

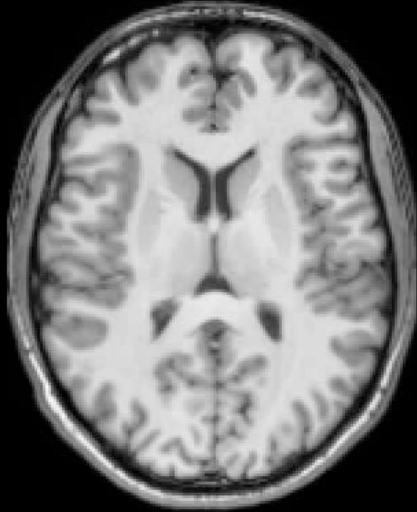
Brain morphometry using diffusion MRI

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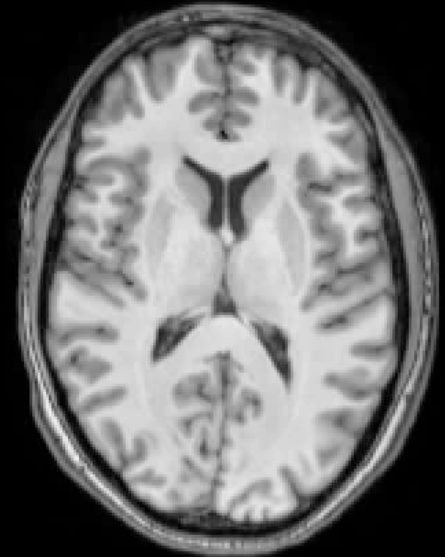
Spatial normalization



Subject 1

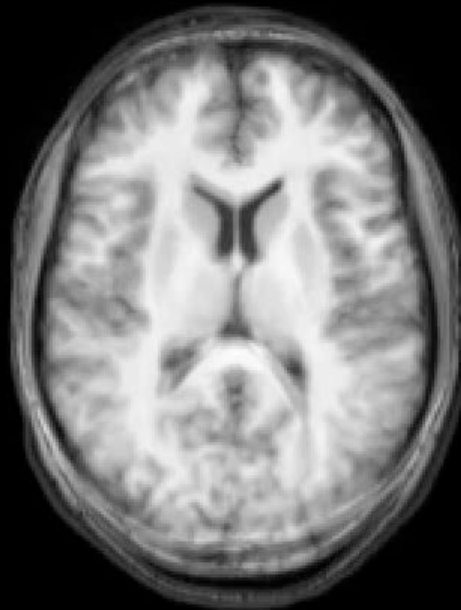


Subject 2



Subject 3

Population
Atlas

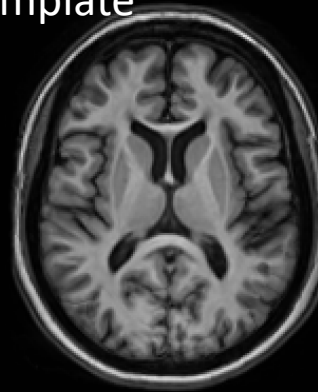


Computational Neuroanatomy

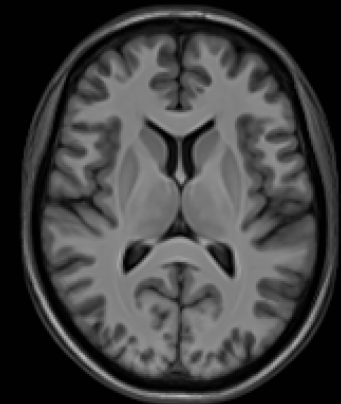
With the increasing resolution of anatomical scans of the human brain and the sophistication of image processing techniques there have emerged, recently, a large number of approaches to characterizing differences in the shape and neuroanatomical configuration of different brains. One way to classify these approaches is to broadly divide them into those that deal with **differences in brain shape** and those that deal with **differences in the local composition of brain tissue** after macroscopic differences in shape have been discounted. The former use the deformation fields that map any individual brain onto some standard reference as the characterization of neuroanatomy, whereas the latter compare images on a voxel basis after the deformation fields have been used to spatially normalize the images. In short, computational neuroanatomic techniques can **either use the deformation fields themselves** or **use these fields to normalize images that are then entered into an analysis of regionally specific differences**. In this way, information about overall shape (deformation fields) and residual anatomic differences inherent in the data (normalized images) can be partitioned.

Jacobian of the transformation is informative of local changes in volume (Tensor-based-morphometry: TBM)

Single Patient brain or patient template



Control Template



- ANTS software

- (Avants et al. 2008 & 2011)

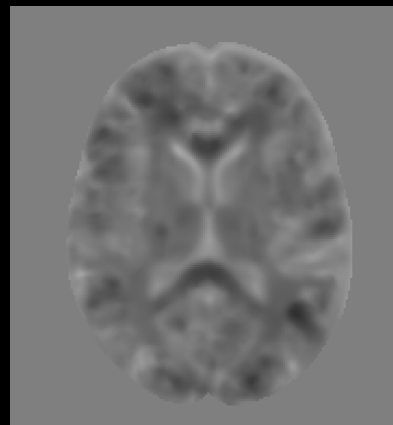
- Similarity metric:

- cross correlation

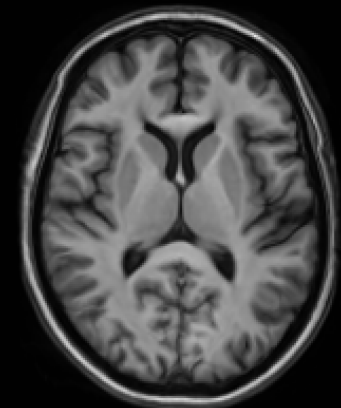
- Transformation model:

- Diffeomorphic (symmetric mapping (Syn))

Log of the Det of the Jacobian of the Transformation



Patient brain registered to the Control template



Applications of TBM based on T1-weighted Images

- Alzheimer disease (Freeborough & Fox 1998)
- Brain development (Thompson et al.2000)
- Huntington (Kipps et al. 2005)
- Fragile X syndrome (Lee et al. 2007)
- Frontotemporal dementia (Brambati 2007)
- Williams syndrome (Chiang et al 2007)
- HIV/AIDs (Chiang et al. 2007, Lepore 2008)
- Schizophrenia (Whitford et al. 2007, Hua et al. 2008)
- TBI (Kim et al. 2008)
- Stress (Hanson et al. 2010)
- ...

Our Hypothesis:

Diffusion MRI provides clear delineation of anatomical structures that can not be separated in T1- and T2-WI (e.g. individual pathways).

Therefore, tensor-based morphometry (TBM) using DTI-driven registration (DTBM) should be more accurate than T1WI-TBM.

Examples in the literature of TBM with registration driven by diffusion MRI data

Registration based only on FA images

Multiple sclerosis and amyotrophic lateral sclerosis (Pagani et al. 2007)

Alzheimer's Disease (Oishi et al. 2011)

Registration based on tensor deviatoric

High-dimensional spatial normalization of diffusion tensor images improves the detection of white matter differences: an example study using amyotrophic lateral sclerosis. Zhang et al. (2007). IEEE transactions on medical imaging, 26(11), 1585-1597.

Only one paper with registration based on all tensor elements

Dense feature deformation morphometry: Incorporating DTI data into conventional MRI morphometry Studholme et al., Medical image analysis 12.6 (2008): 742-751.



Contents lists available at ScienceDirect

NeuroImage

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Investigating white matter fibre density and morphology using fixel-based analysis



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Density

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ABSTRACT

Voxel-based analysis of diffusion MRI data is increasingly popular. However, most white matter voxels contain contributions from multiple fibre populations (often referred to as crossing fibres), and therefore voxel-averaged quantitative measures (e.g. fractional anisotropy) are not fibre-specific and have poor interpretability. Using higher-order diffusion models, parameters related to fibre density can be extracted for individual fibre populations within each voxel ('*fixels*'), and recent advances in statistics enable the multi-subject analysis of such data. However, investigating within-voxel *microscopic* fibre density alone does not account for *macroscopic* differences in the white matter morphology (e.g. the calibre of a fibre bundle). In this work, we introduce a novel method to investigate the latter, which we call fixel-based morphometry (FBM). To obtain a more complete measure related to the total number of white matter axons, information from both within-voxel microscopic fibre density and macroscopic morphology must be combined. We therefore present the FBM method as an integral piece within a comprehensive fixel-based analysis framework to investigate measures of fibre density, fibre-bundle morphology (cross-section), and a combined measure of fibre density and cross-section. We performed simulations to demonstrate the proposed measures using various transformations of a numerical fibre bundle phantom. Finally, we provide an example of such an analysis by comparing a clinical patient group to a healthy



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Article [Talk](#)

Brain morphometry

From Wikipedia, the free encyclopedia

Pattern based morphometry [\[edit \]](#)

Pattern based morphometry (PBM) is a method of brain morphometry first put forth in PBM.^[4] It builds upon DBM a As opposed to typical voxel based approaches which depend on univariate statistical tests at specific voxel location this is that the inferences are not made locally as in VBM or DBM but globally. This allows the method to detect if c single voxels. Also the method is more robust to variations in the underlying registration algorithms as compared to

Surface-based morphometry [\[edit \]](#)

Main article: [Surface-based morphometry](#)

Once the brain is segmented, the boundary between different classes of tissue can be [reconstructed as a surface](#) c results of such analyses can be [projected](#).

Diffusion-weighted MR-based brain morphometry [\[edit \]](#)

Fiber-tracking techniques [\[edit \]](#)

Nerve fiber-tracking techniques are the latest offspring of this suite of MR-based morphological approaches. They c or [diffusion-spectrum imaging](#) (e.g. [Douaud et al., 2007](#) and [O'Donnell et al., 2009](#)).

