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BRAIN NETWORKS OF SPATIAL AWARENESS: EVIDENCE FROM DIFFUSION TENSOR IMAGING TRACTOGRAPHY

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Summary

Left unilateral neglect, a dramatic condition which impairs awareness of left-sided events, has been classically reported after right hemisphere cortical lesions involving the inferior parietal region. More recently, the involvement of long-range white matter tracts has been highlighted, consistent with the idea that awareness of events occurring in space depends on the coordinated activity of anatomically distributed brain regions. Damage to the superior longitudinal fasciculus (SLF), linking parietal to frontal cortical regions, or to the inferior longitudinal fasciculus (ILF), connecting occipital and temporal lobes, have been described in neglect patients. In this study four right-handed patients with right-hemisphere strokes were submitted to a high-definition anatomical MRI with diffusion tensor imaging (DTI) sequences and to a paper-and-pencil neglect battery. We used DTI tractography to visualize the SLF, the ILF and the inferior fronto-occipital fasciculus (IFOF), a pathway running in the depth of the temporal lobe, not hitherto associated with neglect. Two patients with cortical involvement of the inferior parietal and superior temporal regions, but intact and symmetrical fasciculi, showed no signs of neglect. The other two patients with signs of left neglect had superficial damage to the inferior parietal cortex and white matter damage involving the IFOF. These findings suggest that superficial damage to the inferior parietal cortex per se may not be sufficient to produce visual neglect. In some cases, a lesion to the direct connections between ventral occipital and frontal regions (i.e. IFOF) may contribute to the manifestation of neglect by impairing the top-down modulation of visual areas from frontal cortex.

Introduction

Left visual neglect is a frequent consequence of right hemisphere lesions, entailing a defective awareness for left-sided events. Lesions determining neglect often overlap on the temporo-parietal junction (TPJ)[1, 2]. Conflicting evidence, however, indicates lesions of more rostral parts of superior temporal gyrus (STG)[3, 4]. Signs of neglect can also occur after lesions of the ventrolateral prefrontal cortex (VLPFC),[5] of the medial temporal lobe,[2] of the occipital lobe and the corpus callosum,[6] or after damage to two major rostro-caudal brain pathways, the superior[7, 8] and inferior[9] longitudinal fasciculi. Thus, rather than damage to single cortical modules, dysfunction of large cortical networks[10, 11] can be the crucial antecedent of neglect[7, 8, 12-14].

Diffusion tensor imaging (DTI) tractography can be used to track the long-range white matter pathways[15] and then explore, in a standardized brain space, their relationships with the lesions found in stroke patients with standard, anatomical MRI. A recent meta-analysis[13] of previous lesion overlapping studies demonstrated that the subcortical lesions of neglect patients invariably overlapped at or near the SLF. Disconnection between cortical modules might thus be a general mechanism of neglect[12]. This possibility is also consistent with the results of monkey studies,[16, 17] rodent studies[18] and of computer simulations of attention[19]. Here we describe four patients with strokes in the right hemisphere, two of whom showed signs of extrapersonal neglect on paper-and-pencil tests. We used DTI tractography to directly visualize the SLF, the ILF and the inferior fronto-occipital fasciculus (IFOF), a pathway running in the depth of the temporal lobe, not hitherto associated with neglect.

Methods

Four right-handed patients with right hemispheric vascular stroke gave written informed consent to participate to this study, which was approved by the ethics committee of the Hôtel-Dieu Hospital in Paris, France. Patients performed a paper-and-pencil neglect battery including tests of line

bisection, target cancellation, identification of overlapping figures and the copy of a landscape drawing (See Table 1 and the supplementary material for demographic and clinical data). MRI data were acquired using echo-planar imaging at 1.5T and diffusion tensor imaging (DTI) was acquired using 36 independent directions (full details of the MRI and DTI acquisition and processing are available in the supplementary material). Fibre tracking of the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) was performed with Brainvisa 3.0.2 (http://brainvisa.info/), using a two-regions of interest (ROIs) approach[20]. The reconstructed tracts were displayed in 3D and the number of streamlines (a surrogate marker of tract volume) was counted for each fasciculus in both hemispheres (see Supplementary Material).

