

## Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography

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### ABSTRACT

The purpose of this study is to create a white matter atlas of the human brain using diffusion tensor imaging (DTI) tractography and to describe the constant and variable features of the major pathways. DTI was acquired from 40 healthy right-handed adults and reconstructed tracts mapped within a common reference space (MNI). Group effect maps of each tract defined constant anatomical features while overlap maps were generated to study inter-subject variability and to compare DTI derived anatomy with a histological atlas. Two patients were studied to assess the localizing validity of the atlas. The DTI-derived maps are overall consistent with a previously published histological atlas. A statistically significant *leftward* asymmetry was found for the volume and number of streamlines of the cortico-spinal tract and the direct connections between Broca's and Wernicke's territories (long segment). A statistically significant *rightward* asymmetry was found for the inferior fronto-occipital fasciculus and the fronto-parietal connections (anterior segment) of the arcuate fasciculus. Furthermore, males showed a left lateralization of the fronto-temporal segment of the arcuate fasciculus (long segment), while females had a more bilateral distribution. In two patients with brain lesions, DTI was acquired and tractography used to show that the tracts affected by the lesions were correctly identified by the atlas. This study suggests that DTI-derived maps can be used together with a previous histological atlas to establish the relationship of focal lesions with nearby tracts and improve clinico-anatomical correlation.

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### Introduction

Until the advent of diffusion tensor imaging (DTI), our knowledge of white matter anatomy was based on a small number of influential 19th and early 20th century post-mortem dissection atlases (Burdach, 1819; Déjerine, 1895). In common with their contemporary counterparts (Talairach and Tournoux, 1988), these atlases emphasize the constant or average anatomy of representative subjects at the expense of normal variability between subjects. Few post-mortem histological studies addressed the variability of the tracts between the two hemispheres and reported asymmetries for the cortico-spinal tract (CST) (Flechsig, 1876; Yakovlev and Rakic, 1966; Rademacher et al., 2001), the optic radiations

(Bürgel et al., 1999), and the uncinate (Highley et al., 2002). Bürgel et al. (2006) showed that a significant inter-subject variability also exists for each tract within the single hemispheres. Little is known about whether such anatomical variability differs between genders and extends to other tracts underlying complex cognitive functions.

Diffusion tensor imaging has allowed the study of the in vivo anatomy of white matter tracts in the human brain (Catani et al., 2002; Mori et al., 2002, 2005; Wakana et al., 2004; Catani and Thiebaut de Schotten, 2008; Ciccarelli et al., 2008; Lawes et al., 2008) and addressed some of the questions that were difficult to answer with post-mortem dissections such as the location, asymmetry and inter-subject variability of white matter tracts (Ciccarelli et al., 2003; Barrick et al., 2007; Catani et al., 2007; Wakana et al., 2007; Verhoeven et al., 2010). In the recent years several groups have used DTI to produce group atlases of the major white matter tracts (Hua et al., 2008; Lawes et al., 2008; Verhoeven et al., 2010; Wassermann et al., 2010). These atlases contain maps of the major white matter tracts that have a good correspondence with post-mortem blunt

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dissections. However, none of the previous atlases have addressed the inter-subject variability between left and right hemisphere in relation to gender.

The aim of this study was to create a normative atlas of white matter human connections for clinical and research purposes on a large age-matched population of male and female participants. We combine for the first time complementary approaches to address the question whether the lateralization of the association and projection fibres differs between genders and hemispheres. A comparison between the DTI-derived atlas and a previously published post-mortem histological atlas (Bürgele et al., 2006) is also presented and limitations of both approaches discussed. An atlas of the anatomical variability in the normal population could help improve localization of white matter lesions in brain disorders and understand mechanisms of brain recovery and plasticity (Amunts and Willmes, 2006).

## Materials and methods

### Subjects

Our Institutional Review Board approved the study, and informed consent was obtained from all subjects. Forty healthy right-handed volunteers (20 males and 20 females) aged between 18 and 22 years were recruited. To assess the localizing validity of the atlas in patients with brain lesions DTI was also acquired in a 68 year-old female patient with right hemiplegia due to a glioblastoma multiforme and a 61 year-old male patient with chronic neglect due to right hemisphere stroke.

### DTI acquisition and processing

A total of 60 contiguous near-axial slices were acquired on a GE Signa 1.5-T LX MRI system (General Electric, Milwaukee, WI) with 40-mT/m gradients, using an acquisition sequence fully optimized for DTI of white matter, providing isotropic ( $2.5 \times 2.5 \times 2.5$  mm) resolution and coverage of the whole head. The acquisition was peripherally-gated to the cardiac cycle with an echo time of 107 ms and an effective repetition time of 15 R-R intervals. At each slice location, 7 images were acquired with no diffusion gradient applied, together with 64 diffusion-weighted images in which gradient directions were uniformly distributed in space. The diffusion weighting was equal to a b-value of  $1300 \text{ s mm}^{-2}$ . Full details of this sequence are given in (Jones et al., 2002). BrainVISA (<http://brainvisa.info/>) was used to correct for eddy current distortion of raw diffusion-weighted data and to calculate the diffusion tensor and the fractional anisotropy (FA) for each voxel. A tractography algorithm based on Euler integration (Jones et al., 2002) (step length 0.5 mm; FA threshold of 0.2, angle threshold of  $45^\circ$ ) was used to propagate streamlines from “seed” regions of interest (ROIs) manually-defined on Anatomist (<http://brainvisa.info/>). To ensure that the operator was blind to hemisphere during the ROIs delineation, and therefore provide protection against subjective bias, half of the datasets were reflected along the midline. Following previously described criteria (Catani et al., 2002, 2003, 2005; Catani and Thiebaut de Schotten, 2008) ROIs were delineated around areas of white matter that represent “obligatory passages” along the course of each tract. This allows visualizing all streamlines of a single tract without constraining its terminal projections, which may vary from subject to subject.

A one-ROI approach was used for the anterior commissure, corpus callosum, arcuate, cingulum, internal capsule and fornix. A two-ROI approach was used for the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinata, cortico-spinal tract, optic radiations, and cerebellar tracts (cortico-ponto-cerebellar, spino-cerebellar, and superior-cerebellar). A two-ROI approach was also used to separate the three segments of the arcuate fasciculus: a direct long segment between Wernicke’s and Broca’s territories an indirect posterior segment connecting Wernicke’s to Geschwind’s territories (inferior parietal lobule), and an indirect

anterior segment connecting Geschwind’s to Broca’s territories (Catani et al., 2007).

