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Visualization of disconnection syndromes in humans

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ABSTRACT

Knowledge of the relationship between structure and function is essential to the exploration of the architecture of cognition. Cognitive processes require the coordinated activity of large-scale brain networks consisting of distant cortical regions, connected by long-range white matter tracts. Despite decades of connectional tracing studies in monkeys, the backwardness of human anatomy makes it difficult to draw conclusions from lesion studies and functional neuroimaging when brain connectivity is at issue. We propose an approach to clinico-anatomical correlation, based on a standardized atlas of white matter tracts derived from diffusion tensor imaging tractography. Using OVER-TRACK, a method based on tracking and overlapping white matter tracts, we mapped the course of three rostro-caudal association pathways in the Montreal Neurological Institute space. For each voxel we defined the probability of finding fibers belonging to individual tracts. This method is defined to localize in the white matter the overlapping lesion derived from a group of patients with brain damage. Our study provides a general approach for establishing anatomo-functional correlations by estimating the cortical areas connected in normal subjects, or disconnected by white matter lesions. This method will help researchers and clinicians to identify the neural bases of cognitive abilities and the behavioral consequences of brain lesions.

1. Introduction

Research on the neural correlates of human behavior has recently witnessed an enormous expansion thanks to the increasingly precise descriptions of patterns of performance of patients with focal brain lesions and to the development of neuroimaging techniques, such as positron emission tomography and magnetic resonance imaging, used to study

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normal subjects while performing cognitive tasks. It is currently widely accepted that cognitive abilities are not related to single cortical areas, but to distribute cortical networks, often including brain structures remote from each other and connected by long-range association bundles in the cerebral white matter (Geschwind, 1965a,b; Catani and Ffytche, 2005; Mesulam, 1990). Thus, knowledge of the organization of these pathways is essential to make inferences about structure/function relationships in the human brain (Mesulam, 2004). For example, models of language implicate the left arcuate fasciculus (AF) (Benson et al., 1973), damage to which typically results in conduction aphasia (Naeser et al., 1982; Kempler et al., 1988; Schmahmann and Pandya, 2006), whereas its temporary electrical inactivation during neurosurgery induces anomic errors (Duffau et al., 2002). Damage to the superior longitudinal fasciculus (SLF) in the right hemisphere is correlated with left unilateral neglect (Doricchi and Tomaiuolo, 2003b), a disabling condition entailing the lack of awareness of events occurring in the left contralesional, side (Bartolomeo and Chokron, 2001; Mesulam, 1999; Heilman et al., 1993; Parton et al., 2004) and temporary inactivation during brain surgery of this same parieto-frontal pathway also induced signs of left neglect (Thiebaut De Schotten et al., 2005).

The course and projections of the SLF are well known in the monkey (Schmahmann and Pandya, 2006), but the terminations of its components in the human brain can only be extrapolated from the data available from non-human primates (Makris et al., 2005).

Until recently, the study of white matter organization in humans was based on neuropathological examination of post-mortem brain tissue (Nieuwenhuys et al., 1988; Déjerine, 1895; Bossy, 1991), but it has now received new momentum from the utilization of diffusion tensor imaging (DTI) (Basser et al., 1994). DTI reflects the diffusion in space of water in the living brain. Water tends to diffuse preferentially along the axonal fibers, allowing for inference of the pathway followed by the fibers (Basser et al., 1994; Mori et al., 2005). Using this method, long-range pathways of superior associative fibers have been visualized in human individuals (Catani et al., 2002) or small groups of subjects (Catani et al., 2005; Makris et al., 2005; see also Jones, 2008, this issue).

DTI is well adapted for a general description of subcortical white matter architecture in the human brain (Xu et al., 2002; Jones et al., 2002; Catani et al., 2005), but current study using this approach on brain damaged patients has several limitations: (1) the position within a standard system of reference is difficult to establish (Catani et al., 2002; Catani et al., 2005; Mori et al., 2005; Wakana et al., 2004); and (2) when evaluating the white matter lesions of brain damaged patients, white matter damage typically perturbs the anisotropy signal, thus rendering it difficult to reconstruct the fasciculi in traditional DTI approaches and consequently to decide whether a particular bundle is lesioned or not in an individual patient.

