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Normalized perfusion MRI to identify common areas of dysfunction: patients with basal ganglia neglect

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Perfusion-weighted imaging (PWI) is used to identify brain regions that are receiving enough blood supply to remain structurally intact, but not enough to function normally. Previous observations suggest that spatial neglect due to subcortical stroke can be explained by dysfunction of cortical areas rather than through the neuronal loss in the subcortical structures itself. The present study aimed to identify the dysfunctional cortical regions induced by basal ganglia stroke in patients with spatial neglect. In a patient group with stroke lesions centring on the basal ganglia, we examined the common area(s) of structurally intact but dysfunctional cortical tissue by using spatial normalization of PWI maps as well as symmetric voxel-wise inter-hemispheric comparisons. These new techniques allow comparison of the structurally intact but abnormally perfused areas of different individuals in the same stereotaxic space, and at the same time avoid problems due to regional perfusion differences and to possible observer-dependent biases. We found that strokes centring on the right basal ganglia which provoke spatial neglect induce abnormal perfusion in a circumscribed area of intact cortex that typically involves those three regions that have previously been described to provoke spatial neglect when damaged directly by cortical infarction: the superior temporal gyrus, the inferior parietal lobule and the inferior frontal gyrus. The data suggest that spatial neglect following a right basal ganglia lesion typically is caused by the dysfunction of (part of) these specific cortical areas.

Keywords: spatial neglect; basal ganglia; attention; visual search; exploration; perfusion-weighted imaging; human

Abbreviations: PWI = perfusion-weighted imaging; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion-recovery

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Introduction

To explain behavioural defects after stroke, MRI and CT are used to determine brain areas of irreversible damaged neural tissue. The idea that the left hemisphere is dominant for language processing while the right is specialized for spatial orientation is linked to the observation that lesions of cortical structures straddling the sylvian fissure in the left hemisphere typically induce aphasia, while right-sided damage of these structures typically causes spatial neglect. Beyond cortical structures, lesions restricted to the basal ganglia or thalamus have been reported to induce the same behavioural disorders (see recent overviews in Karnath *et al.*, 2002; Radanovic and Scaff, 2003).

However, for a precise understanding of the representation of brain functions, it might be helpful to analyse not only the irreversible damage but also the pattern of (structurally intact but) dysfunctional tissue in stroke patients. Advanced magnetic resonance imaging techniques now provide new, non-invasive methods to address this issue. Diffusion-weighted imaging (DWI) is sensitive to shifts of water between extracellular and intracellular spaces and, thus, can detect brain

regions undergoing irreversible cell death (the 'ischaemic core region') very early after stroke onset and shows high accuracy in predicting final infarct size (Ricci *et al.*, 1999; Schaefer *et al.*, 2002). For acute/subacute cerebral infarcts T2-weighted fluid-attenuated inversion-recovery (FLAIR) images provide high sensitivity in detecting such regions (Brant-Zawadzki *et al.*, 1996; Noguchi *et al.*, 1997). On the other hand, perfusion-weighted imaging (PWI) measures the amount and latency of blood flow reaching different regions of the brain. It allows identification of structurally intact but abnormally perfused brain tissue. In the acute stage of a stroke, regions with normal diffusion but abnormal perfusion, i.e. regions showing a PWI/DWI mismatch, often surround the irreversibly damaged ischaemic core region and are thought to represent the 'ischaemic penumbra' (Schlaug *et al.*, 1999). Such regions not only are observed with ischaemic strokes but also can occur with intracerebral haemorrhage (Sills *et al.*, 1996; Kidwell *et al.*, 2001). Neurons in these 'mismatch areas' are undergoing potentially reversible cellular changes due to reduced availability of essential nutrition and oxygen. They represent zones that are receiving enough blood supply to remain structurally intact, but not enough to function normally. For example, local EEG signals disappear if blood flow is reduced from an average of 50 to 15–20 ml/100g/min (Hossmann, 1994). Moreover, the size of the tissue with perfusion abnormalities has been found to correlate with the general behavioural dysfunction measured by stroke scales (Barber *et al.*, 1998; Tong *et al.*, 1998; Beaulieu *et al.*, 1999; Neumann-Haefelin *et al.*, 1999; Baird *et al.*, 2000). It has also been shown that perfusion deficits in Wernicke's area following subcortical stroke predict language dysfunction (Hillis *et al.*, 2001).

