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Genetic Influences on Language Cortices: Preliminary Results from a Volumetric Twin Study

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Introduction

Twins constitute an ideal population to investigate genetic and epigenetic contributions to the development of brain structures and pathways. While dizygotic (DZ) twins share, on average, only 50% of their genotype, monozygotic (MZ) twins have identical genotypes. The genetic influences on the variability of brain structures in adolescence are not well known. It has been shown that white matter (WM) volume increases throughout adolescence while gray matter (GM) begins to decrease in early adolescence. Such a pattern holds for the entire brain with the exception of the GM of the temporal and occipital lobes, which increases throughout adolescence (Giedd et al., 1999). A few studies have suggested a genetic influence on the temporal lobe (Hulshoff Pol et al., 2006; Wright et al., 2002; Eckert et al., 2002), and only one has shown high heritability for Broca's and Wernicke's areas, but this result was obtained in older adults (Thompson et al., 2001). We have embarked on the study of a large teenage population of MZ and DZ twins in which we address the genetic influences on the different lobes and their subcomponents. Today we report on the methods used in this study, both for structural volumetric comparisons among MZ and DZ twins in language related regions, and for the approach used to study white matter connections among language related regions.

Methods

1) Subjects:

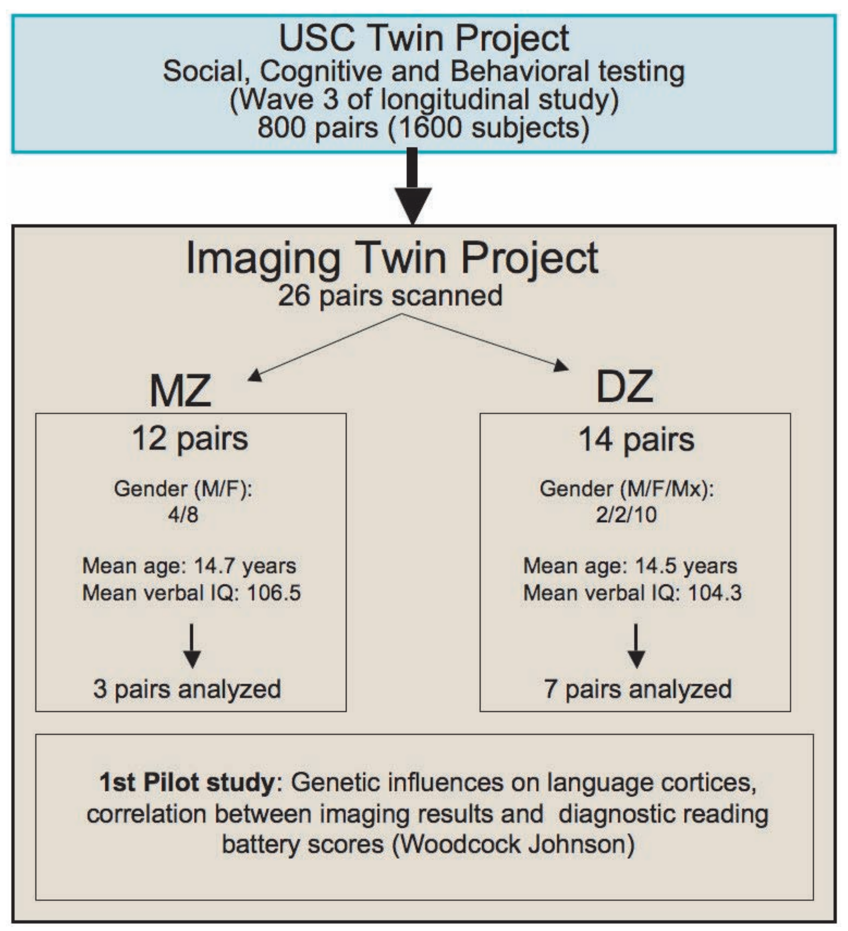

Figure 1: *Demographic criteria of subjects scanned to date. MZ: monozygotic; DZ: dizygotic; M: male; F: female; Mx: mixed pairs (1male/1female)*

2) MRI:

All subjects are scanned on a 3-Tesla Siemens scanner at the Dornsife Cognitive Neuroscience Imaging Center (USC) (see Table 1 for acquisition parameters). Because of a scanner upgrade to a TIM system, the scanning parameters have changed slightly from pair 13 onward. The following scans are obtained:

