

# Atlasing the frontal lobe connections and their variability due to age and education: a spherical deconvolution tractography study

K. Rojkova · E. Volle · M. Urbanski ·  
F. Humbert · F. Dell'Acqua · M. Thiebaut de Schotten

Received: 23 July 2014 / Accepted: 2 February 2015  
© Springer-Verlag Berlin Heidelberg 2015

**Abstract** In neuroscience, there is a growing consensus that higher cognitive functions may be supported by distributed networks involving different cerebral regions, rather than by single brain areas. Communication within these networks is mediated by white matter tracts and is particularly prominent in the frontal lobes for the control and integration of information. However, the detailed mapping of frontal connections remains incomplete, albeit crucial to an increased understanding of these cognitive functions. Based on 47 high-resolution diffusion-weighted

imaging datasets (age range 22–71 years), we built a statistical normative atlas of the frontal lobe connections in stereotaxic space, using state-of-the-art spherical deconvolution tractography. We dissected 55 tracts including U-shaped fibers. We further characterized these tracts by measuring their correlation with age and education level. We reported age-related differences in the microstructural organization of several, specific frontal fiber tracts, but found no correlation with education level. Future voxel-based analyses, such as voxel-based morphometry or tract-based spatial statistics studies, may benefit from our atlas by identifying the tracts and networks involved in frontal functions. Our atlas will also build the capacity of clinicians to further understand the mechanisms involved in brain recovery and plasticity, as well as assist clinicians in the diagnosis of disconnection or abnormality within specific tracts of individual patients with various brain diseases.

**Electronic supplementary material** The online version of this article (doi:[10.1007/s00429-015-1001-3](https://doi.org/10.1007/s00429-015-1001-3)) contains supplementary material, which is available to authorized users.

K. Rojkova · E. Volle · M. Urbanski · M. Thiebaut de Schotten (✉)  
CNRS UMR 7225, Inserm, UPMC-Paris6, UMR\_S 1127, CRICM,  
GH Pitié-Salpêtrière, 75013 Paris, France  
e-mail: michel.thiebaut@gmail.com

K. Rojkova · M. Thiebaut de Schotten  
Natbrainlab, Brain and Spine Institute, Paris, France

M. Urbanski  
Service de Médecine et de Réadaptation Gériatrique et  
Neurologique, Hôpitaux de Saint-Maurice, Saint-Maurice,  
France

F. Humbert  
Centre de Neuroimagerie de Recherche CENIR, Groupe  
Hospitalier Pitié-Salpêtrière, Paris, France

F. Dell'Acqua  
Department of Neuroimaging, Institute of Psychiatry,  
Natbrainlab, King's College London, London, UK

M. Thiebaut de Schotten  
Natbrainlab, Sackler Institute of Translational  
Neurodevelopment, Institute of Psychiatry,  
King's College London, London, UK

**Keywords** White matter · Frontal lobe · Atlas · Aging ·  
Fasciculi · U-shaped tracts · Tractography · Diffusion-  
weighted imaging

## Introduction

The study of frontal lobe connections is essential to understand the role and the organization of the frontal lobes' distinct subregions. The functions of the frontal subregions emerge from an interaction with other cortical areas, on which it exerts its control, and from which it receives information to integrate. These interactions are supported by short- and long-range white matter connections. While most of the recent data and theories regarding the functional organization of the frontal lobes have been supported

by functional imaging, its anatomical connectivity has yet only been scarcely investigated.

In 1985, a breakthrough came with the emergence of a new magnetic resonance imaging (MRI) modality: the diffusion-weighted MRI (Le Bihan and Breton 1985). This non-invasive technique offers a unique approach to investigate *in vivo* the structure of brain tissues by measuring the diffusion of water molecules along different directions. This exciting technical advance not only reproduced reliably known anatomy in the living human brain (Catani et al. 2002; Catani and Thiebaut de Schotten 2008), but also refined the description of large fiber bundles (Catani et al. 2005). Moreover, it also gave rise to studies of intersubject variability (Ciccarelli et al. 2003; Thiebaut de Schotten et al. 2011; Verhoeven et al. 2010; Wakana et al. 2007), asymmetries (Barrick et al. 2007; Catani et al. 2007), behavioral correlates (Barrick et al. 2007; Catani et al. 2007; Johansen-Berg et al. 2007; Thiebaut de Schotten et al. 2014a) and pathological differences (Craig et al. 2009; Thiebaut de Schotten et al. 2014a). While several fiber populations cross almost everywhere in the brain (Dell'Acqua et al. 2013; Jeurissen et al. 2013), standard diffusion tensor tractography models follow the principal direction of fibers, leading to incomplete or erroneous reconstructions of white matter features (Thiebaut de Schotten et al. 2011) that may bias tract-specific measurements (Dell'Acqua and Catani 2012; Vos et al. 2012). New developments in tractography and diffusion modeling can circumvent this issue by extracting the orientation distribution of different populations of fibers within the same voxel (Dell'acqua et al. 2010; Descoteaux et al. 2007; Tournier et al. 2004; Tuch et al. 2003; Wedeen et al. 2005). These new methods allow the depiction of tracts that better correspond to postmortem dissections (Dauguet et al. 2006, 2007; Lawes et al. 2008; Thiebaut de Schotten et al. 2011) and simian axonal tracing (Thiebaut de Schotten et al. 2012) with good reliability (Kristo et al. 2013b). More recently, a novel nomenclature of the frontal lobe U-shaped connection was made possible through preliminary results that combined postmortem Klingler dissection (Klingler 1935) with high-resolution spherical deconvolution tractography (Catani et al. 2012). However, intersubject variability and aging effects could not be assessed due to the small sample size of participants studied. New tract-specific measurements taking into account the crossing of fibers also followed these advances in diffusion imaging tractography (e.g., apparent fiber density or hindrance modulated orientational anisotropy (HMOA) Raffelt et al. 2012; Dell'Acqua et al. 2013). These new measurements are specific to the direction followed by the tractography, therefore providing a true tract-specific index to characterize white matter diffusion when crossing. These indices could offer a more precise characterization of the

underlying microstructural organization and, consequently, be more sensitive to age-related differences of individual tracts when compared with traditional diffusion tensor imaging indices, such as fractional anisotropy (FA).

The study of the frontal connections is also of particular interest for the neurosciences of aging. With aging, neuronal loss and small vessel alteration lead to progressive and subtle white matter changes associated with cognitive decline in the elderly (Pantoni 2010; Xiong and Mok 2011). Cognitive decline affects predominantly many executive functions but not all (Geerligs et al. 2014), and brain changes seem to distribute unevenly, affecting predominantly the frontal region (Bishop et al. 2010; Curiati et al. 2009; Draganski et al. 2011; Giorgio et al. 2010; Good et al. 2001; Moscovitch 1992; Raz et al. 2000, 2004; West 1996) suggesting that the latest developed brain areas are especially susceptible to show an accelerated aging (Tammes et al. 2010). Previous cross-sectional studies using tract-specific measurements confirmed this “frontal lobe hypothesis” for the white matter by revealing a slow decrease with aging in the FA for frontal callosal tracts (Hsu et al. 2008; Hasan et al. 2009b; Lebel et al. 2010; Bastin et al. 2008; Michielse et al. 2010) and for long tracts connecting the frontal lobe (Jones et al. 2006; Hasan et al. 2010, 2009a), affecting more prominently the frontal portion of these tracts (Davis et al. 2009). The same result was corroborated with voxel-based statistics showing a negative correlation between aging and FA in specific, but not all areas of the frontal lobes (Giorgio et al. 2010; Madden et al. 2004, 2007; O'Sullivan et al. 2001; Phillips et al. 2013; Raz 2005; Salat et al. 1999). Nevertheless, it is important to note that the “frontal lobe hypothesis” has also been contested by a 2-year longitudinal study showing no evidence of an accelerated decline in the frontal lobe region in the aging population (Barrick et al. 2010). Hence, aging may affect some, but not all, tracts of frontal white matter. This explains the contrasted results reported in the literature. Further, age-related differences are not taken into account in atlases built from populations with a restricted age range; this bias may hamper the use of these atlases in various clinical populations. One way to circumvent this issue is to build a normative global atlas based on a healthy population with a large age range. The effects of age may also differ according to some factors, such as compensatory networks (Stern et al. 2005, 2008) or increased functional connectivity in existing networks (Bastin et al. 2012), providing a partial protection called “cognitive reserve” (Stern 2002, 2009). Higher education seems to also be an important factor delaying aging effects on the brain and cognitive decline (Brayne et al. 2010; Coffey et al. 1999), and preliminary evidences suggest structural connectivity changes associated with cognitive reserve in the elderly (Fischer et al. 2014). However it is unknown whether specific tracts support these changes.

Therefore, the aim of our study was to map, in a sample of healthy participants, all the association, projection and short U-shaped tracts previously described in the frontal lobe. We also estimated the effect of age and level of education on these tracts using measures of the volume, FA and HMOA. The final atlas of the human frontal lobe can be used for future clinical–neuroanatomical correlation in patients of various age ranges and levels of education.

## Materials and methods

### Participants

This study was approved by the local ethics committee. Participants were recruited via advertising in the Salpêtrière Hospital and on the web site [www.risc.cnrs.fr](http://www.risc.cnrs.fr). All participants were right-handed healthy adults with no history of neurological or psychiatric disorder, no cognitive complaints, and no cognitive impairments or depression, as assessed using translated versions of the Mini Mental State (Folstein et al. 1975) and the MADRS (Montgomery and Asberg 1979). Participants were not included if their MMSE score was lower than 27 and if they had a history of neurological or psychiatric symptoms.

All subjects had an MRI scan including 3D T1-weighted images in addition to diffusion images (acquisition, pre-processing, rules for dissections as well as the approach employed to map white matter tracts are reported in supplementary material). All brain images were examined by a neuroradiologist. Millimetric T1-weighted and diffusion-weighted images did not show any significant signal abnormalities evocative of a small vessel disease or of an evolving neurological disease. Subjects with abnormalities on MRI were excluded.