In order to explain behavioural defects after stroke, PWI thus seems to complement the information about irreversible damaged tissue deriving from MRI and CT. The present article focuses on the phenomenon of spatial neglect due to stroke centring on the right basal ganglia. Spatial neglect is a lateralized disorder of space-related behaviour in stroke patients that describes a characteristic failure to explore the side of space contralateral to the lesion, and to react or respond to stimuli or subjects located on this side (Karnath and Zihl, 2003). The patients typically show spontaneous deviation of the head and the eyes towards the ipsilesional side and orient towards that side when addressed from the front or the left (Fruhmann-Berger and Karnath, 2005).

Within the basal ganglia, the right putamen and caudate nucleus were identified to be the crucial structures associated with spatial neglect (Karnath *et al.*, 2002). First, metabolic, single photon emission computed tomography (SPECT) studies of patients with such infarcts revealed a decrease in cortical cerebral blood flow of the ipsilesional, right hemisphere in those stroke patients who showed spatial neglect but not (or significantly less) in those without the disorder (Weiller *et al.*, 1990, 1993). Using DWI and PWI Hillis *et al.* (2002) recently confirmed these observations. The authors evaluated patients with and without spatial neglect who suffered from right hemisphere subcortical strokes either in the basal ganglia, in the subcortical white matter, or in the thalamus. They found abnormal perfusion at the cortical level in the seven patients who had spatial neglect, while the other seven patients without neglect did not show cortical perfusion abnormalities. In conclusion, the observations obtained from SPECT and from PWI analyses consistently suggest that spatial neglect due to subcortical stroke indeed can be explained by dysfunction of cortical areas rather than through the neuronal loss in the subcortical structures themselves.

If so, the question arises as to exactly which cortical structures are dysfunctional? Are the same structures involved that are known to provoke spatial neglect when damaged by cortical infarction (Heilman *et al.*, 1983; Vallar and Perani, 1986; Husain and Kennard, 1996; Karnath *et al.*, 2001, 2003, 2004*a*, *b*; Mort *et al.*, 2003)? One way to answer this question is to define discrete anatomical or vascular cortical regions and determine the frequency of their involvement. Using either SPECT (Demeurisse *et al.*, 1997) or PWI (Hillis *et al.* 2002, 2005) this procedure has been applied to patient groups with subcortical strokes. However, since this procedure does not always allow the entire area of abnormal perfusion to enter the analysis, information might be lost. Moreover, each of the patient groups investigated so far possessed a mixture of different lesion sites, including thalamic, basal ganglia, internal capsule, and white matter, in order to determine the area of cortical dysfunction related to this composite of various subcortical lesion sites in subjects with aphasia (Hillis *et al.*, 2002) and in subjects with spatial neglect (Demeurisse *et al.*, 1997; Hillis *et al.*, 2002, 2005). The present study thus uses spatial normalization, which is a common tool in fMRI analyses of group data. The entire area of abnormal perfusion in each individual is taken to plot the common cortical site(s) of structurally intact but abnormally perfused tissue in groups of patients with and without spatial neglect for a high resolution analysis in Talairach space (Talairach and Tournoux, 1988). The present study uses this technique to identify the dysfunctional cortical regions induced by right basal ganglia stroke in patients with spatial neglect.

Methods

Subjects

Ten patients with stroke lesions centring on the basal ganglia consecutively admitted to the University Hospital in Tübingen were included in the study. Patients with a haemodynamically relevant stenosis in the internal carotid arteries, i.e. $\geq$70%, demonstrated by Doppler sonography were excluded. Stenoses have been shown to produce false-positive depictions of perfusion deficits, especially in time-to-peak perfusion images (Yamada *et al.*, 2002). Following a standardized testing for spatial neglect (see below), the 10 patients were divided into groups with and without spatial neglect (cf. Table 1). The neglect group and the group without spatial neglect were comparable with respect to age ($U = 12.0$, $P = 0.92$), the mean time from the onset of stroke until testing ($U = 9.0$, $P = 0.46$), the