Table 1: Demographical and clinical data, with lesion location on structural MRI (see Supplementary Fig. 1)

Case	Lesion location	Clinical diagnosis of neglect	Visual Field	Gender / age / education (years of schooling)	Onset of illness (days)	Line bisection (% deviation)	Line cancellation (max 30 / 30)	Bells cancellation (max 15 / 15)	Letter cancellation (max 30 / 30)	Overlapping figures (max 10 / 10)	Landscape drawing (max 6)
1	pI, STG, IPL, pMTOG	NO	Normal	F / 45 / 14	9	-3.10	30 / 30	15 / 15	29 / 30	10 / 10	6
2	pI, TP, STG, MTG, ITG	NO	Normal	M / 60 / 14	5	+4.80	30 / 30	15 / 15	28 / 29	10 / 10	6
3	Subinsular and temporal stem WM, BG, CR, IPL	YES	LE	F / 59 / 10	9	+15.70*	29 / 30	0 / 6*	0 / 13*	6 / 10*	4.5*
4	IPL, SPL, precuneus, cuneus, MTOG, pITG	YES	LH	F / 80 / 17	729	+1.00	30 / 30	1 / 15*	9 / 28*	9 / 10*	3.5*

pI, posterior part of the insula; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule; pMTOG, posterior part of the middle temporo-occipital gyrus; TP, temporal pole; WM, white matter; BG, basal ganglia; CR, corona radiata; LE, left extinction; LH, left hemianopia. * Pathological score[20, 21]. For the line bisection test, the cumulated percentage of deviation from the true centre of all the lines was calculated, with rightward deviations carrying a positive sign and leftward deviations having a negative sign. For the cancellation tests and the overlapping figures test, the number of items cancelled (or identified) on each half of the page or of the central figure is reported. For the landscape copy, 2 points were assigned to the complete copy of the house and 1 point to the complete copy of each tree, 0.5 point were given to items whose only right half was copied, and 0 points to items completely omitted.