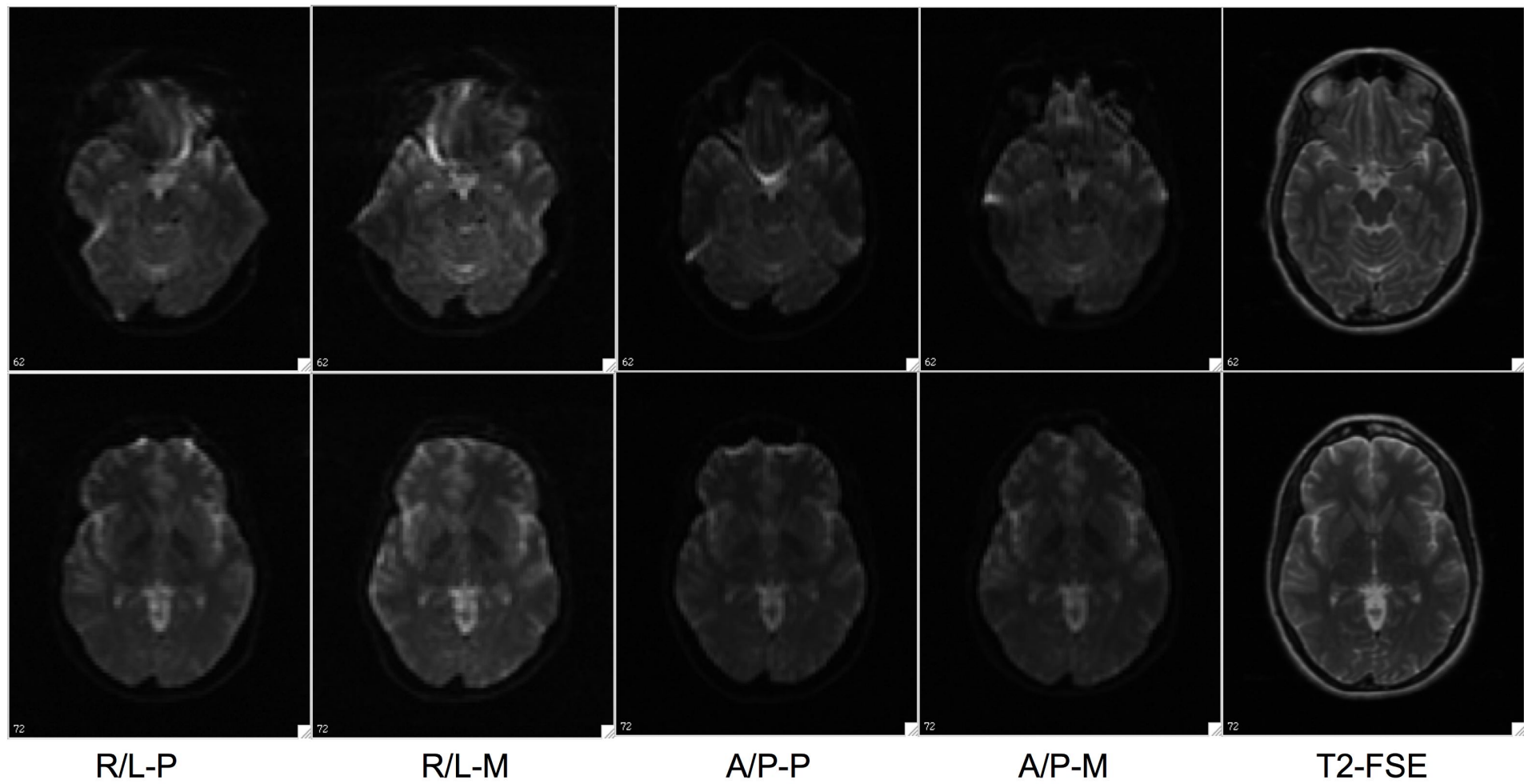
Diffeomorphometry [\[edit \]](#)

[Diffeomorphometry](#)^[5] is the focus on comparison of shapes and forms with a metric structure based on diffeomor registration,^[7] introduced in the 90's, is now an important player with existing codes bases organized around ANTS actively used computational codes for constructing correspondences between coordinate systems based on sparse:

Goal:

Achieve a robust and accurate diffusion MRI based registration that could be used to perform TBM-DTI.

Prerequisite: solve the issue of EPI distortions in DWI

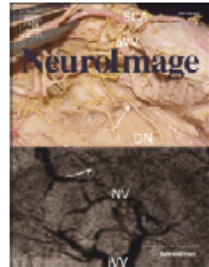




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Effects of image distortions originating from susceptibility variations and concomitant fields on diffusion MRI tractography results

M. Okan Irfanoglu ^{a,b,*}, Lindsay Walker ^{a,b}, Joelle Sarlls ^c, Stefano Marengo ^d, Carlo Pierpaoli ^a

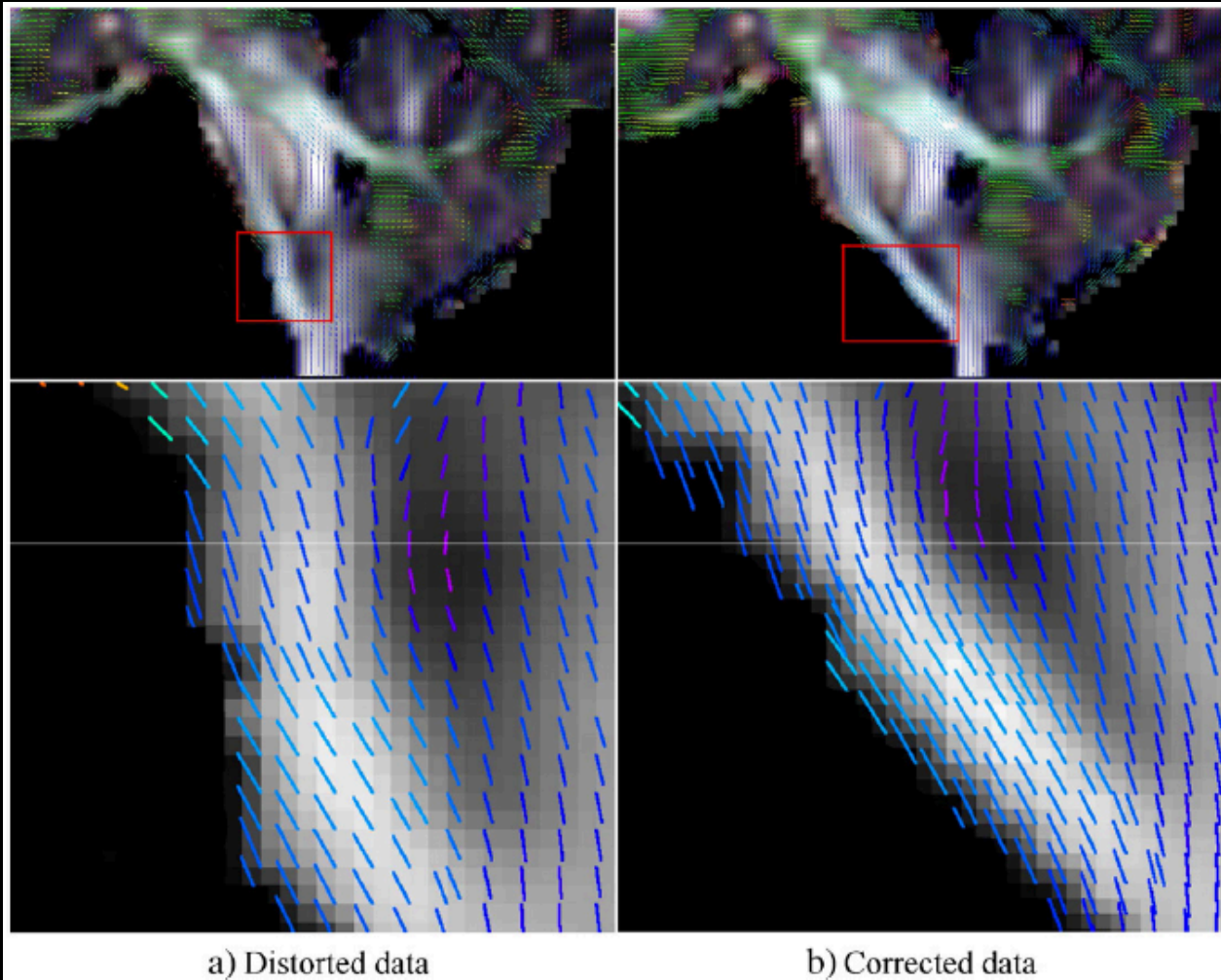
^a Program on Pediatric Imaging and Tissue Sciences, NICHD, National Institutes of Health, Bethesda, MD, 20892, USA

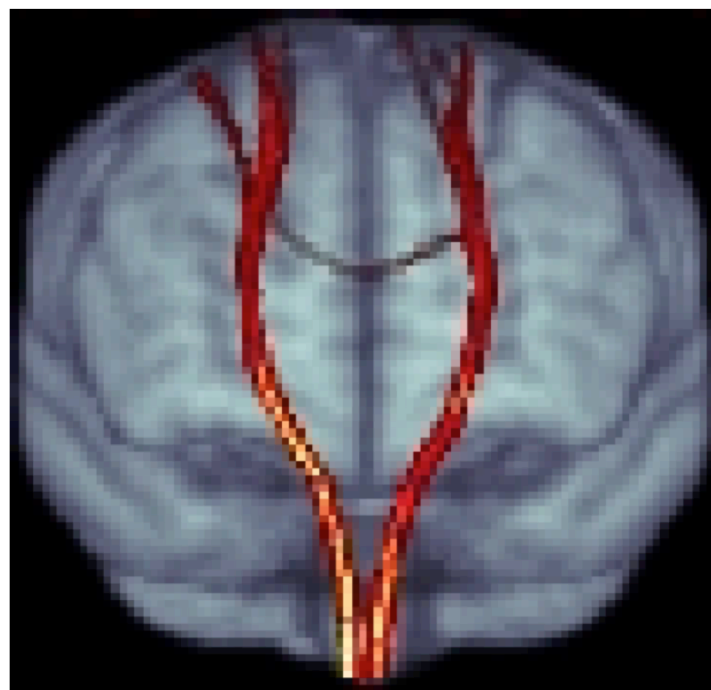
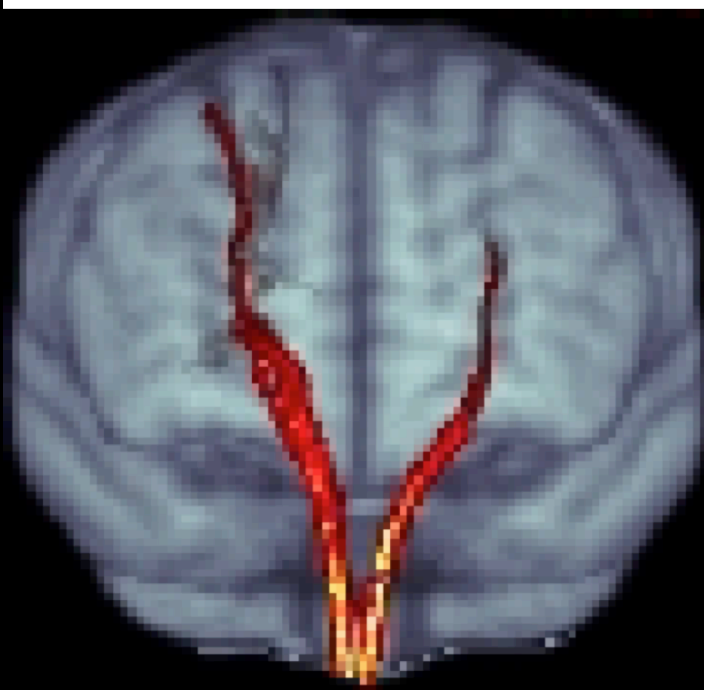
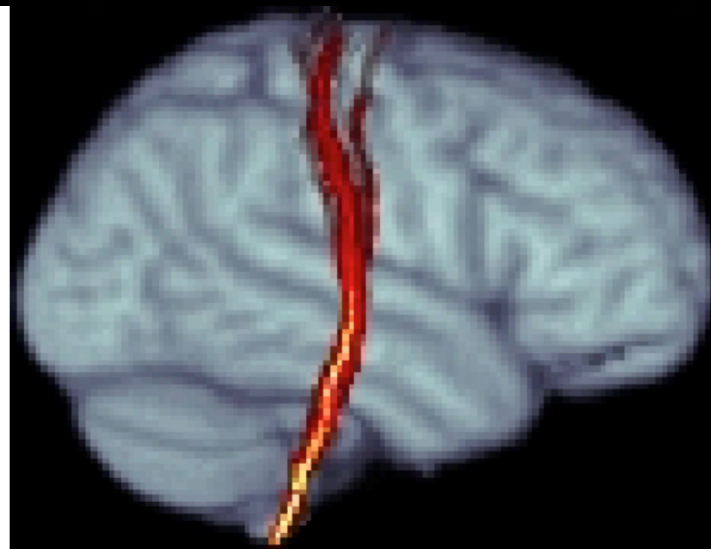
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^d Section on Clinical Studies, National Institute of Mental Health, National Institute of Health, Bethesda, MD, 20892, USA

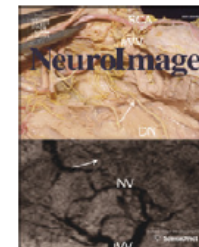
EPI distortions & Tensors





Before correction

After correction



DR-BUDDI (Diffeomorphic Registration for Blip-Up blip-Down Diffusion Imaging) method for correcting echo planar imaging distortions



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Reversed phase encoding

Diffeomorphic image registration

ABSTRACT

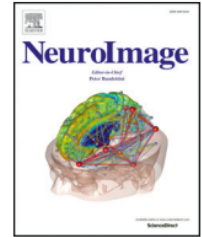
We propose an echo planar imaging (EPI) distortion correction method (*DR-BUDDI*), specialized for diffusion MRI, which uses data acquired twice with reversed phase encoding directions, often referred to as blip-up blip-down acquisitions. *DR-BUDDI* can incorporate information from an undistorted structural MRI and also use diffusion-weighted images (DWI) to guide the registration, improving the quality of the registration in the presence of large deformations and in white matter regions. *DR-BUDDI* does not require the transformations for correcting blip-up and blip-down images to be the exact inverse of each other. Imposing the theoretical “blip-up blip-down distortion symmetry” may not be appropriate in the presence of common clinical scanning artifacts such as motion, ghosting, Gibbs ringing, vibrations, and low signal-to-noise. The performance of *DR-BUDDI* is evaluated with several data sets and compared to other existing blip-up blip-down correction approaches. The proposed method is robust and generally outperforms existing approaches. The inclusion of the DWIs in the correction process proves to be important to obtain a reliable correction of distortions in the brain stem. Methods that do not use DWIs may produce a visually appealing correction of the non-diffusion weighted images, but the directionally encoded color maps computed from the tensor reveal an abnormal anatomy of the white matter pathways.