To address both issues, we developed OVER-TRACK, a method to localize the damage of long-range white matter pathways in the human brain. Using this method and based on a new high-resolution dataset, we aim to construct an atlas of the human white matter in MNI space. Here, we applied OVER-TRACK to the mapping of three major caudal-rostral associative bundles. We normalized directly the image of the voxels included in the long-range association fibers in the native space of each participant's brain (Davatzikos, 1998). We subsequently overlapped them in order to define the probability of finding these specific fibers in each voxel of the MNI space. Using this method, we estimated the trajectory of the AF and of two components of the SLF in each hemisphere of the standard human brain defined by the MNI space. Importantly, OVER-TRACK is defined to be used in clinico-anatomical correlation studies where tracts can not be visualized, thus allowing the researcher to take into account possible hodological mechanisms of deficit (Catani and Ffytche, 2005). In this line of idea, the present method permits one to visualize and determine the location of damage within white matter pathways in disconnection syndromes (see also Rudrauff et al., 2008, this issue). As an example, we provided a re-analysis of a previous lesion overlapping study (Doricchi and Tomaiuolo, 2003a), which permitted the identification of the white matter bundles typically damaged in patients with left unilateral neglect, a neurological syndrome resulting from right brain damage.

2. Materials and methods

2.1. Subjects and data acquisition

Twenty-four right-handed subjects (12 males and 12 females; mean age, 28.0 ± 7.0 years; range, 18–42 years) gave written informed consent to participate in the study, which was approved by the local ethics committee. No subject had radiological signs of cerebral lesions on conventional MRI. MRI data were acquired using echo-planar imaging at 1.5 T (General Electric, Milwaukee, WI) with a standard head coil for signal reception. DTI axial slices were obtained using the following parameters: repetition time, 10 s; echo time, 88 ms; flip angle, 90°; matrix, 128×128; field of view, $380 \times 380\ mm^2$; slice thickness, 3 mm with no gap; in plane pixel size, $3 \times 3\ mm^2$ (isotropic voxels); acquisition time, 320 s and 30 slices (not including the cerebellum). Four averages were used with signal averaging in the scanner buffer. Diffusion weighting was performed along six independent directions, with a b-value of $900\ s/mm^2$.

2.2. Tractography: definition of the regions of interest (ROI)

Fiber tracking was performed using two manually drawn ROIs in the native space: (1) a global ROI based on a previously published method (Catani et al., 2005); and (2) selective ROIs, which permitted us to differentiate the fasciculi (Fig. 1B).

Raw diffusion-weighted data were corrected for geometric distortion secondary to eddy currents using a registration technique based upon the geometric model of distortions (Mangin et al., 2002a). Brainvisa 3.0.2 (http://brainvisa.info/) software was used to calculate diffusion tensors and anisotropy data, to define the ROIs and to perform fiber tracking using likelihood algorithm (Mangin et al., 2002b). Fiber tracking was performed using the following steps: firstly, we defined a large ROI including all superior frontal, parietal and temporal associative fibers, as illustrated on a RGB map, the color of

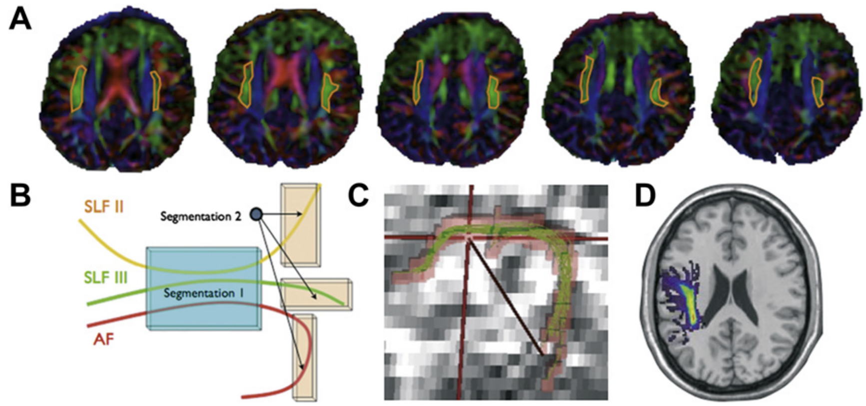

Fig. 1 – (A) ROI including the whole fibers of the three fasciculi used as starting region for the tractography. (B) Selective ROI applied after the tracking to select the fasciculus of interest. (C) Overall mask applied on the fasciculus. (D) Percentage visitation maps.