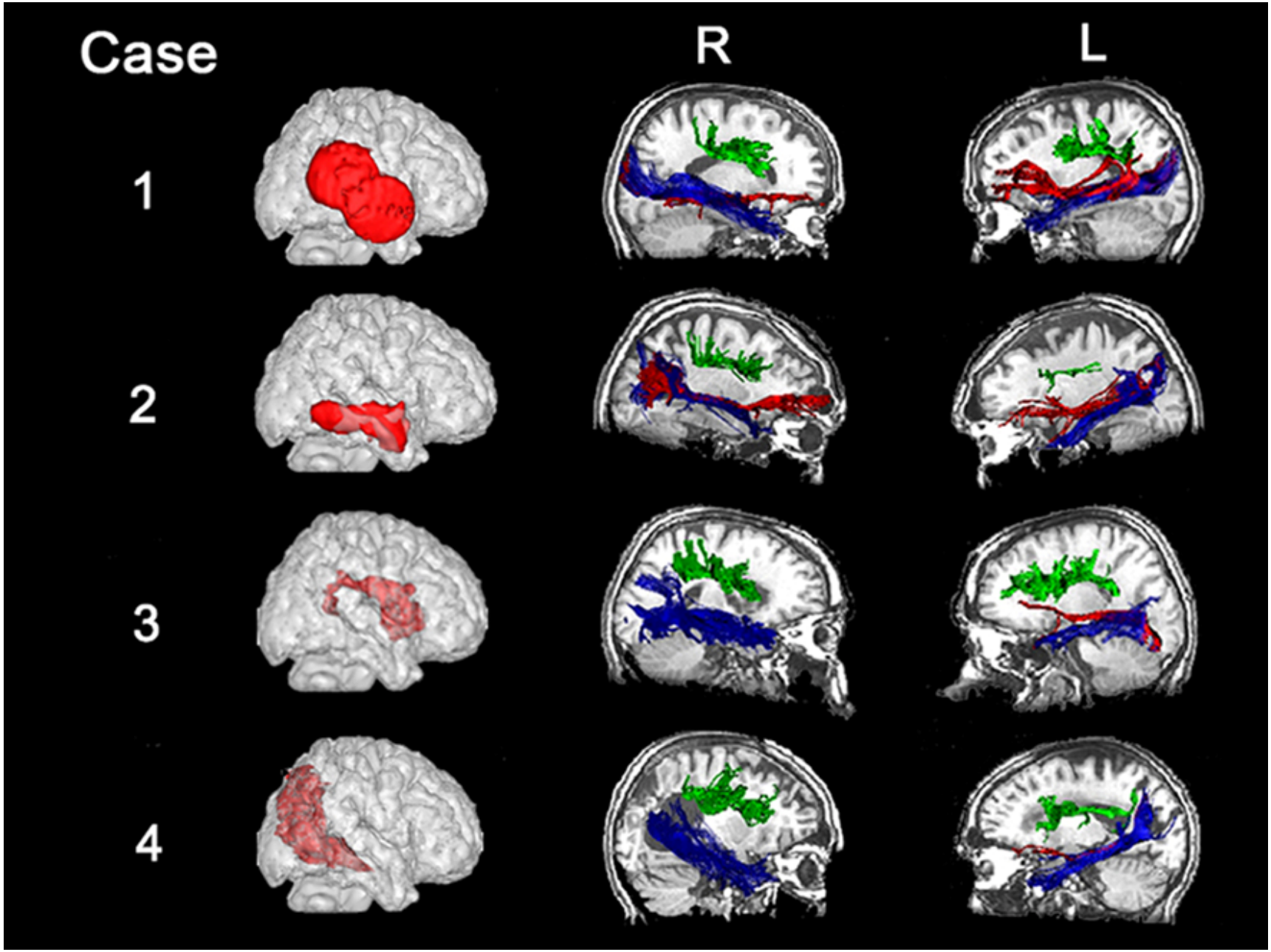
Case
R
L
1
2
3
4

Figure 1: Three-dimensional anatomical reconstruction of the patients' lesions and lateral views (right hemisphere, R; left hemisphere, L) of the DTI tractography of the SLF (in green), the ILF (in blue) and the IFOF (in red) for the four patients studied. For each hemisphere, the three fasciculi are displayed on a T1 sagittal native MRI slice in the anterior/posterior commissure referential.

Results

Cases 1 and 2 demonstrated no signs of neglect on paper-and-pencil tests; cases 3 and 4 had signs of left neglect in more than three tests of the neglect battery (Table 1). Fig. 1 displays three-dimensional reconstructions of the lesions and DTI tractography (see also the supplementary material).

Case 1 displayed no signs of extinction or neglect on neuropsychological testing nine days after the onset of an ischemic stroke affecting both the inferior parietal and the superior temporal cortices, both of which has been considered as the crucial lesional correlate of neglect[1, 4]. The tractography reconstruction visualized bilaterally intact SLF, IFOF and ILF.

Similarly, case 2 had no signs of extinction or neglect when assessed five days after clinical onset. The lesion involved the posterior part of the insula, the whole temporal pole and the superior, middle and inferior temporal gyri, including the temporo-parietal junction. Subcortical white matter was also affected, but long-range association tracts (SLF, IFOF and ILF) were intact.

Case 3 had left visual and tactile extinction and signs of severe left neglect with anosognosia. The lesion involved the subinsular and temporal stem white matter, the body of the caudate nucleus, the lenticular nucleus, the middle part of the corona radiata and the inferior parietal lobe with the underlying white matter. The tractography reconstruction showed intact ILF and SLF in both hemispheres, and complete absence of the right IFOF. At follow-up testing 34 and 41 days after clinical onset, case 3 still showed signs of left neglect (see Supplementary Material).

Case 4 had a right haemorrhagic occipital-parietal stroke. Two years after onset, she still had left hemiparesis and signs of left neglect. The lesion involved the inferior and superior parietal lobe with underlying white matter, the cuneus and precuneus, the middle temporo-occipital gyrus and the posterior part of the inferior temporal gyrus. The tractography reconstruction showed intact ILF and SLF and complete absence of the right IFOF.