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DR-TAMAS: Diffeomorphic Registration for Tensor Accurate Alignment of Anatomical Structures



M. Okan Irfanoglu^{a,c,*}, Amritha Nayak^{a,c}, Jeffrey Jenkins^{a,c}, Elizabeth B. Hutchinson^{a,c}, Neda Sadeghi^a, Cibü P. Thomas^{a,b}, Carlo Pierpaoli^a

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Diffeomorphic image registration

Fiber tractography

ABSTRACT

In this work, we propose *DR-TAMAS* (Diffeomorphic Registration for Tensor Accurate alignment of Anatomical Structures), a novel framework for intersubject registration of Diffusion Tensor Imaging (DTI) data sets. This framework is optimized for brain data and its main goal is to achieve an accurate alignment of all brain structures, including white matter (WM), gray matter (GM), and spaces containing cerebrospinal fluid (CSF). Currently most DTI-based spatial normalization algorithms emphasize alignment of anisotropic structures. While some diffusion-derived metrics, such as diffusion anisotropy and tensor eigenvector orientation, are highly informative for proper alignment of WM, other tensor metrics such as the trace or mean diffusivity (MD) are fundamental for a proper alignment of GM and CSF boundaries. Moreover, it is desirable to include information from structural MRI data, e.g., T_1 -weighted or T_2 -weighted images, which are usually available together with the diffusion data. The fundamental property of *DR-TAMAS* is to achieve global anatomical accuracy by incorporating in its cost function the most informative metrics locally. Another important feature of *DR-TAMAS* is a symmetric time-varying velocity-based transformation model, which enables it to account for potentially large anatomical variability in healthy subjects and patients. The performance of *DR-TAMAS* is evaluated with several data sets and compared with other widely-used diffeomorphic image registration techniques employing both full tensor information and/or DTI-derived scalar maps. Our results show that the proposed method has excellent overall performance in the entire brain, while being equivalent to the best existing methods in WM.

DR-TAMAS main features

Uses all features of the diffusion tensor to achieve good alignment of white matter, gray matter, and CSF

Large deformation mapping capabilities

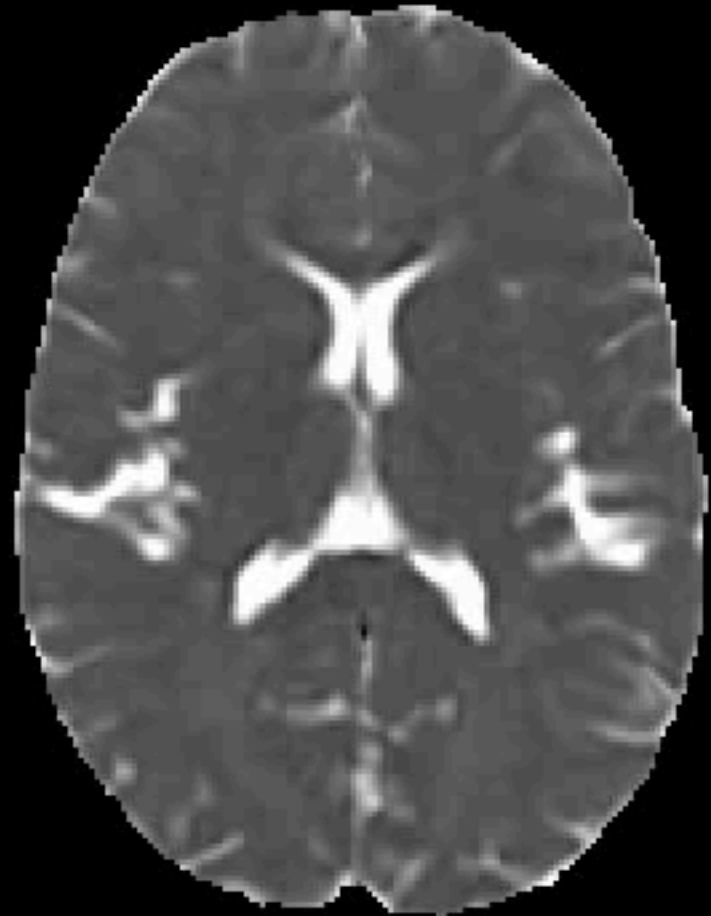
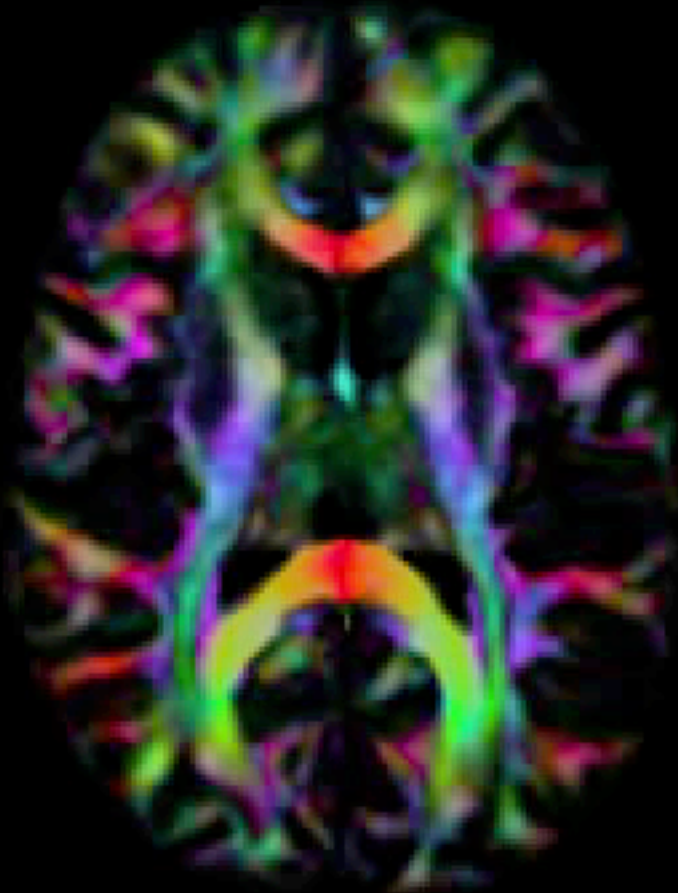
Tensor reorientation during optimization

If desired, can use complementary information from anatomical images such as T1W or T2W structural images

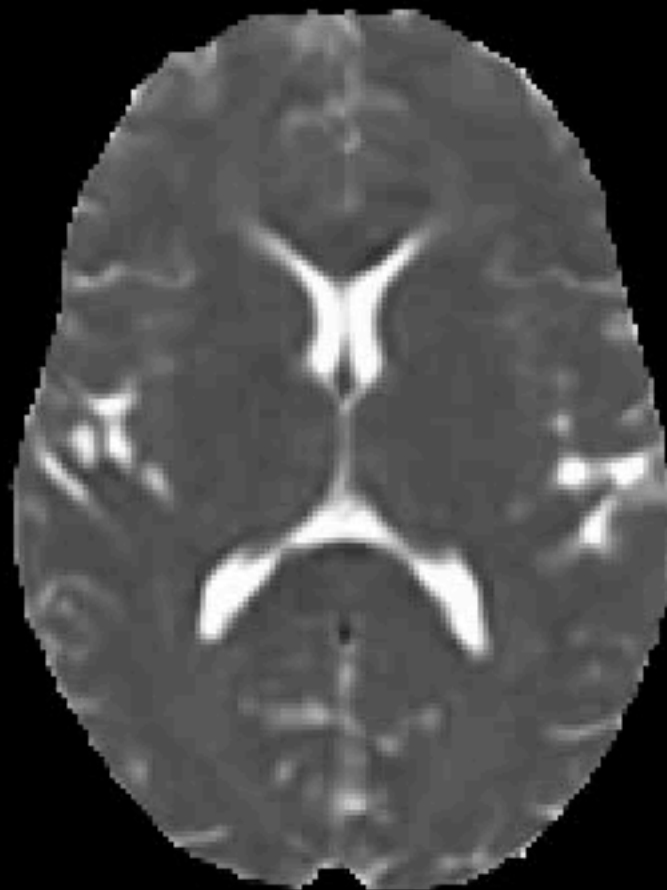
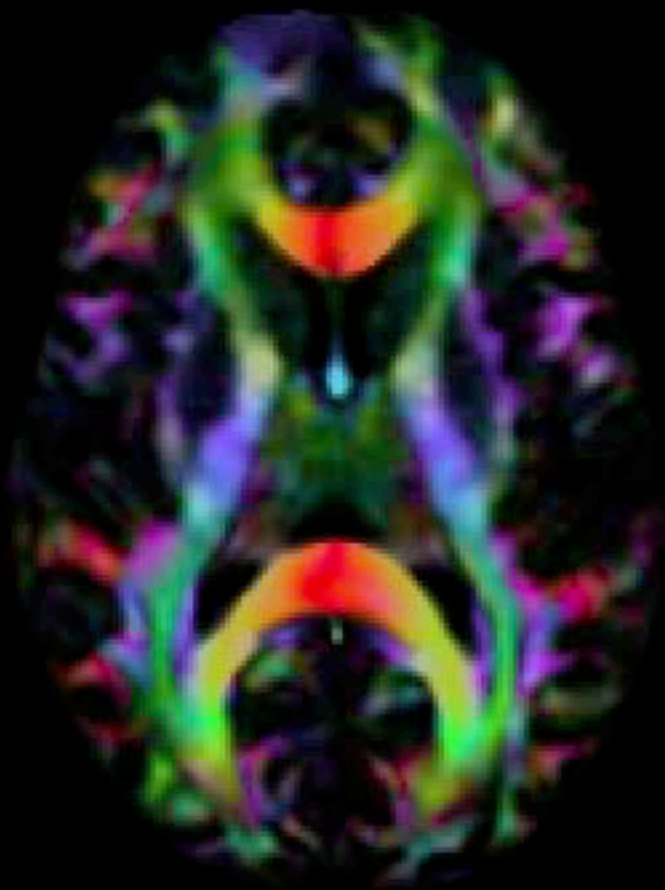
Provides robust atlas creation strategies

Can deal with lesion regions (e.g. tumors) or missing tissue.