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

	Neglect	No neglect
Number	5	5
Sex	2f, 3m	1f, 4m
Age (year)		
Mean (SD)	59 (15.5)	57.8 (8.2)
Aetiology	4 Infarct	3 Infarct
	1 Hemorrhage	2 Hemorrhage
Time since lesion (d)-MRI		
Mean (SD)	3.8 (4.5)	5.6 (4.0)
Lesion volume (ccm)		
Mean (SD)	80.7 (39.8)	50.9 (33.3)
Paresis of contralesional side		
% present	100	80
Somatosensory deficit of contralesional side (touch)		
% present	60	40
Visual field deficit		
% present	0	0
Letter cancellation		
Left; mean (SD)	10 (5.9)	30
Right; mean (SD)	26.8 (2.2)	30
Bells test		
Left; mean (SD)	2.2 (1.8)	13.6 (2.0)
Right; mean (SD)	12.0 (2.6)	14.6 (0.5)
Copying (% omitted)		
Mean (SD)	37.5 (19.8)	0

f, female; m, male.

frequency of additional visual field defects, lesion size (U = 7.0, P = 0.25) and the frequency of contralateral motor and somatosensory deficits (Fisher's exact test: P = 1.00 both) (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 behaviour, such as orienting towards the ipsilesional side when addressed from the front or the left and ignoring of contralesionally located people or objects. In addition, all patients were further assessed with the following tests: the 'Letter cancellation' task, the 'Bells test' and a copying task. Line bisection, Albert's test and star cancellation were not used as screening tools (cf. Ferber and Karnath, 2001). (i) 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 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. (ii) The Bells Test (Gauthier *et al.*, 1989). This consists of seven columns each containing five targets (bells) among 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 were asked to cancel all targets and the number of targets found was reported. The presence of more than five left-sided target omissions was taken to indicate neglect. (iii) Copying Task (Johannsen and Karnath, 2004). 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 8. A score >1 (i.e. more than 12.5% omissions) was taken to indicate neglect.

Neglect patients had to fulfil the criterion for spatial neglect in at least two of these three clinical tests. Visual field deficits, paresis and somatosensory defects were assessed using standardized neurological examination.

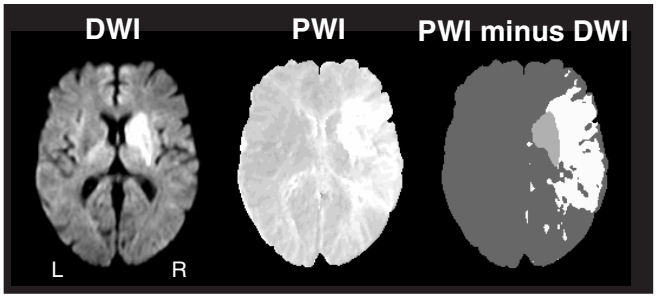

Fig. 1 Example from one patient's imaging data. *Left panel:* normalized DWI map; *Middle panel:* normalized PWI map; *Right panel:* the zone of structurally intact but dysfunctional neural tissue used for the present analyses (*white area*), was determined by subtracting the hyperintense area of the normalized DWI map (*light grey area*) from the region of abnormal perfusion revealed from the normalized PWI (TTP delay) map.

MR imaging and analysis

The MR protocol included DWI, FLAIR sequences and PWI. For lesion delineation, we used DWI imaging within the first 48 h post-stroke and FLAIR sequences when imaging was conducted 48 h or later after the stroke (Brant-Zawadzki *et al.*, 1996; Noguchi *et al.*, 1997; Ricci *et al.*, 1999; Schaefer *et al.*, 2002). The mean time between stroke and imaging used for the present analyses was 3.8 days (SD 4.5) in the neglect group and 5.6 days (SD 4.0) in the control group. Scans were obtained on a 1.5-T echoplanar imaging (EPI) capable system (Magnetom Sonata, Siemens, Erlangen, Germany). The FLAIR sequence was acquired with 20 axial slices (thickness 5 mm; interslice gap 1 mm), a field of view (FOV) of 175 × 220 mm^2, matrix 204 × 256, a repetition time (TR) of 9000 ms and an echo time (TE) of 118 ms. DWI was performed with a single-shot EPI spin echo sequence (TR 3200 ms; TE 87 ms; FOV 230 × 230 mm^2; matrix 128 × 128; slice thickness 5 mm; gap 1 mm; b-value 1000 s/mm^2). The boundary of the lesion was delineated directly on the individual MRI image for every single transverse slice using the MRIcro software (Rorden and Brett, 2000) (http://www.mricro.com). In order to illustrate the common region of involvement per group, both the scan and lesion shape were then transferred into stereotaxic space using the spatial normalization algorithm provided by SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). For determination of the transformation parameters, cost-function masking was employed (Brett *et al.*, 2001). Figure 1 gives an example of the normalized DWI images.