Neither patient 1 nor 2 presented language deficits after stroke, which renders unlikely the

possibility of them having an unusual pattern of hemispheric lateralization.

The 2-ROIs approach to tractography dissections allows dissecting long-range pathways, but it may underestimate the involvement of more superficial (U-shaped) fronto-parietal connections. Hence, we have overlapped the lesions of the four patients to probabilistic maps of fronto-parietal connections as derived from a normative dataset (see Supplementary Fig. 2). This analysis showed that in all four subjects the lesions extended into superficial fronto-parietal connections, sparing deep long range SLF fibres.

Discussion

We used DTI-tractography to show direct evidence of disconnection of major rostro-caudal white matter pathways in neglect patients with vascular lesions. Previous studies demonstrating white-matter disconnection in neglect patients had relied on anatomical[7, 9, 22] or functional[14] MRI, and inferred the localization of tract lesion either from general anatomical knowledge,[7] or from DTI in normal subjects[9]. Compared to previous attempts, the use of DTI tractography allowed us to identify more precisely the white matter pathways that were damaged in neglect patients.

The present results suggest that (1) complete damage of the IFOF can be associated with chronic visual neglect, and (2) cortical lesions sparing the SLF and IFOF, but damaging at least part of IPL and STG, two areas previously indicated as the critical cortical loci for spatial awareness,[1, 4, 23] do not necessarily cause chronic visual neglect.

The limited number of subjects in this study do not allow us to generalise from these preliminary findings to the all neglect patients; nevertheless they do suggest that the neuroanatomical correlates of neglect may be more complex than previously thought and brings up important hypotheses on the role of direct connections between occipital and frontal lobes in spatial processing.

The involvement of the IFOF in left neglect has not been previously described. The IFOF connects the VLPFC and medial orbitofrontal cortex to the occipital lobe[20] and represents the only direct connection between occipital and frontal lobes in humans[15]. The inferior-lateral portion of the

frontal lobe, a cortical end-station of the IFOF, has been frequently associated with frontal neglect.[24] Lesions to the occipital origin of the IFOF have also described in left neglect[24]. Finally, as the central part of the IFOF runs in the stem of the temporal lobe, it is possible to hypothesise an occipito-frontal disconnecting mechanism in those neglect patients with large lesions of the temporal lobe[24]. It remains to be seen whether a lesion of the IFOF per se is sufficient to cause neglect, without involvement of other cortical and subcortical regions. In our patients the inferior parietal cortex and the underlying U-shaped fibres were affected, which is in keeping with previous evidence from monkey studies[16] and human patients[7, 8, 13]. However, the extension into the deep white matter of parietal lobes is a factor that has not been considered before and future studies in larger series should clarify the relationship between clinical manifestations of neglect and extension of white matter lesions to fronto-parietal connections.

Interestingly, we observed that the two patients with IFOF lesion show little asymmetry of performance on the line cancellation test (i.e. a test without distracters), whereas they omitted most contralateral targets on the bells and letter cancellation tests. In the latter tests a target/distracter discrimination is required, an additional factor that neglect patients with predominantly frontal lesion seem to find particularly difficult[5]. IFOF disconnection may deafferent the ventral frontal cortex from more posterior sources of visual input, related, for example, to object identification. In the monkey, neuron populations in the lateral prefrontal cortex respond both to the location and to the identity of previously presented visual objects, thus allowing the integration of "what" and "where" information[25]. Regions in the human VLPFC, which constitute a projection site for the IFOF, show lateral selectivity in the short-time retention of spatial information[26] and may be important to resolve perceptual ambiguity[27]. Damage to these regions in the right hemisphere may bias towards the right the mental reconstruction of a number line[28]. Furthermore, the right VLPFC is a cortical endpoint of the ventral spatial attentional network, which is important for the response to previously unattended targets, and whose dysfunction leads to neglect behavior[14]. The right

VLPFC may represent a convergence zone of three streams of visual processing: (1) the occipito-temporal stream, dedicated to object processing,[29, 30] through the IFOF and the uncinate fasciculus,[31] (2) the ventral parieto-frontal attentional network,[14] presumably connected by the human homologue of the third branch of the SLF (described in the monkey by Schmahmann and Pandya[32]) and (3) the dorsal parieto-frontal attentional network,[14] linked by the human homologue of the second branch of the SLF[8, 32] .