which indicated the main diffusion directions (Catani et al., 2005). Fibers passing through this ROI were reconstructed into three-dimensional (3-D) bundles. Secondly, we created a virtual dissection of this package of bundles in both hemispheres using an atlas of fibers (Bossy, 1991) and previous descriptions (Catani et al., 2005). We separated the fibers into three fasciculi presenting a convexity directed: (1) upward: the AF (Déjerine, 1895; Bossy, 1991; Catani et al., 2002, 2005); (2) downward: the SLF II (Schmahmann and Pandya, 2006); and (3) mesially: the SLF III (Catani et al., 2005; Bossy, 1991). In order to track these three fasciculi individually, three ROIs per hemisphere were created directly on the fibers of interest at the level of the caudal part of their convexity (Fig. 1B).

Only bundles having more than 20 mm of length were kept in order to remove artefacts and to preserve long and valid fibers.

2.3. *DTI template creation*

We created a homemade template using statistical parametric mapping software (SPM2, Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/), in association with MATLAB version 6.5 (The Mathworks, Inc., MA, USA). The DTI images with no diffusion gradient (EPI T_2-weighted images obtained for $b = 0$) of all subjects were used to build the template. Images were spatially normalized to the standard EPI template provided in SPM2 using the default parameters of SPM2 (no weighting; 25 mm cutoff; medium regularization; 16 nonlinear iterations; bounding box −78:78 −112:76 −50:85; voxel size 2 * 2 * 2; trilinear interpolation; no wrap). The normalized EPI images were visually checked for misregistration (anterior and posterior commissure coordinates). Misregistered images, those with incorrect values of anterior and posterior commissure coordinates, were excluded from the analysis ($n = 1$). Then we averaged and smoothed (filter width at half maximum isotropic Gaussian kernel: 12 mm) the 23 normalized EPI images to create an EPI template (Thivard et al., 2006).

2.4. *Spatial normalization and superposition of fibers*

Three stages were necessary to draw the percentage overlap maps of the long-range connections: (1) the elaboration of an individual mask for each fasciculus (see Fig. 1C); (2) the spatial normalization of the masks to the homemade template, which approximates the space defined by Talairach and Tournoux (1988) to the MNI space; and (3) the averaging of the normalized masks for each fasciculus (see Fig. 1D).

First, a 3-D mask was created for each fasciculus using DTI images in the native space. This mask included all voxels crossed by fibers of the fasciculus of interest. Then, we normalized all DTI images as previously described (using the default parameters of SPM2: no weighting; 25 mm cutoff; medium regularization; 16 non-linear iterations; bounding box −78:78 −112:76 −50:85; voxel size 2 * 2 * 2; trilinear interpolation; no wrap) using our homemade EPI template and applied the deformation matrix to the 3-D masks of each fasciculus. The normalized EPI images were again visually checked for misregistration. Misregistered images, i.e., those with incorrect values of anterior and posterior commissure coordinates ($n = 2$), were excluded from the analysis. The EPI deformation field was applied to the fasciculi masks of the remaining 21 participants. Normalized masks were transformed to binary images with the voxels inside the masks having a value of 1 and the other voxels of the images set to 0. For each hemisphere, we averaged the masks of each of the three fasciculi (AF, SLF III and SLF II) for all subjects. The resulting maps showed for each voxel the percentage of subjects having a fiber passing through it using Brainvisa. The final maps displayed the percentage of fasciculus overlap for each voxel (range, 0%–50%).

