

The subcortical anatomy of human spatial neglect: putamen, caudate nucleus and pulvinar

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Summary

Various studies have documented that right hemispheric lesions restricted to the basal ganglia or to the thalamus may evoke spatial neglect. However, for methodological reasons, the exact anatomical correlate of spatial neglect within these two subcortical structures still remained uncertain. The present study identified these locations by comparing the anatomy of subcortical lesions to the basal ganglia or thalamus between neglect and control patients. Analysis revealed that the putamen, the pulvinar and, to a smaller degree, the caudate nucleus are

the subcortical structures typically associated with spatial neglect in humans. All these structures have direct anatomical connections to the superior temporal gyrus (STG), which recently has been identified as the neural correlate of spatial neglect in the human cortex. Therefore, it is assumed that the right putamen, caudate nucleus, pulvinar and STG form a coherent cortico-subcortical anatomical network in the genesis of spatial neglect in humans.

Keywords: attention; temporal lobe; parietal lobe; brain damage; human

Abbreviations: STG = superior temporal gyrus; TPO = temporoparieto-occipital

Introduction

Spatial neglect is a lateralized disorder of space-related behaviour in patients, characterized by failure to explore the side of space contralateral to the lesion, and to react or respond to stimuli or subjects located on this side. Full blown spatial neglect is rarely found following lesions of the left hemisphere. The underlying function thus can be regarded as being asymmetrically represented in the human brain, i.e. predominantly in the right hemisphere (Mesulam, 1999). The disorder is not only associated with cortical injury but is also observed after lesion of the right hemisphere's subcortical nuclei. Various case and group studies have documented that, independently of concomitant cortical damage, lesions restricted to the basal ganglia (Hier *et al.*, 1977; Damasio *et al.*, 1980; Heaton *et al.*, 1982; Vallar and Perani, 1986; Ferro *et al.*, 1987; Perani *et al.*, 1987; Caplan *et al.*, 1990; Donnan *et al.*, 1991; Weiller *et al.*, 1993; Leibovitch *et al.*, 1998; Kumral *et al.*, 1999; Chung *et al.*, 2000) or to the thalamus (Miller Fisher, 1961; Watson and Heilman, 1979; Cambier *et al.*, 1980; Watson *et al.*, 1981; Graff-Radford *et al.*, 1985; Hirose *et al.*, 1985; Bogousslavsky *et al.*, 1986; Motomura *et al.*, 1986; Vallar and Perani, 1986; Waxman *et al.*, 1986; Rafal and Posner, 1987; Kumral *et al.*, 1995;

Chung *et al.*, 1996; Leibovitch *et al.*, 1998; Karussis *et al.*, 2000) may induce contralesional neglect. However, the exact anatomical correlate within these two subcortical structures still remains uncertain. It is thus still unclear whether or not there is a coherent anatomical system of cortical and subcortical areas associated with spatial neglect. Some evidence suggests that infarcts in the territory of the lateral lenticulostriate arteries from the middle cerebral artery (Hier *et al.*, 1977; Damasio *et al.*, 1980; Heaton *et al.*, 1982; Caplan *et al.*, 1990; Kumral *et al.*, 1999; Chung *et al.*, 2000) may be critical for the appearance of spatial neglect with basal ganglia lesions. In the thalamus, various lesion locations have been associated with spatial neglect. Specifically, the posterolateral or the ventral lateral thalamus (Graff-Radford *et al.*, 1985; Motomura *et al.*, 1986; Kumral *et al.*, 1995; Chung *et al.*, 1996; Karussis *et al.*, 2000) as well as the medial thalamic nuclei (Watson *et al.*, 1981; Graff-Radford *et al.*, 1985; Motomura *et al.*, 1986; Kumral *et al.*, 1995) were suggested.

In order to identify the structures within the basal ganglia and the thalamus that are typically associated with human spatial neglect, it is necessary not only to describe the overlap

Table 1 Demographic and clinical data of the right brain-damaged patients with and without spatial neglect suffering from lesions of either the basal ganglia or the thalamus

		Basal ganglia		Thalamus	
		Neglect	Controls	Neglect	Controls
Number		9	9	7	7
Sex		6 F, 3 M	4 F, 5 M	3 F, 4 M	1 F, 6 M
Age (years)	Median (range)	77 (39–81)	67 (49–72)	74 (61–79)	70 (51–75)
Aetiology		9 Infarct	8 Infarct 1 Haemorrhage	7 Haemorrhage	4 Infarct 3 Haemorrhage
Time since lesion at testing (days)	Median (range)	10 (1–49)	2 (1–22)	5.5 (1–18)	3 (1–6)
Paresis of contralesional side	% present	100	78	86	100
Arm	Median (range)	2.3 (0–4.5)	4.5 (0–5)	2.5 (0–5)	3.5 (0–5)
Leg	Median (range)	3.8 (0–4.5)	5 (1.5–5)	2.5 (0–5)	4.5 (1–5)
Somatosensory deficit of contralesional side (touch)	% t.n.p.	22	0	0	0
Arm	% present	44	33	71	57
Leg	% present	44	33	86	71
Visual field defect	% present	0	0	0	0
Letter cancellation					
Left	Median (range)	2 (0–17)	29 (23–30)	0 (0–16)	29 (22–30)
Right	Median (range)	22 (6–28)	29 (25–30)	14 (9–30)	30 (27–30)
Bells test					
Left	Median (range)	1 (0–15)	14 (12–15)	0 (0–9)	15 (13–15)
Right	Median (range)	11 (7–15)	15 (13–15)	8 (2–15)	15 (13–15)
Baking tray task					
Left	Median (range)	2.5 (0–9)	8 (6–9)	5 (0–8)	8 (6–8)
Right	Median (range)	14 (7–16)	8 (7–10)	11 (8–16)	8 (8–10)
Copying (% omitted)	Median (range)	50 (13–88)	0*	25 (0–75)	0 (0–13)