In conclusion these preliminary findings suggest that neglect is a syndrome with a heterogeneous clinical presentation and complex anatomical correlates, where damage to fronto-parietal and possibly occipito-frontal connections may impair at different levels visuo-spatial processing.

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Supplementary Material

Neglect battery

Patients underwent a paper-and-pencil neglect battery [1] including a line bisection test consisting in eight lines horizontally disposed in a vertical A4 sheet in a fixed random order (three 60 mm samples, three 100 mm samples and two 180 mm samples)[2]; three cancellation tests in which patients were asked to cancel stimuli of various sort: (1) lines[3], (2) As among other letters[4], (3) silhouettes of bells among other objects[5]; an overlapping figures task[6], in which patients where requested to identify five patterns of overlapping linear drawings of common objects (one central and a pair of objects over each of its sides); a copy of a linear drawing representing a central house and four trees (a pair of trees over each of its side) presented on a horizontal A4 sheet[19].

MRI acquisition

MRI data were acquired using echo-planar imaging at 1.5T (General Electric) with a standard head coil for signal reception. DTI axial slices were obtained using the following parameters: repetition time, 6575ms; echo time, 74.3ms; flip angle, 90°; matrix, 128 x 128 ; slice thickness, 4mm with no gap; FOV, 28 cm; acquisition time, 250s . One average was used with signal averaging in the scanner buffer. Diffusion weighting was performed along 36 independent directions, with a b-value of 700s/mm2. High-resolution 3-D anatomical images were used for display and anatomical localization (114 axial contiguous inversion recovery three dimensional fast SPGR images, 1.2mm thick; inversion time, 450ms; flip angle, 15°; matrix, 256 x 256; FOV, 28cm; acquisition time, 370s).

Diffusion Tensor Data Analysis

Data were analysed on an independent workstation (Linux PC, kubuntu 6.06 LTS). Raw diffusion-weighted data were corrected for geometric distortion secondary to eddy currents using a registration

technique based upon the geometric model of distortions[7]. Brainvisa 3.0.2 (http://brainvisa.info/) software was used to calculate diffusion tensors and anisotropy data, define the ROIs and perform fibre tracking.

