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Spatial orienting by left hemisphere language areas: a relict from the past?

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During evolution, the human brain developed remarkable functional differences between left and right hemispheres. Due to this lateralization, disorders of spatial orienting occur predominantly after right brain damage and disorders of language after left brain damage. In contrast to this general pattern, few individuals show disturbed spatial orienting (spatial neglect) after left brain damage. Using a voxel-based lesion analysis approach, we found that neglect after acute left brain damage is represented in areas typically serving language functions, namely the superior and middle temporal gyri, inferior parietal lobule and insula. Since all except one of these patients also suffered from aphasia, we conclude that lateralization is not just reversed but that both functions (language and spatial orienting) rather are represented in the same left hemisphere regions. We speculate that a representation of spatial orienting in left hemisphere language areas might be a phylogenetic relict in humans, though this representation stays subdominant in the vast majority of individuals.

Keywords: hemispheric specialization; spatial neglect; aphasia; lateralization; left brain damage

Introduction

During evolution, the human brain has developed fascinating functional differences between the left and right hemisphere. Language is the oldest and the best-known example for such a lateralization. The first historical findings about left cerebral dominance for language come from post-mortem examinations in neurological patients (e.g. Broca, 1861; Dax, 1865). The nature of the mechanisms underlying these cerebral asymmetries still remains unclear (Badzakova-Trajkov *et al*., 2010). Genetic models claim that the RS gene, for example, might be responsible for the asymmetry of the language system. If this gene is present, it supports lateralization for a dominant left hemisphere for language; if the opposite is true, lateralization occurs by chance (Alexander and Annett, 1996). Several authors have suggested that the left lateralization of language causes other functions such as spatial orienting to be lateralized in the right hemisphere (e.g. Corballis and Morgan, 1978; Corballis, 1981; Cook, 1984). Hellige (1990) assumed that at birth the right hemisphere is more mature than the left. The right hemisphere thus is more influenced from incoming visual information and is specialized for attentional processes rather than for language. Previc (1991) hypothesized that there is a developmental right ear advantage at birth that leads to language dominance in the left hemisphere, whereas a developmental otholith advantage on the left side causes dominant representation of visuospatial functions in the right hemisphere.

The hemispheric lateralization of cognitive functions is evident in brain injury. Disorders of language (aphasia) occur predominantly after left brain damage and disorders of spatial orienting and

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attention (spatial neglect) predominantly after right brain damage (Dax, 1865; Marsh *et al*., 2006; Becker and Karnath, 2007). Also, functional MRI studies in healthy subjects have revealed a clear lateralization of language in the left and spatial orienting and attention in the right hemisphere. However, these studies have also demonstrated—though less prominently—involvement of homologous areas in the respective 'non-dominant' hemisphere, i.e. the right for language and the left for spatial orienting (e.g. Himmelbach *et al*., 2006; Vigneau *et al*., 2006; Tzourio-Mazoyer *et al*., 2010).

The role of this activity in the respective non-dominant hemisphere is still unclear. Thus investigation of individuals who—in contrast to the general pattern—show disturbance of lateralized cognitive functions after a lesion in the non-dominant hemisphere is interesting. The present study concentrates on disturbed spatial orienting and attention following left brain damage. While the vast majority of patients with spatial neglect suffer from right hemisphere damage, some individuals show spatial neglect after left brain damage (Becker and Karnath, 2007). These subjects demonstrate a bias in perception and action towards the ipsilesional left side of space and typically fail to address stimuli located on the right. The existence of such patients demonstrates that the group of subjects with disturbed spatial orientation is not a homogenous group (as is the case for the observation of patients with aphasia following right brain damage). These 'exceptions from the rule' provide an opportunity to gain deeper insights into the representation of spatial orienting in the human brain.

Despite its impact for our understanding of hemispheric lateralization of cognitive functions, little is known about neglect after left brain damage (Beis *et al*., 2004; Kleinman *et al*., 2007). It was reported to be less severe than neglect after right brain damage (Ogden, 1987) or that patients with neglect with left brain damage show a different pattern in cancellation tasks compared with patients with right brain damage with neglect (Gainotti *et al*., 1990; Halligan *et al*., 1992). Symptoms typically associated with spatial neglect after left brain damage are aphasia, apraxia and/or disturbed prosody (e.g. Selnes *et al*., 1982, 1991; Kellar and Levick, 1985; Fischer *et al*., 1991). Also, little is known about the brain areas within the left hemisphere that cause spatial neglect when lesioned. Most studies reported single cases or small groups. Lesions of these patients were described to be large, covering frontal, temporal and parietal regions (Selnes *et al*., 1982, 1991; Kellar and Levick, 1985; Junqué *et al*., 1986; Cohen *et al*., 1991; Fischer *et al*., 1991; Posteraro and Maravita, 1996; Kleinman *et al*., 2007). Only few studies investigated larger samples of patients with left brain damage with spatial neglect. Ogden (1985) compared 28 patients with left brain damage and 20 patients with right brain damage with neglect and suggested that neglect patients with left brain damage have more anterior located lesions than neglect patients with right brain damage. Maeshima *et al*. (1992) investigated 20 cases with spatial neglect after left brain damage. They found lesion sites that included temporal, parietal and occipital regions as well as the basal ganglia and/or the thalamus. The 34 neglect patients with left brain damage studied by Beis *et al*. (2004) were characterized having anterior, posterior, anteroposterior or subcortical lesion locations. Ringman *et al*. (2004) studied 17 patients with severe and 60 with moderate neglect suffering from left brain damage. Their lesion locations were described as being mainly temporal, occipital, parietal and thalamic, but also frontal and basal ganglia.