Furthermore, 50 repetitions of perfusion-weighted EPI sequences (TR 1440 ms; TE 47 ms; FOV 461 × 461 mm^2; matrix 256 × 256;

12 axial slices; slice thickness 5 mm; gap 1 mm) were obtained with 20 ml gadolinium diethyl triamineene pentaacetic acid (Gd-DTPA) bolus power injected at a rate of 4 ml/s. Time-to-peak (TTP) was calculated representing the time at which the largest signal drop occurs in the signal intensity curve with respect to the first image. To superimpose individual TTP maps in order to identify common regions of perfusion abnormality in a group of patients, they were transferred into stereotaxic space using the spatial normalization algorithm provided by SPM2. For SPM normalization, we used a template featuring symmetrical left–right hemispheres (cf. Aubert-Broche *et al.*, 2003) in order to perform voxel-wise inter-hemispheric comparisons (see below). Figure 1 gives an example of the normalized TTP maps.

In order to take into account regional and grey-white matter differences of perfusion characteristics within each hemisphere, differences in injection time relative to the beginning of the measurement, and other inter- and intraindividual differences such as heart rate, cardiac output etc. we performed voxel-wise inter-hemispheric comparisons for each individual before extracting perfusion deficit volumes of interest. For the normalized TTP maps, we subtracted from each voxel of the affected right hemisphere its mirrored voxel in the unaffected left hemisphere. The resulting values are termed 'TTP delay' in the following.

For the determination of volumes with perfusion abnormalities we defined the threshold for TTP delays $\geq$3.0 s. The TTP delay threshold was based on previous observations that TTP delays >2.5 s in Wernicke's area were associated with language dysfunction (Hillis *et al.*, 2001), and that the general functional impairment of stroke patients correlated best with the volume of PWI abnormality for TTP delays $\geq$4s (Neumann-Haefelin *et al.*, 1999). The area of mismatch between DWI/FLAIR and PWI abnormalities, i.e. the zones of structurally intact but dysfunctional neural tissue, was determined by subtracting for each subject the normalized DWI/FLAIR map from the normalized TTP delay map (example in Fig. 1). Finally, we compared perfusion abnormalities in the patient groups with and without spatial neglect. For this purpose, the superimposed mismatch images of the group without spatial neglect were subtracted from the neglect group's overlap mismatch images (details concerning the subtraction technique are given in Rorden and Karnath, 2004).

Results

In Fig. 2, overlay plots are presented showing the spatially normalized DWI/FLAIR abnormalities for the groups of patients with and without spatial neglect suffering from lesions centring on the right basal ganglia. The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet (n = 1) to red (n = 5).

The spatially normalized perfusion abnormalities accompanying these lesions, i.e. the zones of mismatch between DWI/FLAIR and PWI abnormalities, are illustrated in Fig. 3. Partly different from previous observations (Hillis *et al.*, 2002, 2005), we did not find abnormal cortical perfusion (increased TTP delays) in *every* subject with spatial neglect. While four neglect patients had marked (n = 3) or slight (n = 1) cortical perfusion abnormalities, one out of five subjects did not show relevant cortical perfusion abnormalities in addition to her lesion.