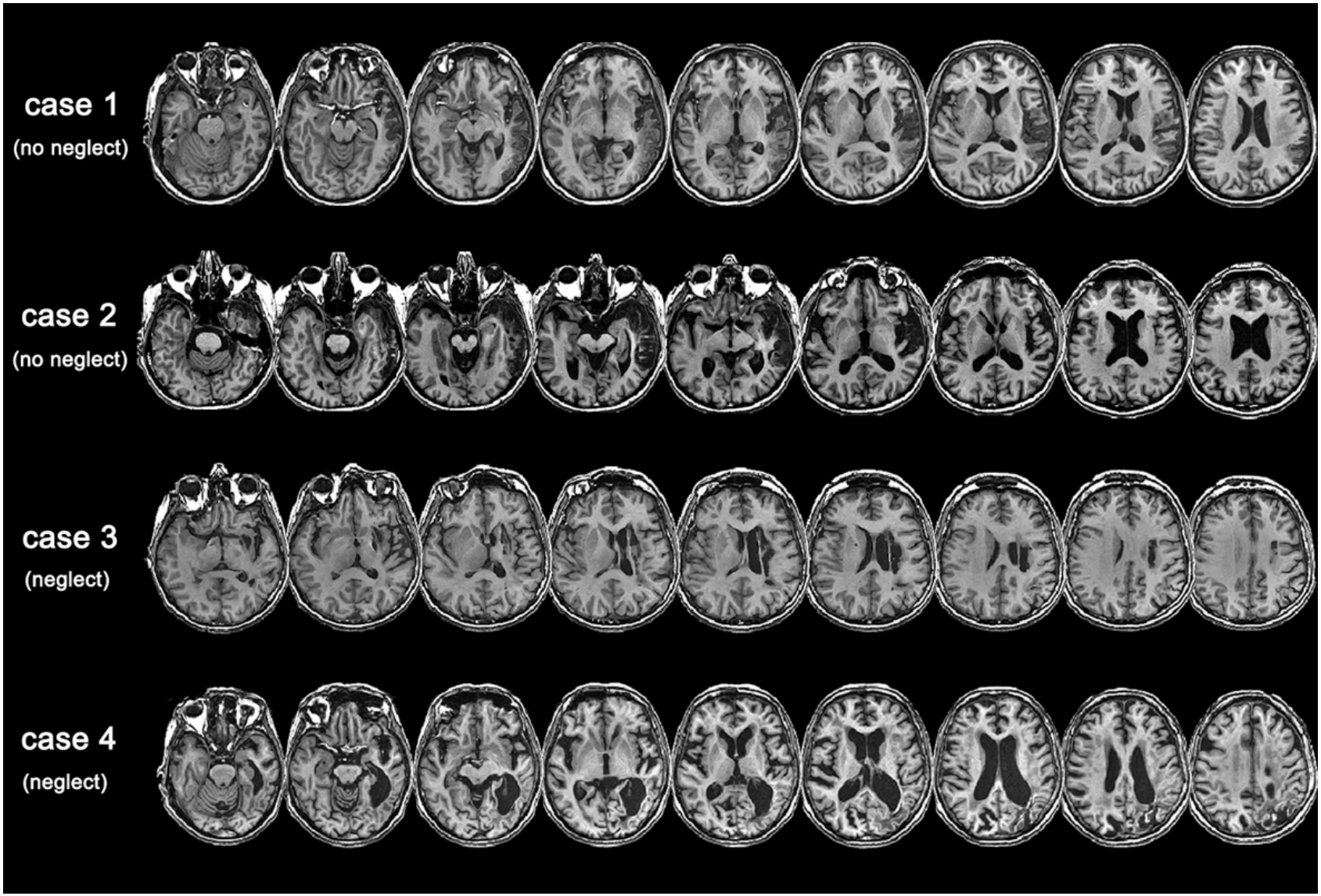
Tractography

Fibre tracking of the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) was performed using previously described ROIs[8]. A "two regions of interest" approach was used for each fasciculus tracking. The procedure[9] consisted in defining a second ROI, at a distance from the first ROI, such that it contained at least a section of the desired fasciculus but did not contain any fibres of the undesired fasciculus that passed through the first ROI. Fibre tracking was performed using a Diffusion Tensor model with a likelihood algorithm. A number of 5 points was put in each voxel of the ROIs used to track each fasciculus. At each tracking step, the algorithm moved the main tensor direction by 0.546875mm (default parameter in BrainVisa). Pathways were traced out until the fractional anisotropy of the tensor fell below an arbitrary threshold of 0.20.
For the SLF, a single ROI was used to visualise the entire arcuate fasciculus, then a two-ROIs approach was used to visualise subcomponents of the SLF[10]. For the two-ROI approach, the first ROI was placed in the white matter underlying Broca territory and the second ROI was drawn caudally including the white matter under the Geschwind and the Wernicke territory[10]. For the ILF, the first ROI was drawn in the occipital white matter and the second ROI was placed in the white matter underlying the rostral temporal regions[11]. For the IFOF, the first ROI was placed in the occipital white matter and the second ROI was drawn rostrally in the white matter of the anterior floor of the external capsule[8].
DTI and high-resolution 3-D anatomical images were registered using Brainvisa 3.0.2. The derived tracts were displayed using Anatomist 3.0.2 (http://brainvisa.info/) and indirect measurements of tract volumes were obtained by counting the number of streamlines for each tract in both hemispheres.