Informed and written consent to participate in this study was provided by 57 right-handed volunteers. Participants were excluded from the analysis for medical reasons (anomalies on neuropsychological testing or on the brain MRI) or for head movements during the MRI acquisition. The average age of the 47 remaining participants (24 males and 23 females) was 45.45 years ( $\pm 14.79$  years; aged between 22 and 71 years) and their education level was 15.36 years of education ( $\pm 3.00$  years; range between 10 and 26 years), noting that a French bachelor's degree corresponds to 12 years of education. Subjects from our sample had relatively high education levels, independently of their gender ( $t_{(45)} = 1.203$ ;  $p = 0.235$ ) but with a trend of correlation with age, with younger participants having a slightly but not significantly higher educational level than older participants ( $r = -0.259$ ;  $p = 0.079$ ). Therefore, partial correlation statistics were carried out for controlling for age or education when appropriate.

### Statistical analysis

To test whether white matter differences distribute unevenly, affecting predominantly the frontal region, we used SPSS software (SPSS, Inc., Chicago, IL, United States of America) to carry on a repeated ANOVA between tracts emerging from the frontal lobe and tracts not involving the frontal lobe using age and education as covariates.

For each of the following statistics, we employed a false discovery rate (FDR) correction (Benjamini and Hochberg 1995) for multiple comparisons; this is available as a tool on the Signed Differential Mapping website (<http://www.sdmproject.com/>).

Gaussian distribution of the data using the Shapiro–Wilk test (Shapiro and Wilk 1965) was not confirmed for all variables in our group of participants. Therefore, two-tailed partial Spearman rank correlation coefficients (Spearman 1904) were performed between the measurements of each dissected single tract and age, controlling for the education level of the participants. Similarly, partial Spearman ranking correlation coefficients were performed between the measurements of each dissected single tract and the education level controlling for age (FDR corrected for 55 tracts).

## Results

We successfully identified and mapped, in the MNI reference space, 55 frontal tracts: 16 interlobar association tracts, 1 commissural tract, 8 frontal projection tracts and 30 frontal short U-shaped tracts for both hemispheres (Fig. 1). Maps are provided as an online digital supplementary material (freely available, please send a request to [michel.thiebaut@gmail.com](mailto:michel.thiebaut@gmail.com)) and projections of these tracts are provided in Figs. 2, 3 and 4. Percentage of success for the reconstruction of each tract and tract-specific measurements are tabulated in supplementary Table 1. This percentage was calculated as follows:

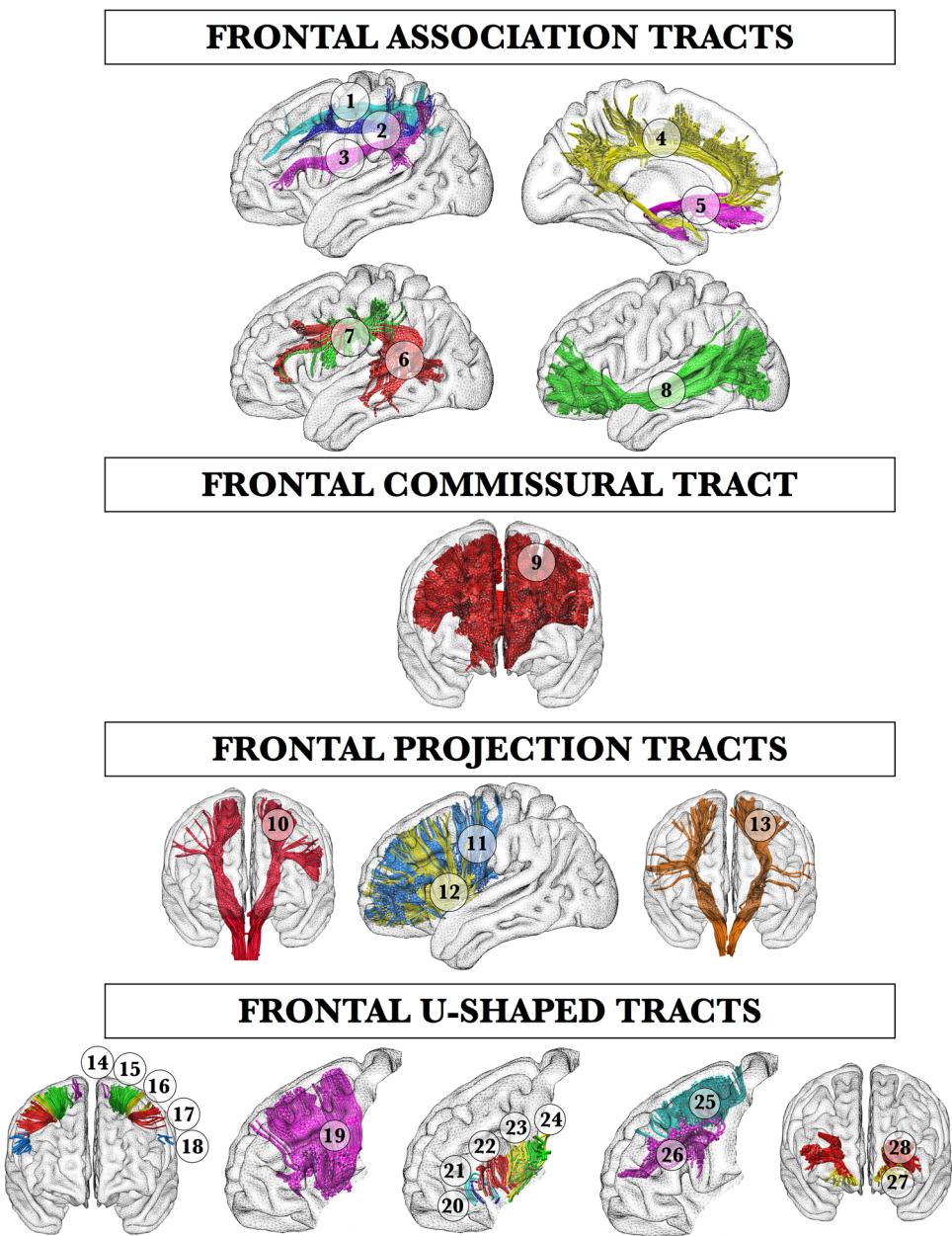
$$\text{Percentage of success} = \frac{\text{Number of successful reconstructions of the tract}}{\text{number of participants}} \times 100$$

### Frontal interlobar association tracts

#### *Superior longitudinal fasciculus (SLF)*

We reconstructed a system, composed of three parallel longitudinal branches passing through the dorsolateral portion of the white matter, situated above the ventricles and the lateral sulcus, and connecting the parietal and the frontal lobes. The

**Fig. 1** Spherical deconvolution tractography of frontal white matter connections. For each tract a single participant map is supplied as a representative example of the individual anatomy. First (SLF I, light blue, no. 1), second (SLF II, dark blue, no. 2) and third (SLF III, pink, no. 3) branches of the superior longitudinal fasciculus; cingulum (yellow, no. 4); uncinate (pink, no. 5); long (LS, red, no. 6) and anterior (AS, green, no. 7) segments of the arcuate fasciculus; inferior fronto-occipital fasciculus (IFOF, no. 8); frontal corpus callosum (CC, no. 9); corticospinal tract (CST, no. 10); fronto-thalamic projections or anterior thalamic radiations (blue, no. 11); fronto-striatal projections (yellow, no. 12); fronto-pontine projections (no. 13); paracentral U tract (pink, no. 14); hand superior (green, no. 15), middle (yellow, no. 16) and inferior (red, no. 17) U tract; face U tract (blue, no. 18); frontal aslant tract (pink, no. 19); fronto-insular tract 1 (FIT 1, light blue, no. 20), 2 (FIT 2, dark blue, no. 21), 3 (FIT 3, red, no. 22), 4 (FIT 4, yellow, no. 23) and 5 (FIT 5, green, no. 24); frontal superior longitudinal (FSL, light blue, no. 25); frontal inferior longitudinal (FIL, pink, no. 26), frontal orbito-polar tract (FOP, yellow, no. 27) and fronto-marginal tract (FMT, red, no. 28). The overall visualization and screenshots were performed in Anatomist (<http://brainvisa.info>)