Tract-specific measurements were extracted (i.e. number of streamlines, volume, and fractional anisotropy) and a lateralization index calculated (Parker et al., 2005; Powell et al., 2006; Catani et al., 2007; Vernooij et al., 2007; Makris et al., 2008; Matsumoto et al., 2008; Rodrigo et al., 2008; Sivaswamy et al., 2008; Lebel and Beaulieu, 2009) according to the following formula (for example for the number (N.) of streamlines):

$$\frac{(N. \text{ streamlines Right} - N. \text{ streamlines Left})}{(N. \text{ streamlines Right} + N. \text{ streamlines Left})}$$

Analysis of the differences between the left and right hemispheres of each tract and the two genders was performed using repeated measure ANOVA. The lateralization index of each tract was set as a within-subjects factor (14 tracts) and the gender as a between-subjects factor. Statistical significance of the degree of the lateralization was determined using a one-sample *t* test for each tract. Only results that survived Bonferroni correction are presented.

### Creation of the atlas based on group effect and variability maps

The B0 images of each subject were normalized to the Montreal Neurological Institute space (MNI <http://www.bic.mni.mcgill.ca/>) using the T2 template provided in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>). Then the affine (12 degrees of freedom) and elastic (16 iterations) transformation matrix derived from the normalization of the B0 images was applied to each FA map and an average FA template was created. This average FA template was used to normalize the individual FA maps to generate a normalized FA template. This new FA template was used to normalize again the individual FA maps. This process was repeated five times to generate a sharper final normalized FA template (Ashburner, 2007).

The binary visitation maps were created for each tract by assigning each voxel a value of 1 or 0 depending on whether the voxel was intersected by the streamlines of the tract (Catani et al., 2007; Lawes et al., 2008; Thiebaut de Schotten et al., 2008). The binary visitation maps of each subject were normalized to the MNI space using the transformation matrix derived from the process of normalization of the FA maps described above. The visitation maps were then analyzed following two complementary approaches (Ciccarelli et al., 2003): (i) a group effect statistic; (ii) a percentage overlap. The first analysis aims to create *group effect maps* following smoothing of the normalized binary maps with a 4-mm (full width at half maximum) isotropic Gaussian kernel. Smoothing has been classically applied to imaging analysis to obtain an approximately Gaussian distribution of the data (Worsley et al., 1992). In our analysis Gaussian distribution of the data was confirmed for three voxels along the inferior fronto-occipital fasciculus using the Shapiro–Wilk test (Shapiro and Wilk, 1965). This allows the use of standard parametric statistics in our dataset to draw statistical inferences (Ashburner and Friston, 2000) about the constant anatomy of the tract. The individual smoothed images were then entered into a design matrix for a one-sample *t*-test corrected for Family Wise Error (FWE).

The second method creates *percentage overlap maps* by summing at each point in the MNI space the normalized visitation maps from each subject. In this case the visitation maps are binary and unsmoothed, hence the overlap of the visitation maps varies according to inter-subject variability. This is the method that was also used by Bürgele et al. (2006) to create a histological atlas of white matter tracts. Hence, by following their method we were able to produce percentage maps to compare side-by-side our *in vivo* atlas with their histological atlas ([http://www.fz-juelich.de/inb/inb-3//spm\\_anatomy\\_toolbox](http://www.fz-juelich.de/inb/inb-3//spm_anatomy_toolbox)). Only maps with an overlap threshold of >50% were used for comparisons.

3D rendering of the brains were calculated using the T1 pipeline in BrainVISA. 3D rendering of the maps were obtained using the online command AimsClusterArg in BrainVISA. The overall visualization and screenshots were performed in Anatomist (<http://brainvisa.info>).

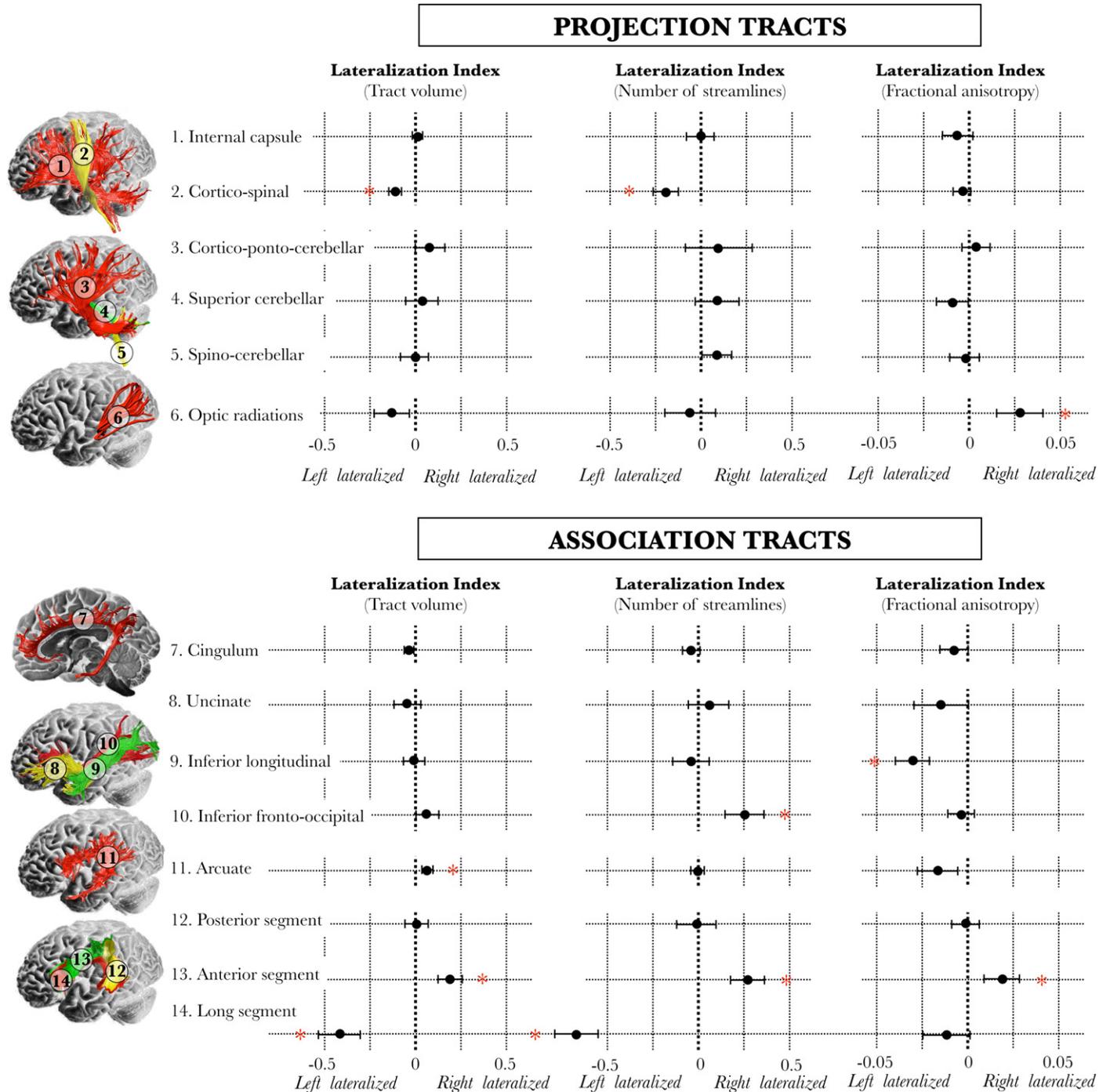
To obtain preliminary data on the localizing validity of the atlas, the T1 or T2 structural images of two patients with brain lesions were normalized in the MNI with SPM5 using affine (12 degrees of freedom) and elastic (16 iterations) transformation and superimposed onto the corresponding slices from the atlas. Then DTI tractography dissections (FA>0.2) of the tract affected by the pathology were performed in the native space of each patient to verify that the atlas localized the tract affected by the lesion correctly.