To narrow these rather gross anatomical descriptions, in recent years the voxel-based lesion-behaviour mapping approach has been established as a powerful method to serve this purpose (Bates *et al*., 2003; Rorden *et al*., 2007, 2009). Without *a priori* assumptions, voxel-based lesion-behaviour mapping computes for every voxel of the entire brain whether or not injury to that voxel predicts a behavioural symptom. The present study used this statistical approach to uncover anatomo-functional relationships in order to identify the neural correlate typically associated with spatial neglect in the left hemisphere. We analysed an unselected sample of left hemisphere stroke patients showing, as well as not showing, spatial neglect to different degrees (Rorden and Karnath, 2004).

Materials and methods

Subjects

Neurological patients consecutively admitted to the Centre of Neurology at Tübingen University were screened for an acute left-hemisphere stroke. Patients with a right-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 total, 424 patients with left brain damage were screened. Seventeen patients with left brain damage and spatial neglect were identified and recruited for the present study. Three of these patients had a basal ganglia stroke; three patients had a thalamic lesion. The lesions were documented by MRI and/or spiral-CT. Figure 1 shows conventional lesion density plots for the patients with neglect with cortical/subcortical strokes. Thirty-two additional patients with first ever circumscribed left-hemisphere stroke, but without spatial neglect, were randomly selected to match the following variables of the patients with spatial neglect: age, handedness, the frequency of aphasia, hemiparesis and visual field defects (Tables 1 and 2). In addition, 10 of these latter subjects were selected to match the lesion locations of the six patients with neglect suffering from strokes restricted to either the basal ganglia or the thalamus (Table 2). All subjects gave their informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964).

Clinical examination

The following clinical tests for spatial neglect were applied: Letter Cancellation Task (Weintraub and Mesulam, 1985), Bells test (Gauthier *et al*., 1989), Albert's test (Albert, 1973) and a Copying Task (Johannsen and Karnath, 2004). All four 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 distractors. Patients were asked to cancel all of the targets. The Bells Test requires identifying 35 bell symbols distributed within a field of other symbols. The Albert's test consists of seven columns of black lines that the patients had to cancel. For these three tests, we calculated the centre of cancellation, using the procedure and software by Rorden and Karnath (2010; www.mricron.com/cancel/). The centre of

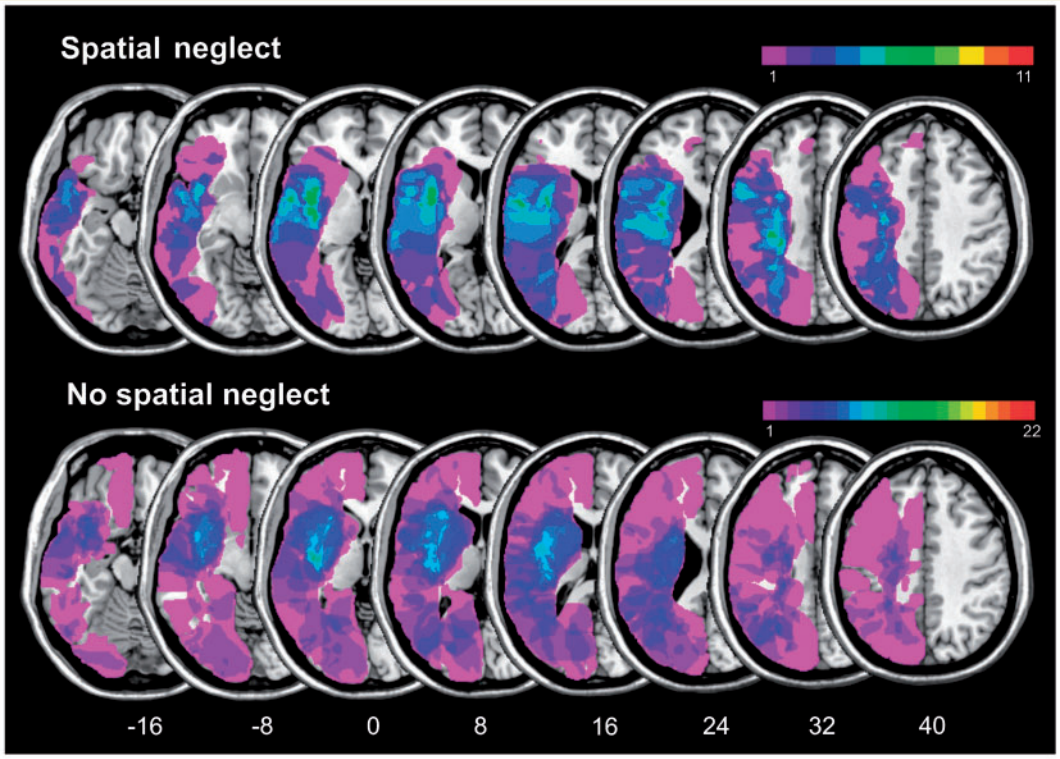

Figure 1 Overlapping lesion plots of the cortical/subcortical left brain-damaged patients with spatial neglect ($n = 11$) and without spatial neglect ($n = 22$). The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet ($n = 1$) to red (n = max.).