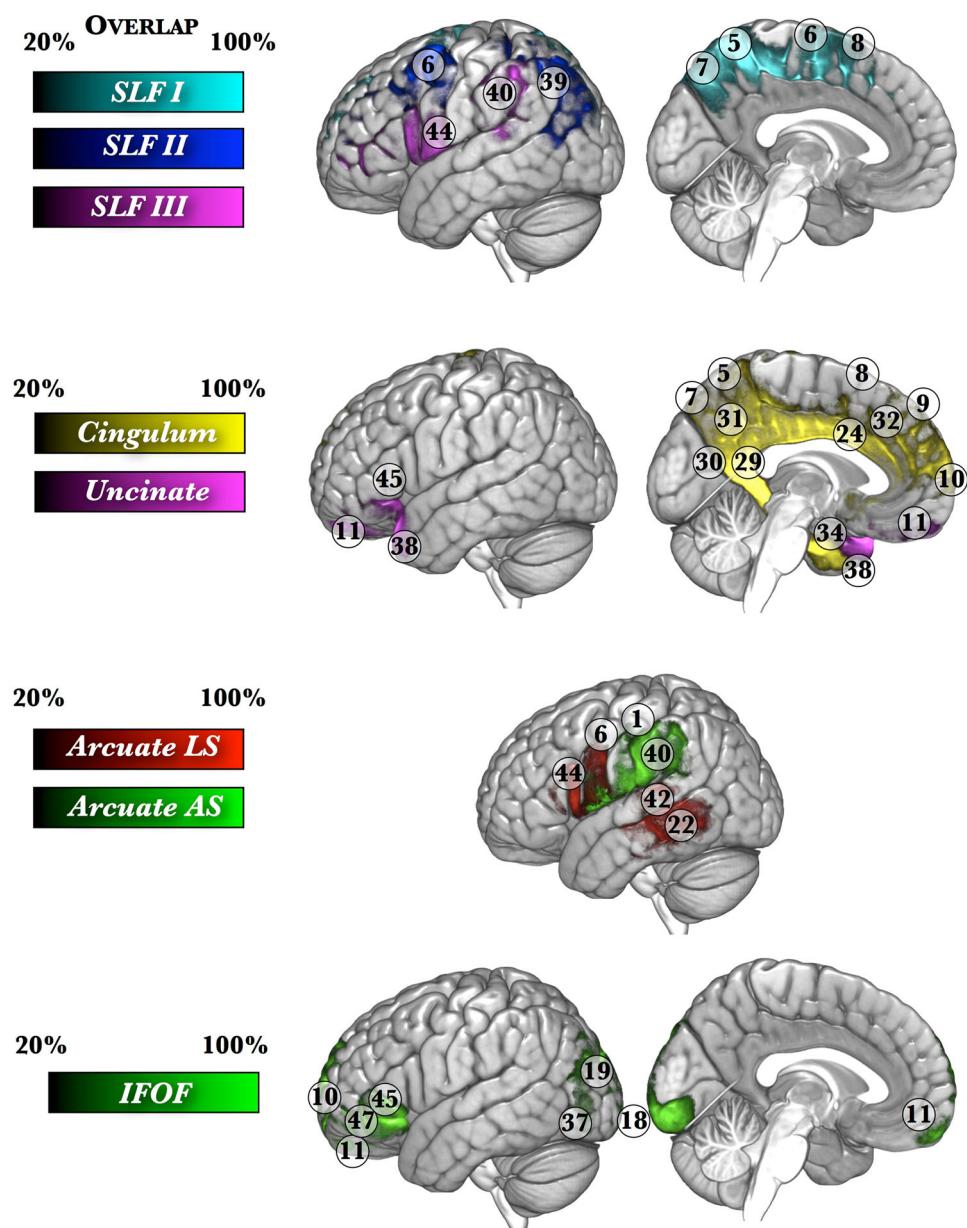


superior branch (SLF I; no. 1 in Fig. 1 and Fig. 2) runs from the superior parietal lobule and the precuneus (Brodmann area, BA7 and BA5) to the superior frontal gyrus (BA6, BA8, BA9 up to BA10). More ventrally, the middle branch (SLF II; no. 2 in Fig. 1 and Fig. 2) connects the angular gyrus (BA39) to the posterior regions of the middle frontal gyrus (BA6). Few projections continue further into the middle frontal gyrus up to BA46. The inferior branch (SLF III; no. 3 in Fig. 1 and Fig. 2) originates in the supramarginal gyrus (BA40) and terminates in the pars opercularis (BA44), triangularis (BA45) and the inferior frontal gyrus (BA47).

Cingulum (no. 4 in Fig. 1 and Fig. 2)

We identified a long medial fiber bundle running within the cingulate gyrus, all around the corpus callosum that contains fibers of different lengths. The longest fibers run from the parahippocampal gyrus and the uncus (BA34) to the medial portion of the orbitofrontal (BA11) cortex. The cingulum also contains short U-shaped fibers that connect the medial frontal (BA32, BA8, BA9, BA10) and parietal (BA31, BA5, BA7) to different portions of the cingulate gyrus.

**Fig. 2** Cortical projection in the MNI stereotaxic space of the frontal interlobar tracts [*top to bottom* the three branches of the superior longitudinal fasciculus (SLFI, SLFII and SLFIII), the cingulum, the uncinate, the arcuate long segment (arcuate LS), the arcuate anterior segment (arcuate AS) and the inferior fronto-occipital fasciculus (IFOF)]. Color brightness depends on overlap percentage. A 50 % overlap in a voxel means that the tract is present in 50 % of participants for this voxel. The numbers on the tridimensional reconstruction correspond to Brodmann areas. The overall visualization and screenshots were performed in MRIcroGL (<http://www.cabiatl.com/mricrogl/>)



#### Uncinate (no. 5 in Fig. 1 and Fig. 2)

The fibers of the uncinate originate from the temporal pole (BA38), parahippocampal gyrus, uncus (BA34) and amygdala. After a U-turn, they enter the external capsule, then reach the lateral and ventral orbital cortex (BA11, BA12) and frontal pole (BA10).

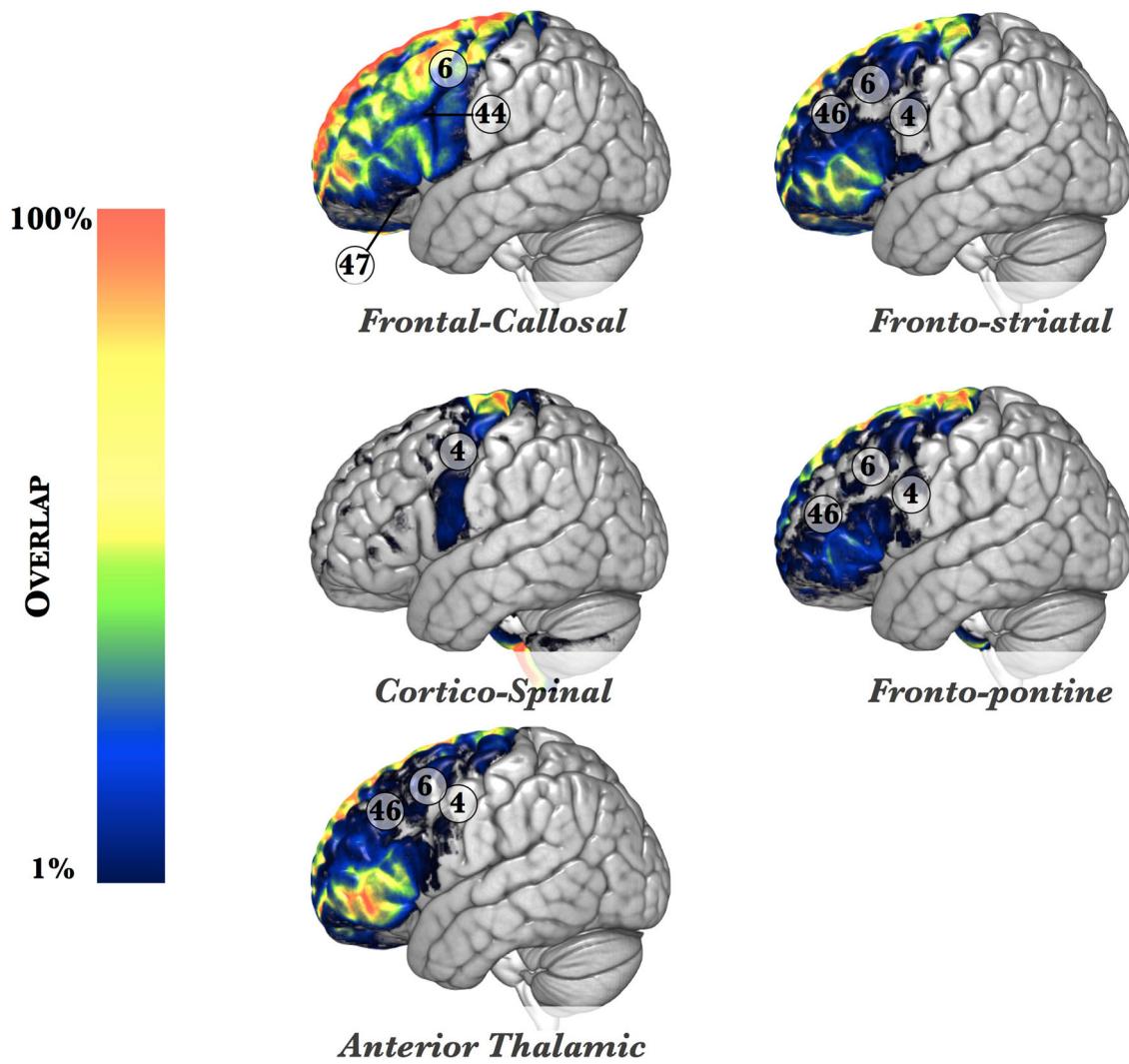
#### Arcuate fasciculus

The fronto-temporal portion of the arcuate fasciculus connects the pars opercularis (i.e., Broca area, BA44) to the auditory cortex (BA22) and the posterior portion of the middle and inferior temporal gyri (BA21, BA37). It forms the long

segment (LS; no. 6 in Fig. 1 and Fig. 2) of the arcuate fasciculus, arching around the Sylvian fissure. Shorter fronto-parietal fibers link the ventral portion of the precentral gyrus (BA6) to the postcentral gyrus (BA1) and the supramarginal gyrus (BA40). These fibers form the anterior segment (AS; no. 7 in Fig. 1 and Fig. 2) of the arcuate fasciculus.

#### Inferior fronto-occipital fasciculus (IFOF, no. 8 in Fig. 1 and Fig. 2)

The inferior fronto-occipital fasciculus is a long-ranged bow tie-shaped tract connecting the occipital lobe to the frontal lobe. It originates from the occipital pole (BA18), the lingual gyrus and the inferior and middle occipital gyri



**Fig. 3** Cortical projection in the MNI stereotaxic space of the commissural and projection tracts. The numbers located beneath the figure refer to the MNI coordinates of different slices displayed. We used a rainbow color code to indicate the percentage overlap. The

numbers displayed on the tridimensional reconstruction correspond to Brodmann areas. The overall visualization and screenshots were performed in MRICroGL (<http://www.cabiatl.com/mricrogl/>)

(BA19). As it leaves the occipital lobe, IFOF narrows and its fibers gather at the level of the extreme capsule. As it enters the frontal lobe, its fibers spread to the inferior frontal gyrus. Its ventral fibers reach the orbital gyrus (BA11) and the frontal pole (BA10), whereas its dorsal fibers terminate in the anterior superior frontal gyrus (most anterior part of BA9 and dorsal BA10).

#### Frontal commissural and projection tracts

Commissural and projection tracts are difficult to follow with tractography as they intertwine with one another and cross-association fibers. Despite spherical deconvolution being designed to circumvent this fiber-crossing issue, their complex configuration may occasionally lead to an underestimation of their true extent. Note that the validity and

limitations of these results will be highlighted in the discussion.