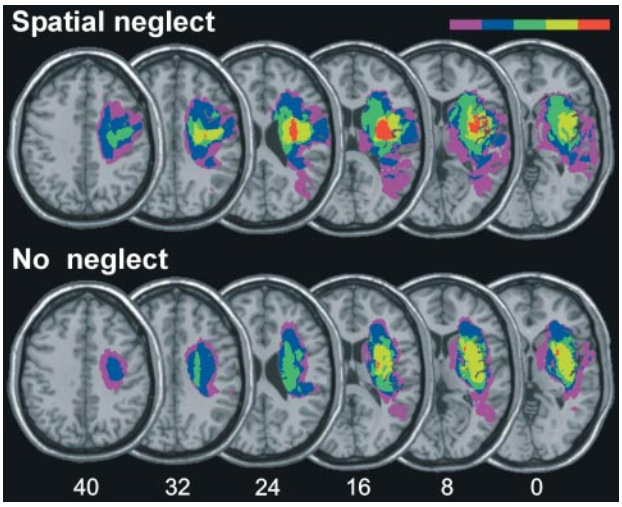

Fig. 2 Conventional lesion overlay plots for the group of five patients with spatial neglect and the group of five patients without neglect, based on normalized DWI or FLAIR images. The number of overlapping lesions is illustrated by different colours, coding increasing frequencies from violet (n = 1) to red (n = 5). Talairach z-coordinates (Talairach and Tournoux, 1988) of the transverse sections are given.

The mismatch images of all individuals in the group of patients with neglect and in the group without neglect were superimposed, creating an overlap image showing the common regions of structurally intact (no DWI/FLAIR abnormalities) but abnormally perfused tissue in each group (Fig. 3A). To illustrate the common area of abnormal perfusion in the patients with spatial neglect in direct contrast to those abnormally perfused areas that were present in the patients who did not show the disorder, we subtracted the overlay mismatch images of the latter group from the overlap mismatch images of the neglect group. The resulting subtraction images specifically highlight structurally intact regions that were both typically dysfunctional in patients with spatial neglect as well as typically spared in patients without the disorder (Fig. 3B and C). We found the maximum of abnormal perfusion in the superior and middle temporal gyri (STG, MTG), the inferior parietal lobule (IPL) and the inferior frontal gyrus (IFG; Fig. 3B and C).

The anatomical parcellation of the MNI single-subject brain by Tzourio-Mazoyer *et al.* (2002) implemented in MRIcro was further used to determine the extent of abnormal perfusion within these regions in each subject. We found clear differences in involvement between the groups of patients with versus without spatial neglect. Figure 4 illustrates the individual and mean percentage of structurally intact but dysfunctional tissue in the IPL, STG, MTG and IFG for both the groups. The statistical comparison of both groups (n = 5 subjects each) revealed a Mann–Whitney U-value of 6.0 (P = 0.111, one-tailed) for the IPL, U = 3.0 (P = 0.028) for the STG, U = 5.5. (P = 0.076) for the MTG and U = 3.0 (P = 0.028) for the IFG.