Table 1 Demographic and clinical data of patients with left-sided cortical/subcortical lesions

	Spatial neglect	No spatial neglect	*P*-values[§]
n	11	22	–
Sex (F/M)	8/3	14/8	–
Age, mean (range) (years)	67 (21–83)	63 (32–86)	0.490
Aetiology	9 infarct, 2 haemorrhage	18 infarct, 4 haemorrhage	–
Handedness	10 right, 1 ambidextrous	22 right	0.170
Time since lesion—scanning, mean (SD) (days)	3.7 (3.4)	4.2 (6.0)	0.818
Time since lesion—clinical examination, mean (SD) (days)	4.4 (3.5)	4.3 (3.2)	0.942
Lesion volume (percentage of left hemisphere)	11	8	0.311
Paresis of contralesional side (per cent present)	91	77	0.338
Aphasia (per cent present)	91	86	0.706
Hemianopia (per cent present)	18	18	1.000
Neglect severity,[a] mean (SD)	−19.45 (17.3)	−0.24 (0.5)	0.004*
Letter cancellation (centre of cancellation), mean (SD)	−0.34 (0.3)	0.00 (0.0)	0.015*
Bells test (centre of cancellation), mean (SD)	−0.34 (0.2)	0.00 (0.0)	0.004*
Albert's test (centre of cancellation), mean (SD)	−0.59 (0.3)	−0.01 (0.0)	0.006*
Copying task (per cent omitted), mean (SD)	45 (27)	7 (15)	0.001*
Eye in head orientation on MR/CT scans, mean (SD) (°)	−6.9 (7.3)	−1.7 (6.7)	0.046*

a z-transformed and averaged outcomes of letter cancellation, Bells test, Albert's test and copying task.
[§]*t*-test or χ^2-test, respectively.
*$P < 0.05$.

cancellation score expresses the mean horizontal coordinate for the detected items of each test. The centre of mass is calculated in terms of pixels in the test image. Thus, individuals who miss no items or show a symmetrically distributed pattern of errors receive a centre of cancellation score near zero. Individuals who only detect the leftmost items, i.e. show very severe right-sided neglect, receive a score close to −1. In the copying task, patients were asked to copy a complex multi-object scene consisting of four figures (a fence, a car,

Table 2 Demographic and clinical data of the patients with left-sided basal ganglia or left-sided thalamic lesions

	Basal ganglia		Thalamus	
	Spatial neglect	No spatial neglect	Spatial neglect	No spatial neglect
n	3	7	3	3
Sex (F/M)	2/1	4/3	2/1	1/2
Age, mean (range) (years)	52 (33–81)	58 (45–64)	75 (74–76)	60 (47–68)
Aetiology	3 haemorrhage	4 infarct, 3 haemorrhage	1 infarct, 2 haemorrhage	1 infarct, 2 haemorrhage
Handedness	3 right	6 right, 1 ambidextrous	3 right	3 right
Time since lesion—scanning, mean (SD) (days)	9.3 (10.4)	3.6 (5.5)	1.7 (2.1)	1.3 (1.5)
Time since lesion—clinical examination, mean (SD) (days)	2.3 (1.5)	4.1 (4.5)	7.0 (8.7)	9.7 (4.9)
Lesion volume (per cent left hemisphere)	2	2	2	1
Paresis of contralesional side (per cent present)	100	86	100	67
Aphasia (per cent present)	66	86	100	67
Hemianopia (per cent present)	0	0	0	0
Neglect severity,[a] mean (SD)	−23.54 (21.7)	−0.06 (0.3)	−29.03 (23.3)	−0.49 (0.3)
Letter cancellation (centre of cancellation), mean (SD)	−0.09[b]	0.00 (0.0)	−0.57 (0.6)	0.01 (0.0)
Bells test (centre of cancellation), mean (SD)	−0.11[b]	0.01 (0.0)	−0.99[b]	−0.03 (0.05)
Alberts test (centre of cancellation), mean (SD)	−0.81 (0.0)	0.00 (0.0)	−0.88 (0.1)	0.00[b]
Copying task (per cent omitted), mean (SD)	88[b]	0 (0)	25[b]	0 (0)
Eye in head orientation on MR/CT scans, mean (SD) (°)	−1.5 (4.2)	−0.5 (7.4)	−10.3 (7.3)	−2.6 (6.0)

a *z*-transformed and averaged outcomes of letter cancellation, Bells test, Albert's test and copying task.
b Data of just one subject (refer to the 'Materials and methods' section for details).

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. Further, we measured the patients' eye-in-head position on the initial clinical scans taken at admission, applying the procedure by Becker and Karnath (2010). Visual field defects were examined by the common neurological confrontation technique. Handedness was investigated by means of the Edinburgh handedness inventory (Oldfield, 1971). 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. Aphasia was assessed conducting a bedside examination that evaluated spontaneous speech, auditory and reading comprehension, picture naming, reading and oral repetition (Weniger, 2006).

The centre of cancellation scores resulting from the Letter Cancellation Task, the Bells test and the Albert's test as well as the outcome of the copying task were *z*-transformed and averaged to serve as a measure for neglect severity. An important aspect of the present study was to avoid an anatomical *a priori* bias due to the systematical exclusion of patients suffering from severe aphasia. Therefore, we accepted that patients were also included who—due to severely disturbed comprehension—could only perform the Albert's test. This latter test can easily be explained to patients with even severe aphasia, using non-verbal gestures and examples of the required cancellation behaviour performed by the examiner. In 8 of the 49 stroke patients, aphasia was so severe that only the Albert's test could be performed. In these subjects, the standardized centre of cancellation score from the Albert's test served as the only measure for neglect severity. All other subjects completed at least two of the four different paper-and-pencil tests for spatial neglect (median number = 3).

Imaging and lesion analysis

All patients had circumscribed left-hemisphere brain lesions due to ischaemic stroke or haemorrhage demonstrated by MRI ($n = 29$) or by computed tomography (spiral CT; $n = 20$). To fit approximately the canonical anterior commissure–posterior commissure orientation of the magnetic resonance 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. Under both protocols, the initial scanning was repeated optionally 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. Lesion location was evaluated using MRIcron software (Rorden *et al.*, 2007, www.mricron.com). 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 sequences when imaging was conducted 48 h or later after stroke onset (Karnath *et al.*, 2004). The mean time between stroke onset and imaging used for the present analyses was 4.1 days (SD 5.4).

In the subjects who underwent MRI scanning at admission, the boundaries of the lesions were delineated directly on the individual MRI scans. 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/). For determination of the transformation parameters, cost–function masking was employed (Brett *et al.*, 2001). In those patients with spiral-CT scanning at admission, lesions were drawn directly by one experimenter 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 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 the closest matching axial slices of each individual.