**Results**

The outcome variables of the tract-specific measurements were used to describe the interhemispheric and gender differences. Both group effect and percentage overlap maps were used to describe the constant and variable features of the dissected tracts and to compare the DTI-derived reconstructions with the post-mortem histology maps.

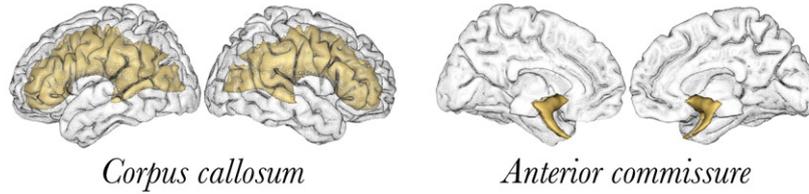
*Hemispheric asymmetries and between gender differences*

The lateralization indexes for the volume, number of streamlines, and FA of the dissected tracts are shown in Fig. 1. A statistically significant leftward asymmetry was found for the volume ( $T_{(39)}=6$



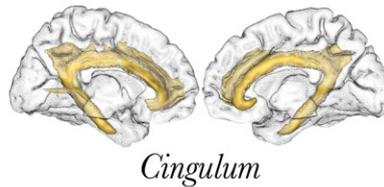
**Fig. 1.** Lateralization index for the volume, number of streamlines, and fractional anisotropy (mean ± 95% confidence interval) of the projection and association pathways. \* $p < 0.05$  after correction for multiple comparisons.

