Microscopic damage to the left hemisphere contributes in determining neglect in patients with a right focal lesion

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Introduction

Using transcranial magnetic stimulation (TMS) and diffusion MRI in combination, we recently provided, in healthy subjects, neurophysiological and microstroctural evidence for a right-left functional asymmetry between parietal cortices (1). This observation is not only interesting from a speculative view-point, but it may also contribute to explain, by disconnection mechanism, the occurrence of 'hemispatial neglect' in the presence of right hemispheric damage. To test this hypothesis, we investigated, using tract-based spatial statistics (TBSS, http://www.fmrib.ox.ac.uk/fsl/), the white matter (WM) microstructure in the left hemisphere (spared by macroscopic lesions) in a group of patients suffering from right-sided stroke and neglect. Aim of the study was therefore to quantify the presence and extension of microstructural WM disconnection, and its potential role in determining the presence and severity of hemispatial neglect.

Materials and methods: We recruited 10 patients suffering from stroke in the right hemisphere [m/f=7/3; mean (SD) age=61.1(9.0) years; all right-handed], and 11 healthy matched controls. All patients were preliminarily examined by the Behavioural Inattention Test (BIT), a validated battery to assess the presence and quantify the severity of hemispatial neglect. All subjects had an MRI scan at 3T including: i) conventional MRI (dual-echo, FLAIR); ii) DTI (TR= 7 s, TE=85 ms, number of diffusion directions=61; max b factor=1000 smm^{-2}); and iii) T1-weighted volume (3D MDEFT, TR=1338 ms, TE=2.4 ms). Dual-echo and FLAIR scans were used to exclude the presence of macroscopic lesions in patients' left hemisphere. The right-hemisphere lesion was outlined on T1-weighted volumes using a semi-automated contouring technique (www.xinapse.com). The volumes were then warped to MNI space using FLIRT (http://www.fmrib.ox.ac.uk/fsl/) to produce a map of the spatial extension and overlap of the lesions across subjects (Fig.1). Every subject's FA image was edited to remove the right hemisphere. Likewise, a left hemisphere FA template was obtained by removing the right hemisphere from the template provided with FSL. In order to avoid boundary effects, part of the right hemisphere next to the mid-sagittal section was left intact (see Fig 2), although results from those brain regions were ignored. The TBSS pipeline was then applied these left hemisphere images. Statistical analysis was carried out on the resulting skeletonized images to assess: i) the presence and extension of changes in fractional anisotropy (FA; an index of microscopic WM integrity) in the left hemisphere of patients compared to controls; and ii) to investigate, by correlation analysis, whether this damage might account for the presence and severity of neglect, as assessed by the Behavioural Inattention Test. Statistical analysis was based on permutation tests, and P-values were accepted as significant if lower than 0.05 corrected for multiple comparisons using the threshold free cluster enhancement (TFCE) (4).

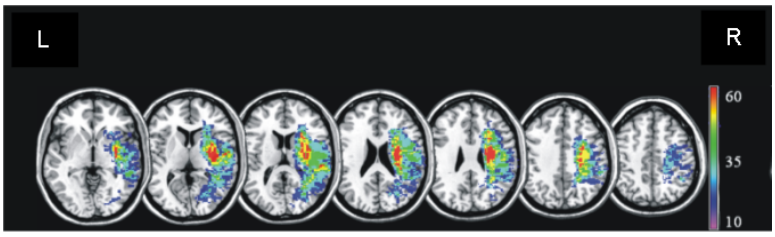

Fig.1 Patients lesion distribution assessed on T1-w volumes. The colour scale indicates the percentage of overlapping lesions across patients.

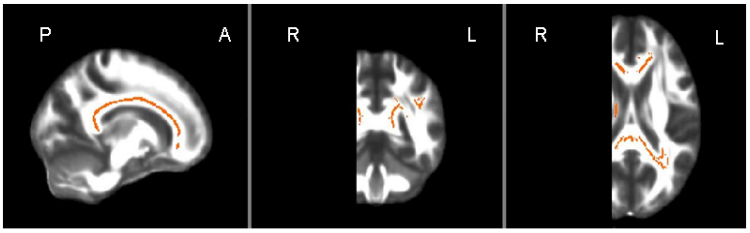

Fig.2 Red voxels represent the areas where FA values of neglect patients are significantly reduced with respect to those of healthy controls.

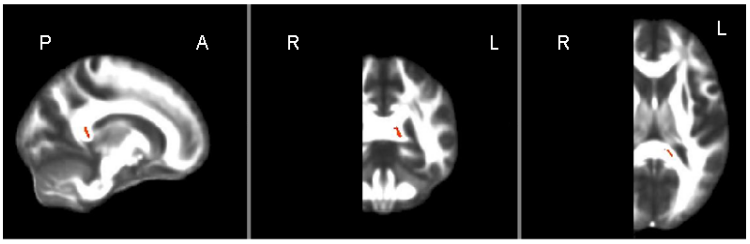

Fig.3 Correlation between FA reduction and BIT scores in neglect patients.

Results: None of the patients had any macroscopic abnormality in the left hemisphere. Conversely, TBSS analysis revealed a diffuse reduction of FA in most of their left hemisphere tracts, with a predominant involvement of the corpus-callosum (CC) and its parietal projections (Fig.2). In the patient group, a trend to statistical significance (p=0.08) was found in the correlation analysis between scores obtained at the BIT and regional FA in the fifth portion of the CC (Fig.3).

Discussion: Despite the absence of macroscopic tissue damage, the left hemisphere of patients with right-side stroke shows a widespread pattern of micro-structural abnormalities. These WM changes, preferentially located within the CC, are likely to be due to axonal degeneration, and might reflect the neurobiological substrate for inter-hemispheric disconnection, thus accounting for the clinical manifestations of neglect. This hypothesis is reinforced by the association found between FA values in the posterior part of the CC and BIT scores reported by patients. This area of the CC, which resulted from a data-driven analysis (without any a priori anatomical assumption), is indeed critical for the structural connection between the parietal cortices In conclusion, the present study supports the hypothesis that symptoms of 'neglect' are due to an unbalance of interhemispheric interactions between the two parietal cortices rather than a mechanism of hemispheric specialization.

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