F = female; M = male; t.n.p. = testing not possible. Hemiparesis: paresis was scored with the usual clinical ordinal scale, where '0' stands for no trace of movement and '5' for normal movement. *No variation in data.

of lesions in neglect patients, but also to contrast these sites directly with those of patients who also suffer from lesions restricted to the basal ganglia or to the thalamus but who do not exhibit spatial neglect. Without this comparison, observed regions of maximal overlap may reflect vulnerability of certain regions in the basal ganglia and the thalamus to injury (e.g. due to the vasculature of these regions) rather than any particular involvement with neglect. Only two of the previous studies offer a direct comparison between neglect and control patients (Motomura *et al.*, 1986; Weiller *et al.*, 1993). Unfortunately, the analysis of Weiller *et al.* (1993) confounded lesion location of patients with spatial neglect with those suffering aphasia, examining patients with both right and left hemisphere damage, while the other study (Motomura *et al.*, 1986) illustrated lesion location with two separate figures of superimposed plots (one highlighting lesion locus for the neglect patients, and the other indicating the regions impaired in the control group). However, within compact anatomical regions such as the thalamus or the basal ganglia, this procedure is not sufficient for precise localization.

The present study aimed to identify the subcortical structures critically involved in spatial neglect. In contrast to previous studies, the analysis did not merely divide the subcortical structures into only discrete anatomical or vascu-

lar sections and calculate the frequency of their involvement in the individual CT lesions of the patients with and without neglect for statistical comparison; rather, we used the entire lesioned area of each individual subject to plot the critical lesion site(s) in spatial neglect for a high resolution analysis in Talairach space (Talairach and Tournoux, 1988). The comparison of lesion location in patients with and without neglect was carried out by extending a free software package [MRIcro (Rorden and Brett, 2001)] to allow a direct subtraction of lesion overlap of one group of subjects from another group. This technique has been used previously for anatomical comparison between patient groups (e.g. Weiller *et al.*, 1990, 1993; Adolphs *et al.*, 2000). It allows us to illustrate the centre of overlap in patients with spatial neglect in direct visual contrast to those areas in the basal ganglia and the thalamus that do not induce neglect when lesioned.

Methods

Subjects and clinical investigation

We examined 49 acute stroke patients with severe spatial neglect but no visual field defects following circumscribed unilateral right hemispheric brain lesions, consecutively admitted over a 5-year period from a well-defined recruitment

area belonging to the University Hospital in Tübingen. From this group, 25 had cortical lesions without involvement of the basal ganglia or the thalamus and were thus not suitable for the current study. Their data were reported elsewhere (Karnath *et al.*, 2001). Also not included in the present analysis were eight of the 49 admitted neglect patients who had lesions involving both subcortical and cortical structures.

Sixteen patients with spatial neglect but no visual field defects showed brain lesions restricted to either the basal ganglia (nine patients) or the thalamus (seven patients). Demographic and clinical data for these patients are presented in Table 1. The neuroanatomical findings of these subjects were analysed and contrasted with a sample of 16 acute right hemisphere stroke patients consecutively admitted in the same 5-year period, who showed no neglect but also had lesions restricted to either the basal ganglia or the thalamus (Table 1) (control groups). All subjects were right-handed. They 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.

Patients were classified as having spatial neglect when they showed the typical clinical features such as (i) a spontaneous deviation of the head and eyes toward the ipsilesional side; (ii) orienting towards the ipsilesional side when addressed from the front or the left; and (iii) ignoring contralesionally located people or objects. In addition to the evaluation of these characteristic manifestations of spatial neglect in spontaneous behaviour, all patients were assessed further using the following four tests; and (iv) fulfilled the criterion in at least two of them.

The four standard tests used were as follows (i) The letter cancellation test (Weintraub and Mesulam, 1985): 60 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. Patients were asked to cancel all of the targets. The number of targets found was reported for the left and right sides of the page. Patients were classified as suffering from spatial neglect when they omitted at least five left-sided targets. (ii) The bells test (Gauthier *et al.*, 1989): this consists of seven columns each containing five targets (bells) and 40 distractors. Three of the seven columns (= 15 targets) are on the left side of a horizontally oriented 21×29.7 cm sheet of paper, one is in the middle and three are on the right (= 15 targets). Again, patients are asked to cancel all of the targets, and the number of targets found was reported. More than five left-sided target omissions was taken to indicate neglect. (iii) The baking tray task (Tham and Tegnér, 1996): patients had to place 16 identical items as evenly as possible on a blank test sheet (21×29.7 cm). The number of items distributed within each half sheet is reported, with the ideal score being 8. As suggested by the authors (Tham and Tegnér, 1996), any distribution that was more skewed than seven items in the left half and nine on the right was considered a sign of neglect. (iv) Copying task: patients were asked to copy a complex multi-object scene consisting of four figures (a fence, a car, a house and a tree), two in each

half of a horizontally oriented 21×29.7 cm sheet of paper. Omission of at least one of the left-sided features of each figure was scored as 1, and omission of each whole figure was scored as 2. One additional point was given when left-sided figures were drawn on the right side. The maximum score was 8. A score higher than 1 (i.e. >12.5% omissions) was taken to indicate neglect.

Table 1 gives an overview of these data. Visual field defects were excluded using standardized neurological examination and/or Tübingen perimetry.

Lesion analysis

Brain lesions were identified by MRI, including diffusion-weighted and T₂-weighted MRI or CT. Patients with diffuse or bilateral brain lesions or with tumours, and those in whom MRI or CT scans revealed no obvious lesion or very small lesions that were obviously lacunes, were excluded. The lesions were mapped using MRIcro software (Rorden and Brett, 2001) (www.psychology.nottingham.ac.uk/staff/cr1/micro.html). The lesions were drawn manually on slices of a template MRI scan from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view), which is based on 27 T₁-weighted MRI scans from a single subject. This template is oriented approximately to match Talairach space (Talairach and Tournoux, 1988). It is distributed with SPM99 (www.fil.ion.ucl.ac.uk/spm/spm99.html) and has become a popular template for normalization in functional imaging. Therefore, our findings have a strong degree of correspondence to the published literature from functional imaging studies.