To relate the statistical map from the voxel-based lesion-behaviour mapping analyses to grey matter structures, we overlaid it with the AAL atlas (Tzourio-Mazoyer *et al*., 2002) distributed with MRIcron. To identify the white matter fibre tracts that overlapped with the resulting statistical map, we used the fibre tract maps from the human probabilistic cytoarchitectonic atlas (Bürgel *et al*., 2006). This atlas is in the same space as the MNI reference brain with each atlas map illustrating the relative frequency with which a certain fibre tract of 10 normal post-mortem human brains was histologically present. The number of overlapping voxels was determined using MRIcron software.

Results

Cortical/sub-cortical strokes

To evaluate the relationship between lesion location and neglect severity a voxel-based lesion-behaviour mapping analysis was performed by using the *t*-test statistic implemented in the MRIcron toolset and by including all 33 subjects with cortical/subcortical lesions. For this analysis, neglect severity was determined as a continuous variable by using the *z*-transformed and averaged scores from the clinical neglect tests (see above). We controlled for multiple comparisons using the false discovery rate correction; all results presented in the following survived a 1% false discovery rate cut-off threshold. Figure 2 illustrates the results. In total, 72% of the statistical map affected cortical grey matter structures; the remaining voxels covered white matter territory.

We found voxels with the highest *z*-scores in the superior temporal gyrus area (around $x = -68$, $y = -24$, $z = 8$). Twenty-four per cent of the statistical map affected this area (Fig. 2A). Beyond, regions significantly damaged involved the middle temporal gyrus (12% of the statistical map), the inferior parietal lobule (5%), as well as the precentral and the post-central gyri (8 and 16%, respectively). Regions that revealed percentages of overlap $<5\%$ were the rolandic operculum (4%), the insula (2%) and the inferior frontal gyrus (1%).

Regarding the brain's white matter, the superior longitudinal fascicle (6% of the statistical map) turned out to be the fibre tract showing the highest *z*-scores (around $x = -38$, $y = -32$, $z = 32$) (Fig. 2B). In addition, small parts of the inferior occipito-frontal fascicle (1%), and the superior occipitofrontal fascicle (1%) were found to be significantly damaged. The primary motor, auditory and visual projection tracts were also affected (corticospinal tract: 14%, acoustic radiation: 10%, optic radiation: 3%).

Basal ganglia or thalamic strokes

Due to the low number of subjects in the groups with basal ganglia and with thalamic strokes, two subtraction lesion analyses were performed, respectively (Rorden and Karnath, 2004). Subtraction plots directly contrast patients with neglect (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 patients with neglect as well as being typically spared in control patients. Here, we subtracted the overlap images of patients with basal ganglia lesion but no neglect from the subjects with basal ganglia lesions group showing neglect. The same procedure was applied to the two patient groups with thalamic lesions.

Figure 3A shows conventional lesion density plots of the patients with and without spatial neglect suffering from basal ganglia strokes. Within the basal ganglia, the subtraction analysis revealed small areas in the posterior putamen (14% of the subtraction plot) and the posterior pallidum (4%) that were more frequently injured in the patients with spatial neglect than in controls (Fig. 3B). Areas affected in the vicinity of the basal ganglia were the insula (25%) and a very small part of the rolandic operculum (1%). The white matter analysis revealed the superior longitudinal fascicle (15%) and the inferior occipitofrontal fascicle (2%) being more frequently lesioned in the basal ganglia patients with neglect than in those without.

Figure 4A shows the overlay plots for patients with and without spatial neglect suffering from thalamic strokes. Within the thalamus, the subtraction analysis revealed different areas (52% of the subtraction plot) that were more frequent in the patients with spatial neglect than in controls (Fig. 4B), namely the posterior and anterior part of the ventral nucleus, parts of the anterior nucleus and the mediodorsal nucleus at the border to the pulvinar. Further, the white matter analysis revealed the superior occipito-frontal fascicle (10%) and superior longitudinal fascicle (2%) being more frequently affected in the thalamic patients with spatial neglect than in those without.

Discussion

The cortical areas involved in spatial neglect after left brain damage were the superior and middle temporal gyri, as well as the inferior parietal lobule, and the insula. Thus, spatial neglect appears to be represented in homologous regions in the human left and right hemisphere. In the right hemisphere also, spatial neglect is known to occur with lesions of the superior temporal gyrus, middle temporal gyrus and insula (Karnath *et al*., 2001, 2004, 2011; Corbetta *et al*., 2005; Committeri *et al*., 2007; Sarri *et al*., 2009; Chechlacz *et al*., 2010), as well as inferior parietal lobule and temporo-parietal junction (Heilman *et al*., 1983; Vallar and Perani, 1986; Mort *et al*., 2003; Chechlacz *et al*., 2010; Karnath *et al*., 2011). Beyond, the inferior frontal gyrus was observed to correlate with spatial neglect in the right hemisphere (Husain and Kennard, 1996; Committeri *et al*., 2007), while the present study found only a very small part of it affected with spatial neglect in the left hemisphere.