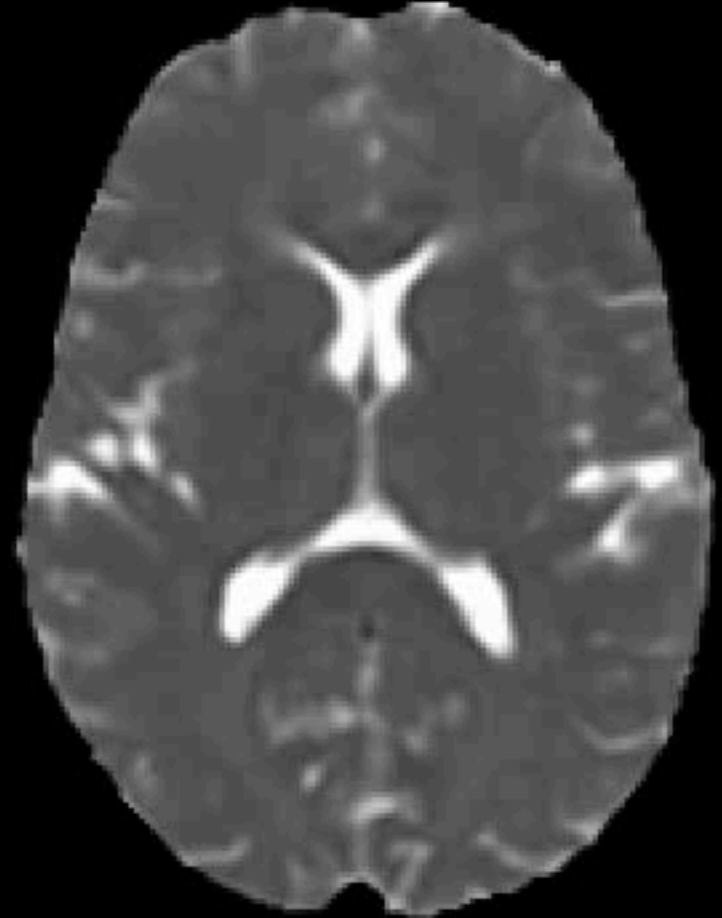
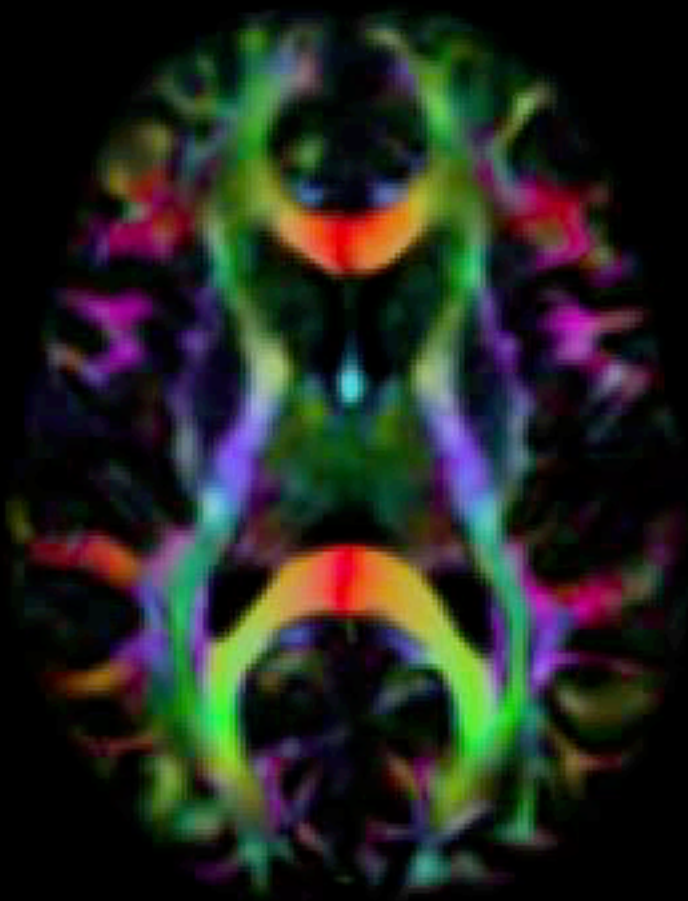
Native morphology (AC-PC aligned)



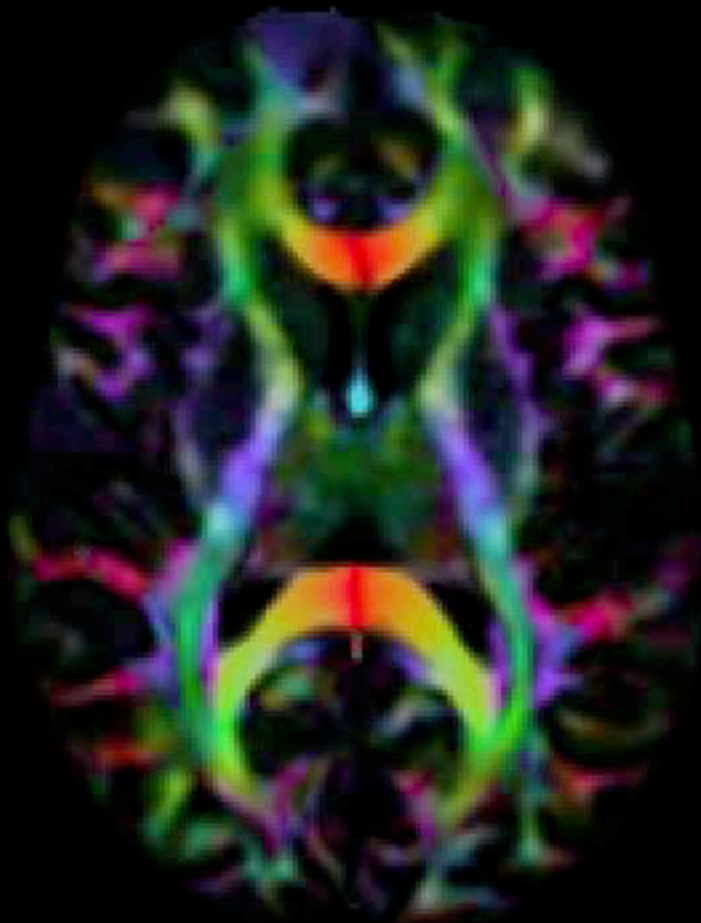
Registered using FA (FSL)

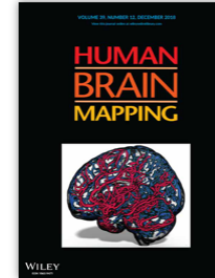


Registered using deviatoric tensor (DTI-TK)



Registered using DR-TAMAS





RESEARCH ARTICLE

Tensor-based morphometry using scalar and directional information of diffusion tensor MRI data (DTBM): Application to hereditary spastic paraplegia

Neda Sadeghi , Filippo Arrigoni, Maria Grazia D'Angelo, Cibu Thomas, M. Okan Irfanoglu, Elizabeth B. Hutchinson, Amritha Nayak, Pooja Modi, Maria Teresa Bassi, Carlo Pierpaoli

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Application to Hereditary Spastic Paraplegia

DTBM localizes disease to specific white matter pathways

DTBM results are consistent with selective involvement of long range white matter pathways

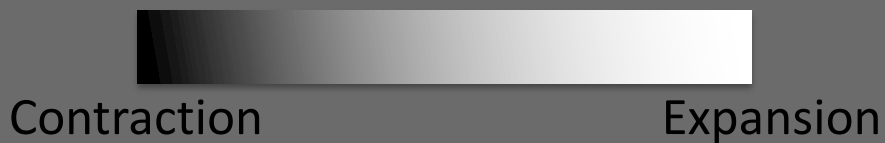
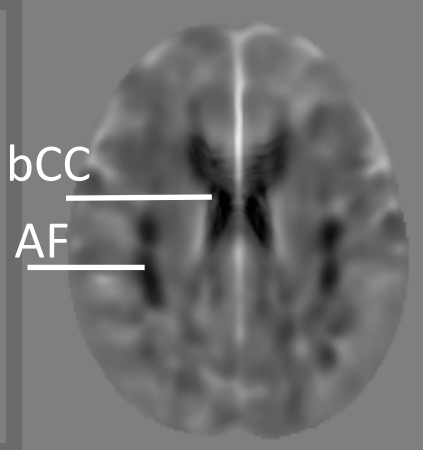
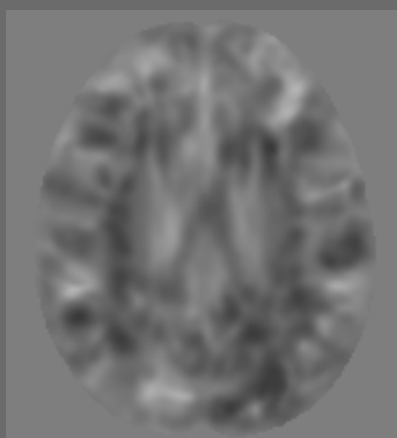
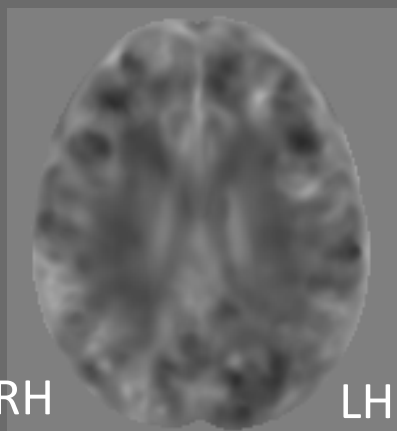
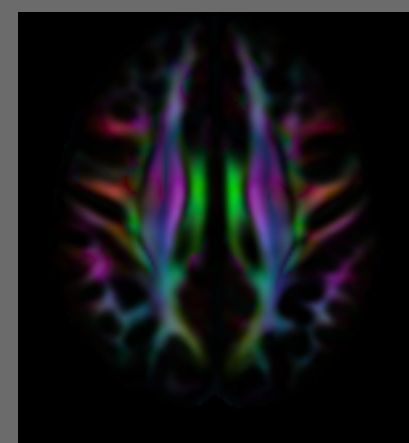
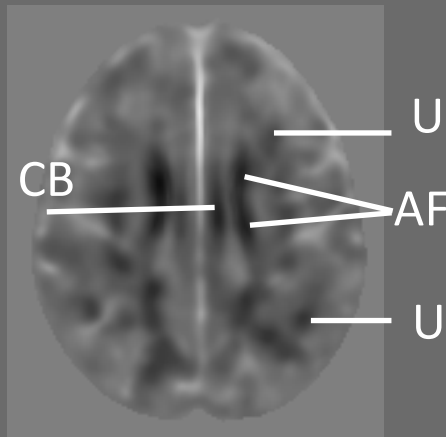
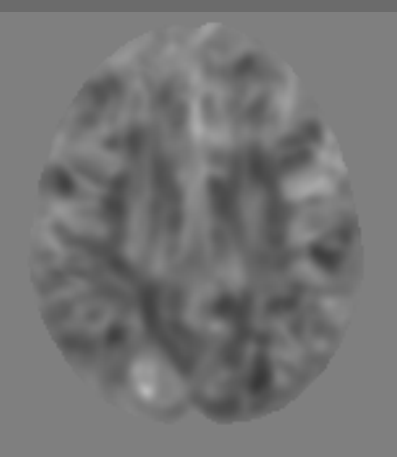
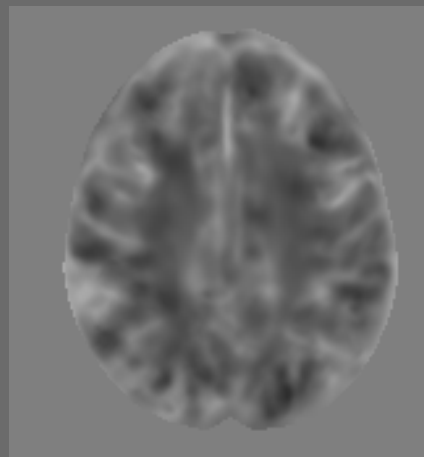
- Hereditary Spastic Paraplegia (HSP) is a group of neurodegenerative disorders characterized by lower limb weakness & spasticity.
- The pure form has only motor involvement
- SPG11 is a subtype of HSP with mutation in the SPG11 gene which encodes for a protein involved in the maintenance of axons.
- HSP-SPG11 patients also exhibit other neurological problems in addition to spasticity, for example intellectual disability
- Conventional MRI findings:
 - None in the pure form
 - Thinning of corpus callosum and Enlargement of ventricles in SPG11