	T1-weighted	DIFFUSION
12 first pairs	Sagittal, 8-channel phase array coil, 1mm isotropic voxels, TR=2070, TE=4, TI=900, FLIP=7, NEX=1, FOV=256x256, BW=140Hz, slices: 192; time: 9 min	Angular resolution: 48, TR=8000ms, TE=104ms, Bandwidth=1930Hz/Px, 51 axial slices, Slice thickness=2.5mm, FOV=240x 240mm, Matrix=96 x96, b=1000 s/mm^2, time: 7min
13 subsequent pairs	Coronal, 12-channel matrix coil, 1mm isotropic voxels, TR=2530, TE=3, TI=800, FLIP=10, NEX=1, FOV=256x256, BW=220Hz, slices: 208; time: 11min;	Angular resolution: 128, TR=9600ms, TE=150ms, Bandwidth=1396Hz/Px, 50 axial slices, Slice thickness=2.5mm, FOV=224x 224mm, Matrix=128 x128, b=5000 s/mm^2, time: 21min

Table 1: *Acquisition parameters obtained before and after the scanner upgrade*

3) Image Processing and ROI delineation:

Each brain volume is corrected for radio frequency field homogeneity and oriented to the AC-PC line, but not resized to Talairach space. The brain is manually extracted using Brainvox software (Frank et al., 1997) and a 3D volume is created for each subject. A rater, blind to zygosity, traces the following sulci on the 3D brain volumes (Fig. 2):

- In the temporal lobe: the sylvian fissure (SF); the superior temporal sulcus (STS); the transverse temporal sulci (separating Heschl's gyrus from the posterior sector of the superior temporal gyrus — planum temporale, and from the anterior sector — planum polare);
- In the frontal lobe: the inferior frontal sulcus (IFS), the ascending and horizontal terminal branches of the SF, used as landmarks to delineate the pars opercularis and the pars triangularis (Broca's area).