2.5. *Visualization of disconnection results*

Using this approach, neuroimaging results can be projected to the normalized white matter maps. This offers the possibility to take into consideration the possible damage to long-range white matter pathways in studies based on anatomical images, which do not allow the direct visualization of these pathways. As an example, we provide a re-analysis of the results of a study (Doricchi and Tomaiuolo, 2003b), which investigated the anatomical correlates of spatial neglect. In the original study, the Talairach atlas (Talairach and Tournoux, 1988) was used to match the patients' lesions with normal anatomical structures, and neglect patients' lesions were found to overlap on the SLF, thus suggesting an important role for fronto-parietal disconnection in left neglect (Thiebaut De Schotten et al., 2005; Bartolomeo et al., 2007; Bartolomeo, 2006). Doricchi and Tomaiuolo kindly provided us with their original data, consisting of the maximum lesion overlap (as detected by T1-weighted MRI scans) of 21 patients with unilateral right hemisphere damage and signs of left neglect on tasks of line bisection and letter cancellation, in the absence of homonymous hemianopia. Patients' lesions were overlapped to create a map defining for each voxel of the MNI space the percentage of neglect patients whose lesion affected that voxel. We plotted the statistical map lesions on the full mask (without any threshold) of the three normalized fasciculi, AF, SLF III and SLF II. A lesioned voxel was considered to correlate with neglect if it was damaged in at least 80% of the neglect patients, and to be independent of neglect if it was lesioned in less than 5% of the patients. A chi-square test on the number of voxels implicated or not in full mask overlap of each fasciculus was performed to discriminate the relative contribution to neglect of damage to that fasciculus.

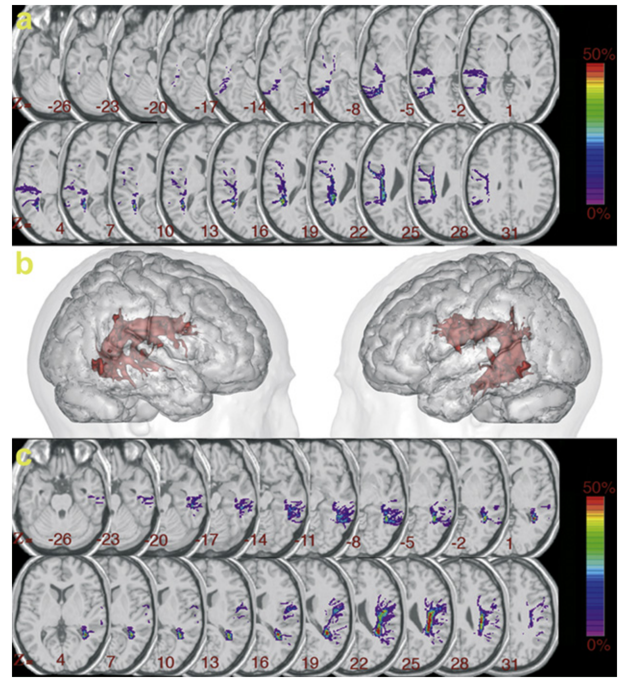

Fig. 2 – Probabilistic maps (in percentage of overlapping) for the AF in (a) the right hemisphere (12 normalized fasciculi) and (c) the left hemisphere (14 normalized fasciculi) in different axial sections of the MNI space. (b) 3-D reconstruction of the full overlap.

3. Results

Following the terminology proposed by Schmahmann and Pandya (2006), we describe in a ventral-to-dorsal direction an estimation of the visitation maps and projections in the MNI of the AF (Fig. 2), the SLF III (Fig. 3) and the SLF II (Fig. 4).

3.1. *Analysis of white matter damage in left unilateral neglect*

The re-analysis of a previous lesion overlapping study of left neglect (Doricchi and Tomaiuolo, 2003b), which we provide as an example of application of our approach, demonstrated a different implication in unilateral neglect for the three fascicles (Table 1 and Fig. 5; chi-square value, 6961.05; d.f., 2; $P < 0.0001$).