T1W-TBM

FA-TBM

DTI-TBM

Control DEC Map

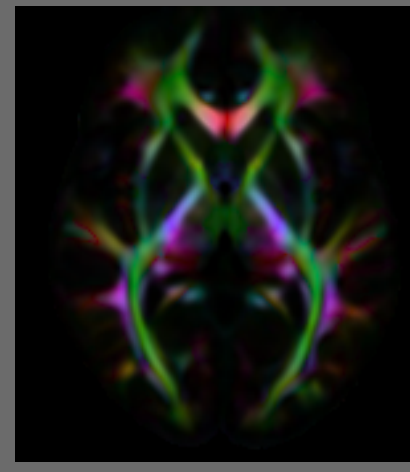
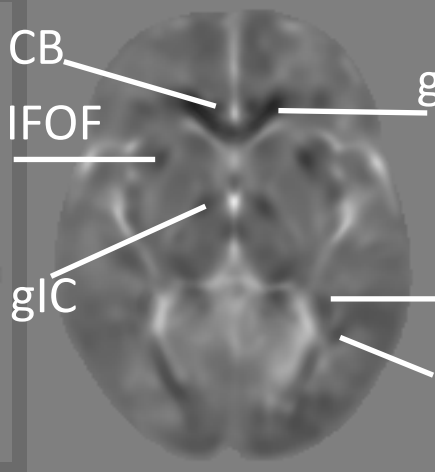
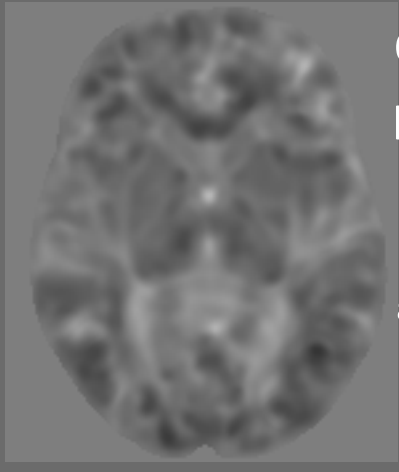
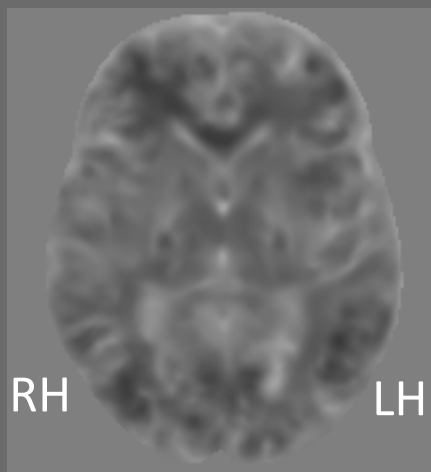
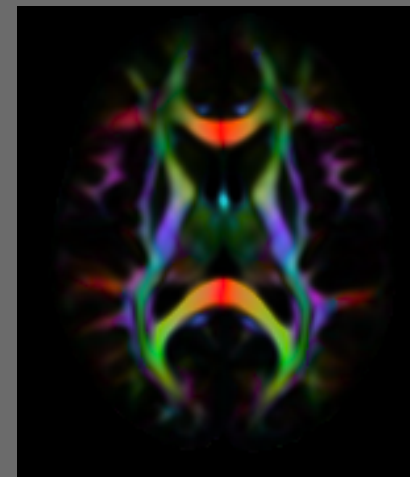
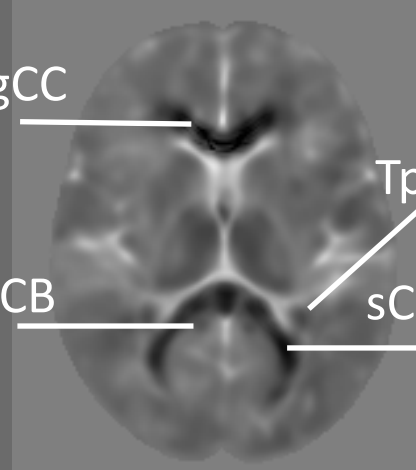
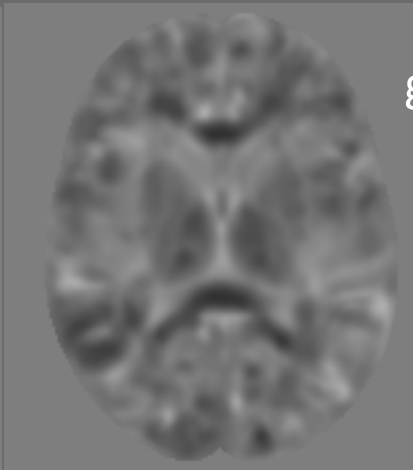
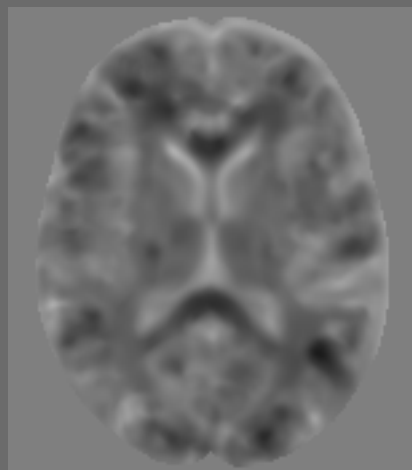