## COMMISSURAL PATHWAYS

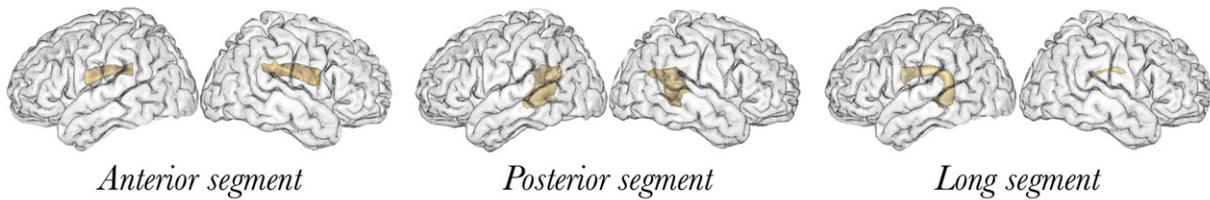


## ASSOCIATIVE PATHWAYS

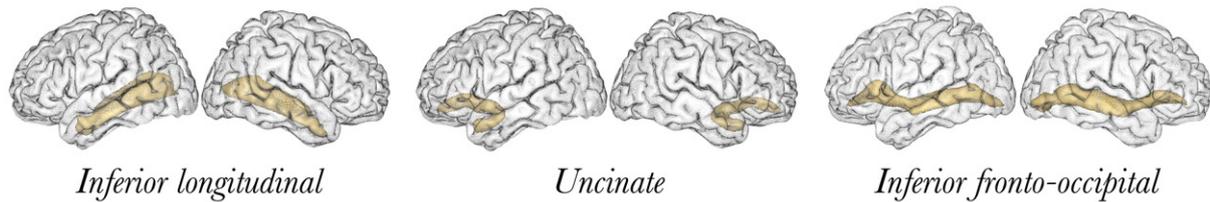
### MEDIAN NETWORK



### PERISYLVIAN/ARCUATE NETWORK



### INFERIOR NETWORK



## PROJECTION PATHWAYS

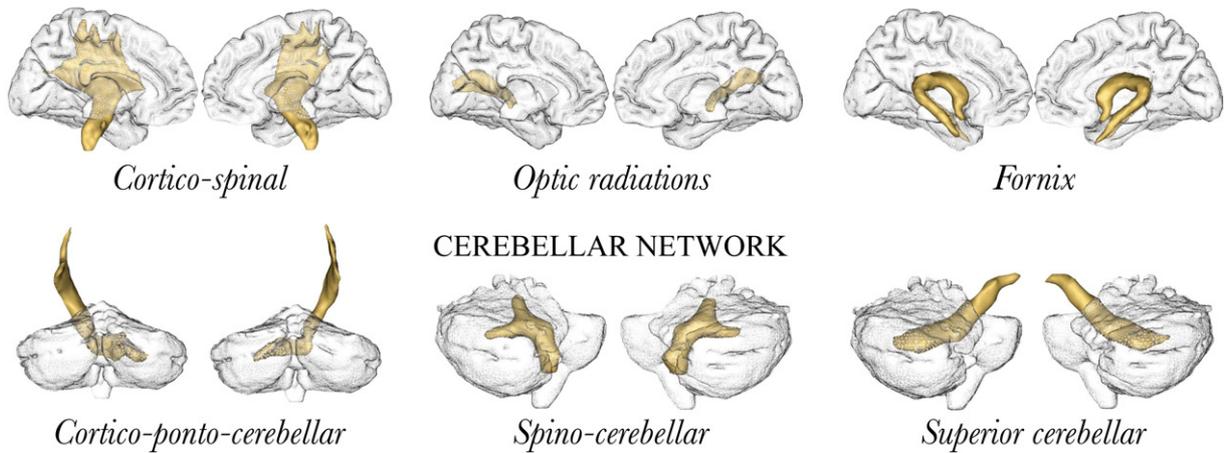
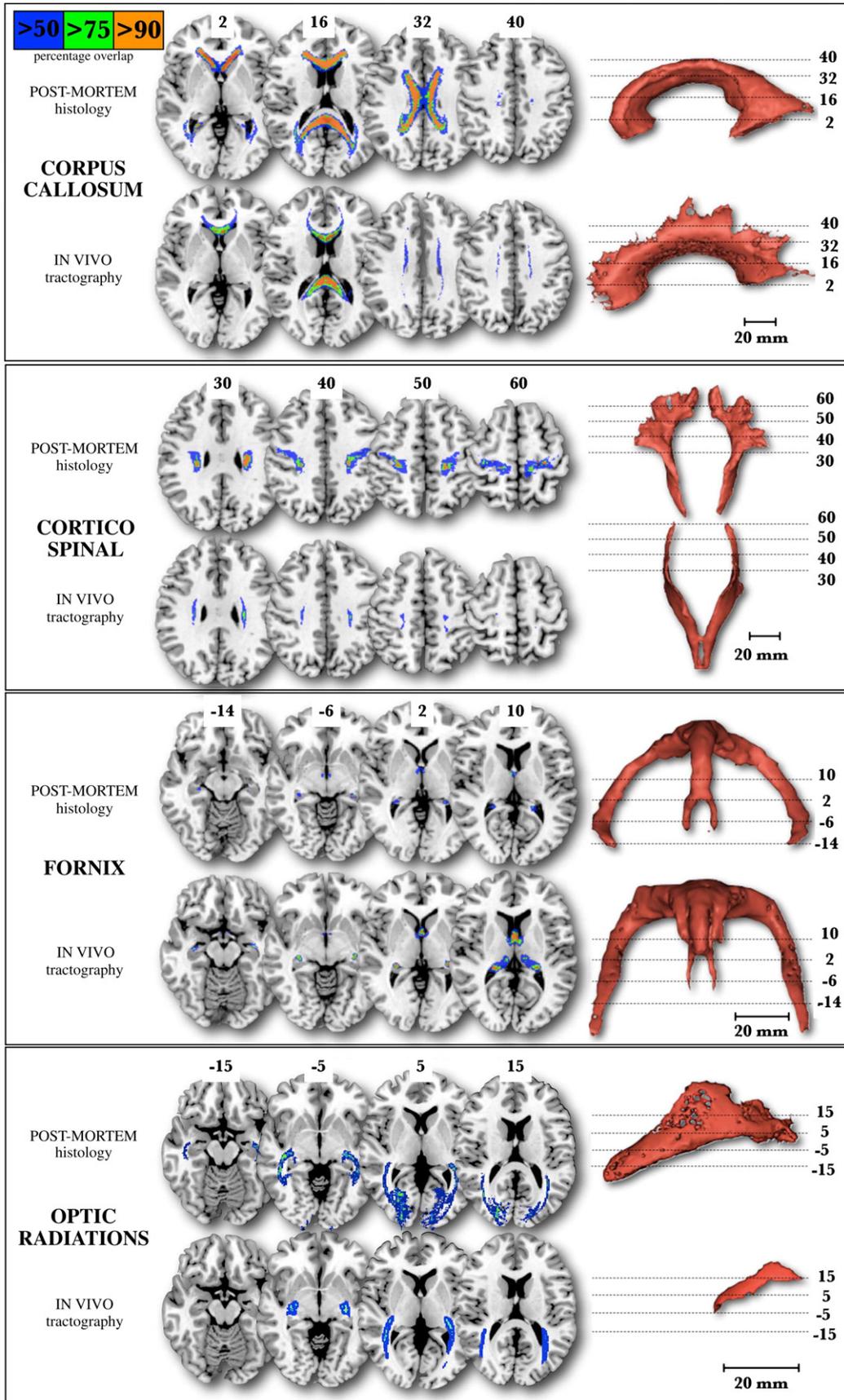


Fig. 2. 3D reconstruction of the major commissural, associative and projection pathways revealed by the group effect maps.

## COMMISSURAL AND PROJECTION PATHWAYS



**Fig. 3.** Comparison between percentage maps based on post-mortem histology (upper rows) (Bürgel et al., 2006) and DTI tractography (lower rows) of the major commissural and projection tracts (the anterior commissure was not available for the histological maps). Numbers above each slice refer to MNI co-ordinates. On the right, tridimensional reconstructions of two sets of maps (>50% subjects' tract overlaps) are shown.