The pattern of affection of the white matter fibre tracts in the left hemisphere also corresponds well to what is known from the right hemisphere. The present study revealed the left superior longitudinal fascicle, inferior occipitofrontal fascicle and superior occipitofrontal fascicle to be associated with spatial neglect. In the human right hemisphere, case and small group studies (Thiebaut de Schotten *et al*., 2005; He *et al*., 2007; Urbanski *et al*., 2008; Shinoura *et al*., 2010) as well as a recent voxel-based lesion-behaviour mapping group analysis of a large sample of 140 patients (Karnath *et al*., 2009) likewise have revealed the involvement of the superior longitudinal fascicle, inferior occipitofrontal fascicle as well as the superior occipitofrontal fascicle with spatial neglect. Interestingly, these tracts form a dense perisylvian

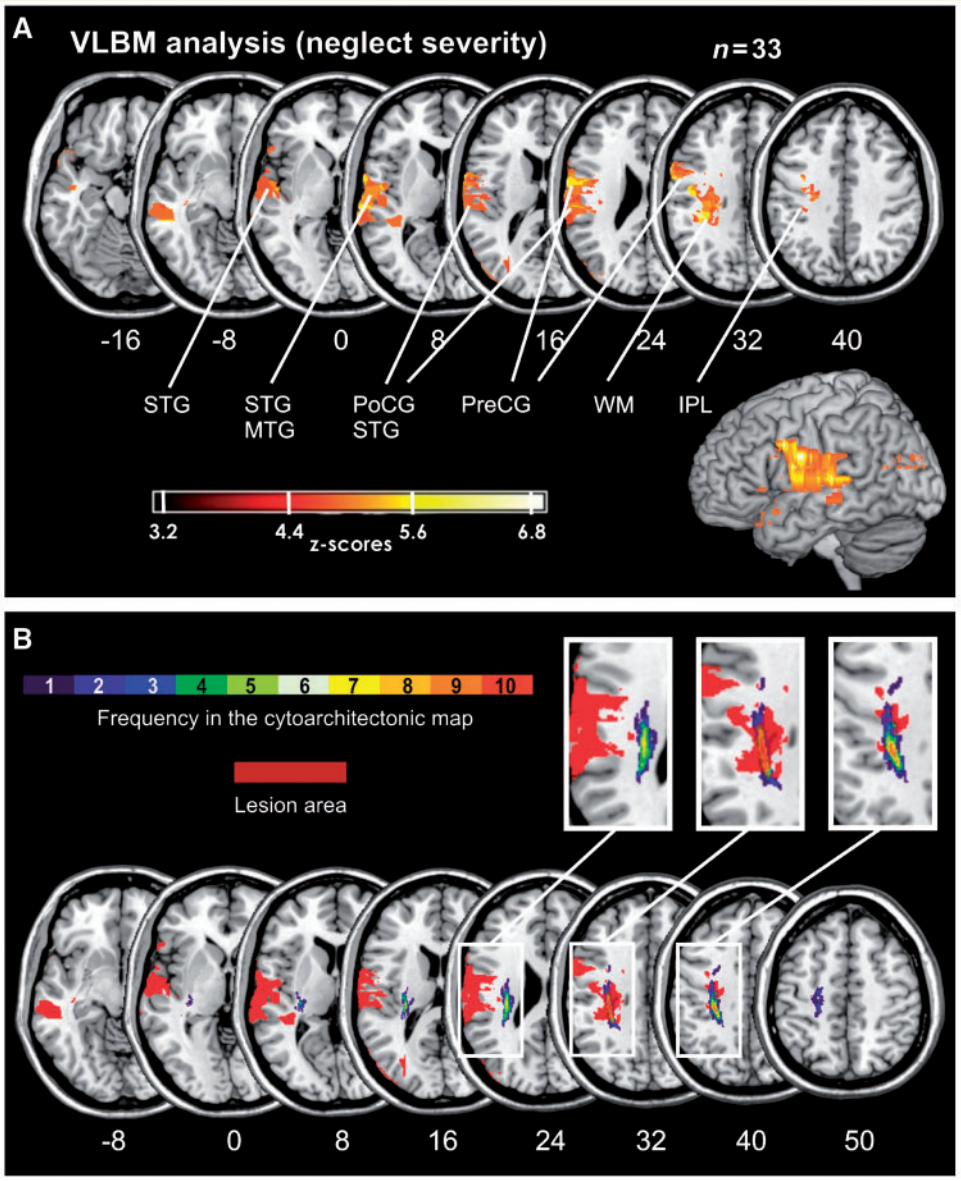

Figure 2 (**A**) Statistical voxelwise lesion-behaviour mapping (VLBM) analysis for the 33 patients with cortical/subcortical left brain damage with respect to neglect severity (*t*-test statistic). For this analysis, neglect severity was determined as a continuous variable by using the *z*-transformed and averaged scores from the clinical neglect tests (refer to 'Materials and methods' section). Presented are all voxels that survived a correction for multiple comparisons using a 1% false discovery rate cut-off threshold ($z > 3.12$). No voxels were found that were significantly more likely to be damaged in patients without neglect than in patients with neglect. MNI coordinates of the transverse sections are given. (**B**) Overlap of the statistical map from this voxel-based lesion-behaviour mapping analysis (voxels from **A** now in homogenous brown colour) with the map of the left superior longitudinal fascicle from the Jülich atlas. 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, the superior longitudinal fascicle was histologically present (e.g. a 30% value of the fibre tract in a certain voxel of the reference brain indicates that the fibre tract was present in that voxel in 3 out of 10 post-mortem brains). MNI coordinates of the transverse sections are given. IPL = inferior parietal lobule; MTG = middle temporal gyrus; PoCG = postcentral gyrus; PreCG = precentral gyrus; STG = superior temporal gyrus; WM = white matter.

network in both hemispheres, interconnecting the three cortical sites associated with spatial neglect, namely the superior/middle temporal gyri, inferior parietal lobule and inferior frontal gyrus (for review see Karnath, 2009).