T1W-TBM

FA-TBM

DTI-TBM

Control DEC Map

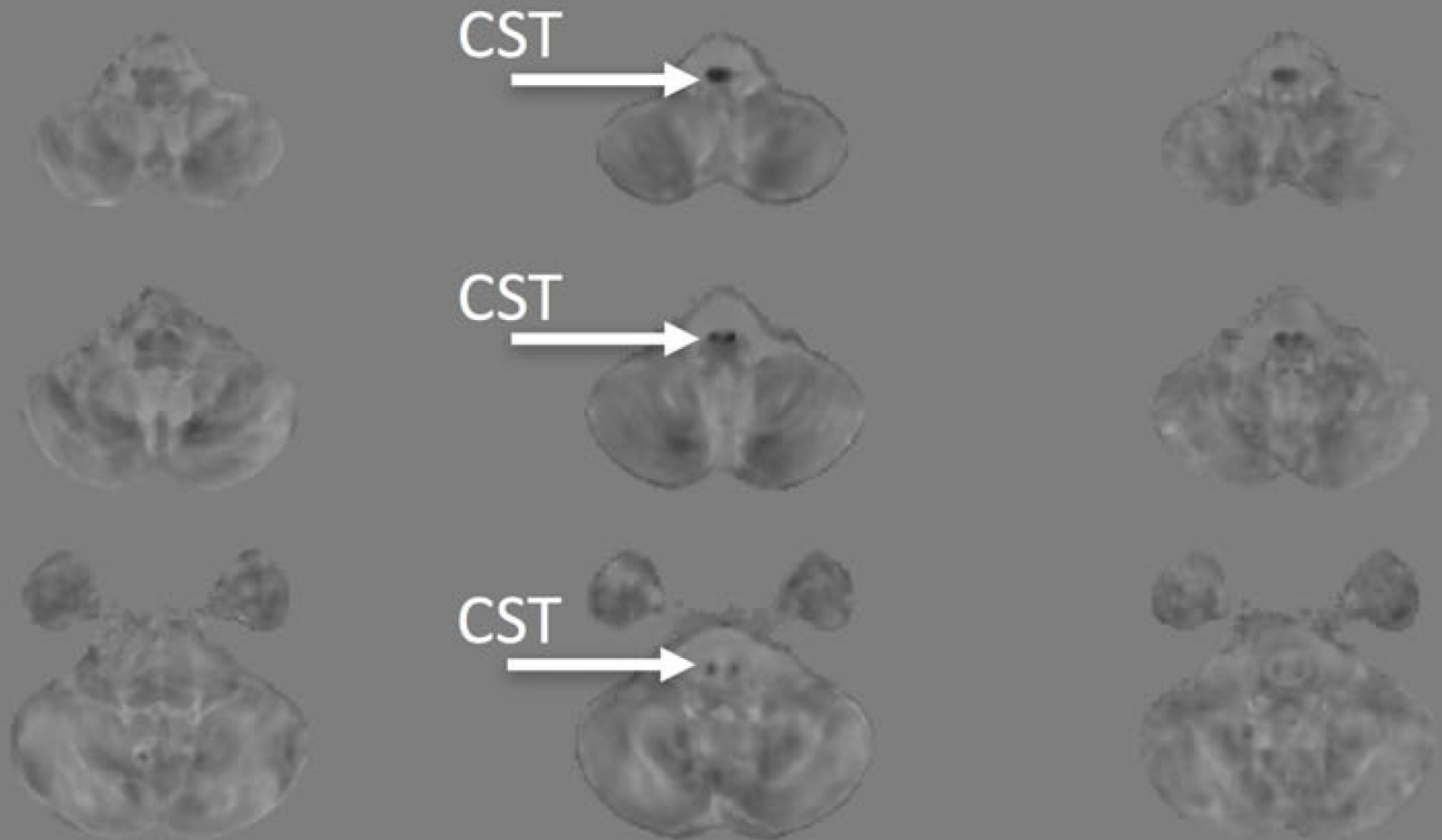


Effect Size

T1W-TBM

DTBM

FA-TBM



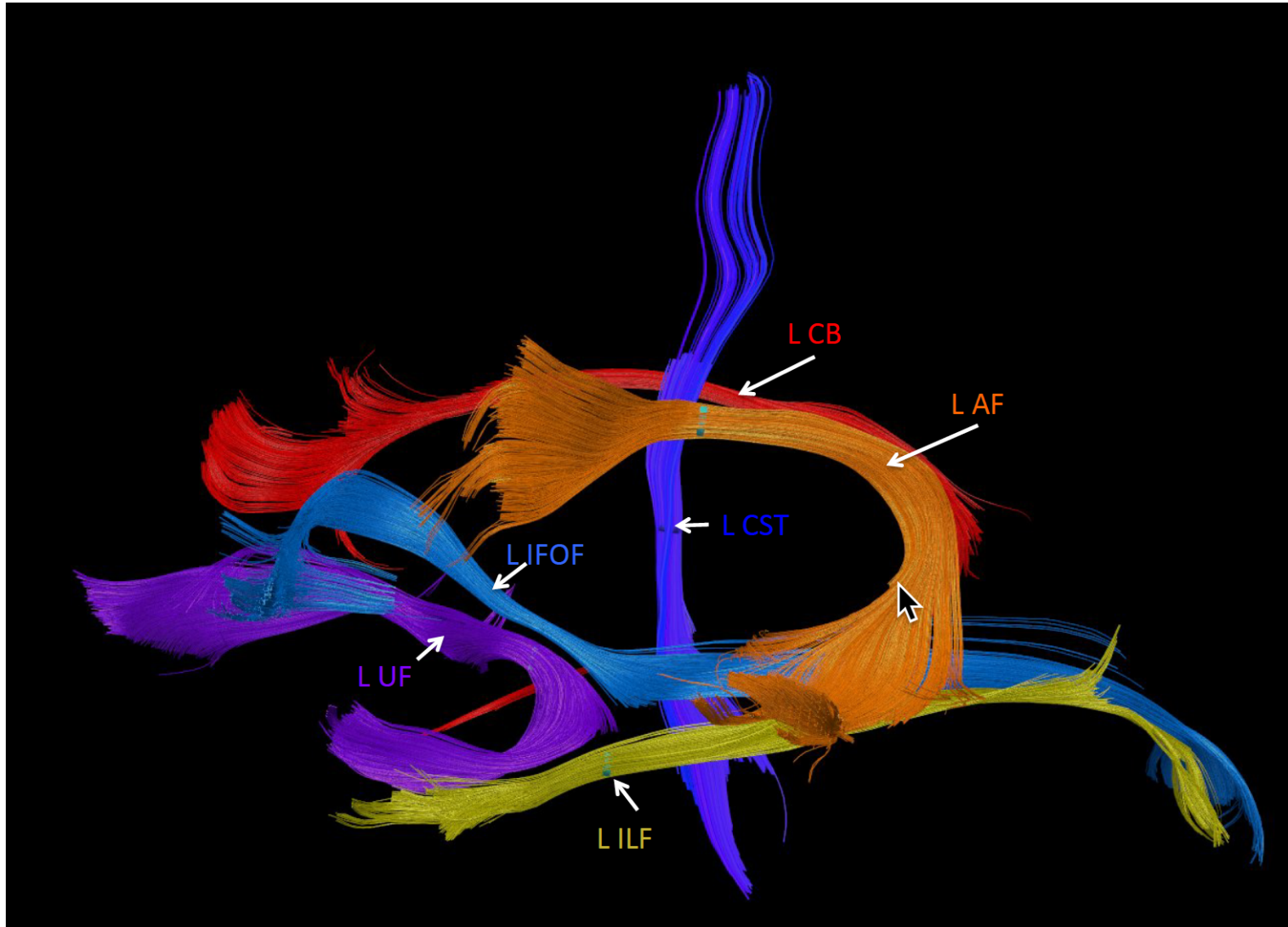


Figure 6: Fiber tracts located in regions of atrophy in the left hemisphere. AF: arcuate fasciculus; CB: cingulum bundle; CST: corticospinal tract; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; UF: uncinate fasciculus.

Application to Normal Brain development

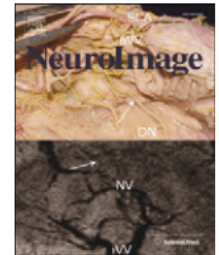
DTBM changes generally correlate with FA changes but the regression slope changes in different pathways



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The diffusion tensor imaging (DTI) component of the NIH MRI study of normal brain development (PedsDTI)



Lindsay Walker ^a, Lin-Ching Chang ^{a,1}, Amritha Nayak ^a, M. Okan Irfanoglu ^a, Kelly N. Botteron ^b, James McCracken ^c, Robert C. McKinstry ^d, Michael J. Rivkin ^e, Dah-Jyuu Wang ^f, Judith Rumsey ^g, Carlo Pierpaoli ^{a,*}, the Brain Development Cooperative Group

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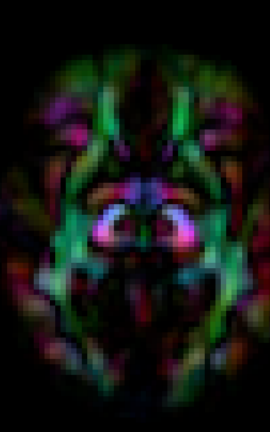
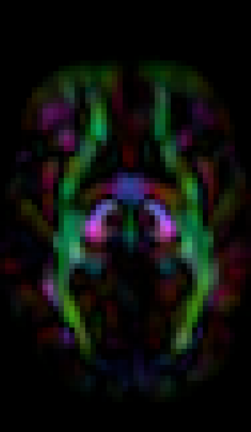
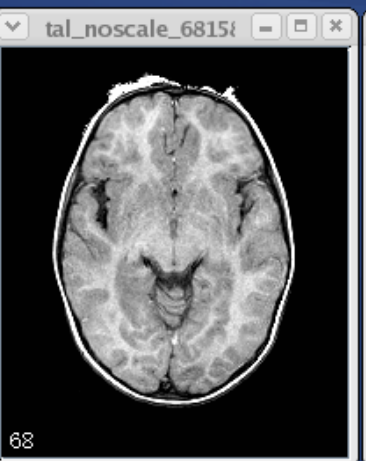
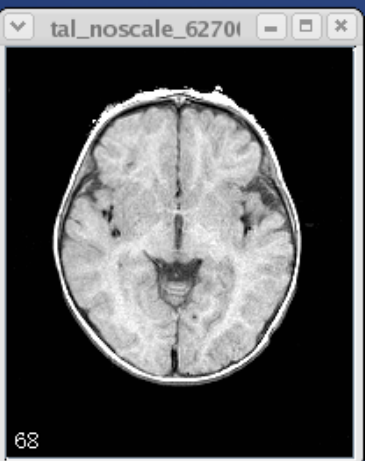
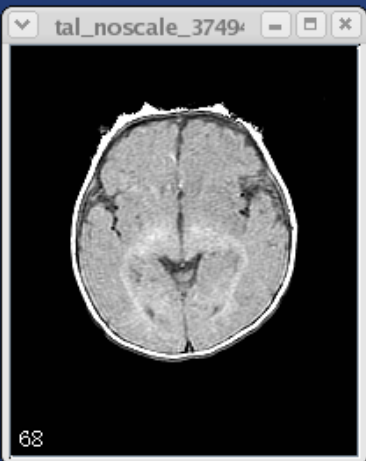
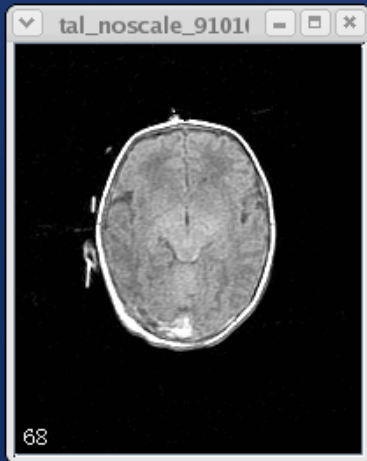
^c Department of Child Psychiatry, University of California in Los Angeles, Los Angeles, CA, USA

^d Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA

^e Departments of Neurology, Psychiatry and Radiology, Boston Children's Hospital, Boston, MA, USA

^f The Children's Hospital of Philadelphia, Philadelphia, PA, USA

^g Clinical Neuroscience Research Branch, Division of Translational Research, NIMH, NIH, Bethesda, MD, USA