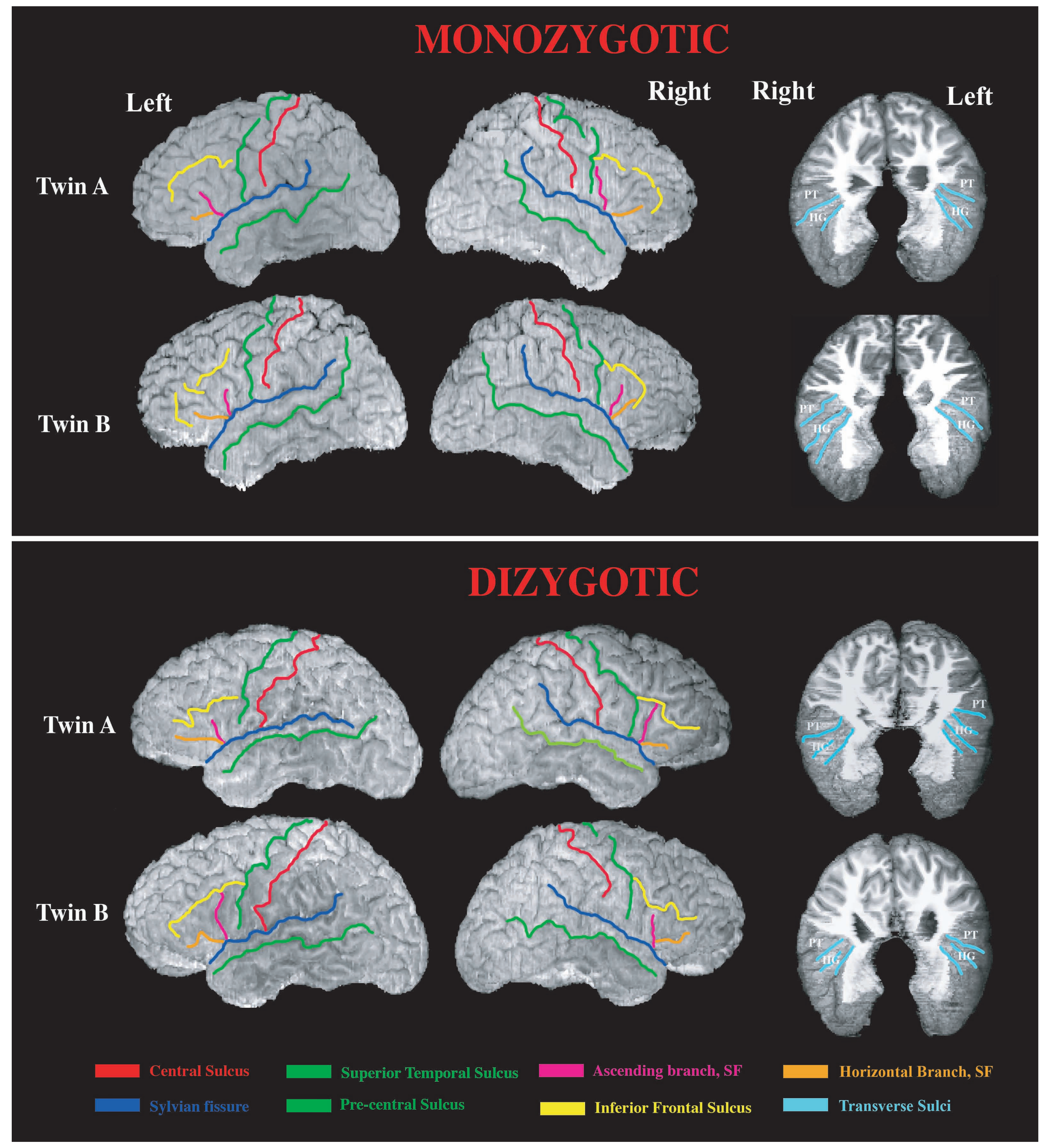

Figure 2: *Sulci are traced on the brain surface of each twin, on both hemispheres. Here, the sulci are shown for one MZ and one DZ pair picked randomly from our sample. Heschl's gyrus (HG) and Planum Temporale (PT) are identified by cutting out the frontal and parietal lobe (right panel)*

Sulci traced on the surface of the 3D volume using the 2D orthogonal images (axial, sagittal and coronal) in Brainvox are checked for accuracy using BrainSuite software, which allows the sulci to be followed "in depth" (Shattuck et al., 2002).

BrainSuite provides the possibility to work on mid-cortex surfaces (surfaces created by removing half of the outer GM). In brief, to create these surfaces, each volume is processed as follows: both white matter and whole brain (extracted from non brain tissues) surfaces are generated in Freesurfer (Fischl et al., 2001, 1999) and averaged in Matlab to calculate the GM thickness (3mm in average). From that average, a midcortex surface is generated by removing 1.5mm of outer GM.

To trace a sulcus, the trajectory of the curve is generated using the mid-cortical surface (Fig. 3c). This approach allows the clear identification of the sulcus and of its possible true (or false) interruptions.

Such interruptions are often difficult to interpret when only the GM/CSF surface is available, as is the case in Brainvox. The combination of Brainvox and Brainsuite allows for a much higher degree of accuracy in the precise delineation of cortical sub-sectors (Fig. 3d,e,f).