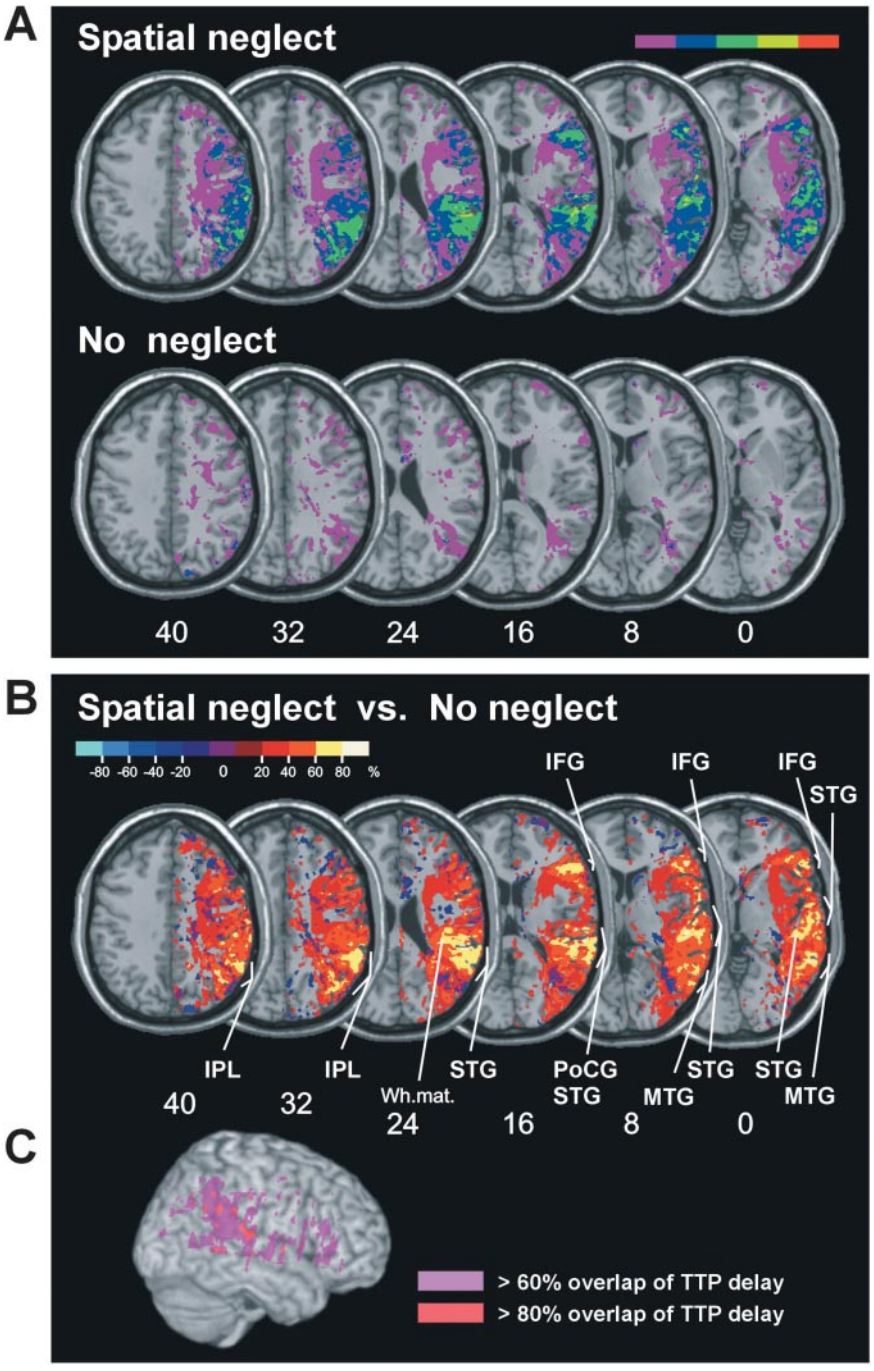

Fig. 3 (**A**) Overlay plots showing the common regions of mismatch between DWI/FLAIR and PWI abnormalities, i.e. of structurally intact but abnormally perfused tissue, for the group of five neglect patients and the group of five patients without spatial neglect. The number of overlapping areas with abnormal perfusion is illustrated by different colours, coding increasing frequencies from violet ($n = 1$) to red ($n = 5$). Talairach *z*-coordinates (Talairach and Tournoux, 1988) of the transverse sections are given. (**B**) Overlay plots of the subtracted superimposed mismatch images of the neglect group minus the mismatch images of the group without neglect. The percentage of overlapping areas of structurally intact but abnormally perfused tissue in the neglect group after subtraction is illustrated by five different colours, coding increasing frequencies from dark red (difference = 1–20%) to white–yellow (difference = 81–100%). Each colour represents 20% increments. The different colours from dark blue (difference = −1% to −20%) to light blue (difference = −81% to −100%) indicate regions abnormally perfused more frequently in patients without neglect than in the neglect group. Purple (middle of the colour bar) designates regions where there is an identical percentage of abnormal perfusion in both groups (= 0%). Talairach *z*-coordinates (Talairach and Tournoux, 1988) of the transverse sections are given. IFG, inferior frontal gyrus; PoCG, postcentral gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; IPL, inferior parietal lobule; and Wh.mat., white matter. (**C**) Lateral surface view of the maximum of common regions of structurally intact but abnormally perfused tissue after subtraction between the two groups. Please note that the figure illustrates the interpolated result derived from the spatial normalization algorithm provided by SPM2 based on the 5 mm thick perfusion-weighted EPI sequence slices.