Post-hoc tests showed a difference between the AF and each of the two components of the SLF (chi-square value, 4028.11; d.f., 1; $P < 0.0001$). The SLF III and the SLF II did not differ between themselves (chi-square value, <1). Thus, in this patient series unilateral neglect was related to damage to the right SLF III and II, but not to the AF. The present analysis permitted us to refine the original interpretation of the results as showing a link between neglect and fronto-parietal disconnection (Doricchi and Tomaiuolo, 2003b) by identifying precisely the critical branches of the SLF whose damage brought about neglect signs.

4. Discussion

The concept of disconnection syndromes, introduced during the 19th century and reinvented by the charismatic work of Norman Geschwind (1965a,b), has been central in the

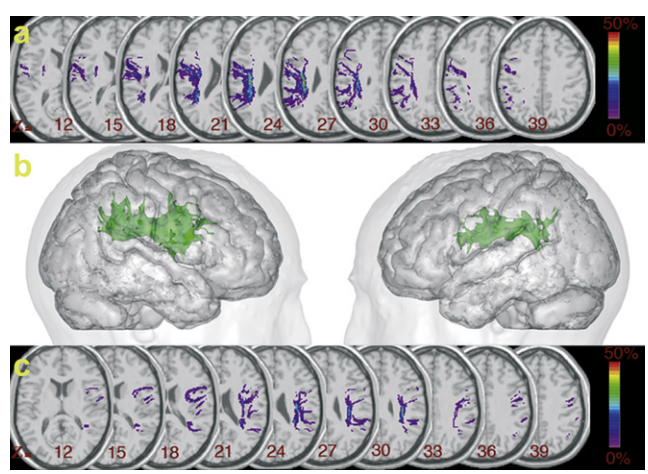

Fig. 3 – Probabilistic maps (in percentage of overlapping) for the SLF III in (a) the right hemisphere (16 normalized fasciculi) and (c) the left hemisphere (15 normalized fasciculi) in different axial sections of the MNI space. (b) 3-D reconstruction of the full overlap.

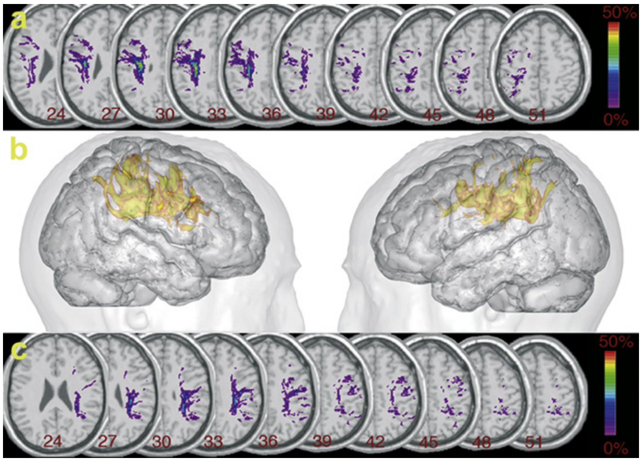

Fig. 4 – Probabilistic maps (in percentage of overlapping) for the SLF II in (a) the right hemisphere (19 normalized fasciculi) and (c) the left hemisphere (19 normalized fasciculi) in different axial sections of the MNI space. (b) 3-D reconstruction of the full overlap.

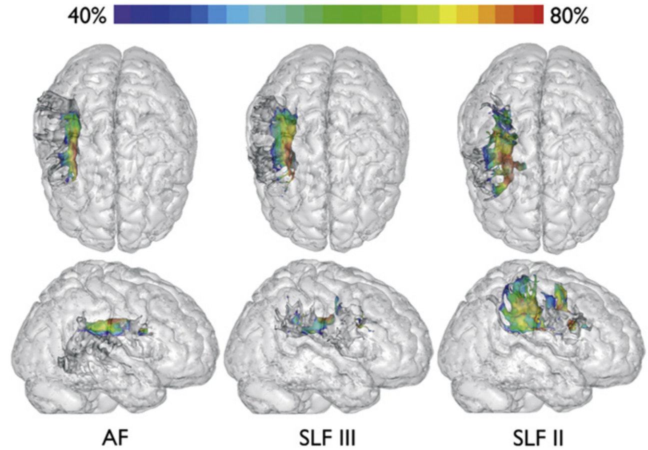

Fig. 5 – Percentage lesion overlaps of patients with left neglect from a previous study (Doricchi and Tomaiuolo, 2003b), plotted on the three long-range pathways in MNI space.