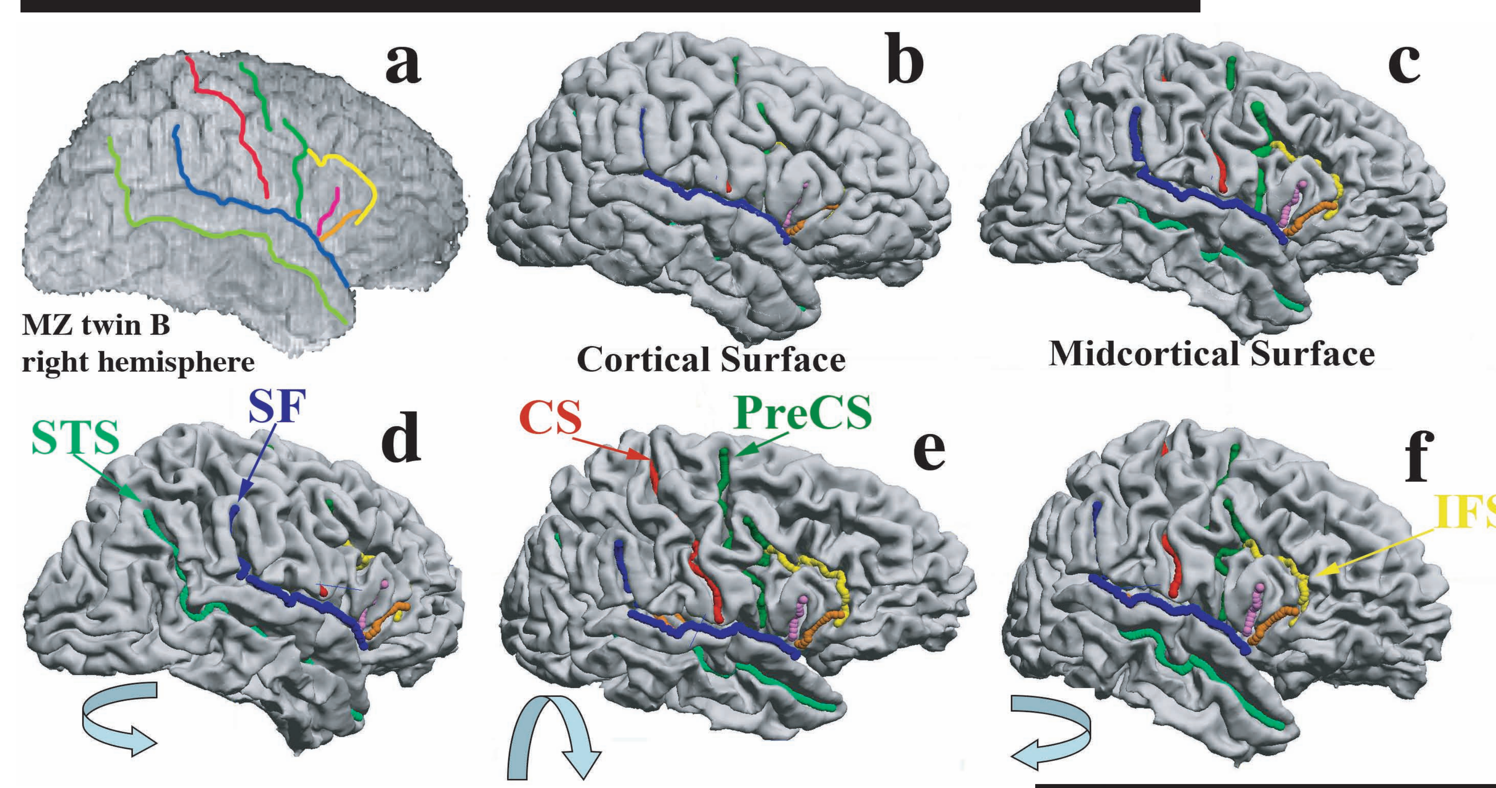

Figure 3: *Example (MZ twin B right hemisphere from Fig. 2) showing the advantages of using a midcortical surface in BrainSuite to guide sulci identification. Sulci traced on the cortical surface (a) are also traced in "depth" on the midcortical surface (c) obtained from the automatic extracted volume (b) along with the white matter volume. The midcortical surface is rotated to help the visualization of the sulci and the localization of the true (or false) interruptions (rotation towards the back in (d) helps the identification of the posterior part of the SF and the STS, towards the top (e) helps the identification of the CS and preCS and towards the front in (f) helps the identification of the IFS).*

Using the sulci as landmarks, the following regions of interest (ROIs) are traced in Brainvox: (1) superior temporal gyrus, Heschl's gyrus and planum temporale (Fig.4, cuts (3) & (4)); (2) inferior frontal gyrus, pars opercularis and triangularis (Fig. 4, cuts (1) & (2)). Mask volumes of each ROI are generated from the tracings and retained for both volumetric and diffusion analyses.

Each brain is segmented into GM, WM and cerebrospinal fluid (Grabowski et al., 2000). The mask volume of each ROI is used to calculate the amount of each of the segmented tissue components in each ROI (Fig. 4 cut (3) left).