To explore more in detail in the present patients the possible involvement of the SLF[12-14], we also projected their lesions to the normalized white matter percentage maps of the SLF (ranging from 0 to 50%) based on DTI tractography of 16 normal subjects[15].

Case reports and supplementary results

Case 1 showed left motor deficit, left somatosensory extinction and dysarthria as a consequence of an ischemic stroke in the territory of the right middle cerebral artery, affecting both the inferior parietal and the superior temporal cortices (see Table 1 and Supplementary Figure 1). Despite the localization of the cortical lesion, nine days after clinical onset case 1 displayed no signs of extinction or neglect on neuropsychological testing.



Supplementary Figure 1. MRI axial slices of the lesions in the right hemisphere for the four patients (neurological convention: left hemisphere is on the left side

Case 2 was admitted to hospital with dysarthria, left upper limb motor deficit, and extinction for left visual and tactile stimuli as a consequence of an ischemic stroke in the territory of the right middle cerebral artery affecting the temporal lobe (see Table 1 and Supplementary Figure 1). Five days later, a mild motor deficit persisted. Orientation in time and space was normal and there were no more signs of visual field deficit, sensory extinction or left neglect.

Case 3 was admitted to hospital with left hemiparesis predominant in the arm, left Babinski sign, rightward deviation of the head, signs of left neglect and anosognosia as a consequence of an ischemic stroke in the territory of the right middle cerebral artery (see Table 1 and Supplementary Figure 1). Nine days later, case 3 still had left visual and tactile extinction, signs of severe left neglect and anosognosia. When describing from memory of a map of France,[16] she produced 8 items on the left side and 7 items on the right side, thus showing no evidence of imaginal neglect[17]. At follow-up testing 34 days after clinical onset, case 3 still showed signs of left neglect. She found 2 targets on the left and 11 on the right on the bells cancellation test[5], 16 targets on the left and 29 on the right on the letter cancellation test[18], deviated rightward by 15% on line bisection[2], omitted the leftmost tree and the left extremity of the house on the landscape drawing copy[19], made no omission on the line cancellation[3] and on the overlapping figure tests[6], and showed left visual and tactile extinction. On further testing one week after, she performed in a similar manner. She found 2 targets on the left and 15 on the right on the bells cancellation test, 15 targets on the left and 25 on the right on the letter cancellation test, deviated rightward by 20% on line bisection, had identical performance on the landscape drawing, made no omission on the line cancellation and on the overlapping figure tests, and had left visual and tactile extinction.

Case 4 had a right hemorrhagic occipital-parietal stroke, which resulted in left homonymous hemianopia

(see Table 1 and Supplementary Figure 1). A small medial occipito-parietal lesion was also present in the left hemisphere (Supplementary Figure 1). Two years after clinical onset, she had left hemiparesis and signs of left neglect. She was anosognosic and did not explore the left hemispace to compensate for her hemianopia. Neuropsychological examination revealed no deficit of memory or language.