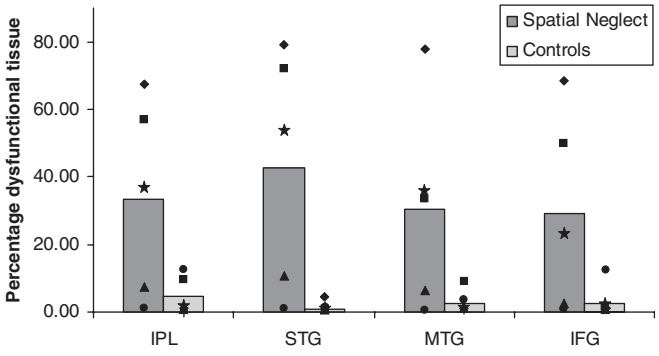

Fig. 4 Individual (five different symbols) and mean (bars) percentage of structurally intact but dysfunctional tissue in the inferior parietal lobule (IPL), superior temporal gyrus (STG), middle temporal gyrus (MTG) and inferior frontal gyrus (IFG). Regions were defined by the anatomical parcellation for the MNI single-subject brain by Tzourio-Mazoyer *et al.* (2002).

Discussion

The present study used normalized PWI to identify the common area(s) of structurally intact but dysfunctional cortical neural tissue in a group of patients with spatial neglect, suffering from lesions centring on the right basal ganglia. We found that the lesions in such a group induce abnormal perfusion (increased TTP delays) in a circumscribed, structurally intact cortical area that typically involves those three regions that have been described to provoke spatial neglect when damaged directly by cortical infarction: (i) the right STG, (ii) the IPL and (iii) the IFG.

Lesion studies in patients with cortical damage and spatial neglect suggest that the IPL and the temporo-parietal junction (TPJ) (Heilman *et al.*, 1983; Vallar and Perani, 1986; Leibovitch *et al.*, 1998, 1999; Mort *et al.*, 2003), as well as the IFG (Husain and Kennard, 1996; Samuelsson *et al.*, 1997) comprise the areas for multimodal representation of space used in exploration and spatial perception. By employing voxel-wise statistical comparisons between large patient groups with and without a bias in exploration, the STG and insula of the right hemisphere have recently been identified as being critically related to spatial neglect (Karnath *et al.*, 2004*b*). Evidence for the involvement of these areas in tasks related to spatial orienting and exploration also is reported from a recent experiment using functional magnetic resonance imaging (fMRI) in healthy subjects (M. Himmelbach, M. Erb, H.-O. Karnath, manuscript submitted). This study investigated the subjects' cortical pattern of activation in an exploratory task that closely resembled clinical procedures known to be sensitive to the neglect patients' behavioural bias. The authors used visual exploration of a letter array similar to the cancellation task of Weintraub and Mesulam (1985) and contrasted the behaviour and brain activity with the execution of stepwise horizontal and vertical saccades. Significant differences of the measured BOLD signal between the conditions were located at the TPJ, the middle part of the STG and the ventral aspect of the IFG.

The present study cannot decide which of the three cortical regions with abnormal perfusion observed in the group of neglect patients with basal ganglia strokes—the IPL, the STG and MTG, and the IFG—is the crucial cortical area provoking the disorder. It is possible that dysfunction in only one of these regions leads to neglect. However, it is also possible that the combined dysfunction of more than one (maybe of all three) cortical areas provokes spatial neglect following a stroke of the right basal ganglia. Further research has to clarify this issue.