development of cognitive neurosciences (see also Catani and Mesulam, 2008a,b, this issue). The advent of functional neuroimaging, with its focus on cortical modules, has weakened the interest on the connection systems in the brain. A partial reversal of this trend has been initiated with the advent of diffusion tensor imaging and tractography (Catani and Ffytche, 2005), but knowledge on the real connectivity of the human brain and its relationship to normal and impaired cognition remains enigmatic (Mesulam, 2004). Our approach is an attempt at a better localization of brain lesions in neurological patients or foci of metabolic activation in neuroimaging studies on normal individuals, despite the vast inter-subject variability in brain anatomy, and taking into proper consideration the long-range white matter pathways in the brain.

It remains questionable whether the current DTI technology does provide data comparable with post-mortem anatomical studies, but encouraging results in this sense were provided by two recently published studies, which compared tractography with autoradiography following injection of isotope in monkey, and found good inter-technique reliability (Dauguet et al., 2006; Schmahmann et al., 2007).

The present approach is notably different from previous tracking studies (Catani et al., 2002, 2005; Mori et al., 2005; Wakana et al., 2004), because we first tracked the fiber bundles in the subjects' native space and then normalized the resulting tracks into a standard space (see also Catani and Thiebaut de Schotten, 2008, this issue). In this way, we were able to work in the native DTI space, and not in a space reconstructed and interpolated by normalization. As pooling subjects together minimize artefacts, in OVER-TRACK, we lower the FA threshold (from usual 0.2 to 0.1) in order to increase the size of the reconstructed fasciculi. Although we acknowledge the limit of using only six directions for the DTI acquisition, the identification of the probability of presence for each voxel of the MNI space of three long-range fasciculi in each hemisphere of the living human brain constitute a first step towards the construction of a white matter atlas in the MNI space. However, a high-resolution DTI dataset is necessary to increase the reliability between the diffusion tensor tractography and the real white matter anatomy.

Table 1 – Number of voxels for each of the three fascicles implicated, respectively, in < 5% and > 80% of patients with left neglect from a previous lesion overlap study (Doricchi and Tomaiuolo, 2003b)

	AF	SLF III	SLF II
<5%	5866	6	23
>80%	370	631	1792

OVER-TRACK may offer the opportunity to re-examine previously published results obtained with lesion overlapping in stroke patients or fMRI in order to consider a structural connectivity explaining disconnection syndromes and functional networks activity. Without any consideration for an eventual age effect, as an example, we plotted the maximum lesion overlap in neglect patients (Doricchi and Tomaiuolo, 2003b) on the 3-D visitation maps. We demonstrated a joint implication of the SLF III and of the SLF II, consistent with neurosurgical stimulation data (Thiebaut De Schotten et al., 2005) and suggesting the possibility that both of these parieto-frontal pathways may be important to spatial cognition (see also Doricchi et al., 2008, this issue). Thus, the present approach permitted to take into consideration those hodological factors (Catani and Ffytche, 2005), which, in addition to topological factors resulting from cortical damage or deafferentation, may lead to neglect behavior (Bartolomeo et al., 2007). This should not be taken to imply that disconnection alone can cause neglect, or that the SLF is the only pathway implicated. Further work is necessary to disentangle the contributions of different lesional sites on different forms of neglect.

In vivo functional anatomy in humans, combining hodological, functional imaging and clinical evidence, is a major challenge of cognitive neuroscience (Catani and Ffytche, 2005; Mesulam, 2004). Our results confirm and extend the reconstructions of the stem portions of the fasciculi based on RGB maps (Makris et al., 2005) and preliminary results on the asymmetry of some components (Catani et al., 2007). These maps will help clinicians and researchers to better define the location of subcortical brain lesions and their anatomical relationship with association pathways. Future results obtained with this method are likely to bring attention to the functional role of cortico-cortical association pathways in defining the architecture of the large brain networks, which shape human sensory-motor and cognitive processes.

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