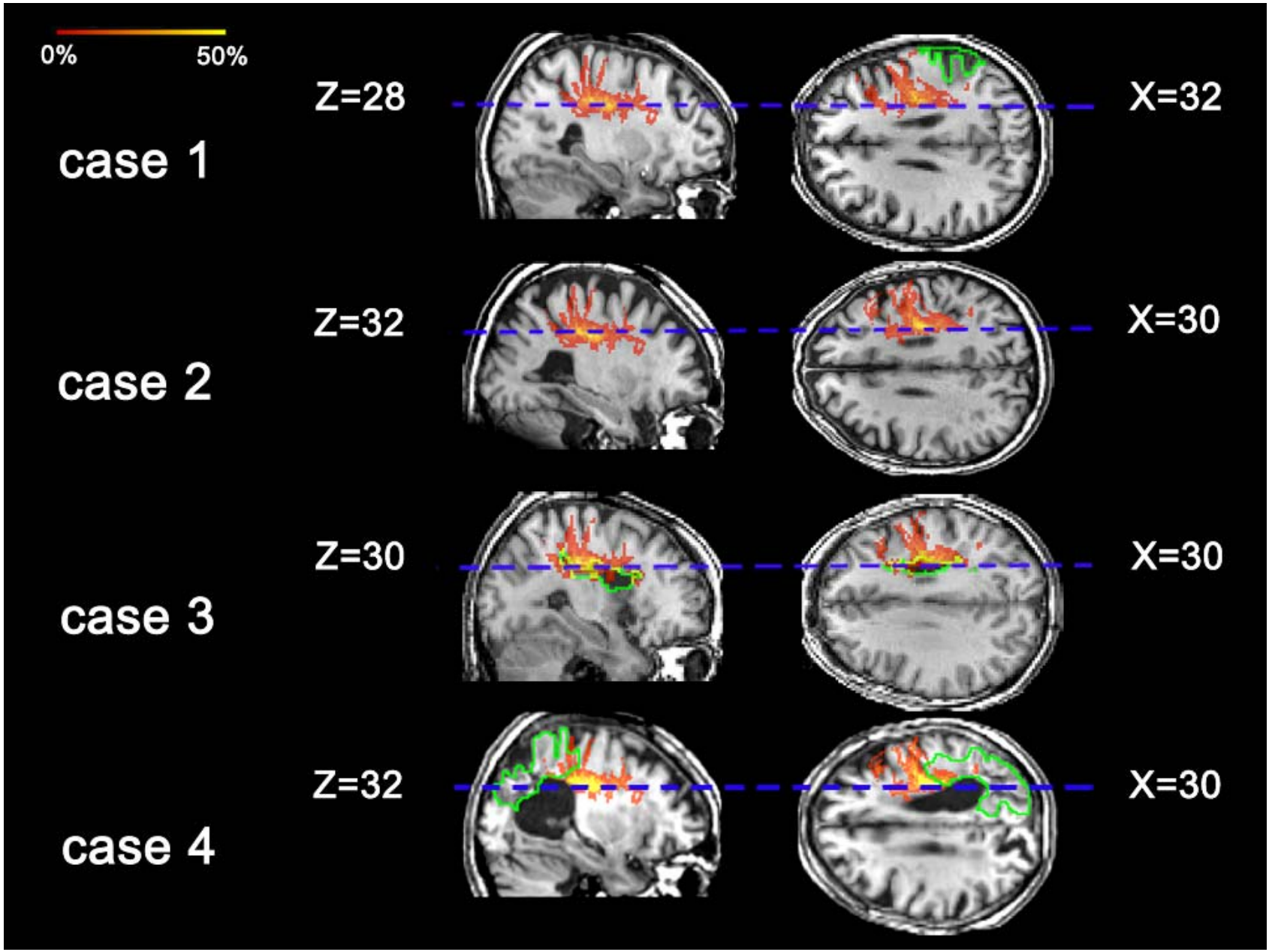
The supplementary Table reports the number of streamlines for each fasciculus. The small number of streamlines in the left hemisphere of case 4 likely resulted from the concomitant left occipito-parietal lesion in this patient.

Supplementary Table. Number of streamlines for the three fascicles tracked in the left (L) and the right (R) hemisphere of each patient

	SLF		*IFOF*		*ILF*	
Case	*L*	*R*	*L*	*R*	*L*	*R*
1	796	575	286	165	2566	1041
2	25	693	47	248	1090	718
3	2051	1874	61	0	714	4684
4	365	991	4	0	608	3228

SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus

Supplementary Figure 2 illustrates how the lesions of cases 3 and 4, but not of cases 1 and 2, overlap with the likely normal localisation[20] of the SLF. This might suggest partial damage to the SLF in cases 3 and 4.


0%
50%
Z=28
X=32
case 1
Z=32
X=30
case 2
Z=30
X=30
case 3
Z=32
X=30
case 4

Supplementary Figure 2. Overlay of the patients' lesions (outlined in green) and of the normalized percentage maps of the SLF localisation (red-yellow colour scale) for 16 normal subjects[20] in the MNI referential space (http://www.mni.mcgill.ca). An axial and a sagittal MRI slices are shown for each patient. For case 2, there was no slice containing both the SLF and the lesion.

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