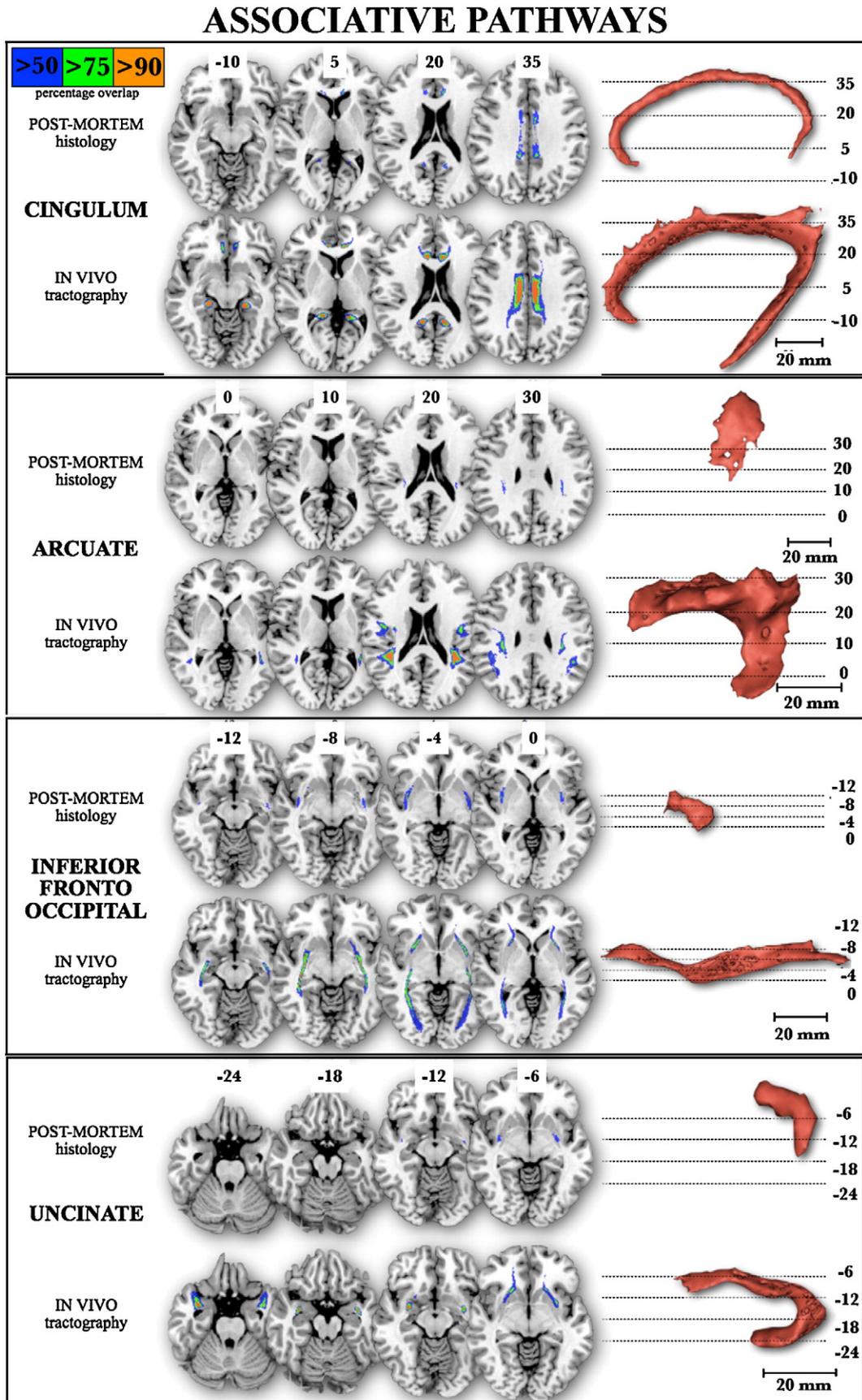
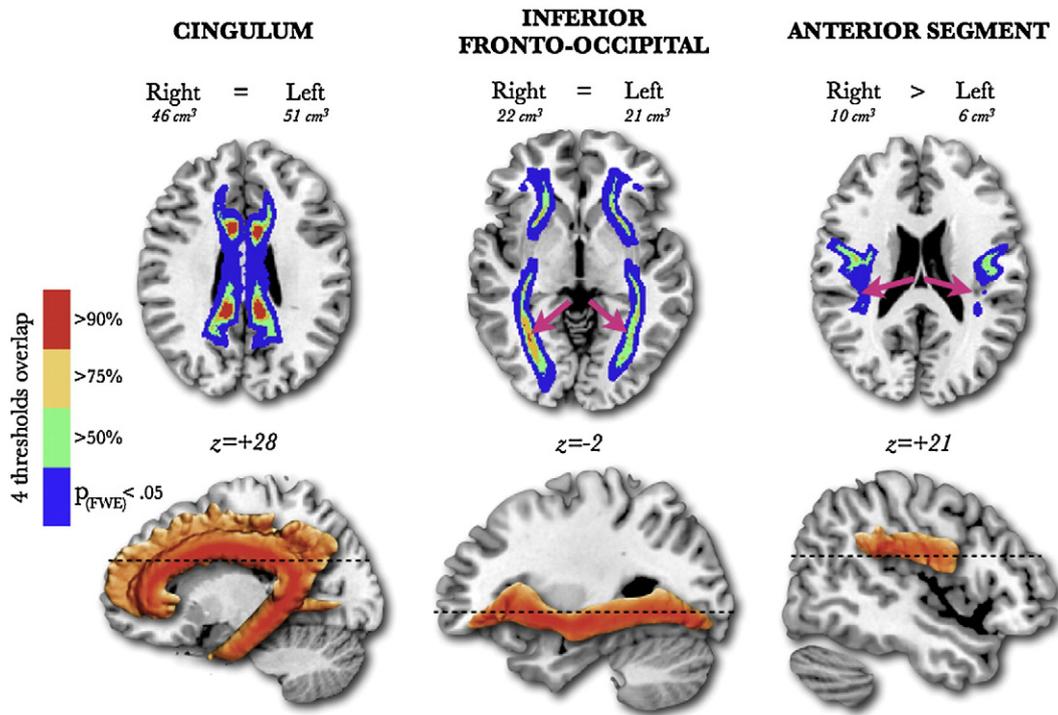


Fig. 4. Comparison between percentage maps based on post-mortem histology (upper rows) (Bürgel et al., 2006) and DTI tractography (lower rows) of the major association tracts. Numbers above each slice refer to MNI co-ordinates. On the right, tridimensional reconstructions of two sets of maps (>50% subjects' tract overlaps) are shown.



**Fig. 5.** The composite maps of the DTI-derived atlas reveal that the left–right differences in volume of the bilateral tracts do not always correlate with the left–right distribution of the percentage overlap maps. The cingulum, for example, shows an almost symmetrical distribution for both volume and percentage overlap maps, while the inferior fronto-occipital fasciculus shows similar left–right volumes but greater overlap in the right side (i.e. lower inter-subject variability) (pink arrows). Finally the anterior segment shows rightward asymmetry for both volume and percentage maps (pink arrows). On the lower panel the dashed lines indicate in the MNI the plane on the z-axis of the axial slice above.