0-3
months

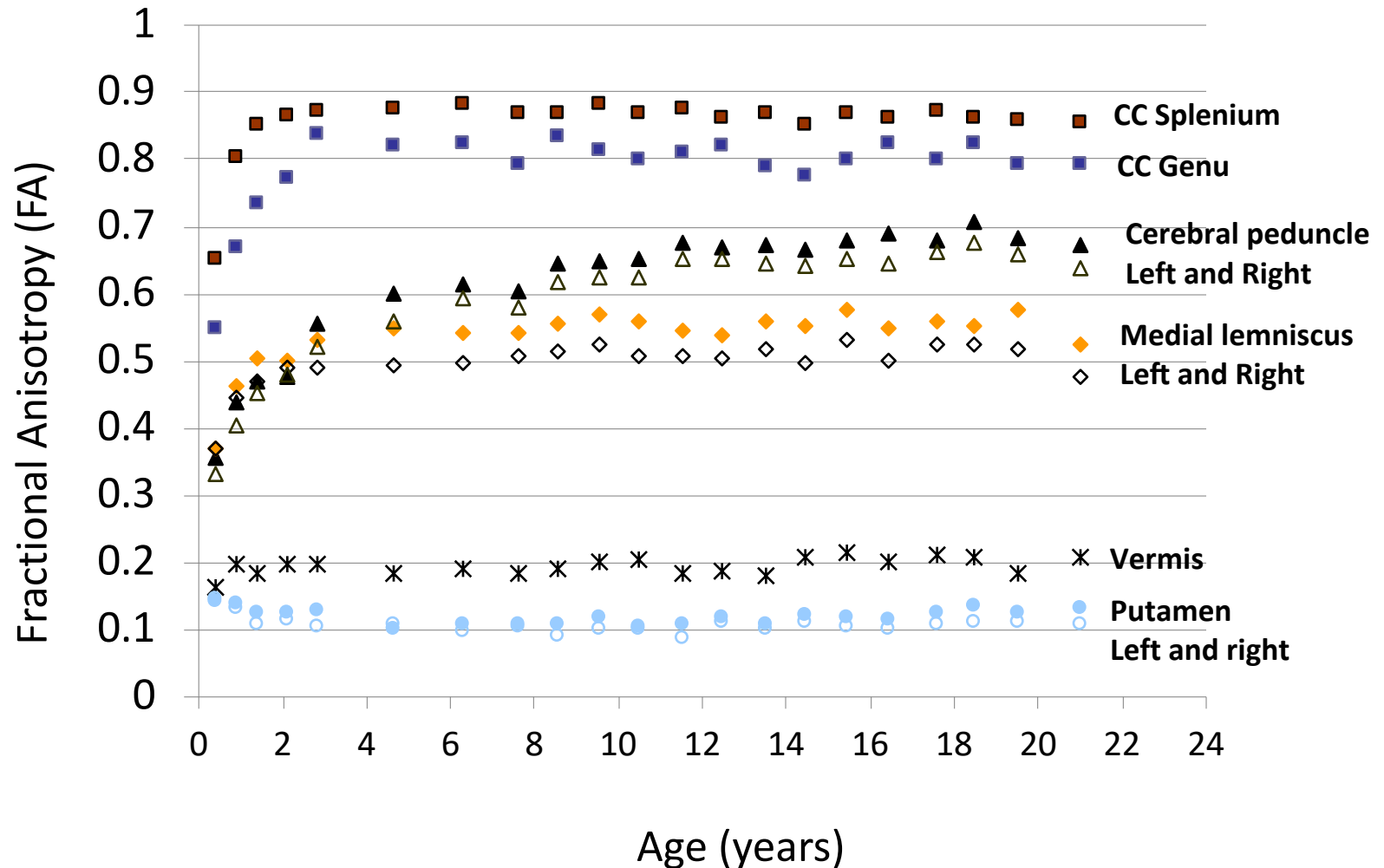
6-12
months

18
months

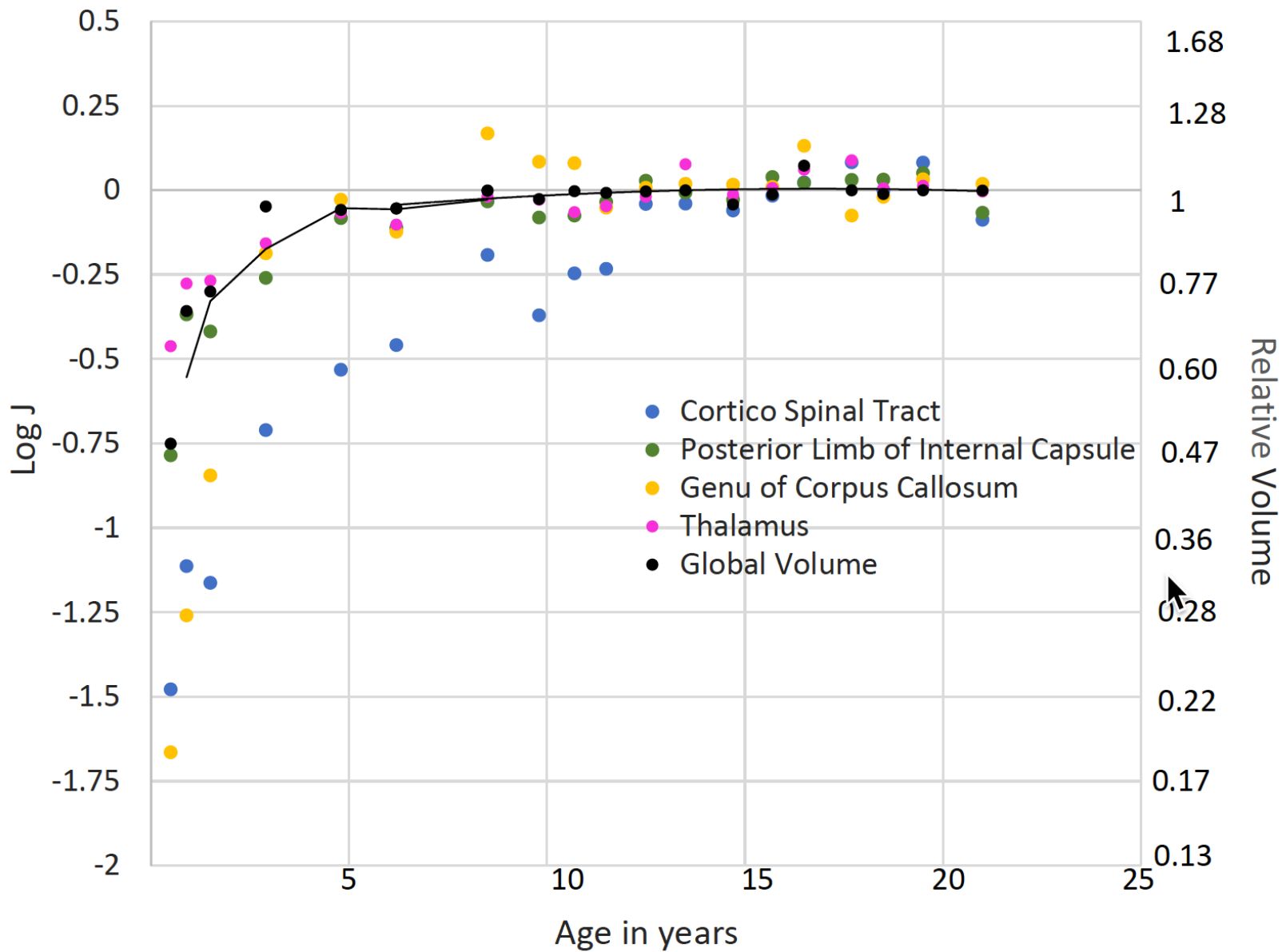
2-4
years

10
years

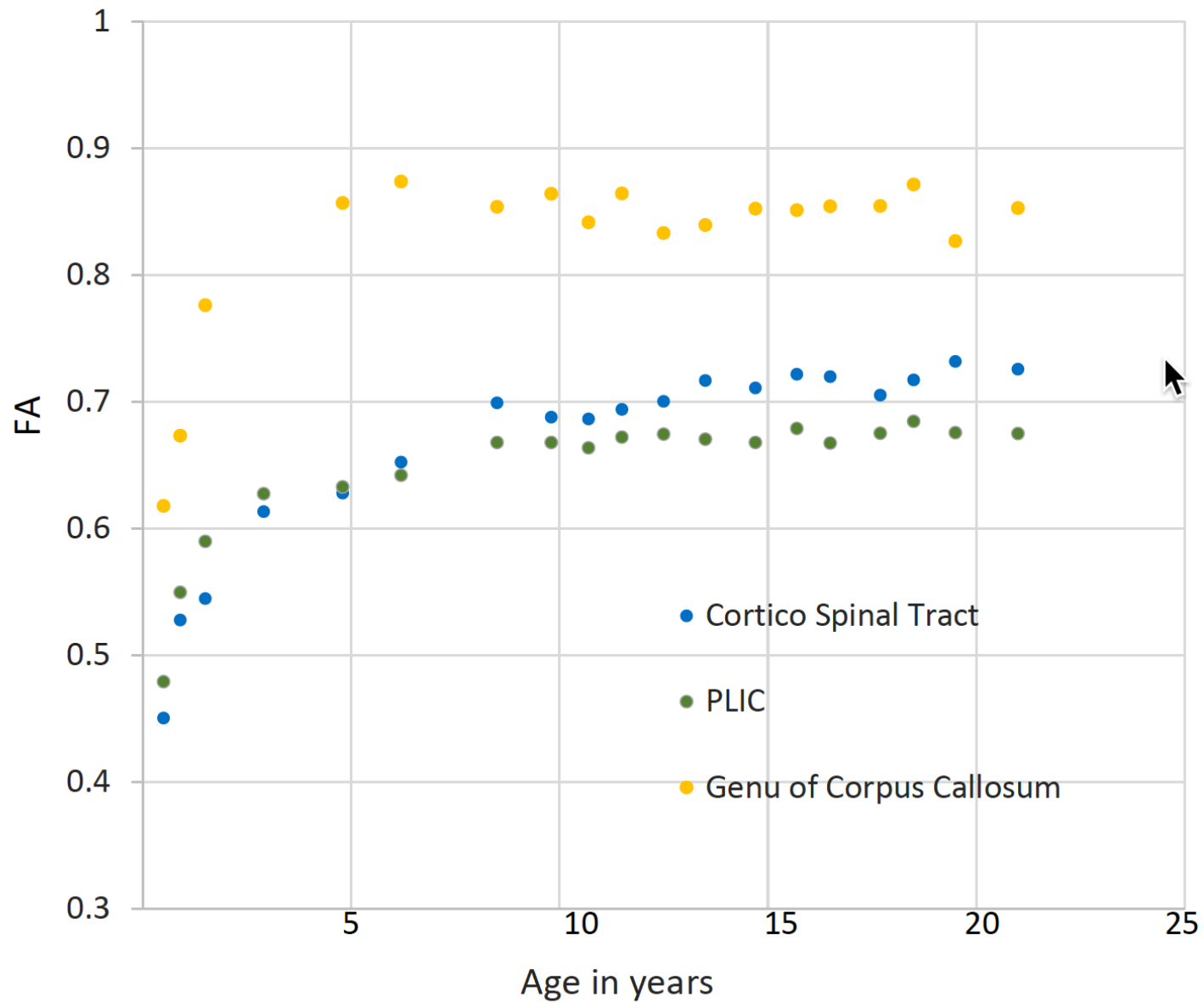
Developmental trajectories



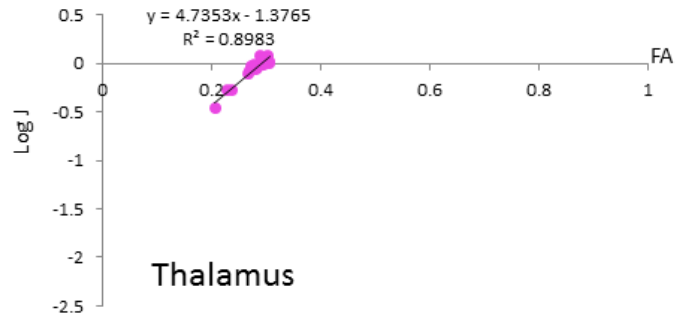
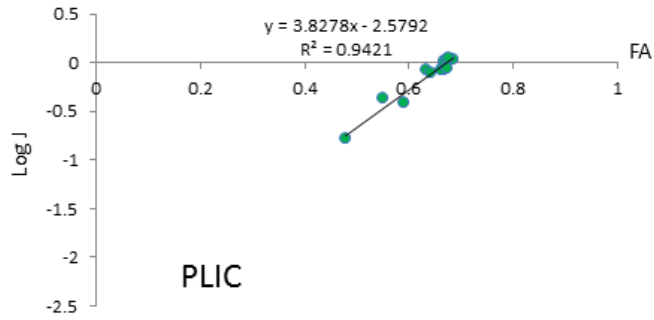
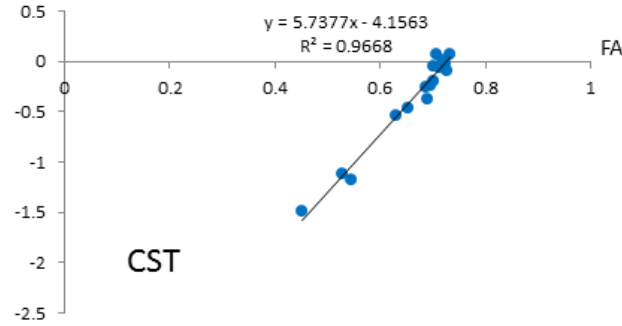
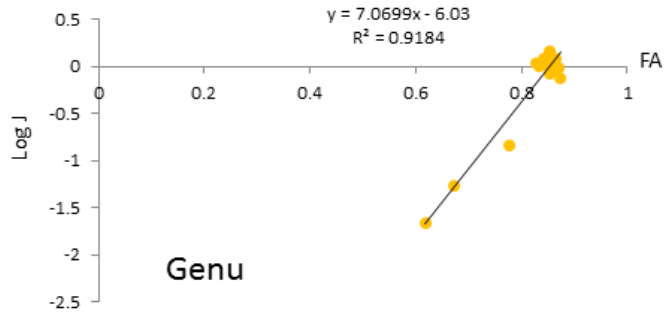
Volume changes of various brain structures as function of age (relative to volume in adults)



FA changes of various white matter structures as function of age



Correlation between FA and Log J



ROIs	Slope	R2
CST	5.7377	0.9667
PLIC	3.827	0.9421
Genu	7.0699	0.9183
Thalamus	4.7353	0.892

Application to Down Syndrome

Dramatic patients vs controls DTBM differences with no FA differences.