It is a long-standing debate whether damage to subcortical structures, such as the basal ganglia, causes cognitive disturbances (e.g. spatial neglect or aphasia) either directly or through functional or metabolic abnormalities in cortical areas via diaschisis (Feeney and Baron, 1986; Stirling Meyer *et al.*, 1993), or through vascular dysfunction. Diaschisis is believed to be a result of reduction of neuronal activity from axonal damage leading to brain dysfunction distant from the stroke. Also vascular disorders such as loss of autoregulation, release of vasoactive substances, and/or abnormally vasoconstricted arterioles and stenosis have been suggested to be occurring with hypoperfusion (Slater *et al.*, 1977; Takano *et al.*, 1988). In fact, perfusion-weighted MRI does not provide the possibility to differentiate between these aetiologies. PWI only measures the amount and latency of blood flow reaching different regions of the brain. It thus allows to identify zones that are receiving enough blood supply to remain structurally intact, but not enough to function normally. However, this technique does not explain the physiology behind the relationship between the neuronal loss in the basal ganglia and the cortical blood flow abnormalities. If the latter is the product of diaschisis, it might suggest that the basal ganglia are indeed a part of the network that when damaged induces spatial neglect. An observation that could support this notion is the finding that one out of the five present patients with spatial neglect did not show relevant cortical perfusion abnormalities in addition to her lesion. However, this discrepancy also could be due to accidental instances or specific demographic or clinical variables not yet apparent between subjects. Nevertheless, very clearly and consistent with earlier findings (Hillis *et al.*, 2002, 2005), the present study found obvious differences of cortical perfusion between the two patient groups with and without spatial neglect. Further studies have to clarify the mechanisms underlying cortical perfusion abnormalities occuring with subcortical neuronal loss. The specific molecular, cellular and vascular changes leading to the cortical dysfunction still are not known.

Our experiment used two new techniques to study perfusion abnormalities in the human brain. To define abnormal perfusion, previous studies used e.g. a 'neutral region', such as the cerebellum (Kluytmans *et al.*, 1998), to control for intra- and inter-individual differences. The most common approach was to use a reference region at the same approximate position as the anticipated area of abnormal perfusion in the unaffected hemisphere (Neumann-Haefelin *et al.*, 1999; Schlaug

et al., 1999; Hillis *et al.*, 2001; Singer *et al.*, 2003). In the case of TTP, the mean or median value calculated from this region was subtracted to obtain standardized values for abnormal perfusion in the subject's affected hemisphere. This approach is problematic because regional intrahemispheric differences exist with respect to metabolic demands. For example, Helenius *et al.* (2003) found that CBF, CBV and MTT not only differ between grey and white matter, but also between cortical and deep grey matter and between different lobes. Regional differences also exist in TTP maps. Thus, voxel-based perfusion abnormality maps based on calculations that use mean values from regions in the unaffected hemisphere necessarily lead to biases. For example, the TTP delay values for regions with generally faster blood supply in the healthy hemisphere compared with the reference mean are underestimated, whereas delays with generally slower blood supply regions are overestimated. A further problem for previous standardization methods is that they need observer-dependent decisions to define the reference regions. To avoid these problems, the present study used voxel-wise inter-hemispheric comparisons per subject. Each voxel of the unaffected left hemisphere was related to its mirrored voxel in the affected right hemisphere. This avoids any averaging procedures to obtain a reference in the healthy hemisphere, and thus also the problem of a priori anatomical region delineation and possible observer-dependent biases.

Moreover, the present study used normalization to analyse the PWI data. This allows to investigate the entire area of abnormal perfusion in each individual by transforming the subjects' brains and respective PWI data to a common standard stereotaxic space so that they become comparable between subjects. This procedure makes it possible to plot the common sites of abnormal perfusion at the group level without any loss of information. It thus provides significant benefits compared with the hitherto existing procedure to define discrete anatomical or vascular cortical regions and determine the frequency of their involvement in the individual PWI scans of a patient group.

In conclusion, to investigate anatomo-functional relationships in humans, PWI seems to complement the information about irreversibly damaged tissue derived from magnetic resonance imaging (DWI, FLAIR, T1). Normalization of the PWI data seems to be a promising technique to identify common areas of abnormal perfusion in patient groups showing the same disorder. Using this new method, we found that strokes centring on the right basal ganglia induce dysfunction in a circumscribed cortical area that typically involves those three regions that have been described to provoke spatial neglect when damaged directly by cortical infarction: (i) the right STG, (ii) the IPL and (iii) the IFG. Together with the previous observation that abnormal perfusion at the cortical level discriminates between subcortical stroke patients with versus without symptoms of spatial neglect (Weiller *et al.*, 1990, 1993; Demeurisse *et al.*, 1997; Hillis *et al.*, 2002), our results seem to indicate that spatial neglect following a right basal ganglia lesion typically is caused by the dysfunction of (part of) these specific cortical areas.

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