$p < 0.001$ ) and number of streamlines ( $T_{(39)} = 5.3$   $p < 0.001$ ) of the cortico-spinal tract and for the volume ( $T_{(39)} = 7.2$   $p < 0.001$ ) and number of streamlines ( $T_{(39)} = 10.9$   $p < 0.001$ ) of the long segment of the arcuate fasciculus. The volume of the optic radiations showed a leftward asymmetry ( $T_{(39)} = 2.7$   $p < 0.01$ ) which did not survive Bonferroni correction.

A statistically significant rightward asymmetry was found for the volume of the arcuate fasciculus ( $T_{(39)} = 3.4$   $p < 0.001$ ) and for the number of streamlines ( $T_{(39)} = 4.4$   $p < 0.001$ ) of the inferior fronto-occipital fasciculus. Of the three segments of the arcuate fasciculus the anterior segment showed a rightward asymmetry in volume ( $T_{(39)} = 5.6$   $p < 0.001$ ) and number of streamlines ( $T_{(39)} = 5.9$   $p < 0.001$ ).

Analysis of the FA measurements revealed a leftward asymmetry for the inferior longitudinal fasciculus ( $T_{(39)} = 6.2$   $p < 0.001$ ). In contrast a rightward lateralization was found for the optic radiations ( $T_{(39)} = 5.1$   $p < 0.001$ ) and the anterior segment of the arcuate fasciculus ( $T_{(39)} = 3.7$   $p < 0.001$ ).

The ANOVA analysis showed a significant interaction between the lateralization index of tract volume and the gender ( $F_{(13,494)} = 2.0742$   $p < 0.05$ ), but no interaction for the lateralization index of the number of streamlines and FA. Post-hoc analysis revealed a statistically significant gender difference in the lateralization index of the volume of the long segment of the arcuate ( $T_{(38)} = 2.57$   $p < 0.05$ ), with males (lateralization index  $-0.56 \pm 0.36$ ) showing a greater left lateralization compared to females (lateralization index  $-0.24 \pm 0.28$ ). However the difference did not survive Bonferroni correction.

#### Group effect and overlap maps

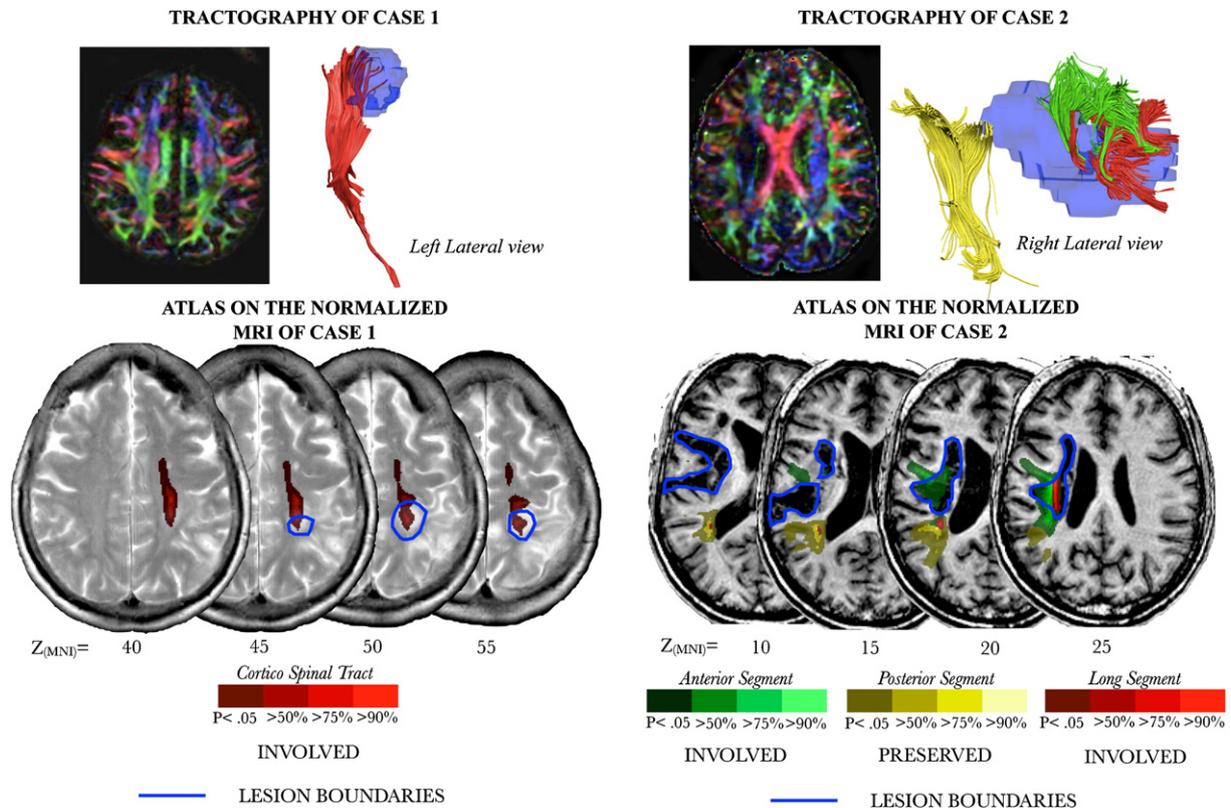
The results of the group effect statistic for the commissural, projection, cerebellar and association tracts are shown in Fig. 2. All tracts were present in each subject except for the long segment of the arcuate on the right hemisphere. Hence, for the right long segment percentage overlap and group effect maps have been derived only from 16 subjects. The DTI percentage overlap maps of projection,

commissural and associative tracts are shown in Figs. 3 and 4. A concentric distribution of the variability maps was observed for all tracts, with a descending gradient from the central portion (overlap more than 90%) to the most peripheral zones (overlap below 50%).

Finally composite maps derived from the overlap of the group effect and the percentage overlap maps were created for each dissected tract. The composite maps provide complementary information about the constant anatomy of the tracts and the inter-individual variability as illustrated by the tracts shown in Fig. 5. The maps of the cingulum, for example, show a symmetrical pattern of both tract volume and percentage overlap maps. For other tracts the lateralization of volume and the degree of overlap differ. This is the case for the inferior fronto-occipital fasciculus where maps show no left–right differences in the tract volume but asymmetrical distribution of the percentage overlap maps. Finally the anterior segment of the arcuate is an example of asymmetry for both volume and percentage maps.