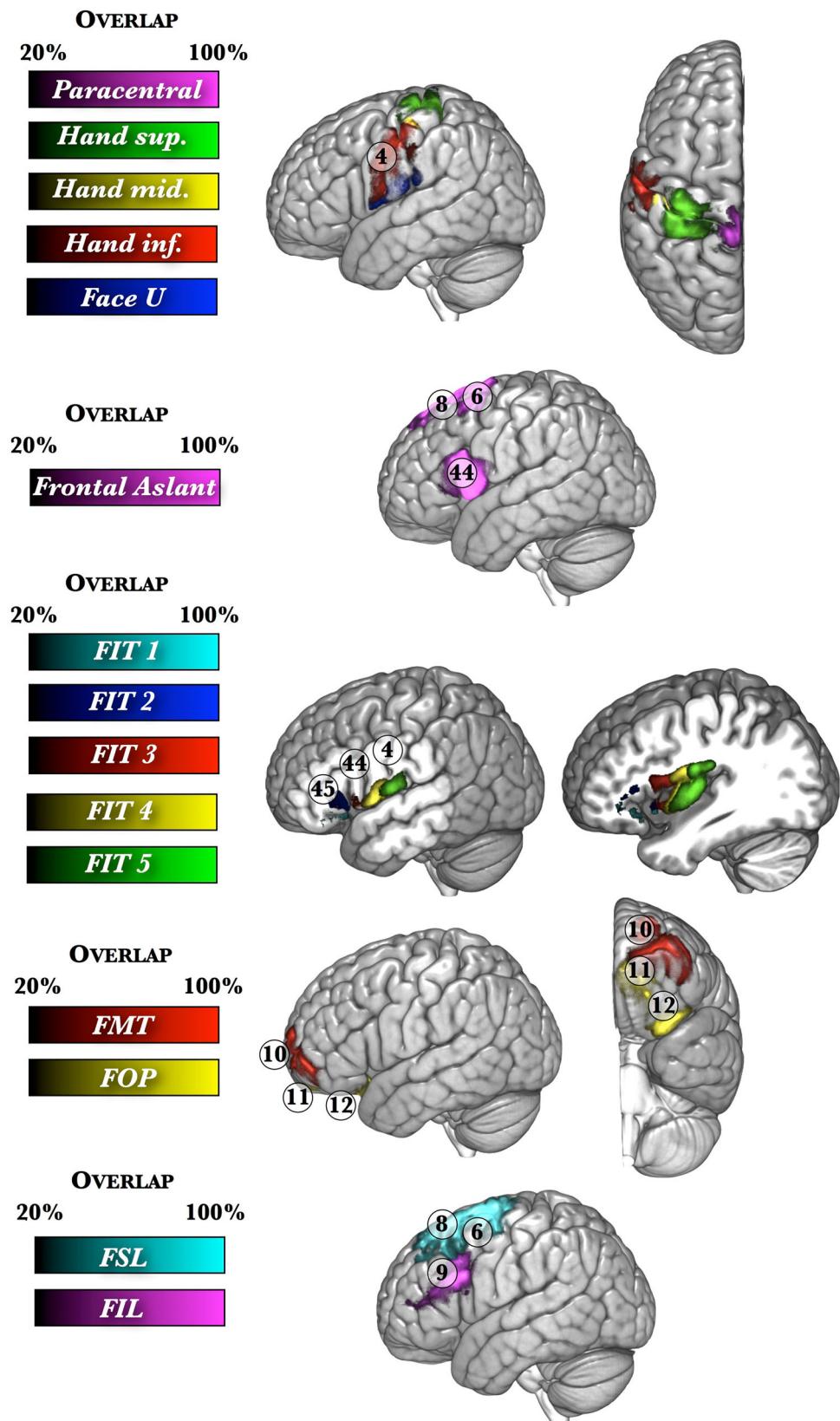
#### *Frontal corpus callosum (no. 9 in Fig. 1 and Fig. 3)*

The frontal portion of the corpus callosum occupies the rostrum, the genu and most of the body of the corpus callosum and projects on to the whole surface of the frontal lobe except for the pars orbitalis (BA 47). These projections also show a reduced probability for the pars opercularis (BA 44) and the frontal eye field (BA 6).

#### *Corticospinal tract (CST, no. 10 in Fig. 1 and Fig. 3)*

The corticospinal tract consists of a fan-shaped set of fibers, passing through the posterior limb of the internal capsule and

**Fig. 4** Cortical projection in the MNI stereotaxic space of frontal short U-shaped tracts (top to bottom: paracentral, hand superior, middle and inferior, face U-shaped, frontal aslant, fronto-insular 1, 2, 3, 4, 5, frontal superior longitudinal, frontal inferior longitudinal, fronto-orbito-polar and fronto-marginal tracts). The numbers located beneath the figure refer to the MNI coordinates of different slices displayed. Color brightness depends on overlap percentage. The numbers displayed on the tridimensional reconstruction correspond to Brodmann areas. The overall visualization and screenshots were performed in MRIcroGL (<http://www.cabiatl.com/mricrogl/>)



projecting from the precentral gyrus (BA4) to the spinal cord. We note that in a third of participants we obtained CST projection onto the whole homunculus in the precentral gyrus; for the remainder of the participants tractography confined its projections to the hand and the lower limb regions.

#### *Fronto-thalamic (anterior thalamic radiations) and fronto-striatal projections (no. 11 and 12 in Fig. 1 and Fig. 3)*

Fronto-thalamic and fronto-striatal projections pass through the anterior limb of the internal capsule and project on to the whole surface of the frontal lobe. These projections also show a reduced probability for the ventral portion of the precentral gyrus and the middle frontal gyrus (BA 6 and 46).

#### *Fronto-pontine projections (no. 13 in Fig. 1 and Fig. 3)*

Fronto-pontine fibers pass through the genu and the anterior limb of the internal capsule and project on to the whole surface of the frontal lobe. As for the fronto-thalamic and fronto-striatal projections, we note a reduced probability of the fronto-pontine projection in the precentral gyrus and the middle frontal gyrus (BA 6 and 46).

#### Frontal U-shaped tracts

##### *Fronto-parietal U tracts*

We mapped a set of five tracts running beneath the central sulcus from the parietal postcentral gyrus (BA1) to the frontal precentral gyrus (BA4), which are organized from the dorsal to ventral as follows: paracentral U-shaped tract (no. 14 in Fig. 1 and Fig. 4), ventral face U-shaped tract (no. 18 in Fig. 1 and Fig. 4) and hand superior, middle and inferior U-shaped tracts (no. 15–17 in Fig. 1 and Fig. 4).

##### *Frontal aslant tract (FAT) (no. 19 in Fig. 1 and Fig. 4)*

The frontal aslant tract is a large tilted tract linking the supplementary and pre-supplementary motor area (BA6) with the frontal operculum (BA44) and the posterior portion of the pars triangularis (BA45).

##### *Fronto-insular tracts (FITs) (no. 20–24 in Fig. 1 and Fig. 4)*

A system composed of five U-shaped tracts dives from the frontal lobe into the external capsule to reach the insula. The four most anterior tracts, 1–4, link respectively the pars orbitalis or BA47 (FIT 1; no. 20 in Fig. 1 and Fig. 4), the pars triangularis or BA45 (FIT 2; no. 21 in Fig. 1 and Fig. 4), the pars opercularis or BA44 (FIT 3; no. 22 in Fig. 1 and Fig. 4) and the precentral gyrus or BA6 (FIT 4; no.

23 in Fig. 1 and Fig. 4) of the frontal lobe with the anterior insula (i.e., anterior short gyrus and middle short gyrus; see Cerliani et al. (2012) for a detailed description of the anatomy of the insula). The most posterior tract (FIT 5; no. 24 in Fig. 1 and Fig. 4) connects the subcentral gyrus (BA43) to the posterior insula (i.e., anterior long gyrus).

#### *Frontal longitudinal system*

Two parallel chains of U-shaped tracts run longitudinally in the frontal lobe: the frontal superior longitudinal tract (FSL; no. 25 in Fig. 1 and Fig. 4) and frontal inferior longitudinal tract (FIL; no. 26 in Fig. 1 and Fig. 4).

The longest fibers of the frontal superior longitudinal tract connect the precentral gyrus to the anterior portion of the superior frontal gyrus, while its shortest fibers link the middle frontal gyrus with the superior frontal gyrus through a series of chain-like U-shaped fibers.

The longest fibers of frontal inferior longitudinal tract connect the precentral gyrus to the anterior portion of the middle frontal gyrus, while its shortest fibers link the dorsal portion of the pars opercularis and triangularis with the middle frontal gyrus through a series of chain-like U-shaped fibers.

#### *Fronto-orbito-polar and fronto-marginal tracts*

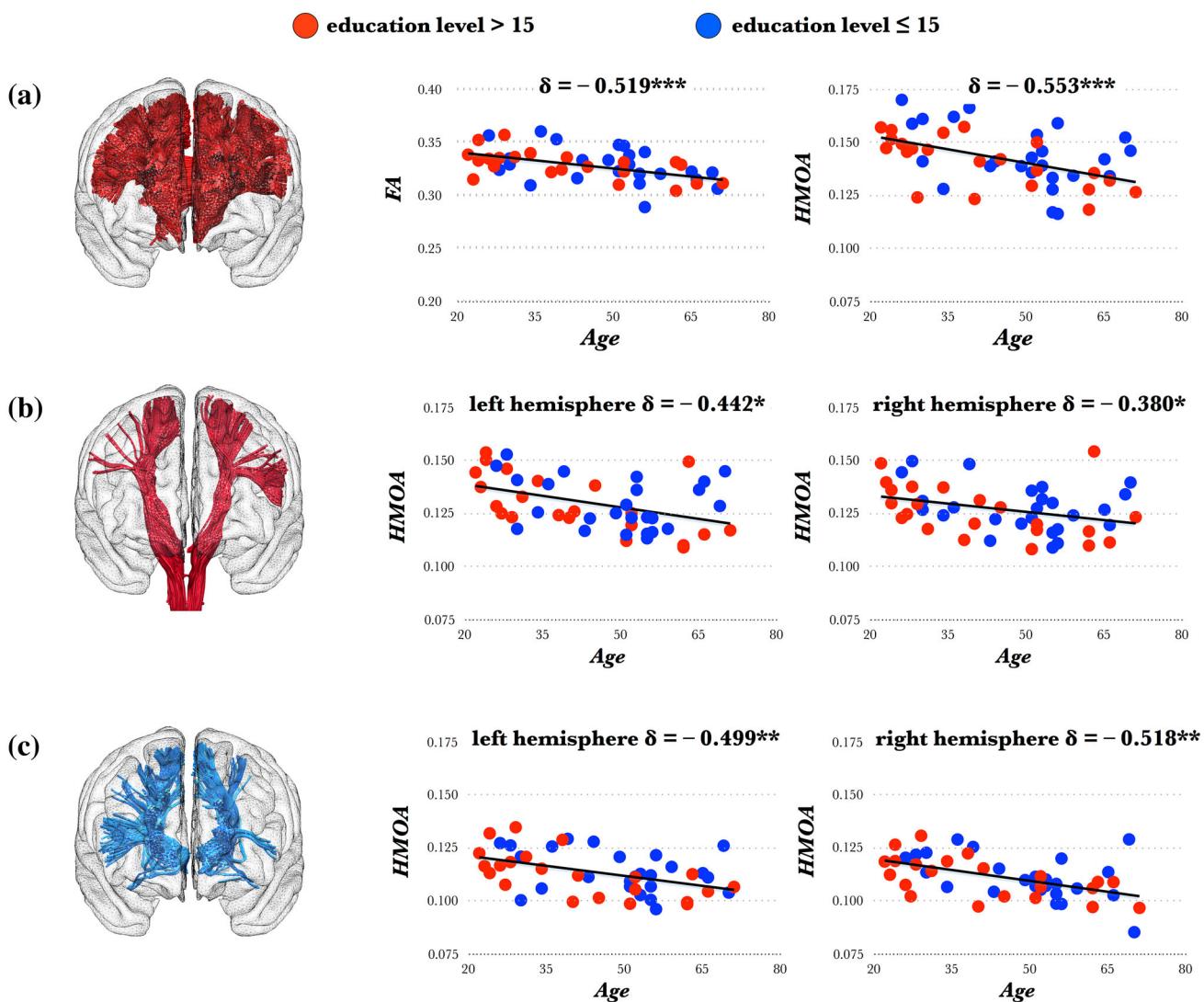
Two intralobar tracts can be observed within the frontal pole. The fronto-orbito-polar tract (FOP; no. 27 in Fig. 1 and Fig. 4) connects the posterior orbital gyrus (BA12) to the anterior orbital gyrus (BA11) and the ventro-medial region of the frontal pole.