Though homologous in location, a marked difference exists between the areas associated with spatial neglect in the human left and right hemispheres. While a lesion of these regions in the human left hemisphere only rarely causes full-blown spatial neglect, the vast majority (>96%) of neglect cases are observed after lesion of these areas in the right hemisphere (Becker and Karnath, 2007). Instead, the left hemisphere structures identified here typically serve language functions in humans and cause

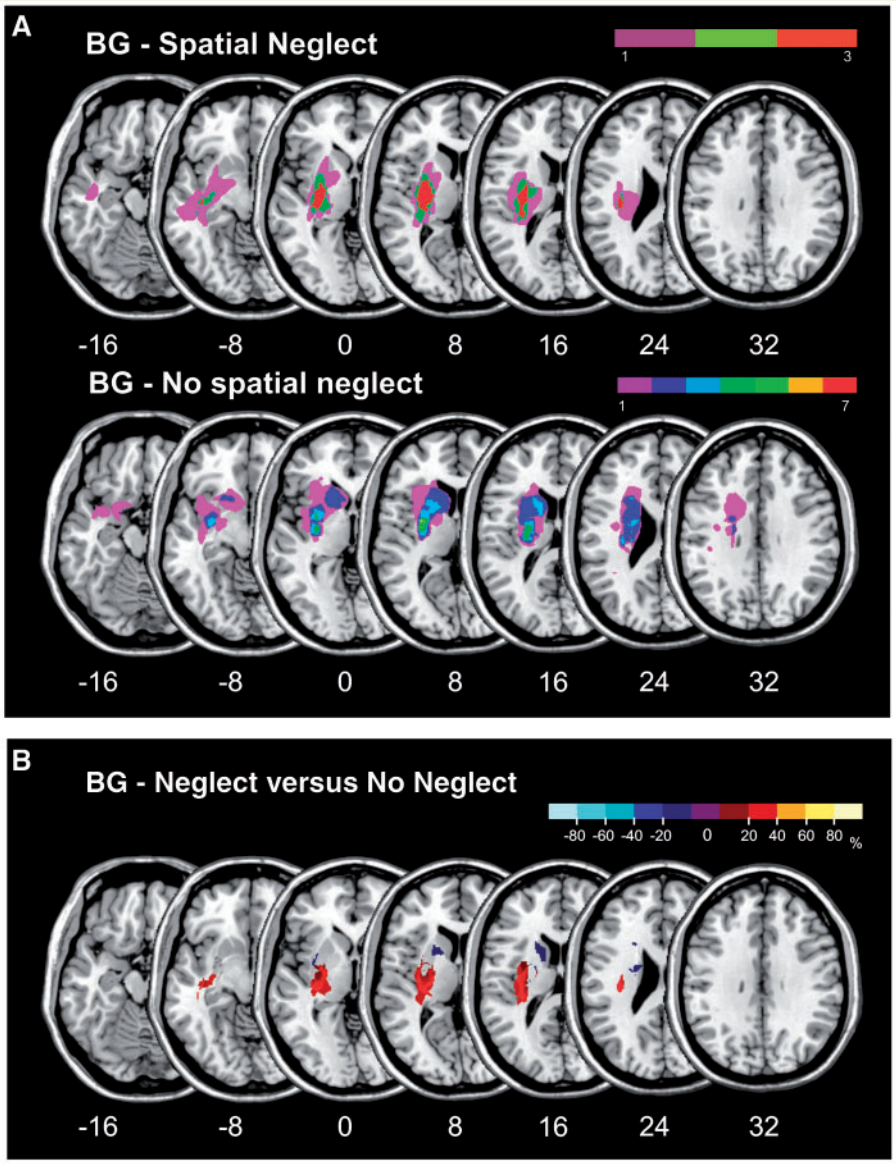

Figure 3 (**A**) Overlapping lesion plots of the patients with left-sided basal ganglia lesions with spatial neglect ($n = 3$) and without spatial neglect ($n = 7$). The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet ($n = 1$) to red (n = max.). (**B**) Subtraction plot illustrating the superimposed lesions of the basal ganglia patients with spatial neglect minus those not showing neglect. The percentage of overlapping lesions of the patients with neglect after subtraction of controls is illustrated by different colours coding increasing frequencies from dark red to white–yellow. The colours from dark blue to light blue indicate regions damaged more frequently in basal ganglia patients not showing neglect than in patients with spatial neglect. MNI coordinates of the transverse sections are given. BG = basal ganglia.

aphasia in the case of a lesion. Studies of cortical lesion localization in stroke patients with aphasia (speech comprehension and/or production disorders) showed involvement of the superior temporal gyrus, middle temporal gyrus, inferior parietal lobule, insula and dorsolateral frontal cortex (Kreisler *et al*., 2000; Dronkers *et al*., 2004; Borovsky *et al*., 2007). Neuroimaging of healthy subjects support these results. A meta-analysis on 129 functional MRI studies addressing different language tasks revealed left frontal, superior and middle temporal, as well as inferior parietal areas to be the most frequently activated areas with phonologic, semantic and syntax processing (Vigneau *et al*., 2006). White matter fibre tracts interconnect these areas. The superior longitudinal fascicle/arcuate fascicle system between superior temporal and prefrontal regions is the most relevant pathway for speech production (Catani and ffytche, 2005; Catani and Mesulam, 2008; Saur *et al*., 2008), while the extreme capsule connecting the middle temporal lobe with the ventrolateral prefrontal cortex is relevant for speech comprehension (Saur *et al*., 2008).