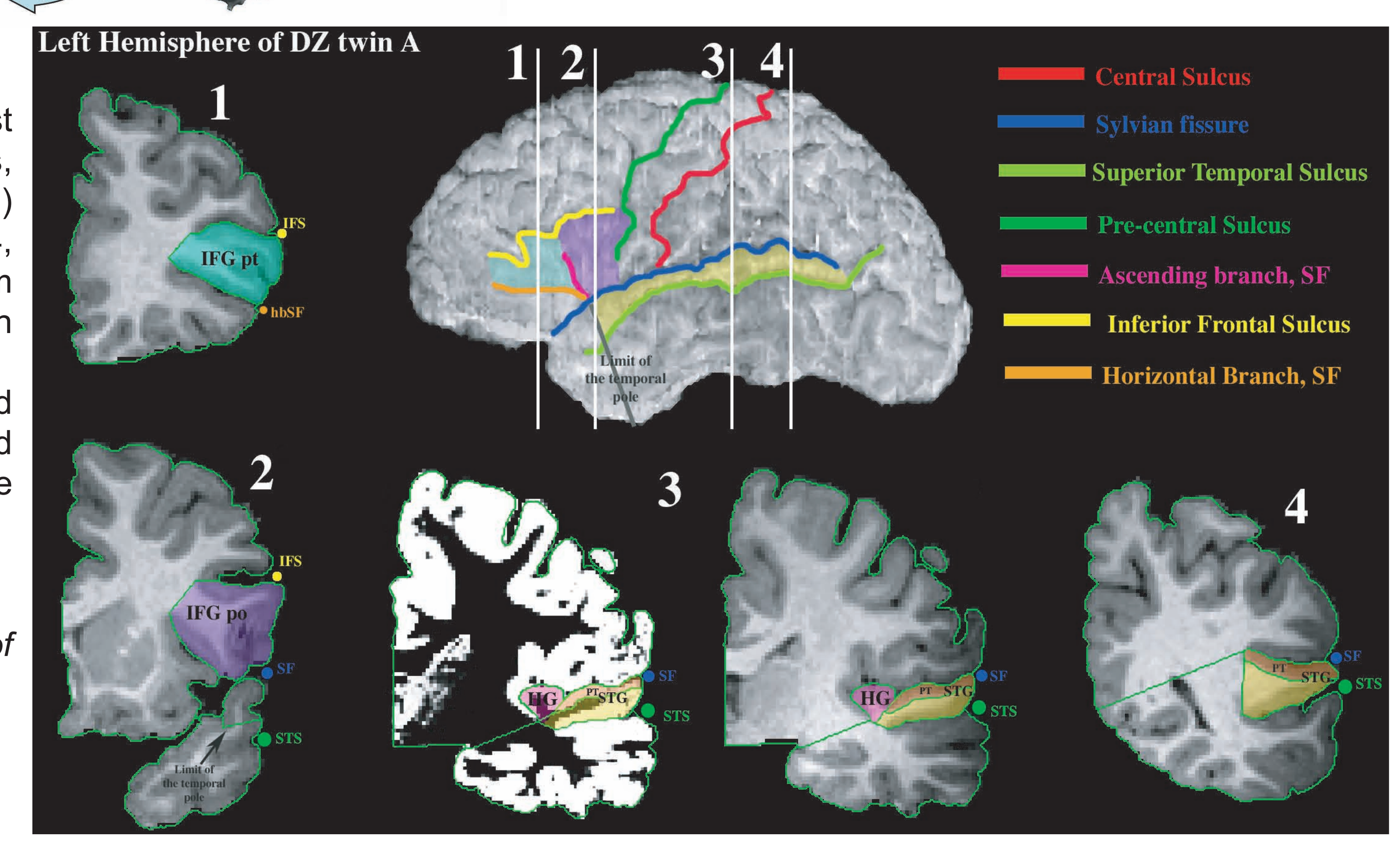

Figure 4: *Example of ROI delineation on the left hemisphere of DZ twin A (Fig. 2).*

4) Processing of the Diffusion Data:

Each diffusion MRI volume is corrected for eddy current distortion using FSL software (Smith et al., 2004). The corrected volumes are then imported into Diffusion Toolkit (Wang and Wedeen, 2007) in which the raw images are reconstructed using the corresponding gradient table (48 gradient directions and 128) to create a set of tensor images, DWI, ADC and FA maps. The reconstruction method uses a linear least-squares fitting method. A track file is generated using 2nd order Runge-Kutta method and smoothed with a B-Spline filter. The generated fiber track data are visualized in Trackvis (Wang and Wedeen, 2007) (see an example in Figure 7).

