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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.

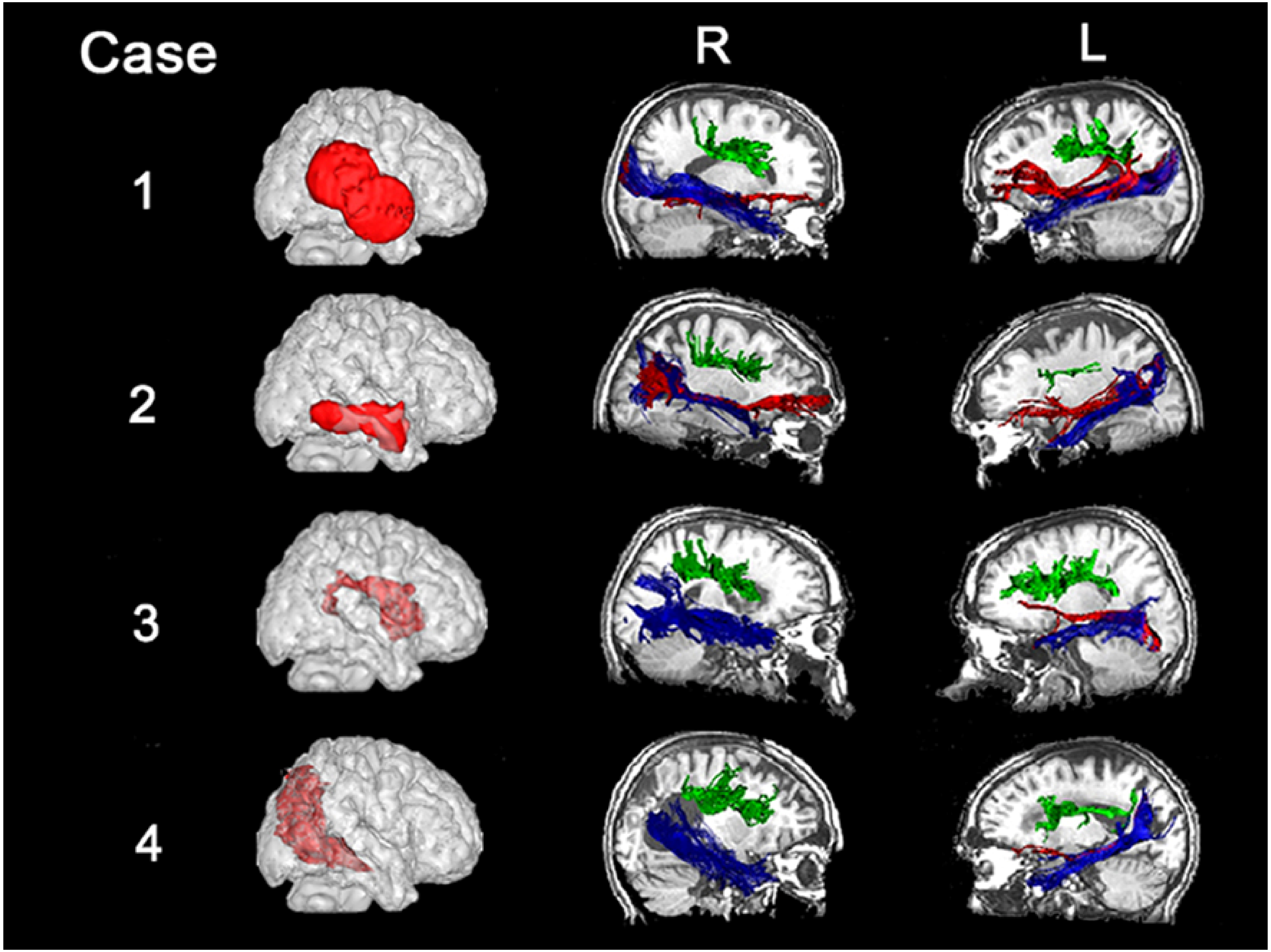
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Figure 1: Three-dimensional anatomical reconstruction of the patients’ lesions and lateral views (right hemisphere, R; left hemisphere, L) of the DTI tractography of the SLF (in green), the ILF (in blue) and the IFOF (in red) for the four patients 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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