The fronto-marginal tract (FMT; no. 28 in Fig. 1 and Fig. 4) runs beneath the fronto-marginal sulcus from the medial to the lateral region of the frontal pole (BA10).

#### Age and level of education effect

Repeated ANOVA between measurement of streamlines emerging from the frontal lobe and streamlines not involving the frontal lobe using age and education as covariates revealed a significant interaction between HMOA measures of frontal and non-frontal tracts and the age of the participants ( $F_{(1,44)} = 6.968$ ;  $p < 0.011$ ). This result demonstrates that microstructural differences related to age are stronger for the tracts emerging from the frontal lobe compared to other tracts. This effect was not significant for FA measure or relative volume measures.

Results presented in the following section are false discovery rate (FDR) corrected for multiple comparisons. Uncorrected  $p$  values are reported in supplementary Table 2. Tract-specific volume measurements did not correlate significantly with aging.



**Fig. 5** Correlation between the participants' age and tract-specific measurements. Participants with higher education are represented by a red dot and participants with a lower education by a blue dot. **a** Frontal corpus callosum; **b** left and right corticospinal tract; **c** left

and right anterior thalamic radiations.  $*p < 0.05$ ,  $^{**}p < 0.01$ ,  $^{***}p < 0.001$  false discovery rate corrected for multiple comparisons. For each tract a single participant 3D reconstruction is supplied as a representative example of the individual anatomy

Partial correlation analyses revealed that aging was significantly associated with a decrease of FA (Spearman rank coefficient partial correlation  $\delta = -0.519$ ,  $p < 0.001$ ) and HMOA ( $\delta = -0.553$ ,  $p < 0.001$ ) in the frontal projections of the corpus callosum. HMOA measures also decreased with aging in the left hemisphere for the frontal inferior longitudinal fasciculus ( $\delta = -0.563$ ,  $p < 0.001$ ), the frontal orbito-polar tract ( $\delta = -0.552$ ,  $p < 0.001$ ), fronto-insular tract 5 ( $\delta = -0.379$ ,  $p = 0.047$ ), the corticospinal tract ( $\delta = -0.442$ ,  $p < 0.014$ ) and fronto-thalamic projections ( $\delta = -0.499$ ,  $p = 0.004$ ) (Figs. 5, 6). No other partial correlation with age was reported as significant.

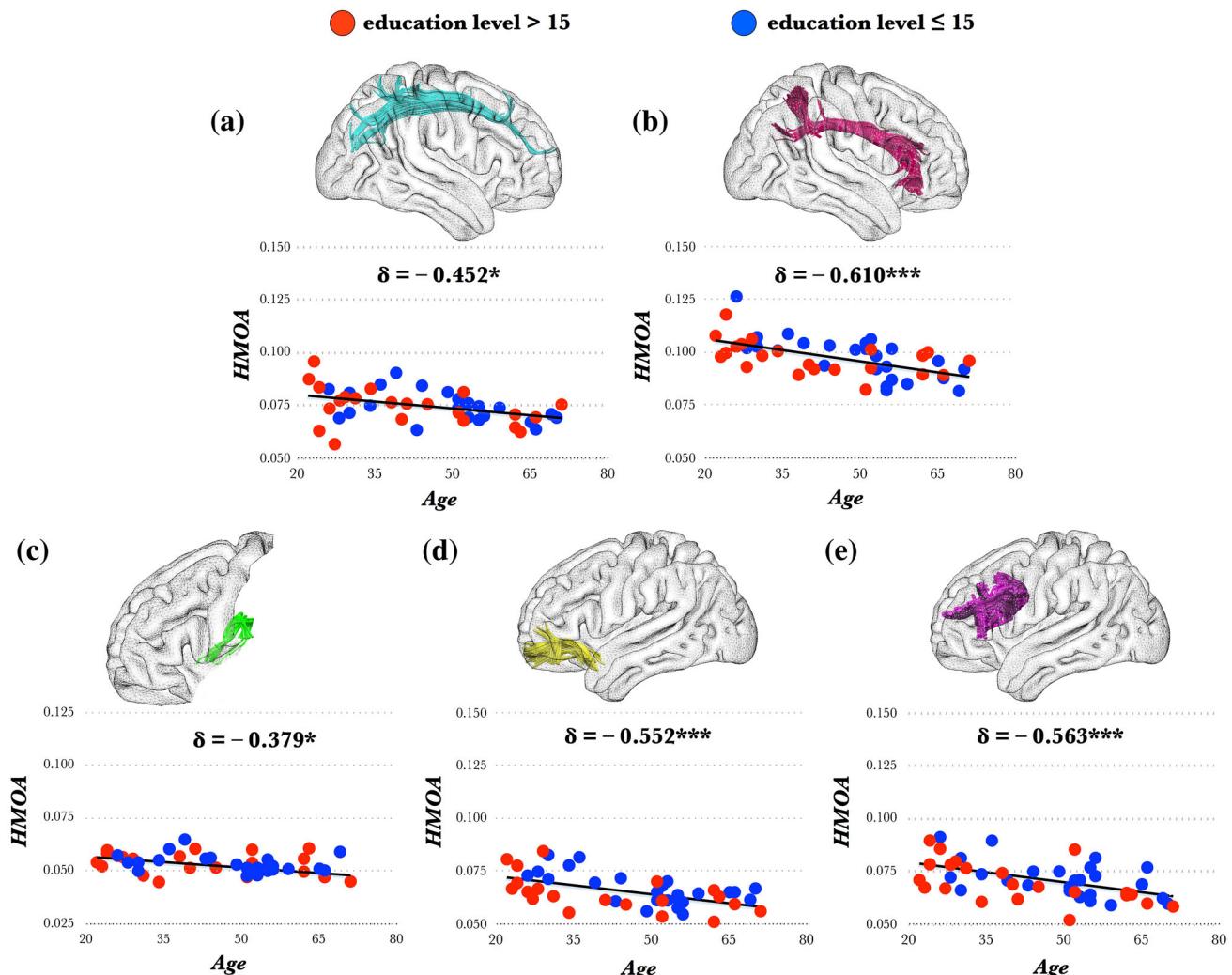
Aging was also associated with a decrease of HMOA in the right frontal lobe including the SLF I ( $\delta = -0.452$ ,

$p = 0.015$ ), SLF III ( $\delta = -0.610$ ,  $p < 0.001$ ) branches of the superior longitudinal fasciculus, the corticospinal tract ( $\delta = -0.380$ ,  $p < 0.046$ ) and fronto-thalamic projections ( $\delta = -0.518$ ,  $p = 0.003$ ) (Figs. 5, 6).

Tract-specific volume, FA and HMOA correlations with education level did not survive FDR correction for multiple comparisons.

## Discussion

In this study we employed advanced spherical deconvolution tractography to dissect 55 white matter pathways within the frontal lobes. We produced a probabilistic atlas



**Fig. 6** Correlation between the participants' age and tract-specific measurements. Participants with higher education are represented by a red dot and participants with a lower education by a blue dot. **a** First branch of the right superior longitudinal fasciculus; **b** third branch of the right superior longitudinal fasciculus; **c** fronto-insular tract 5;

**d** left frontal orbito-polar tract; **e** left frontal inferior longitudinal fasciculus. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  false discovery rate corrected for multiple comparisons. For each tract a single participant 3D reconstruction is supplied as a representative example of the individual anatomy

of the interlobar, commissural, projection and short U-shaped tracts in a population with a large age range. All tracts showed a high intersubject spatial reproducibility (freely available, please send a request to [michel.thiebaut@gmail.com](mailto:michel.thiebaut@gmail.com)). We also replicated correlations between age and microstructural measures of the corpus callosum, bilateral corticospinal tract and frontothalamic projections. For the first time, the use of spherical deconvolution combined with the use of tract-specific HMOA allowed us to report correlations between age and the frontal inferior longitudinal fasciculus, the fronto-insular tract 5 and orbito-polar tract in the left hemisphere and the SLF I and III in the right hemisphere. Education did not correlate with any of the tract-specific measurements. While our maps can be of interest for clinical-

neuroanatomical correlations and functional imaging studies, the correlation with age provides a normative measure for future studies on diseases affecting various age ranges.

#### Probabilistic atlas of the interlobar, commissural, projection and short U-shaped tracts

Our frontal lobe atlas is a probabilistic replication in the stereotaxic space (MNI152) of the original anatomical postmortem and tractography dissection performed on a single brain and reported by Catani et al. (2012). Compared to previous work (Mori et al. 2008; O'Donnell and Westin 2007; Lawes et al. 2008; Thiebaut de Schotten et al. 2011), this atlas provides probabilistic maps of the three branches

of the superior longitudinal fasciculus and many intralobar and U-shaped connections, as well as a full reconstruction of most of the crossing fibers. These maps can be of interest to identify tracts connecting functional activations (Thiebaut de Schotten et al. 2014a) or disconnections caused by strokes (Thiebaut de Schotten et al. 2014b). It may also provide a basis for future studies, which aim to clarify the very debated anatomo-functional organization of the prefrontal cortex for executive functions and cognitive control.