The procedure allowed us to measure normalized lesion volume, superimpose lesions to find regions of mutual involvement and conduct subtraction analysis. Both lesion volume measurement and analysis of lesion overlap are popular techniques and have been described elsewhere (e.g. Rorden and Brett, 2001). Lesion subtraction analysis is not yet widely used (but see, for example, Weiller *et al.*, 1990, 1993; Adolphs *et al.*, 2000) and will therefore be described in greater detail. As noted earlier, lesion overlap techniques that identify the region most often damaged in a group of patients with a specific pathology do not necessarily suggest a functional role for that region. Overlap techniques do not discriminate between regions that are commonly damaged (e.g. due to the vasculature of these regions) and regions that have a role in the function being investigated (e.g. spatial neglect). This is particularly problematic when comparing lesion locations between subjects with damage restricted to only a small and compact anatomical region, such as the basal ganglia or the thalamus.

The logic of the subtraction method is straightforward. First, lesions for both groups of patients are defined on the same template image. Next, the lesions for all the subjects of the first group (e.g. neglect patients) are added together, creating a traditional overlap image showing the regions of mutual involvement. Finally, the lesions for the

control patients are subtracted from the neglect group's overlap image. This method creates an image that shows regions that are damaged commonly in patients with neglect but typically are spared in control patients (coded as positive values), regions specifically damaged in the control patients (coded as negative values) and regions that are damaged/spared in equal proportions between the two groups (values near zero). These results can be plotted graphically on the same template image; we here used progressively brighter shades of orange to highlight positive values, and progressively brighter shades of blue to illustrate negative values. Regions with a value of zero (either where there were equal numbers of patients in each group with this damage, or where none of the observed patients had damage) remain uncoloured. The software we created is freely distributed and documented (www.psychology.nottingham.ac.uk/staff/cr1/mritut.html multiroi).

Results

Basal ganglia

Figure 1A and B illustrates the superimposed lesion plots of the nine neglect patients with lesions located predominantly in the right basal ganglia, together with their nine controls. Measurements of overall lesion volume indicated that the neglect patients, on average, had more extensive lesions (2.1% of right hemisphere volume, SD 1.2) than control patients (0.6%, SD 0.6; Mann–Whitney $U = 11.0$, $P < 0.008$). One possibility is that neglect is a consequence of large lesions in the basal ganglia, regardless of the precise location (an equipotentiality model). On the other hand, it is conceivable that neglect is a consequence of damage to a specific region of the basal ganglia (a locality model). There are two ways to test these models. One test is to examine whether the severity of symptoms in our neglect group correlates with lesion volume (as used, for example, by Henik *et al.*, 1994). The equipotentiality model predicts that neglect will be most severe following large lesions. However, it should be conceded that the locality model might also predict more severe neglect following larger lesions, as the larger lesions are more likely to compromise the critical regions. We calculated the relationship between each of our four neglect tests and lesion volume using Pearson's product moment correlation. None of the tests were significant [$r = 0.049$, 0.343, 0.236, 0.089 for the copying task, letter cancellation, bells test and the baking tray task, respectively; d.f. = 7, where a one-tailed $P < 0.05$ level of significance (not corrected for multiple comparisons) is 0.582]. Thus, there was no clear evidence that lesion volume alone predicts neglect severity in these patients.

A more specific test of the locality model is that it predicts that the neglect patients should suffer damage to specific regions of the basal ganglia. To identify the structures typically involved in neglect patients, we subtracted the

superimposed lesions of the control group (Fig. 1A) from those of the neglect group (Fig. 1A). The result is illustrated in Fig. 1C. The centre of overlap was defined as those voxels in the subtracted lesion overlap that were damaged concurrently in at least five (= 56%) neglect patients (i.e. regions that were damaged in at least five more neglect patients than control patients). In Fig. 1C, this centre is outlined; Table 2 documents its boundaries in Talairach space (Talairach and Tournoux, 1988). The centre of overlap covered the putamen almost entirely. To a much smaller degree, it also involved the caput and the corpus of the caudate nucleus. The globus pallidus, the claustrum, and the anterior and posterior limbs of the internal capsule were not affected (Fig. 1C).