#### Comparison with histology-based variability maps

The percentage overlap maps derived from DTI-tractography were compared with the histological maps from the atlas of Bürgel et al. (2006). Overall there is a good anatomical correspondence between the DTI-tractography and the histological maps for the central portion of the cortico-spinal tract, corpus callosum and fornix. Differences between histological and DTI-tractography derived maps were particularly evident for the association tracts and cortical projections of the cortico-spinal tract. In particular the volume of the optic radiations and the cortico-spinal tract was smaller in the DTI maps compared to the histological maps, whereas volume of all association tracts was greater in the DTI maps compared to the histological maps. Differences in tract volume between the two atlases are due to partial reconstructions (false negatives) or overestimation (false positive) of the tracts due to limitations inherent to each technique.



**Fig. 6.** The composite maps presented in this study can be used for establishing the relationship between focal lesions and the nearby white matter tracts. In the left upper panel the axial directionality (red, green and blue, RGB) map of a patient with right lower limb weakness shows an area of reduced FA in the posterior part of the corona radiata. The overlaying of the cortico-spinal tract maps onto the normalized MR images suggests a direct involvement of the posterior portion of the cortico-spinal tract by the tumour. The involvement of the cortico-spinal tract is in this case confirmed by the tractography reconstruction of the cortico-spinal tract that shows an interruption and intersection with the tumour of the posterior cortico-spinal tract streamlines. In the right upper panel the axial directionality (RGB) map of a patient with hemispatial neglect shows an area of reduced FA in the corona radiata (blue) extending into the most lateral voxels (green) containing fibres of the arcuate fasciculus. The exact involvement of the different components of the arcuate fasciculus is difficult to determine on the directionality maps alone. Below, the structural images show a stroke in the hemisphere that according to the atlas involves both anterior and long segments. The tractography analysis confirms involvement of both segments, which are only partially reconstructed in the most anterior regions.

Examples of the false negative reconstructions of DTI are the lack of lateral cortico-spinal tract projections to the face/tongue region and the lack of callosal fibers projecting to the ventrolateral regions of the frontal, parietal and occipital lobes and posterior temporal lobe (i.e. tapetum). A false negative result of the histological maps is the lack of terminal projections for all association tracts (Figs. 3 and 4).

#### Atlas-based tract localization in brains with pathology

Fig. 6 shows the application of the atlas to two patients presenting with neurological symptoms due to localized brain lesions. The first patient presented with a mass in the left post-central gyrus and right hemiplegia. The atlas overlapped on the patient's normalized T2-weighted images indicated that the tumor was infiltrating the posterior portion of the left cortico-spinal tract at the level of the corona radiata. The DTI color maps and the tractography reconstruction of the projection tracts performed on the patient's own DTI dataset (after placing a ROI in the posterior limb of the internal capsule) confirmed that the tumor involves the streamlines of the cortico-spinal tract at the level of the corona radiata.

The second patient presented with a right middle cerebral artery ischemic stroke and spatial neglect of the left hemisphere. Neglect is a syndrome associated with lesions of the right perisylvian pathways. Overlay of the atlas-derived tract composite maps on the normalized T1-weighted image suggested involvement of the anterior and long segments of the right arcuate fasciculus. Dissections of the patient's DTI confirmed that the lesion involved these two tracts.

#### Discussion

In this study we used DTI-tractography to produce a white matter atlas in the MNI space that describes the in vivo variability of the major association, commissural, and projection connections. Three findings emerge from our work. First, tracts like the cortico-spinal tract and the long segment of the arcuate fasciculus are left lateralized, whereas the anterior segment of the arcuate fasciculus and the inferior fronto-occipital fasciculus are right lateralized. Secondly, we confirmed gender differences for the long segment, which is more left lateralized in males as compared to females. Finally, each tract showed an inter-individual variability that could reflect anatomical differences among the healthy population.

The leftward asymmetry found in the cortico-spinal tract and the long segment of the arcuate fasciculus is in agreement with previous findings from post-mortem dissections (Rademacher et al., 2001), in vivo DTI-tractography (Nucifora et al., 2005; Hagmann et al., 2006; Eluvathingal et al., 2007; Lebel and Beaulieu, 2009), and voxel-based analysis of T1-images (Good et al., 2001; Hervé et al., 2006, 2009). An important question is the extent to which structural differences between the two hemispheres correlate with functional lateralization, and whether the anatomical lateralization of language and sensory-motor pathways reflects differences in language, visuo-spatial processing and handedness. Preliminary studies combining DTI tractography and fMRI reported no correlation between the lateralization of the arcuate fasciculus volume and the degree of functional lateralization as determined by fMRI during tasks of verbal fluency, verb generation and reading comprehension (Powell et al., 2006). The functional lateralization seems to correlate better with the lateralization of the fractional

anisotropy (Powell et al., 2006; Vernooij et al., 2007) and the number of streamlines of the arcuate fasciculus as demonstrated in right-handed healthy individuals (Vernooij et al., 2007) and in patients with temporal lobe epilepsy (Rodrigo et al., 2008).

There are also preliminary findings showing that the extreme left lateralization of the direct long segment (fronto-temporal) is associated with worse performance on a complex verbal memory task that relies on semantic clustering for retrieval (i.e. California Verbal Learning Test, CVLT). The correlation remained significant after splitting the group according to gender, suggesting that the main determinant of CVLT performance is the anatomy (symmetry) of the language pathways, and not the gender. Overall these findings support the notion that lateralization of language to the left hemisphere is an important aspect of human brain organization but paradoxically, a bilateral representation might ultimately be advantageous for certain cognitive functions (Catani et al., 2007).

Higher FA in the anterior part of the superior cingulum has been previously reported in the left hemisphere using tractography (Gong et al., 2005) and voxel based statistics (Park et al., 2004). Our analysis of the whole cingulum shows no significant hemispheric asymmetry, suggesting that overall the cingulum has a symmetrical distribution of the FA with only the anterior region showing a leftward asymmetry (Park et al., 2004; Gong et al., 2005).