Why is it that we find full-blown spatial neglect in the present patients with left brain damage while this is not the case in the vast majority of individuals with lesions of these areas in the left hemisphere? One could assume that the present subjects with

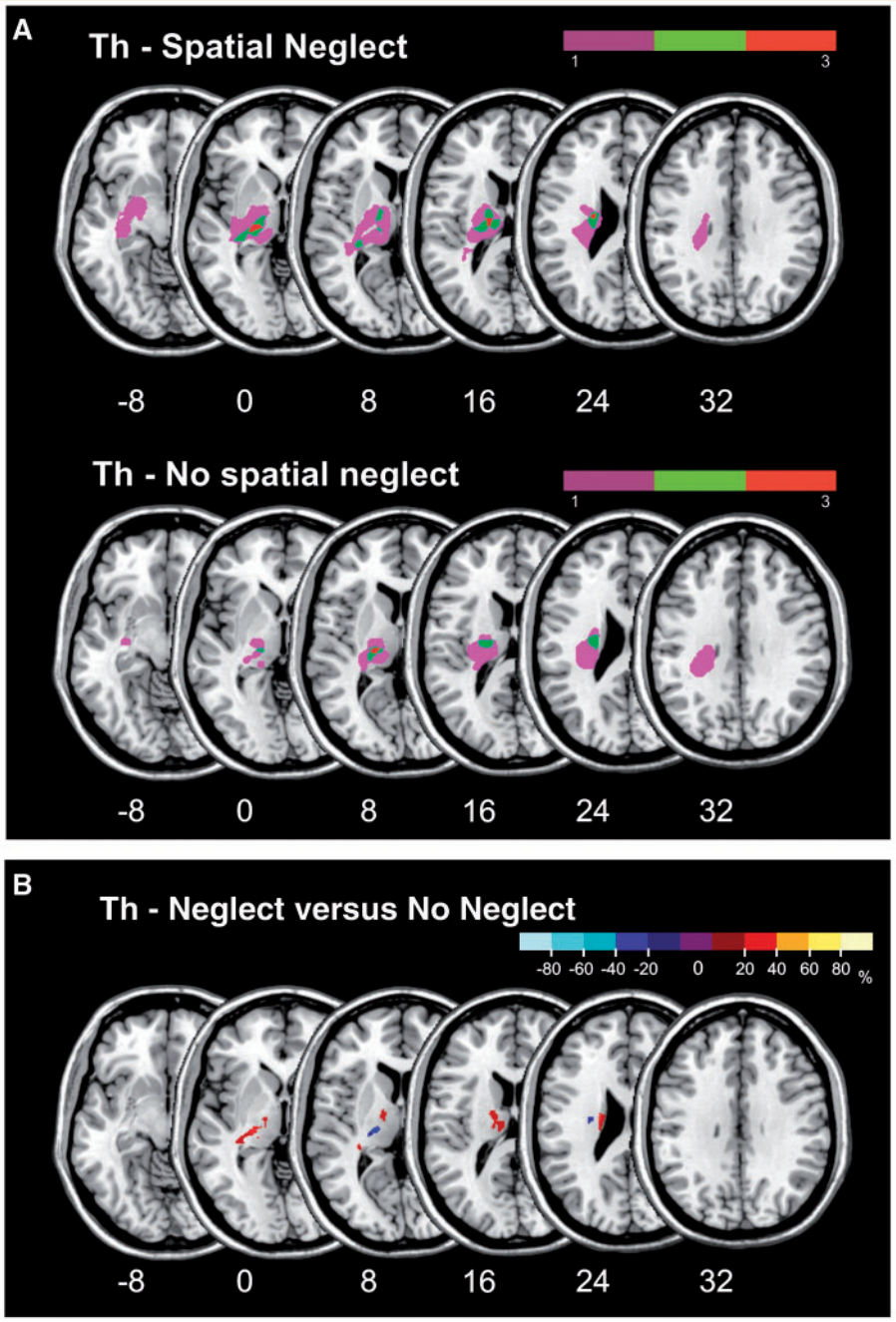

Figure 4 (**A**) Overlapping lesion plots of the patients with thalamic (Th) lesions with spatial neglect ($n = 3$) and without spatial neglect ($n = 3$). The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet ($n = 1$) to red (n = max.). (**B**) Subtraction plot illustrating the superimposed lesions of the thalamic patients with spatial neglect minus those not showing neglect. The percentage of overlapping lesions of the patients with neglect after subtraction of controls is illustrated by different colours coding increasing frequencies from dark red to white–yellow. The colours from dark blue to light blue indicate regions damaged more frequently in basal ganglia patients not showing neglect than in patients with spatial neglect. MNI coordinates of the transverse sections are given.

spatial neglect after left brain damage are unique in that the lateralization of (i) language and (ii) spatial orienting is just reversed, i.e. language functions are dominantly represented in the right and spatial orienting dominantly in the left hemisphere. However, this does not seem to be the case. In our neglect group with left cortical lesions, all except one (=91%) showed aphasia in addition to spatial neglect. This co-occurrence of spatial neglect and aphasia argues against the assumption of reversed lateralization. Both language and spatial orienting rather seem to be represented in the same left hemisphere regions. The co-occurrence of spatial neglect and of aphasia following left brain damage has been previously reported (e.g. Coslett *et al*., 1993; Alexander and Annett,

1996), while there are also some observations of left hemisphere patients with neglect but without aphasia (e.g. Junqué *et al*., 1986; Cohen *et al*., 1991; Posteraro and Maravita, 1996).

What is known about the reversed interhemispheric pattern, namely when a lesion of the human right hemisphere causes aphasia? This so-called 'crossed aphasia' (Bramwell, 1899) is also a rare phenomenon. Reports of incidence vary between 1% and 18% in right handed patients with right brain damage (Mariën *et al*., 2004). In ~50% of the patients with crossed aphasia, attentional deficits and/or spatial neglect were observed in addition. In a review article, Alexander and Annett (1996) reported 17 adult patients with aphasia after right brain damage from whom seven had additional configurational spatial deficits and four out of these seven showed spatial neglect. Mariën *et al*. (2004) reported 49 cases with crossed aphasia [partly overlapping with Alexander and Annett's (1996) patients] from whom 22 suffered from spatial neglect. Thus, it appears as if crossed aphasia cases show additional spatial neglect less frequently compared with the occurrence of aphasia with spatial neglect after left brain damage. One possible reason for this difference could be the two different types of crossed aphasia described to exist after right brain damage. While one type shows a mirrored lesion pattern compared with aphasia after left brain damage, the second type demonstrates lesions in brain areas not typically associated to language functions and only mild language deficits (Alexander *et al*., 1989). Alternatively, a generally more bilateral representation of language compared with spatial orienting could explain the difference.