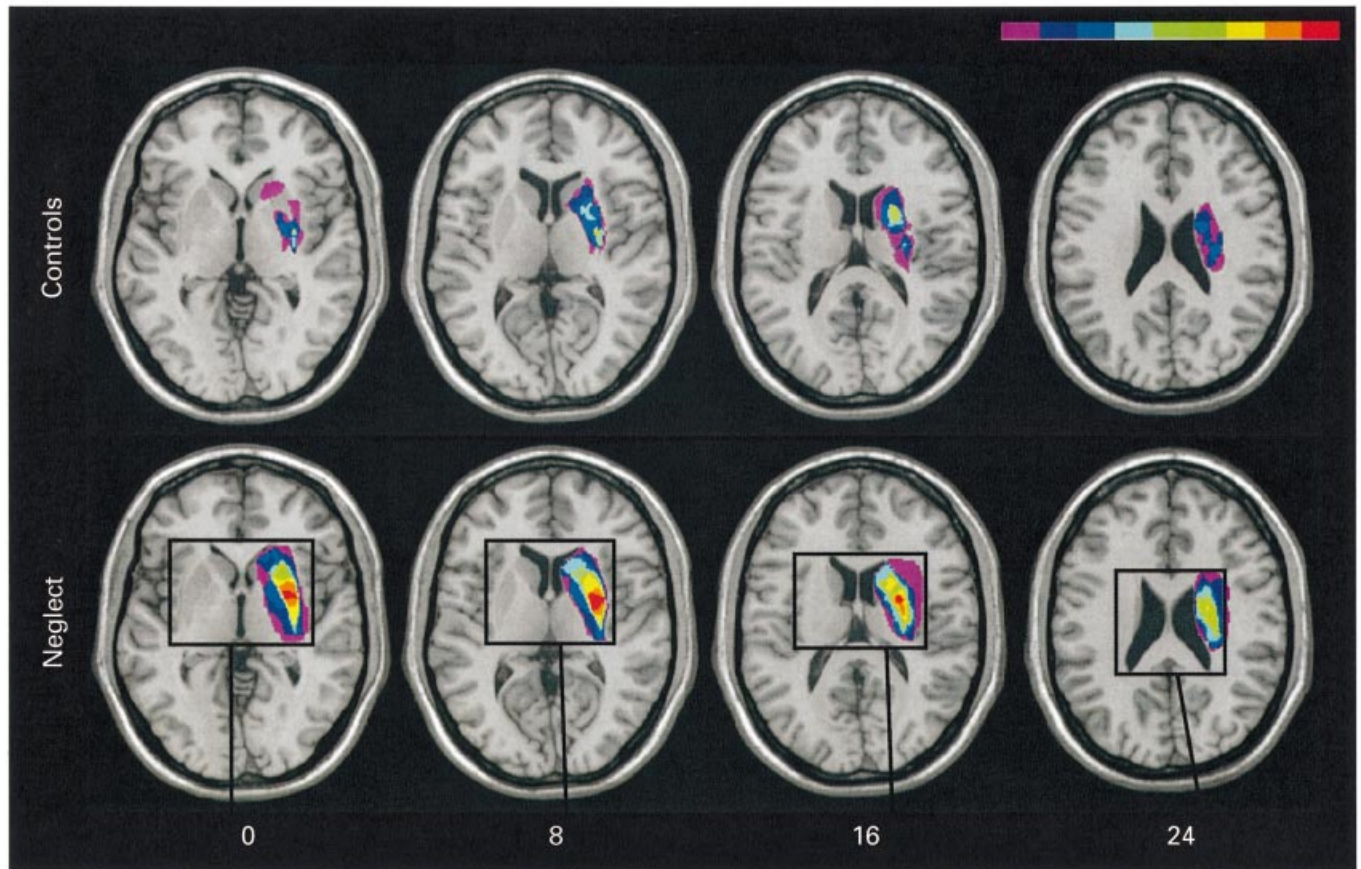
For statistical comparison of putamen and caudate nucleus involvement in the two subject groups, we defined the area of the putamen and the area of the caudate nucleus in Talairach coordinates (Talairach and Tournoux, 1988). Next, we used the MRIcro software package (Rorden and Brett, 2001) to determine the percentage of the damage to these two regions of interest for each patient. The averaged extent of region of interest involvement in the two subject groups is illustrated in Fig. 2. Between-group comparison revealed a highly significant difference for the putamen (Mann–Whitney $U = 1.0$, $P < 0.001$), showing that neglect patients had a 4.6 times greater involvement of the putamen (cf. Fig. 2). The extent of involvement of the caudate nucleus in neglect patients was much smaller (Figs 1 and 2) and the difference between neglect and control patients less obvious. The statistical comparison between both groups revealed a barely significant result ($U = 19.0$, $P = 0.045$).

Thalamus

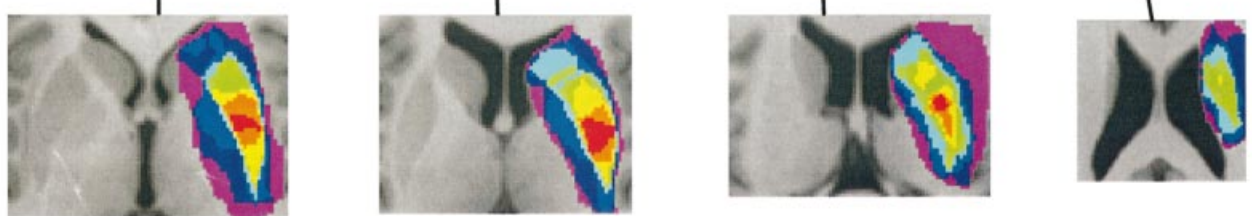
Figure 3A and B illustrates the superimposed lesion plots of the seven neglect patients with lesions located predominantly in the right thalamus, and their seven controls. Analysis of overall lesion volume indicated a non-significant trend for neglect patients to suffer from more extensive lesions (mean volume 1.6% of the right hemisphere, SD 1.0) than the control patients (0.5%, SD 0.3; Mann–Whitney $U = 9.0$, $P = 0.053$). As with the basal ganglia patients, the trend for larger lesions in patients with neglect than controls might be interpreted as support for a model of neural equipotentiality. Again, we explored whether there is a positive correlation between lesion volume and neglect as scored by our clinical neglect tests. Only one out of four tasks showed a significant correlation [$r = 0.12$, -0.05 , -0.157 , 0.775 for the copying task, letter cancellation, bells test and the baking tray task respectively; d.f. = 5, where a one-tailed $P < 0.05$ level of significance (not corrected for multiple comparisons) is 0.669].