Classically, patient studies demonstrate that the prefrontal cortex is critical to executive functions and adaptive goal-directed behaviors (Azuar et al. 2014; Burgess et al. 2009; Stuss and Knight 2013; Volle et al. 2008). Influential cognitive models such as the working memory model postulate a specialization of retro-rolandic and of prefrontal regions along the superior–inferior axis. In the posterior prefrontal regions, dissociation between the processing of spatial (in the superior part) and verbal (in the inferior part) information has been reported in both functional MRI (Curtis and D’Esposito 2003; Sakai and Passingham 2003; Sala et al. 2003; Smith and Jonides 1999) and lesion studies (Volle et al. 2008, 2013). The superior and inferior longitudinal U-shaped tracts evidenced in the current study may support this spatial and verbal specialization, respectively, within the frontal lobe. Posteriorly, separate parietal and temporal inputs to these systems via the superior longitudinal and the arcuate fasciculi may also support this functional segregation. The examination of direct relationship between anatomical tracts and functional dissociations would be of high interest for future studies to disambiguate the organization of prefrontal cortex.

The longitudinal U-shaped tracts are also interesting to consider regarding the proposed postero-anterior serial organization of frontal functions. A U-shaped organization of connections is concordant with caudal–rostral models (Badre and D’Esposito 2007; Badre 2008; Christoff et al. 2009) of lateral prefrontal organization, such as the cascade model of cognitive control (Koechlin and Summerfield 2007; Koechlin et al. 1999, 2003). In these models, more posterior regions correspond to a lower-level module and receive signals from a higher-level module supported by more anterior regions. The processing level of these modules may depend on the level of cognitive control, relational complexity or abstraction of representations. The most anterior region, or rostral prefrontal cortex, is thought to support the highest-level modules and has indeed been consistently shown to be involved in the highest level of cognitive abilities, such as relational reasoning (Smith et al. 2007; Vartanian 2012; Volle et al. 2010), combination of remote information (Gonen-Yaacovi et al. 2013), coordinating goals and subgoals (Koechlin et al. 1999; Kroger et al. 2002) and multitasking (Burgess et al. 2009; Volle et al. 2011). The U-shaped tracts composing the frontal

longitudinal system may constitute the anatomical link between successive modules. This hypothesis may be tested in future studies.

It is also interesting to note that the projection areas of different tracts are not randomly distributed in the frontal lobes, but seem to overlap in preferred locations, such as the inferior frontal junction, the posterior part of the superior frontal sulcus, the inferior frontal gyrus and the rostral prefrontal region. These cortical regions have been well observed in a myriad of functional imaging studies, using various cognitive tasks. They may well be functional hubs, in addition to anatomical hubs.

#### White matter correlations with age and education

We report that age-related white matter differences distribute unevenly, inducing subtle differences in several tracts of the frontal region but not all. Our analysis confirms previous evidence of reduced microstructural organization in the frontal portion of the corpus callosum associated with aging (Lebel and Beaulieu 2011; Lebel et al. 2008, 2010). This commissural decline may explain why increased reaction time is associated with aging, as reported during tasks requiring interhemispheric transfer (Gootjes et al. 2004; Reuter-Lorenz and Stanczak 2000) that may sometimes be compensated by alternative use of a different portion of the corpus callosum (Schulte et al. 2013). Similarly, our analysis confirmed the decreased age-related microstructural measurements of the left and right corticospinal tract recently associated with age-related differences in fine motor control (Holtrop et al. 2014).

Age-related differences reported in the anterior thalamic radiations bilaterally are concordant with the age-related significant decrease of the neuron number in the anterior thalamic nuclei (Panadero and Gonzalo Sanz 1988). The anterior thalamic radiations are also part of a network involving the hippocampus and dedicated to episodic memory (Aggleton et al. 2010; Catani et al. 2013). Hence, the decreased age-related microstructural integrity of the anterior thalamic radiation might be related to the normal aging of episodic memory function (Brickman and Stern 2009; Charlton et al. 2010).

We also explored age-related correlations for new pathways not defined in other atlases. For the first time to our knowledge, we reported an age-related microstructural decreased integrity of two interlobar tracts in the right hemisphere (SLF I and III) and three intralobar tracts in the left hemisphere (the frontal inferior longitudinal fasciculus, the frontal orbito-polar tract and the fronto-insular tract 5). The contrast between the two hemispheres suggest that white matter differences related to age are not similar for the left and the right hemispheres and may be supported by different mechanisms.

Education level did not correlate significantly with tract-specific measurements, even when controlling for the effect of age. This finding suggests that education does not change or strengthen the white matter microstructure of the frontal lobe. Compensation mechanisms to counteract neural decline may therefore be supported by other mechanisms, such as the recruitment of supplementary “compensatory” brain networks (Stern et al. 2005, 2008; Cabeza et al. 2002; Cabeza and Dennis 2012). Comparing the effect of education or measures of general intelligence using task-specific functional connectivity in young adults and the elderly may provide further support to this hypothesis.

#### FA and HMOA tract-specific measurements

Spherical deconvolution tractography produced larger bundles, including voxels where fibers crossed, which indubitably decreased FA and may have biased FA measures. New tract-specific measurements, such as HMOA, are less susceptible to crossing fiber effects. Correlations between age and tract-specific HMOA, but not with FA, suggest that HMOA produces a better estimate of white matter bundle microstructure when crossing with other fiber populations (Dell’Acqua et al. 2013). Therefore, when undertaking tract-specific measurements using advanced fiber-crossing algorithms, it is preferable to use real tract-specific measures, such as HMOA, rather than voxel-specific measures, such as FA.

#### Limitations

We employed a structure-specific approach to quantify age-related changes occurring within frontal tracts instead of a whole brain voxel-based approach. This approach may have missed differences that may occur at the voxel level. However, a structure-specific approach does not suffer normalization approximations and is therefore more sensitive than analysis performed over the whole brain (Catani 2006). New hybrid approaches, such as the one reported in Yushkevich et al. (2008) using true tract-specific indices to characterize white matter diffusion when crossing might bring the best of structure-specific and voxel-based approaches.

We noted that volume measurements have a larger standard deviation than FA or HMOA measurements. This is important as a larger standard deviation reduces the statistical power and decreases the chances of reporting a significant result. The accuracy of tract volume measurements depends on the quality of the dissection, which relies on the reliability of the operator and the quality of the dataset. We employed a semi-automatic approach for the dissection to reduce variability, and subsequently all tracts

were visually inspected to reduce false positives. However, false negatives may still have been the source for this increase in volume variability (Jones et al. 2013; Kristo et al. 2013a).

We also report preliminary results on the distribution of the corpus callosum, corticospinal tract, striatum, pons and thalamus connections to the cortical surface. Axonal tracing studies suggest that a comparable distribution of projection for the corpus callosum (Myers 1965), the striatum (Haber et al. 2000), the thalamus (Barbas and Mesulam 1981) and the pons (Schmahmann and Pandya 1995) also exists in monkeys. Indeed, the frontal corpus callosum decreases its probability of projection for the frontal eye field, the orbito frontal gyrus and the frontal operculum in monkey axonal tracing (Myers 1965) as well as in the map we presented. Similarly, the striatal projection seems to be reduced for the Brodmann areas 9 and 46 (Haber et al. 2000) and lighter projections from the pons were received from the medial and ventrolateral cortices (Schmahmann and Pandya 1995). However, quantitative maps of the fiber density arising from or terminating in the simian cortex are missing in literature and prevent us from drawing firm comparative anatomy conclusions. Furthermore, in most of our participants the corticospinal tract did not connect to the whole motor homunculus. Hence, although spherical deconvolution may put forward an encouraging improvement in the quality of dissections as compared to standard tensor tractography, it is not exempt from limitations. It should be used with caution, especially when reconstructing projection pathways or in clinical applications where edema, tumors, lesions and infarcts are present. In these cases, multiple compartments and partial volume effects will limit and confound spherical deconvolution (Roine et al. 2014).

Finally, our cross-sectional report suggests an heterogeneously distributed age-related microstructural change within the frontal lobe that ideally will require replication in a longitudinal study.

#### Conclusions

This atlas of the frontal lobe connections may help identify tracts connecting functional activations, thus contributing to a better understanding of frontal functions and processes. It may also help clinicians to diagnose the disconnection or abnormality of specific tracts on patients’ MRIs following a wide range of pathologies, including but not limited to stroke, degenerative diseases, traumatic brain injury, multiple sclerosis, tumors, vascular malformations, leukoencephalopathies and infectious diseases. In relation to clinical disorders, our maps could increase understanding of cognitive deficits, as well as mechanisms of brain recovery and plasticity. However, special caution should be

taken when overlapping the atlas maps with the structural data of patients due, for example, to tissue displacement and an altered anatomy (Brett et al. 2001; Clark et al. 2003). Finally, tract-specific correlations with aging produce interesting hypotheses on possible early cognitive decline dissociations that may be tested in elderly patients.

**Acknowledgments** We thank Dr. Marco Catani for his assistance with the anatomical dissection and insightful discussions. We also thank the French Agence Nationale de la Recherche for its support of this project (project CAFORPFC, No. ANR-09-RPDOC-004-01 and project PHENOTYPES, No. ANR-13-JSV4-0001-01). In addition, we also thank the program “Investissements d’avenir” (ANR-10-IAIHU-06) for its generous support.