While we can exclude a reversed lateralization of language and of spatial orienting in our sample with spatial neglect after left brain damage, we cannot decide about further options. It is possible that the language system in these individuals is as dominantly represented in the left hemisphere as this is the case in the vast majority of humans. Alternatively, one or both functions might have a more bilateral representation. While bilateral language representation in left-handers is more frequent, it is known to be <1% in right-handers (Jäncke, 2006). All except one of the present subjects with spatial neglect after left brain damage were right-handed; this could argue against a more bilateral representation of language. Likewise, it is possible that spatial orienting is represented more bilaterally in these individuals. If so, one could expect that its disturbance, i.e. spatial neglect, after a left hemisphere lesion might be less prominent than after a right hemisphere lesion. In fact, weaker spatial neglect after left brain damage compared with neglect after right brain damage has been reported (Ogden, 1987). In further support of this notion, the ipsilesional bias in the cancellation behaviour of the present patients with neglect with acute strokes was less pronounced (*cf*. centre of cancellation values for the letter cancellation and the bells test) than in a typical sample of acute neglect subjects following right brain damage (*cf*. Table 1 in Karnath *et al*., 2011). If we assume that there is indeed a more bilateral representation of spatial attention in these subjects, it raises the next question, namely why this occurs. It might be possible to find an answer in the evolutionary background of development of this function.

Studies in non-human primates have suggested that spatial orienting has been a function represented in both the left and right hemisphere (for review Oleksiak *et al*., 2010). Lesions in the monkey left hemisphere cause spatial neglect towards the right side, while lesions in the monkey right hemisphere evoke spatial neglect towards the left (Luh *et al*., 1986; Watson *et al*., 1994). Evolvement of a new function in the transition from monkey to human, namely the language system, could have caused a formerly bilateral function to (partly) shift to homologous areas in the right hemisphere (Karnath *et al*., 2001). A representation of spatial orienting in left hemisphere language areas thus might be a phylogenetic relict in humans, though this representation stays subdominant in the vast majority of individuals. A lesion of these left hemisphere areas thus only rarely causes full-blown spatial neglect, while the majority of individuals with such lesions do not show an apparent bias, or show such disturbance only extremely short-lasting. But why is it that there are some individuals in whom this left-sided relict is more dominantly represented in the left hemisphere than in others? We can only speculate about an answer to that question. One possible explanation is a differently wired network in these individuals. Catani *et al*. (2007) showed that in humans, different degrees of lateralization of the perisylvian network interconnecting the superior temporal, inferior parietal and inferior prefrontal cortex exists in the left compared with the right hemisphere. This anatomical asymmetry has been confirmed by other studies (e.g. Powell *et al*., 2006; Vernooij *et al*., 2007; Glasser and Rilling, 2008), while some investigations did not find an asymmetry of this network between hemispheres (e.g. Makris *et al*., 2005; Bürgel *et al*., 2006; Hagmann *et al*., 2006; Upadhyay *et al*., 2008). Further possible reasons for the fact that the left-sided relict of spatial orienting is more dominantly represented in the left hemisphere in some individuals might be variations in the organization of higher cognitive functions within and/or between the hemispheres due to genetic or environmental factors.

Basal ganglia/thalamus

With respect to the neural correlates of spatial neglect in subcortical grey matter tissue, we observed the posterior parts of the putamen and the pallidum to be affected more frequently in patients with spatial neglect after basal ganglia lesions. In the left thalamus, regions more frequently affected in neglect were parts of the anterior, ventral and mediodorsal nuclei at the border to the pulvinar. In the right basal ganglia, Karnath *et al*. (2002) found the putamen and—to a smaller part—the caudate nucleus critically associated with spatial neglect. In the right thalamus, these authors had observed the pulvinar as the crucial substrate for spatial neglect (Karnath *et al*., 2002). The present anatomical results thus fit partly to those revealed from studies with patients with right brain damage. However, it has to be noted that due to the small number of patients with neglect with left-sided basal ganglia as well as thalamic lesions, the present anatomical findings should be interpreted carefully. Analysis of a larger cohort would be required.

Based on previous findings in the right hemisphere, we speculate that the mechanism underlying the occurrence of spatial

neglect after a lesion in the left basal ganglia or the left thalamus may be cortical malperfusion. Comparison of patients with subcortical lesions showing versus not showing spatial neglect or aphasia has revealed abnormal perfusion of cortical areas only in those cases that exhibited apparent spatial neglect or aphasia (Weiller *et al*., 1990, 1993; Demeurisse *et al*., 1997; Hillis *et al*., 2005; Karnath *et al*., 2005). This indicated that spatial neglect after subcortical stroke is due to dysfunction of (structurally intact) cortical areas rather than through the neuronal loss in the subcortical structures itself. We expect that this is also the case in the present neglect cases with basal ganglia and with thalamic lesions. However, future studies examining cortical perfusion are required to prove this assumption.

Conclusion

It seems that homologous cortical regions are associated with spatial orienting and attention in the left as well as the right hemisphere. The co-occurrence of spatial neglect and of aphasia in our unselected, continuously recruited sample of left hemisphere patients with neglect suggests that the lateralization of: (i) language and (ii) spatial orienting is not just reversed in these cases. Both functions rather seem to be represented in the same left hemisphere regions. We speculate that a representation of spatial orienting in left hemisphere language areas is not a unique feature of only these few individuals. It might be a phylogenetic relict generally existing in humans, though this left-sided representation of spatial orienting stays sub-dominant in the vast majority of individuals. A lesion of these areas thus only rarely causes full-blown spatial neglect, while the majority of such lesions induce no or only an extremely short-lasting bias.

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