As noted earlier, both the equipotentiality and locality models might predict neglect to be associated with larger lesions. Therefore, it is necessary to examine lesion location to test whether neglect is associated with damage to a specific region of the thalamus. As before, additional analyses were

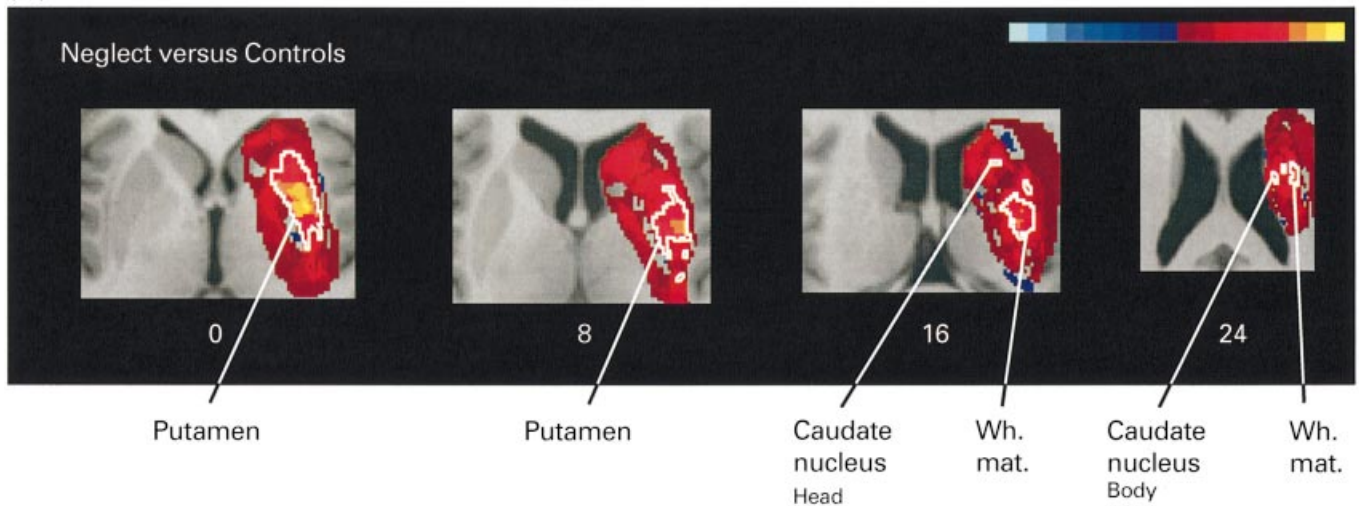
(A)



(B)



(C)



conducted to determine the specific structures that commonly were damaged in neglect patients but typically were spared in control patients. Again, the superimposed lesions of the control group (Fig. 3A) were subtracted from those of the neglect group (Fig. 3A). The result is illustrated in Fig. 3C. The centre of overlap was defined as those voxels in the subtracted template MRI that were lesioned concurrently in at least four (= 57%) neglect patients (after subtraction of controls). In Fig. 3C, this centre is encircled; Table 3 documents its boundaries in Talairach space (Talairach and Tournoux, 1988). The centre of overlap predominantly covered the pulvinar. It extended further into the ventral lateral and the lateral dorsal nuclei.

For statistical comparison of pulvinar involvement in the two subject groups, we defined the area of the pulvinar in Talairach space (Talairach and Tournoux, 1988). Figure 2 shows that the lesions in patients with spatial neglect covered a large part of the pulvinar. The extent of pulvinar involvement was 3.2 times greater in neglect patients than in controls, revealing a significant difference between the groups ($U = 5.5$, $P = 0.012$).

Discussion

The present study analysed the anatomical correlates of spatial neglect following subcortical damage of the right hemisphere. Lesion locations of patients with and without neglect were contrasted in Talairach space (Talairach and Tournoux, 1988). In the right basal ganglia, the putamen was identified as the principal site typically associated with spatial neglect. After subtraction, the centre of lesion overlap covered most of the putamen. To a much smaller degree, we also found the caudate nucleus associated with the pathological behaviour, which corresponds to earlier observations (Caplan *et al.*, 1990; Kumral *et al.*, 1999).

Within the right thalamus, the lesions predominantly affected the pulvinar. Neurophysiological studies in monkeys and functional imaging studies in humans repeatedly have supported a role for the thalamic pulvinar in attentional processes such as filtering (LaBerge and Buchsbaum, 1990) and other selective attentional processes (Chalupa, 1977; Petersen *et al.*, 1985; Corbetta *et al.*, 1991; Robinson, 1993), selective processing of salient or behaviourally important stimuli (Robinson, 1993; Morris *et al.*, 1997) and active visual scanning (Ungerleider and Cristensen, 1979). Moreover, sectorial inactivation within the rhesus monkeys'

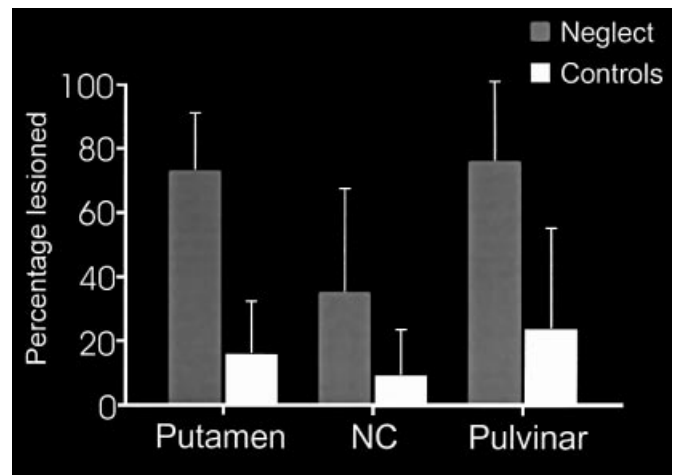


Fig. 2 Average extent of lesioned area within the putamen, the caudate nucleus (NC) and the thalamic pulvinar in the patients with and without spatial neglect.