In addition to the above findings we report, for the first time, a rightward asymmetry for the volume of the fronto-parietal connections (i.e. anterior segment) of the arcuate fasciculus and the inferior fronto-occipital fasciculus. These tracts convey sensory information from parietal and occipital areas respectively, to a more anterior region in the inferior frontal gyrus. Lesions to the projection areas of the fronto-parietal segment of the arcuate fasciculus and the inferior fronto-occipital fasciculus result in neglect (Doricchi et al., 2008), a syndrome characterized by the inability to process visual sensory information in one hemisphere. Neglect occurs mostly with lesions to the right hemisphere and the asymmetry of the fronto-parietal segment of the arcuate fasciculus (Thiebaut de Schotten et al., 2005) and the inferior fronto-occipital fasciculus (Urbanski et al., 2008) may represent the anatomical correlate of right hemisphere dominance for visuo-spatial processing.

We found gender differences in the lateralization of the fronto-temporal long segment of the arcuate, with a more left lateralized pattern in males. Previous studies have also reported gender differences in the lateralization of the cortical volume of language regions (Good et al., 2001; Luders et al., 2004), subcortical white matter anatomy (Good et al., 2001; Hagmann et al., 2006), and activation patterns during linguistic tasks (Shaywitz et al., 1995). It has been suggested that gender differences in the lateralization pattern may reflect a different maturational trajectory during development (Paus, 2009; Perrin et al., 2009). Some, for example, documented significant gender differences in the white matter of the left inferior frontal gyrus, a region containing anterior projections of the arcuate fasciculus: boys but not girls showed a linear age-related increase in the white matter volume in this region (Blanton et al., 2004). However, a recent DTI tractography study found no gender differences for the arcuate in the transition from childhood to adolescence (Lebel and Beaulieu, 2009). Hence, the authors suggested that differentiation between the two hemispheres occur early in life and it is maintained during adolescence.

The inter-individual variability we observed for each tract is likely to reflect differences in tract volume, their course and termination. Other biological factors such as axonal diameter, density, and myelination modulate the diffusion signal and can explain inter-individual variability at a microstructural level (e.g. FA) (Beaulieu, 2009). However other methodological explanations should also be considered. The normalization procedure we employed, which deforms each brain to fit with the referential template, may produce misregistration errors (Ashburner, 2007). Even small misregistration

errors are likely to generate maps with a higher degree of overlap in the central portion of the tracts, and a lower degree of overlap in the peripheral regions. Misregistration is also frequent in datasets where individual brains show structural differences in relation, for example, to age (Stadlbauer et al., 2008) and handedness (Hagmann et al., 2006). In our sample we recruited only right-handed subjects within a relatively narrow age range to reduce this source of variability. The degree of uncertainty in the estimation of the fibre orientation which is typical of DTI-tractography algorithms may also increase variability across subjects. For example, in regions containing crossing fibres the FA decreases as the confidence intervals in fibre orientation (i.e. “cone of uncertainty”) increases (Jones, 2003). In tractography, accumulated uncertainties in fibre orientation have clear potential for leading to erroneous reconstructions of pathways. For example Jones (Jones, 2003) demonstrated that the cone of uncertainty is greater in the most terminal regions of the tracts where the reliability of fibre orientation maps decreases. In this study, we set a FA threshold of 0.2 to exclude most of voxels with a high cone of uncertainty and therefore reduce the probability of artefactual reconstructions.

The similarity between our maps and the histology-based atlas (Rademacher et al., 2001; Bürgel et al., 2006) suggests that true anatomical differences contribute to the variability observed in the healthy population. However, compared to the histological maps, our DTI tractography approach was not able to visualize the lateral projection of the cortico-spinal tract and the most anterior part of the optic radiations. This is due to the limitations of current diffusion tensor models in resolving fibre crossing (McNab et al., 2009); in our case, DTI was unable to visualize the fibres of the cortico-spinal tract crossing the arcuate fasciculus. The use of novel algorithms in tractography reconstructions (e.g. spherical deconvolution) may in part overcome these limitations (Tournier et al., 2004, 2008; Dell'Acqua et al., 2007, 2010). For other tracts, such as the arcuate fasciculus, uncinate and inferior fronto-occipital fasciculus, DTI tractography was able to show anatomical features that are closer to classical post-mortem blunt dissections than post-mortem histology. This may be due to the difficulty of following anterior to posterior tracts on coronal slices using post-mortem myelin staining methods. Differences in the age range between studies may also explain some of the differences we found between the post-mortem (Bürgel et al., 2006) and the DTI tractography results (Jones et al., 2006; Verhoeven et al., 2010). White matter anatomy changes with age and in the older population white matter changes related to atrophy, reduced myelination, gliosis and so forth can affect the ability to obtain reliable dissections. The subjects recruited for our study had a relatively young and narrow age range, and therefore the results of our study may not be representative of white matter anatomy across the lifespan. Future atlases will need to take into account the age-related changes in diffusion measurements (Lebel et al., 2008, 2010; Lebel and Beaulieu, 2009; Verhoeven et al., 2010) and how these changes affect the tracking results.

The atlas could facilitate the identification of the main white matter tracts on T2- and T1-weighted MR images in patients with a wide range of pathologies including stroke, multiple sclerosis, acquired and hereditary leukoencephalopathies, neurodegenerative diseases, tumours and vascular malformations. However, in these patients the overlapping of the atlas maps with the structural data could raise some problems due, for example, to tissue displacement and an altered anatomy secondary to the tumour mass effect (Clark et al., 2003). Hence, the results in these patients should be interpreted with caution. Finally the atlas can also help localize between-group differences derived from voxel based morphometry analysis in psychiatric disorders such as autism (Catani et al., 2008; Pugliese et al., 2009), depression, schizophrenia (Kanaan et al., 2009) and antisocial behaviour (Craig et al., 2009).

In conclusion, a decade ago, radiological information about white matter anatomy could only be inferred from axonal tracing

studies in monkeys and a limited number of histological atlases based on human post-mortem dissections. Our results suggest that DTI-tractography maps can complement the information on the constant and variable features of white matter anatomy derived from quantitative histological atlases. Composite maps of inter-hemispheric asymmetry and interindividual variability have the potential to become a very useful educational and practical tool in establishing the relationship of a lesion with adjacent white matter tracts. This adds a new layer of complexity to the correlation method by linking deficits to inferred dysfunction within distributed networks.

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