvian network. This fibre bundle hooks around the insula to link the temporal pole and the ventral prefrontal cortex. Involvement of the superior longitudinal fasciculus as well as of the inferior occipitofrontal fasciculus/extreme capsule and uncinate fasciculus in stroke patients with acute spatial neglect has been previously reported in studies of single cases or small patient groups (Thiebaut de Schotten *et al*., 2005; He *et al*., 2007; Urbanski *et al*., 2008; Shinoura *et al*., 2009) as well as from a recent VLBM analysis in a large cohort of 140 patients suffering from acute right hemispheric stroke (Karnath *et al*., 2009).

Beyond white matter fibre tracts, integrity of the basal ganglia—namely the putamen, pallidum and caudate nucleus—also seems to be critical for recovery of spatial neglect. We found the basal ganglia critically involved in both the initial and the chronic phases of the stroke. Such injuries to the right basal ganglia can affect the

ipsilesional perisylvian network involved in spatial neglect via functional and/or metabolic abnormalities. Using single photon emission computed tomography (Weiller *et al*., 1990, 1993; Demeurisse *et al*., 1997) and perfusion-weighted imaging (Hillis *et al*., 2002; Karnath *et al*., 2005) it has been shown that only those patients who exhibit spatial neglect following subcortical infarcts suffer from perfusion abnormalities in the ipsilesional cortex. Moreover, it has been found that acute right basal ganglia strokes that provoke spatial neglect induce abnormal perfusion specifically in those (structurally intact) cortical areas that are known to cause the disorder when damaged directly by cortical infarction (Karnath *et al*., 2005), namely the superior temporal gyrus, the inferior parietal lobule and the inferior frontal gyrus, i.e. the entire right perisylvian network involved in spatial neglect. To date it is not certain whether the same functional and/or metabolic abnormalities caused by basal ganglia lesions in distant cortical areas also underlie neglect behaviour in the chronic phase of the stroke. Nevertheless, first indirect evidence that this may be the case has been reported. Several studies found that functional recovery from spatial neglect correlated with an improvement of the cortical metabolism (Vallar *et al*., 1988; Pantano *et al*., 1992; Perani *et al*., 1993; Pizzamiglio *et al*., 1998).

Several recent studies using functional magnetic resonance brain imaging suggest that acute spatial neglect is associated with physiological abnormalities in the dorsal parietal and frontal cortices. Specifically, task-evoked (Corbetta *et al*., 2005) and resting state (He *et al*., 2007; Carter *et al*., 2010) imbalances were reported between the injured and spared hemispheres, with the level of bias correlating with behavioural measures of spatial deficits. These imbalances reduce along with behavioural biases during the chronic stage (Corbetta *et al*., 2005; He *et al*., 2007; Thimm *et al*., 2008). Corbetta *et al.* (2005) postulated that neglect often results from structural damage to a ventral area network (including superior temporal gyrus, middle temporal gyrus and insula) as well as a functional disruption of a dorsal area network that includes the frontal eye fields and parietal regions. According to this model, recovery from neglect is accomplished by a reactivation of the structurally intact dorsal area network. Some interpret these findings to suggest that the injury to the ventral network predicts spatial neglect because they disrupt function of distal regions. In other words, these regions are not merely compensating for ventral network disruption; rather initial ventral network injury directly influences the performance of these critical regions. According to this interpretation, structural anatomical studies did not observe parietal and superior frontal foci due to the low incidence of direct injury to these regions. While we do not personally subscribe to this model, we note that such an interpretation makes distinct predictions that can be resolved in future studies (for example, using transcranial magnetic stimulation to briefly disrupt these areas). Regardless, we suggest that the brain activation findings complement our work based on structural anatomy. For example, an important aspect of our study is to provide practitioners with criteria for a prognosis of the disorder's recovery when examining clinical scans obtained at admission, while these brain activation studies hint at the mechanisms that drive spontaneous recovery.

We wish to note that we used paper-and-pencil tests to identify spatial neglect at both the acute and chronic stages. These tests are clinically popular and easy to apply, but may be less sensitive than computerized tests for detecting subtle attentional deficits, e.g. reaction time differences, at the chronic stage. In theory, the potentially reduced sensitivity of our clinical tests might lead to poor statistical power (causing us to miss some brain regions associated with spatial neglect, but not undermining the statistically significant findings we report here). However, on the other hand, super sensitive computerized tests may detect deficits that are so subtle that they have little clinical implications, while the paper-and-pencil tests identify predictors of profound behavioural deficits in the chronic phase of the stroke.

To conclude, the present results suggest that at the cortical level, the superior and middle temporal gyri not only appear to be important cortical structures when patients show spatial neglect in the initial phase of a stroke but also seem to be critically involved when neglect behaviour becomes a chronic disorder. At the subcortical level, the basal ganglia as well as the white matter fibre tract inferior occipitofrontal fasciculus/extreme capsule likewise appear to play a significant role for both acute/subacute as well as chronic neglect. Beyond, the uncinate fasciculus was critically related to the emergence of chronic spatial neglect. It appears as if brain lesions that do not include these structures but evoke spatial neglect in the initial phase of a stroke are good predictors for a favourable prognosis.

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