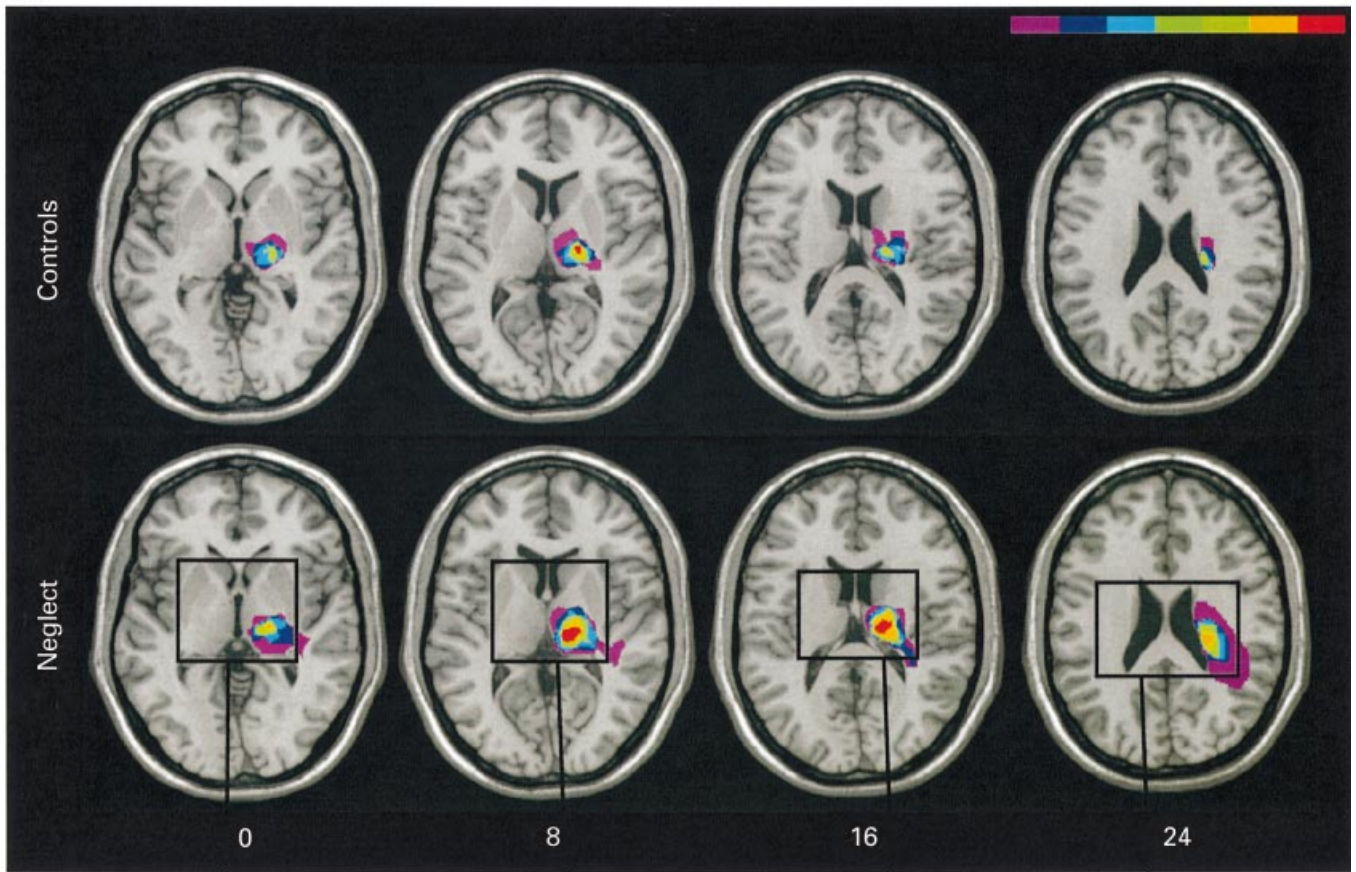
Table 2 Basal ganglia: Talairach coordinates (mm) of neglect patients' overlap area after subtraction of lesion locations in controls

Borders	x	y	Anatomical structure
$z = 0$			
Anterior	22	15	Putamen
Medial	22	-1	Putamen
Lateral	28	2	Putamen
Posterior	27	-12	Putamen
$z = 8$			
Anterior	24	6	Putamen
Medial	22	-6	Putamen
Lateral	28	-3	Putamen
Posterior	24	-12	Putamen
$z = 16$			
Anterior	22	-5	White matter
Medial	21	-9	White matter
Lateral	26	-11	White matter
Posterior	24	-16	White matter
	16	6	Caudate nucleus
$z = 24$			
Anterior	24	-9	White matter
Medial	24	-12	White matter
Lateral	25	-12	White matter
Posterior	25	-15	White matter
	17	-13	Caudate nucleus

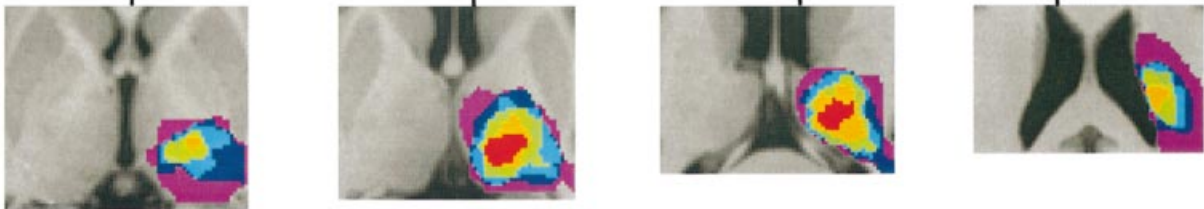
For each transverse section, the borders of the overlap area are given.