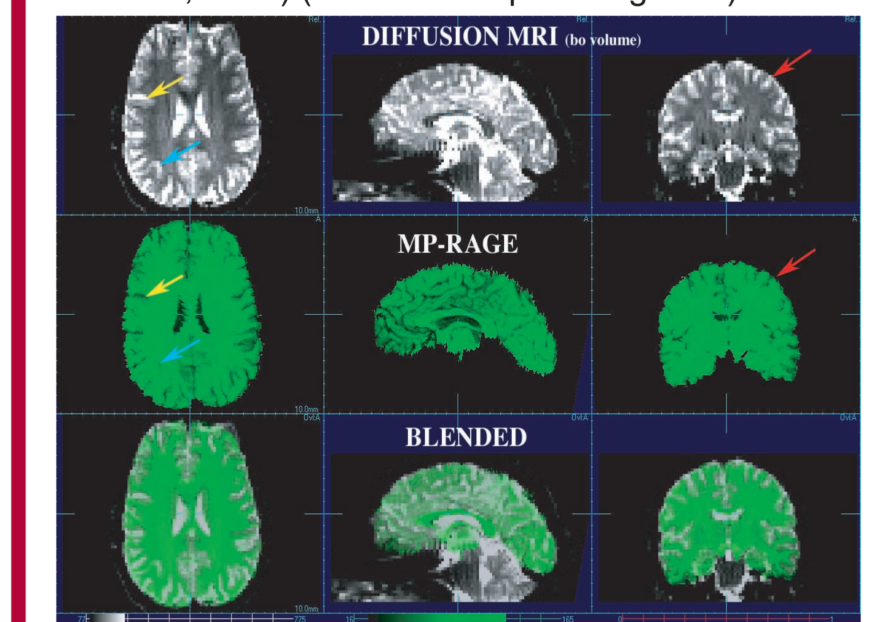

Figure 5: *Example of a co-registration of structural data to diffusion data. Top panel shows the target diffusion b0 volume, the middle panel shows the MP-RAGE volume and the lower panel shows the two co-registered volumes.*

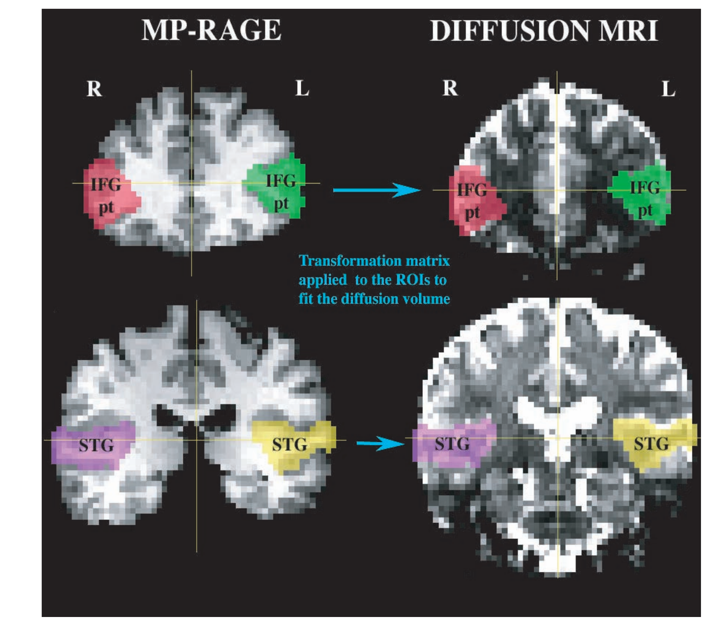

Figure 6: *Example showing the result of the co-registration of the ROIs to the diffusion data.*

5) Co-registration of the Anatomical Data to the Diffusion MRI:

After manual extraction of non-brain tissues, each MP-RAGE volume is co-registered to the b0 diffusion volume using Normalized Mutual Information (Rview software). Figure 5 shows an example of co-registration of an MP-RAGE volume to a corresponding diffusion volume where the arrows point to matching sulcal features. The resulting transformation matrix file is saved and applied to frontal and temporal ROIs to anatomically match the diffusion volume (Fig. 6). The co-registered ROIs are then imported in Trackvis (Fig. 6). We use the ROIs as seed points for tractography and calculate the fractional anisotropy of the white matter in each ROI.