## References

- Aggleton JP, O’Mara SM, Vann SD, Wright NF, Tsanov M, Erichsen JT (2010) Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *Eur J Neurosci* 31(12):2292–2307
- Azuar C, Reyes P, Slachevsky A, Volle E, Kinkingnehu S, Kouneiher F, Bravo E, Dubois B, Koechlin E, Levy R (2014) Testing the model of caudo-rostral organization of cognitive control in the human with frontal lesions. *Neuroimage* 84:1053–1060
- Badre D (2008) Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn Sci* 12(5):193–200
- Badre D, D’Esposito M (2007) Functional magnetic resonance imaging evidence for a hierarchical organization of the pre-frontal cortex. *J Cogn Neurosci* 19(12):2082–2099
- Barbas H, Mesulam MM (1981) Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *J Comp Neurol* 200(3):407–431
- Barrick TR, Lawes IN, Mackay CE, Clark CA (2007) White matter pathway asymmetry underlies functional lateralization. *Cereb Cortex* 17(3):591–598
- Barrick TR, Charlton RA, Clark CA, Markus HS (2010) White matter structural decline in normal ageing: a prospective longitudinal study using tract-based spatial statistics. *Neuroimage* 51(2):565–577
- Bastin ME, Piatkowski JP, Storkey AJ, Brown LJ, MacLullich AM, Clayden JD (2008) Tract shape modelling provides evidence of topological change in corpus callosum genu during normal ageing. *Neuroimage* 43(1):20–28
- Bastin C, Yakushev I, Bahri MA, Fellgiebel A, Eustache F, Landeau B, Scheurich A, Feyers D, Collette F, Chetelat G, Salmon E (2012) Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging. *Neuroimage* 63(2):713–722
- Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Statistical Soc Series B (Methodological)* 289–300
- Bishop NA, Lu T, Yankner BA (2010) Neural mechanisms of ageing and cognitive decline. *Nature* 464(7288):529–535
- Brayne C, Ince PG, Keage HA, McKeith IG, Matthews FE, Polvikoski T, Sulkava R (2010) Education, the brain and dementia: neuroprotection or compensation? *Brain* 133(Pt 8):2210–2216
- Brett M, Leff AP, Rorden C, Ashburner J (2001) Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage* 14(2):486–500
- Brickman AM, Stern Y (2009) Aging and memory in humans. In: S LR (ed) Encyclopedia of neuroscience. Academic Press, Oxford, pp 175–180
- Burgess PW, Alderman N, Volle E, Benoit RG, Gilbert SJ (2009) Mesulam’s frontal lobe mystery re-examined. *Restor Neurol Neurosci* 27:493–506
- Cabeza R, Dennis N (2012) Frontal lobes and aging: deterioration and compensation. In: Stuss D, Knight R (eds) Principles of frontal lobe function, 2nd edn., pp 628–652
- Cabeza R, Anderson ND, Locantore JK, McIntosh AR (2002) Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17(3):1394–1402
- Catani M (2006) Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. *Curr Opin Neurol* 19(6):599–606
- Catani M, Thiebaut de Schotten M (2008) A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex* 44(8):1105–1132
- Catani M, Howard RJ, Pajevic S, Jones DK (2002) Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *NeuroImage* 17(1):77–94
- Catani M, Jones DK, ffytche DH (2005) Perisylvian language networks of the human brain. *Ann Neurol* 57(1):8–16
- Catani M, Allin MP, Husain M, Pugliese L, Mesulam MM, Murray RM, Jones DK (2007) Symmetries in human brain language pathways correlate with verbal recall. *Proc Natl Acad Sci USA* 104(43):17163–17168
- Catani M, Dell’acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M (2012) Short frontal lobe connections of the human brain. *Cortex* 48(2):273–291
- Catani M, Dell’acqua F, Thiebaut de Schotten M (2013) A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev* 37(8):1724–1737
- Cerliani L, Thomas RM, Jbabdi S, Siero JC, Nanetti L, Crippa A, Gazzola V, D’Arceuil H, Keysers C (2012) Probabilistic tractography recovers a rostrocaudal trajectory of connectivity variability in the human insular cortex. *Hum Brain Mapp* 33(9):2005–2034
- Charlton RA, Barrick TR, Markus HS, Morris RG (2010) The relationship between episodic long-term memory and white matter integrity in normal aging. *Neuropsychologia* 48(1):114–122
- Christoff K, Keramati K, Gordon AM, Smith R, Madler B (2009) Prefrontal organization of cognitive control according to levels of abstraction. *Brain Res* 1286:94–105
- Ciccarelli O, Toosy AT, Parker GJ, Wheeler-Kingshott CA, Barker GJ, Miller DH, Thompson AJ (2003) Diffusion tractography based group mapping of major white-matter pathways in the human brain. *NeuroImage* 19(4):1545–1555
- Clark CA, Barrick TR, Murphy MM, Bell BA (2003) White matter fiber tracking in patients with space-occupying lesions of the brain: a new technique for neurosurgical planning? *Neuroimage* 20(3):1601–1608
- Coffey CE, Saxton JA, Ratcliff G, Bryan RN, Lucke JF (1999) Relation of education to brain size in normal aging: implications for the reserve hypothesis. *Neurology* 53(1):189–196
- Craig MC, Catani M, Deeley Q, Latham R, Daly E, Kanaan R, Picchioni M, McGuire PK, Fahy T, Murphy DG (2009) Altered connections on the road to psychopathy. *Mol Psychiatry* 14(10):946–953, 907
- Curiati PK, Tamashiro JH, Squarzoni P, Duran FL, Santos LC, Wajngarten M, Leite CC, Vallada H, Menezes PR, Scauzufca M, Busatto GF, Alves TC (2009) Brain structural variability due to aging and gender in cognitively healthy Elders: results from the São Paulo Ageing and Health study. *AJNR Am J Neuroradiol* 30(10):1850–1856

- Curtis CE, D'Esposito M (2003) Success and failure suppressing reflexive behavior. *J Cogn Neurosci* 15(3):409–418
- Dauguet J, Peled S, Berezovskii V, Delzescaux T, Warfield SK, Born R, Westin CF (2006) 3D histological reconstruction of fiber tracts and direct comparison with diffusion tensor MRI tractography. *Med Image Comput Comput Assist Interv MICCAI Int Conf Med Image Comput Comput Assist Interv* 9(Pt 1):109–116
- Dauguet J, Peled S, Berezovskii V, Delzescaux T, Warfield SK, Born R, Westin CF (2007) Comparison of fiber tracts derived from in-vivo DTI tractography with 3D histological neural tract tracer reconstruction on a macaque brain. *Neuroimage* 37(2):530–538
- Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R (2009) Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *NeuroImage* 46(2):530–541
- Dell'Acqua F, Catani M (2012) Structural human brain networks: hot topics in diffusion tractography. *Curr Opin Neurol* 25(4):375–383
- Dell'acqua F, Scifo P, Rizzo G, Catani M, Simmons A, Scotti G, Fazio F (2010) A modified damped Richardson-Lucy algorithm to reduce isotropic background effects in spherical deconvolution. *Neuroimage* 49(2):1446–1458
- Dell'Acqua F, Simmons A, Williams SC, Catani M (2013) Can spherical deconvolution provide more information than fiber orientations? Hindrance modulated orientational anisotropy, a true-tract specific index to characterize white matter diffusion. *Hum Brain Mapp* 34(10):2464–2483
- Descoteaux M, Angelino E, Fitzgibbons S, Deriche R (2007) Regularized, fast, and robust analytical Q-ball imaging. *Magn Reson Med* 58(3):497–510
- Draganski B, Ashburner J, Hutton C, Kherif F, Frackowiak RS, Helms G, Weiskopf N (2011) Regional specificity of MRI contrast parameter changes in normal ageing revealed by voxel-based quantification (VBQ). *Neuroimage* 55(4):1423–1434
- Fischer FU, Wolf D, Scheurich A, Fellgiebel A (2014) Association of structural global brain network properties with intelligence in normal aging. *PLoS One* 9(1):e86258
- Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12(3):189–198
- Geerligs L, Saliasi E, Maurits NM, Renken RJ, Lorist MM (2014) Brain mechanisms underlying the effects of aging on different aspects of selective attention. *Neuroimage* 91:52–62
- Giorgio A, Santelli L, Tomassini V, Bosnell R, Smith S, De Stefano N, Johansen-Berg H (2010) Age-related changes in grey and white matter structure throughout adulthood. *Neuroimage* 51(3):943–951
- Gonen-Yaacovi G, de Souza LC, Levy R, Urbanski M, Josse G, Volle E (2013) Rostral and caudal prefrontal contribution to creativity: a meta-analysis of functional imaging data. *Front Hum Neurosci* 7:465
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *NeuroImage* 14(3):685–700
- Gootjes L, Van Strien JW, Bouma A (2004) Age effects in identifying and localising dichotic stimuli: a corpus callosum deficit? *J Clin Exp Neuropsychol* 26(6):826–837
- Haber SN, Fudge JL, McFarland NR (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20(6):2369–2382
- Hasan KM, Iftikhar A, Kamali A, Kramer LA, Ashtari M, Cirino PT, Papanicolaou AC, Fletcher JM, Ewing-Cobbs L (2009a) Development and aging of the healthy human brain uncinate fasciculus across the lifespan using diffusion tensor tractography. *Brain Res* 1276:67–76
- Hasan KM, Kamali A, Iftikhar A, Kramer LA, Papanicolaou AC, Fletcher JM, Ewing-Cobbs L (2009b) Diffusion tensor tractography quantification of the human corpus callosum fiber pathways across the lifespan. *Brain Res* 1249:91–100
- Hasan KM, Kamali A, Abid H, Kramer LA, Fletcher JM, Ewing-Cobbs L (2010) Quantification of the spatiotemporal microstructural organization of the human brain association, projection and commissural pathways across the lifespan using diffusion tensor tractography. *Brain Struct Funct* 214(4):361–373
- Holtrop JL, Loucks TM, Sosnoff JJ, Sutton BP (2014) Investigating Age-related changes in fine motor control across different effectors and the impact of white matter integrity. *Neuroimage* 96:81–87
- Hsu JL, Leemans A, Bai CH, Lee CH, Tsai YF, Chiu HC, Chen WH (2008) Gender differences and age-related white matter changes of the human brain: a diffusion tensor imaging study. *Neuroimage* 39(2):566–577
- Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J (2013) Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum Brain Mapp* 34(11):2747–2766
- Johansen-Berg H, Della-Magiore V, Behrens TEJ, Smith SM, Paus T (2007) Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *NeuroImage* 36(Suppl 2):T16–T21
- Jones DK, Catani M, Pierpaoli C, Reeves SJ, Shergill SS, O'Sullivan M, Golesworthy P, McGuire P, Horsfield MA, Simmons A, Williams SC, Howard RJ (2006) Age effects on diffusion tensor magnetic resonance imaging tractography measures of frontal cortex connections in schizophrenia. *Hum Brain Mapp* 27(3):230–238
- Jones DK, Knosche TR, Turner R (2013) White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage* 73:239–254
- Klingler J (1935) Erleichterung der makroskopischen Präparation des Gehirn durch den Gefrierprozess. *Schweiz Arch Neurol Psychiat* 36:247–256
- Koechlin E, Summerfield C (2007) An information theoretical approach to prefrontal executive function. *Trends Cogn Sci* 11(6):229–235
- Koechlin E, Basso G, Pietrini P, Panzer S, Grafman J (1999) The role of the anterior prefrontal cortex in human cognition. *Nature* 399(6732):148–151
- Koechlin E, Ody C, Kouneiher F (2003) The architecture of cognitive control in the human prefrontal cortex. *Science* 302(5648):1181–1185
- Kristo G, Leemans A, de Gelder B, Raemaekers M, Rutten GJ, Ramsey N (2013a) Reliability of the corticospinal tract and arcuate fasciculus reconstructed with DTI-based tractography: implications for clinical practice. *Eur Radiol* 23(1):28–36
- Kristo G, Leemans A, Raemaekers M, Rutten GJ, de Gelder B, Ramsey NF (2013b) Reliability of two clinically relevant fiber pathways reconstructed with constrained spherical deconvolution. *Magn Reson Med* 70(6):1544–1556
- Kroger JK, Sabb FW, Fales CL, Bookheimer SY, Cohen MS, Holyoak KJ (2002) Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. *Cereb Cortex* 12(5):477–485
- Lawes INC, Barrick TR, Murugam V, Spierings N, Evans DR, Song M, Clark CA (2008) Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. *NeuroImage* 39(1):62–79
- Le Bihan D, Breton E (1985) Imagerie de diffusion in vivo par résonance magnétique nucléaire. *Comptes rendus de l'Académie des sciences* 301:1109–1112