Fig. 1 Basal ganglia: lesion analysis of the patients with spatial neglect following basal ganglia damage and their controls. (A) Overlay plots. The Talairach z -coordinates (Talairach and Tournoux, 1988) of each transverse section are given. The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet ($n = 1$) to red ($n = 9$). (B) Enlarged view of the lesion overlap in the neglect patients. (C) Overlay plots of the subtracted superimposed lesions (neglect group minus control group). The centre of overlap is outlined using a white contour. The number of overlapping lesions of the neglect patients after subtraction of controls is illustrated by different colours coding increasing frequencies from dark red (difference +1) to yellow (difference +9). [For example, bright yellow indicates a region that is implicated in all neglect patients (difference +9), but none of the control patients. On the other hand, the bright orange (difference +8) represents both regions damaged in none of the controls and eight of the neglect patients (+8 - 0 = +8), or damaged in all nine neglect patients as well as one control patient (+9 - 1 = +8).] The different colours from dark blue (difference -1) to light blue (difference -9) indicate regions damaged more frequently in control patients than in neglect patients. Wh. mat. = white matter.

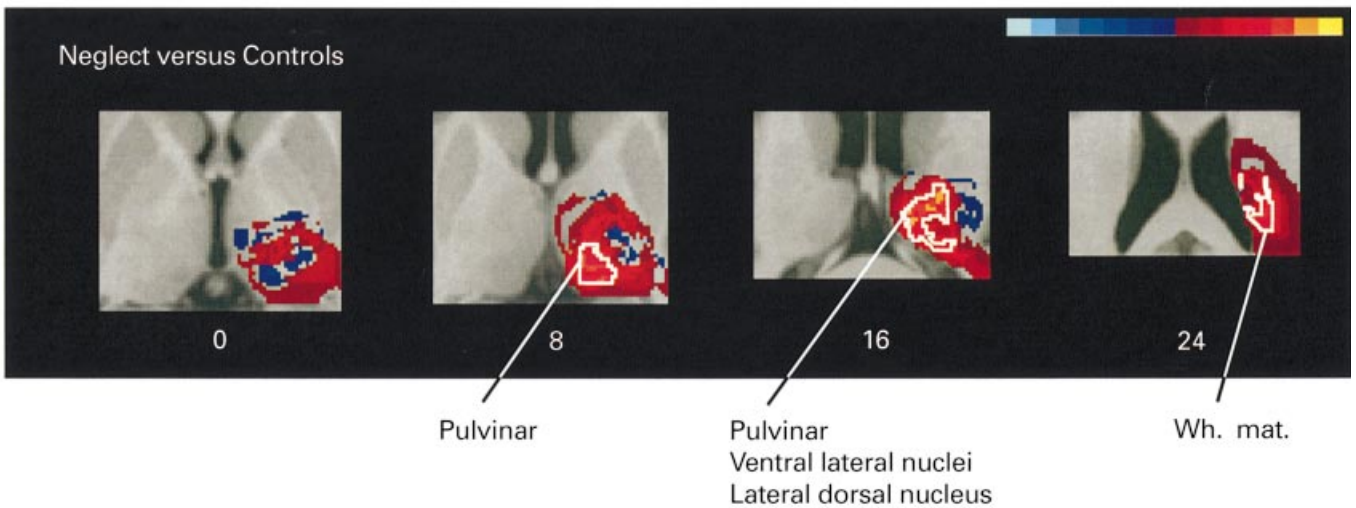
(A)



(B)



(C)



pulvinar using microinjections of muscimol (GABA agonist) revealed a slowing of the shift of attention in the direction contralateral to the hemisphere in which the pulvinar was injected (Petersen *et al.*, 1987). The present results confirm and extend these findings by demonstrating that the pulvinar is involved in processes of space exploration and the orientation of attention in space. They show that the pulvinar is the principal site in the right human thalamus associated with spatial neglect, i.e. with the failure to orient to and actively explore the side of space contralateral to the lesion.

In summary, we have found that the putamen, the pulvinar and, to a smaller degree, the caudate nucleus are the subcortical regions responsible for spatial neglect. It is therefore of considerable interest to examine the cortical connections of these areas in order to increase our understanding of the cortical anatomy of spatial awareness. Cortical neglect traditionally has been associated with lesions to the inferior parietal lobule and the temporoparieto-occipital (TPO) junction (Heilman *et al.*, 1983; Vallar and Perani, 1986). However, these studies have confounded spatial neglect with visual field defects (e.g. 87% of the neglect patients reported by Vallar and Perani also suffered from hemianopia). Lesion localization thus was biased towards posterior brain regions that induce these visual field defects. Karnath *et al.* (2001) illustrated that in the branch territory of the middle cerebral artery, lesions inducing only hemianopia, but no neglect, centre on the inferior parietal lobule and the TPO junction and subcortically extend to the posterior horn of the lateral ventricle, thereby affecting the optic radiation. In a study that specifically studied patients with focal right hemisphere cortical lesions who exhibited spatial neglect but had intact visual fields, Karnath and colleagues (Karnath *et al.*, 2001) have found that lesion location for neglect in humans centres on the superior temporal gyrus (STG) rather than on the inferior parietal lobule or the TPO junction. If the putamen, the caudate nucleus and the pulvinar have direct connections with the STG, this would provide further support for the observation that it is the STG that seems to play the crucial role in spatial neglect.

From anatomical studies in the monkey, we know that the association areas of the STG have direct connections with the putamen and the caudate nucleus (Yeterian and Pandya, 1998). The rostral and middle parts of the STG are connected to the rostroventral and caudoventral portions of the putamen, while the caudal portion of the STG projects more dorsally in the caudal part of the putamen. In addition, the rostral and

middle parts of the STG are connected with ventral portions of the head, body and tail of the caudate nucleus, while the caudal portion of the STG projects more dorsally within its head and body (Yeterian and Pandya, 1998). Thus, the two structures identified here as relevant within the basal ganglia for spatial neglect show dense anatomical connectivity with the entire area of lesion overlap found in patients with spatial neglect after cortical damage (Karnath *et al.*, 2001), namely with the STG.