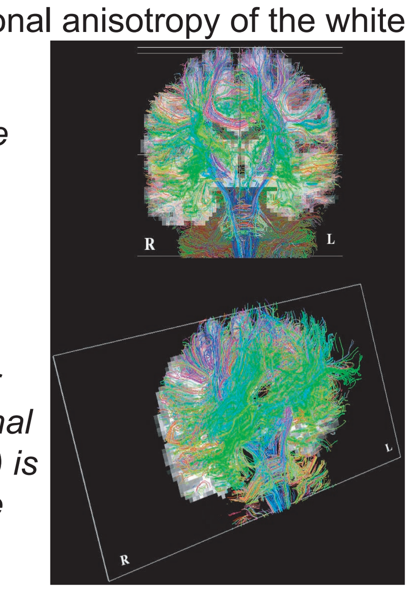

Figure 7: *Visualization of the fiber tracks displayed on the co-registered MP-RAGE of one twin data picked randomly from our sample. The coronal view (upper panel) is slightly tilted to the left (lower panel).*

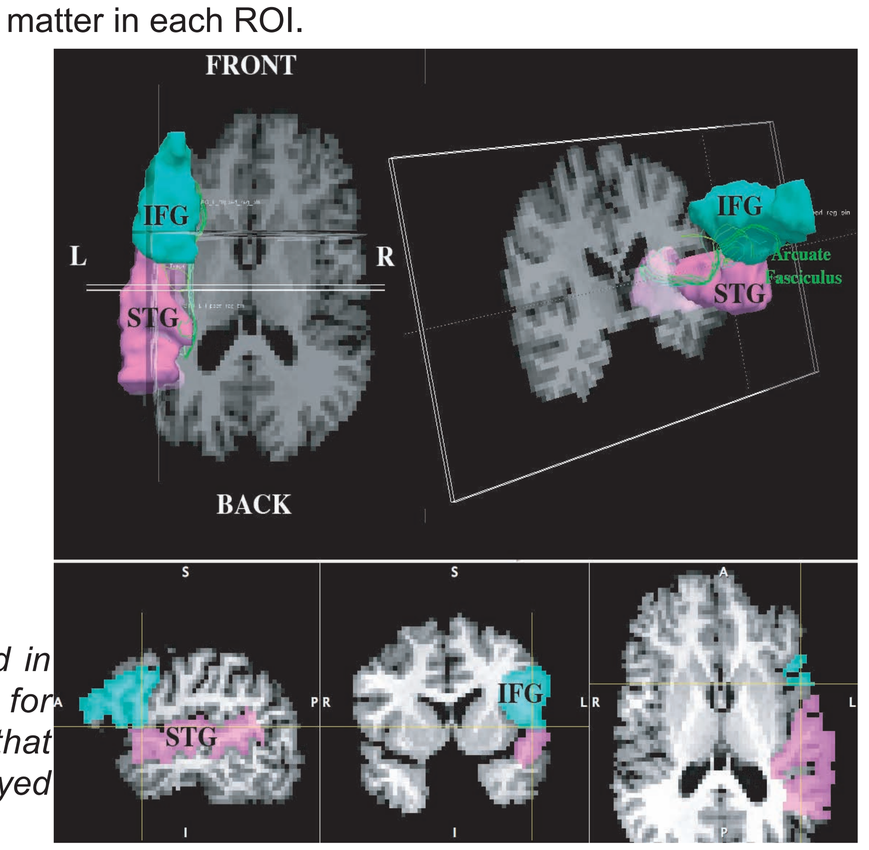

Figure 8: *The IFG and STG ROIs are used in the present example as seed points for tractography. Fibers between both ROIs that represent the arcuate fasciculus are displayed in the upper panel.*

Conclusion

This is a feasibility report with respect to the volumetric study and the white matter study of a large cohort of twins, all the same age, and all studied extensively with neuropsychological measures. To date we have completed the volumetric calculations for the ROIs mentioned and the initial processing of the diffusion data in only 12 pairs of twins. Given that we have only 3 MZ pairs in that initial group it is premature to provide numeric results.

References

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