- Lebel C, Beaulieu C (2011) Longitudinal development of human brain wiring continues from childhood into adulthood. *J Neurosci* 31(30):10937–10947
- Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C (2008) Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage* 40(3):1044–1055
- Lebel C, Caverhill-Godkewitsch S, Beaulieu C (2010) Age-related regional variations of the corpus callosum identified by diffusion tensor tractography. *Neuroimage* 52(1):20–31
- Madden DJ, Whiting WL, Huettel SA, White LE, MacFall JR, Provenzale JM (2004) Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage* 21(3):1174–1181
- Madden DJ, Spaniol J, Whiting WL, Bucur B, Provenzale JM, Cabeza R, White LE, Huettel SA (2007) Adult age differences in the functional neuroanatomy of visual attention: a combined fMRI and DTI study. *Neurobiol Aging* 28(3):459–476
- Michielse S, Coupland N, Camicioli R, Carter R, Seres P, Sabino J, Malykhin N (2010) Selective effects of aging on brain white matter microstructure: a diffusion tensor imaging tractography study. *Neuroimage* 52(4):1190–1201
- Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389
- Mori S, Oishi K, Jiang H, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl PC, Mazziotta J (2008) Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *NeuroImage* 40(2):570–582
- Moscovitch M (1992) Memory and working-with-memory: a component process model based on modules and central systems. *J Cogn Neurosci* 4(3):257–267
- Myers RE (1965) Organization of forebrain commissures. In: Ettlinger EG (ed) Functions of the Corpus Callosum. CIBA Foundation Study Group 20, London, pp 133–143
- O'Donnell LJ, Westin CF (2007) Automatic tractography segmentation using a high-dimensional white matter atlas. *IEEE Trans Med Imaging* 26(11):1562–1575
- O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS (2001) Evidence for cortical “disconnection” as a mechanism of age-related cognitive decline. *Neurology* 57(4): 632–638
- Panadero A, Gonzalo Sanz LM (1988) Memory and aging: changes in the mammillary body and anterior thalamic nuclei due to age. *Rev Med Univ Navarra* 32(4):191–200
- Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 9(7):689–701
- Phillips OR, Clark KA, Luders E, Azhir R, Joshi SH, Woods RP, Mazziotta JC, Toga AW, Narr KL (2013) Superficial white matter: effects of age, sex, and hemisphere. *Brain Connect* 3(2):146–159
- Raffelt D, Tournier JD, Rose S, Ridgway GR, Henderson R, Crozier S, Salvador O, Connelly A (2012) Apparent fibre density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. *Neuroimage* 59(4):3976–3994
- Raz N (2005) The aging brain observed in vivo: differential changes and their modifiers, in: cognitive neuroscience of aging: linking cognitive and cerebral aging. In: Cabeza R, Nyberg L (eds) Cognitive neuroscience of aging. Park DC, New-York, pp 19–57
- Raz N, Williamson A, Gunning-Dixon F, Head D, Acker JD (2000) Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. *Microsc Res Tech* 51(1):85–93
- Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD (2004) Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol Aging* 25(3):377–396
- Reuter-Lorenz PA, Stanczak L (2000) Differential effects of aging on the functions of the corpus callosum. *Dev Neuropsychol* 18(1):113–137
- Roine T, Jeurissen B, Perrone D, Aelterman J, Leemans A, Philips W, Sijbers J (2014) Isotropic non-white matter partial volume effects in constrained spherical deconvolution. *Front Neuroinform* 8:28
- Sakai K, Passingham RE (2003) Prefrontal interactions reflect future task operations. *Nat Neurosci* 6(1):75–81
- Sala JB, Rämä P, Courtney SM (2003) Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. *Neuropsychologia* 41(3): 341–356
- Salat DH, Kaye JA, Janowsky JS (1999) Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. *Arch Neurol* 56(3):338–344
- Schmahmann JD, Pandya DN (1995) Prefrontal cortex projections to the basilar pons in rhesus monkey: implications for the cerebellar contribution to higher function. *Neurosci Lett* 199(3):175–178
- Schulte T, Maddah M, Muller-Oehring EM, Rohlfing T, Pfefferbaum A, Sullivan EV (2013) Fiber tract-driven topographical mapping (FTTM) reveals microstructural relevance for interhemispheric visuomotor function in the aging brain. *Neuroimage* 77:195–206
- Shapiro S, Wilk M (1965) An analysis of variance test for normality (complete samples). *Biometrika* 52(3/4):591–611
- Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. *Science* 283(5408):1657–1661
- Smith R, Keramatian K, Christoff K (2007) Localizing the rostral-lateral prefrontal cortex at the individual level. *Neuroimage* 36(4):1387–1396
- Spearman C (1904) The proof and measurement of association between two things. *Am J Psychol* 15(1):441–471
- Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 8:448–460
- Stern Y (2009) Cognitive reserve. *Neuropsychologia* 47(10): 2015–2028
- Stern Y, Habeck C, Moeller J, Scarmeas N, Anderson KE, Hilton HJ, Flynn J, Sackeim H, van Heertum R (2005) Brain networks associated with cognitive reserve in healthy young and old adults. *Cereb Cortex* 15(4):394–402
- Stern Y, Zarahn E, Habeck C, Holtzer R, Rakitin BC, Kumar A, Flynn J, Steffener J, Brown T (2008) A common neural network for cognitive reserve in verbal and object working memory in young but not old. *Cereb Cortex* 18(4):959–967
- Stuss DT, Knight RT (2013) Principles of frontal lobe function. Oxford University Press, Oxford
- Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tonnessen P, Walhovd KB (2010) Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. *Cereb Cortex* 20(3):534–548
- Thiebaut de Schotten M, Ffytche DH, Bizzi A, Dell'Acqua F, Allin M, Walshe M, Murray R, Williams SC, Murphy DG, Catani M (2011) Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage* 54(1):49–59
- Thiebaut de Schotten M, Dell'acqua F, Valabregue R, Catani M (2012) Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex* 48:82–96
- Thiebaut de Schotten M, Cohen L, Amemiya E, Braga LW, Dehaene S (2014a) Learning to read improves the structure of the arcuate fasciculus. *Cereb Cortex* 24(4):989–995
- Thiebaut de Schotten M, Tomaiuolo F, Aiello M, Merola S, Silvetti M, Lecce F, Bartolomeo P, Doricchi F (2014b) Damage to white matter pathways in subacute and chronic spatial neglect: a group

- study and 2 single-case studies with complete virtual “in vivo” tractography dissection. *Cereb Cortex* 24(3):691–706
- Tournier JD, Calamante F, Gadian DG, Connelly A (2004) Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage* 23(3):1176–1185
- Tuch DS, Reese TG, Wiegell MR, Wedeen VJ (2003) Diffusion MRI of complex neural architecture. *Neuron* 40(5):885–895
- Vartanian O (2012) Dissociable neural systems for analogy and metaphor: implications for the neuroscience of creativity. *Br J Psychol* 103(3):302–316
- Verhoeven JS, Sage CA, Leemans A, Van Hecke W, Callaert D, Peeters R, De Cock P, Lagae L, Sunaert S (2010) Construction of a stereotaxic DTI atlas with full diffusion tensor information for studying white matter maturation from childhood to adolescence using tractography-based segmentations. *Hum Brain Mapp* 31(3):470–486
- Volle E, Kinkingnehus S, Pochon JB, Mondon K, Thiebaut de Schotten M, Seassau M, Duffau H, Samson Y, Dubois B, Levy R (2008) The functional architecture of the left posterior and lateral prefrontal cortex in humans. *Cereb Cortex* 18(10):2460–2469
- Volle E, Gilbert SJ, Benoit RG, Burgess PW (2010) Specialization of the rostral prefrontal cortex for distinct analogy processes. *Cereb Cortex* 20(11):2647–2659
- Volle E, Gonen-Yaacovi G, Costello Ade L, Gilbert SJ, Burgess PW (2011) The role of rostral prefrontal cortex in prospective memory: a voxel-based lesion study. *Neuropsychologia* 49(8): 2185–2198
- Volle E, Levy R, Burgess PW (2013) A new era for lesion-behavior mapping of prefrontal functions. In: D.T. S, Knight RT (eds) *Principles of Frontal Lobe Function*. pp 500–523
- Vos SB, Jones DK, Jeurissen B, Viergever MA, Leemans A (2012) The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. *NeuroImage* 59(3):2208–2216
- Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl PC, Mori S (2007) Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage* 36(3):630–644
- Wedeen VJ, Hagmann P, Tseng W-YI, Reese TG, Weisskoff RM (2005) Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med Off J Soc Magn Reson Med Soc Magn Reson Med* 54(6):1377–1386
- West RL (1996) An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull* 120(2):272–292
- Xiong YY, Mok V (2011) Age-related white matter changes. *J Aging Res* 2011:617927
- Yushkevich PA, Zhang H, Simon TJ, Gee JC (2008) Structure-specific statistical mapping of white matter tracts. *NeuroImage* 41(2):448–461