What about the pulvinar, the region within the thalamus associated with spatial neglect? The thalamic pulvinar is subdivided into medial, lateral, inferior and anterior nuclei (Jones, 1985). The inferior and lateral nuclei receive projections from the superior colliculus, pretectum, as well as the striate and extrastriate visual cortex. In each of these two nuclei, a complete map of the contralateral visual field has been identified (Gattass *et al.*, 1978; Bender, 1981). The other parts of the pulvinar complex are less obviously visual in terms of their connection. The anterior pulvinar nucleus is connected to parts of areas 5 and 7 lying adjacent to the primary sensory cortex. Most interestingly with respect to the cortical correlate of spatial neglect (Karnath *et al.*, 2001), the

Table 3 *Thalamus: Talairach coordinates (mm) of neglect patients' overlap area after subtraction of lesion locations in controls*

Borders	x	y	Anatomical structure
<i>z</i> = 8			
Anterior	10	-23	Thalamus, pulvinar
Medial	7	-27	Thalamus, pulvinar
Lateral	14	-27	Thalamus, pulvinar
Posterior	11	-31	Thalamus, pulvinar
<i>z</i> = 16			
Anterior	17	-11	Thalamus, VL*
Medial	8	-21	Thalamus, LD†
Lateral	18	-13	Thalamus, VL*
Posterior	14	-26	Thalamus, pulvinar
<i>z</i> = 24			
Anterior	26	-23	White matter
Medial	21	-31	White matter
Lateral	27	-31	White matter
Posterior	26	-36	White matter

For each transverse section, the borders of the overlap area are given. VL = ventral lateral nuclei; LD = lateral dorsal nucleus. In the human nomenclature of Hassler (Schaltenbrand and Wahren, 1977): *nuclei ventroorales anterior et posterior (V.o.a / V.o.p), *nuclei ventrointermedii (V.im), *nuclei dorsointermedii (D.im), †nucleus dorsalis superficialis (D.sf).

Fig. 3 Thalamus: lesion analysis of the patients with spatial neglect following thalamic damage and their controls. (A) Overlay plots. The Talairach *z*-coordinates (Talairach and Tournoux, 1988) of each transverse section are given. The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet (*n* = 1) to red (*n* = 7). (B) Enlarged view of the lesion overlap in the neglect patients. (C) Overlay plots of the subtracted superimposed lesions (neglect group minus control group). The centre of overlap is encircled using a white contour. As in Fig. 1, increasingly bright orange, from dark red (difference +1) to yellow (difference +7), is used to represent areas damaged more commonly in neglect patients than in controls. Likewise, increasingly bright blue regions, from dark blue (difference -1) to light blue (difference -7), illustrate regions that are damaged more frequently in controls than in neglect patients. Wh. mat. = white matter.

thalamocortical axons arising in the medial pulvinar nucleus of the monkey project to the entire STG (Burton and Jones, 1976; Eidelberg and Galaburda, 1982; Jones, 1985). The cortical projections of the medial pulvinar stretch from the temporal pole up to the exposed surface of the STG through the anterior bank of the superior temporal sulcus. Thus these connections encompass the entire area of lesion overlap found in patients with spatial neglect after cortical damage (Karnath *et al.*, 2001).

Lesion overlap in the neglect patients with thalamic damage extended into two further thalamic nuclei, the lateral dorsal and ventral lateral nuclei. While the lateral dorsal nucleus is connected reciprocally with the limbic cortex of the cingulate gyrus, the retrosplenial area and the pre- and parasubiculum (Kaitz and Robertson, 1981; Robertson and Kaitz, 1981), the ventral lateral nuclei are part of motor-related pathways (Jones, 1985). The ventral lateral nuclei receive input from the cerebellum and globus pallidus and the efferent fibres project to the primary and premotor cortex, Brodmann areas 4 and 6, probably including the supplementary motor area. Whilst the ventral lateral nuclei seem to be related primarily to motor behaviour and not to attentional processes, the lateral dorsal nucleus, with its connectivity to the cingulate cortex, may be relevant to spatial neglect. However, the clinical incidence of spatial neglect following a lesion restricted to the cingulate cortex is extremely low. To our knowledge, full blown spatial neglect has been observed only twice after such lesions in the right hemisphere (Heilman and Valenstein, 1972; Klatka *et al.*, 1998). Moreover, these lesions did not affect the cingulate cortex exclusively. Rather, the medial, parafalcine portions of the frontal and/or parietal lobes were also damaged. Thus, it seems as if the lateral dorsal nucleus and its projection to the cingulate cortex only play a minor role in the genesis of spatial neglect.

On the basis of these anatomical connections, it can be assumed that the right putamen, caudate nucleus, pulvinar and STG form a coherent corticosubcortical network representing spatial awareness in humans. Damage of any of these interconnected structures evokes the same pathological behaviour, namely spatial neglect. Also, it is possible that subcortical damage of the right putamen, caudate nucleus or pulvinar affects the ipsilesional STG by functional and/or metabolic abnormalities via diaschisis (Feeney and Baron, 1986). In fact, metabolic studies of neglect patients with subcortical infarcts in the basal ganglia (Weiller *et al.*, 1990, 1993; Demeurisse *et al.*, 1997) or in the thalamus (Baron *et al.*, 1986; Perani *et al.*, 1987; Demeurisse *et al.*, 1997) found such a decrease in the patients' ipsilesional cortical cerebral blood flow, and functional recovery seems to correlate with an improvement of the cortical metabolism (Vallar *et al.*, 1988; Pantano *et al.*, 1992; Perani *et al.*, 1993; Pizzamiglio *et al.*, 1998).

In conclusion, the present study identified the right putamen and pulvinar as the subcortical structures whose

damage predominantly leads to spatial neglect in humans. To a smaller degree, the caudate nucleus as well as the thalamic lateral dorsal and ventral lateral nuclei were also identified in the centre of lesion overlap. Since the putamen, caudate nucleus and pulvinar have direct anatomical connections with the STG, it is assumed that these structures form a coherent corticosubcortical anatomical network in the genesis of spatial neglect in humans.

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