DTBM allows the identification of selective hypoplasia of fronto-pontine-cerebellar connections

Subjects

Table 1. Demographic characteristics of the sample

	DS (<i>n</i>=15)			Control (<i>n</i>=29)		
	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>M</i>	<i>SD</i>	<i>Range</i>
Age	17.02	5.47	6-23	16.17	6.40	5-24
Nonverbal IQ	59.53	15.19	34-86	113.59	16.27	89-134
SES (Hollingshead)	35.87	15.62	20-63	39.71	22.24	20-115
	<i>n</i>	<i>%</i>		<i>n</i>	<i>%</i>	
Sex: Female	7	47		16	55	
Race: White, non-Hispanic	10	67		17	59	

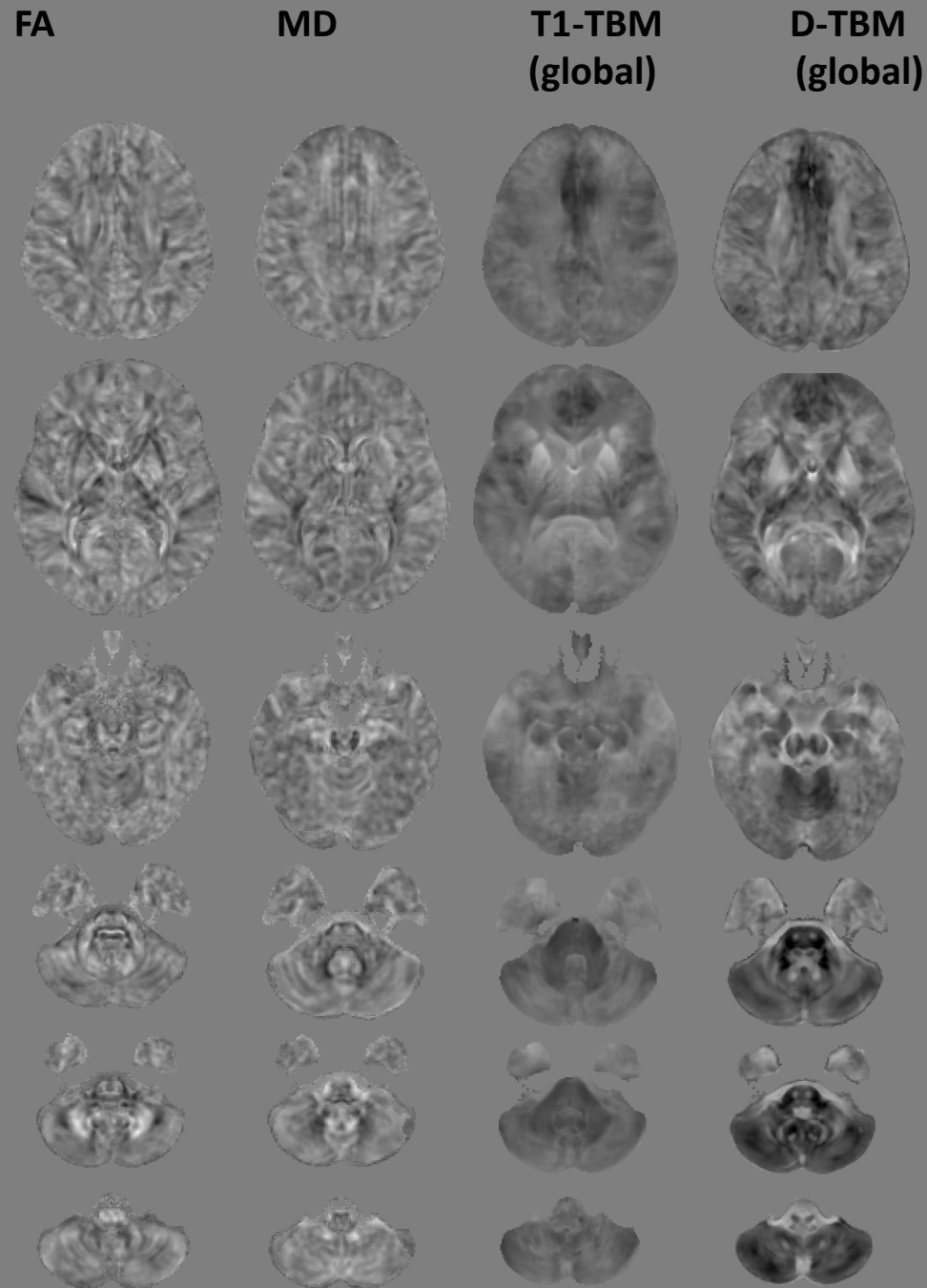
MRI Methods

- DTI datasets consisted of 60 volumes with 6 b=0, 12 b=300, and 42 b=1100s/mm². Resolution was 2.5 mm isotropic
- Control template created using DR TAMAS
- All subjects individually registered to the control template.
- The the log of the determinant of the jacobian was computed from the deformation field maps of each individual subject warped to the control template.
- TBSS and TFCE statistics were computed using FSL randomize program.
- Effect size maps were computed as follows:
$$\frac{(\text{mean patients} - \text{mean controls})}{\text{std dev of the population}}$$

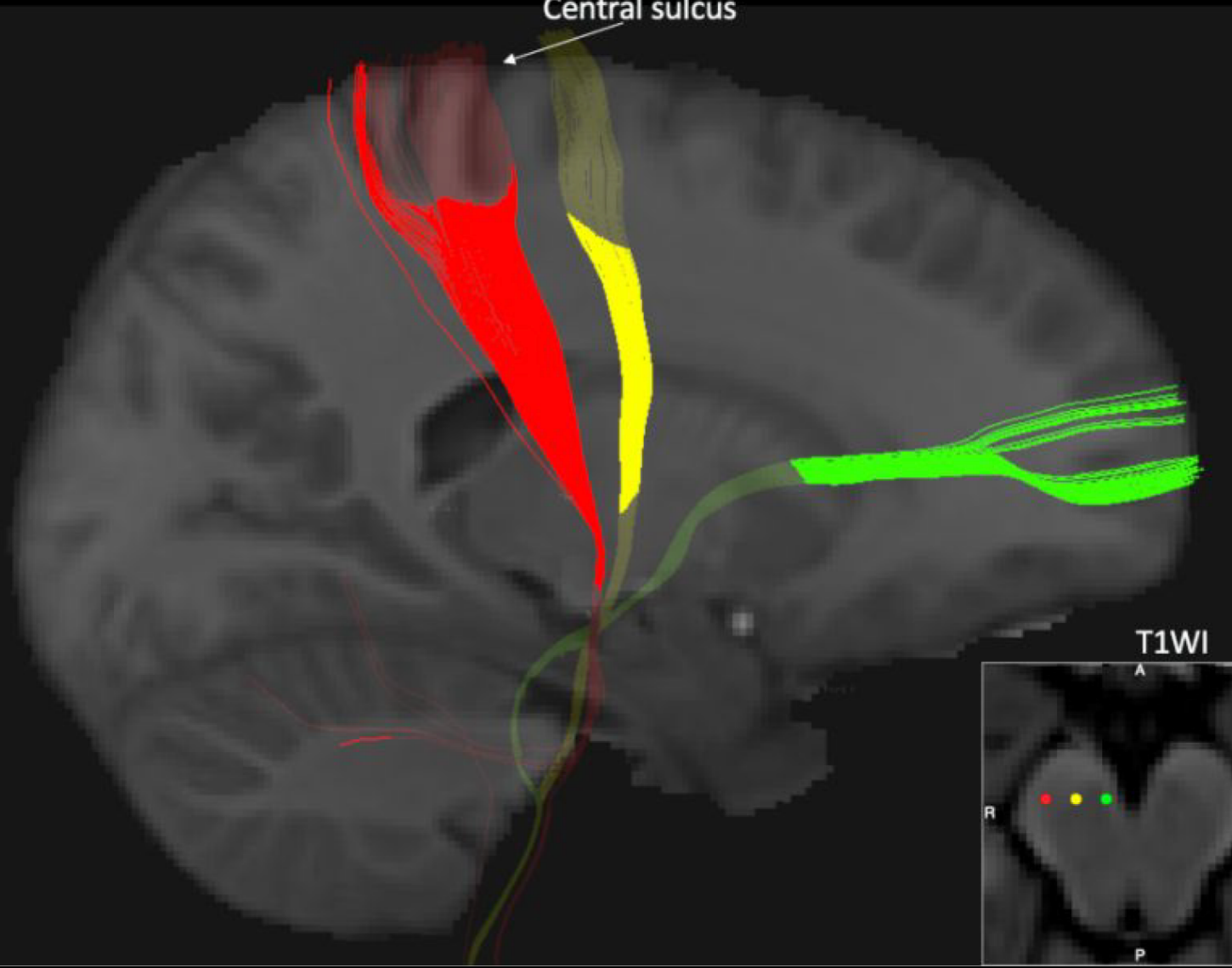
Results

Effect Size
of Patients vs.
Controls
differences

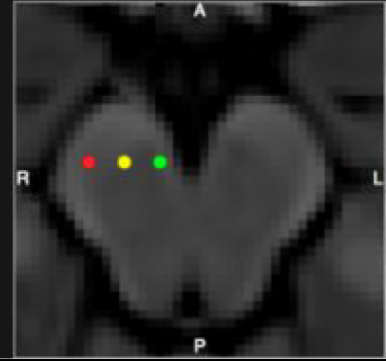
Cohen's d
Scaled between
-3 and 3



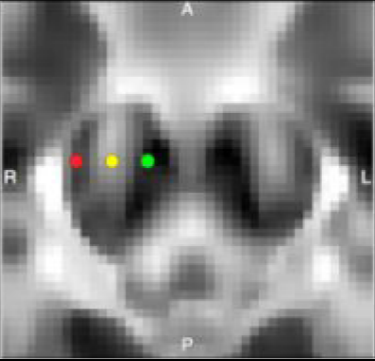
Central sulcus



T1WI



Ln-J

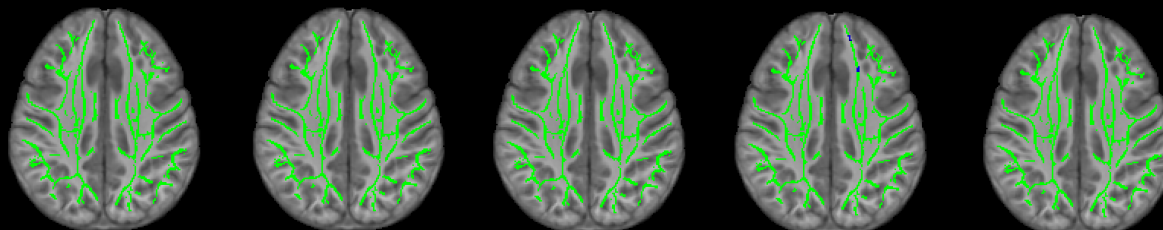


FA

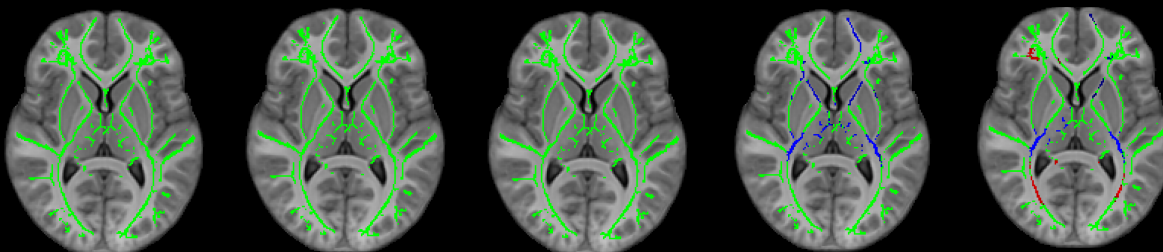
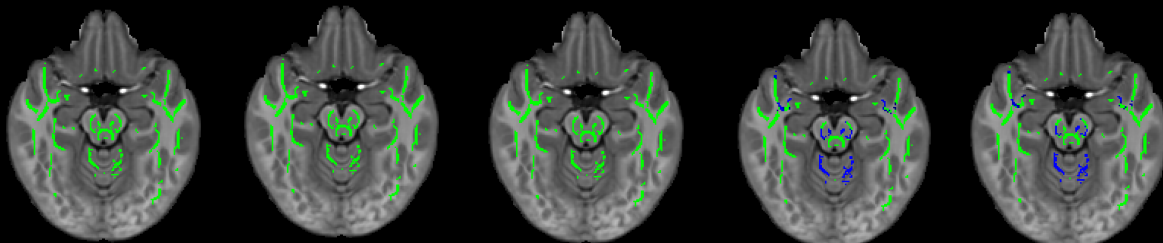
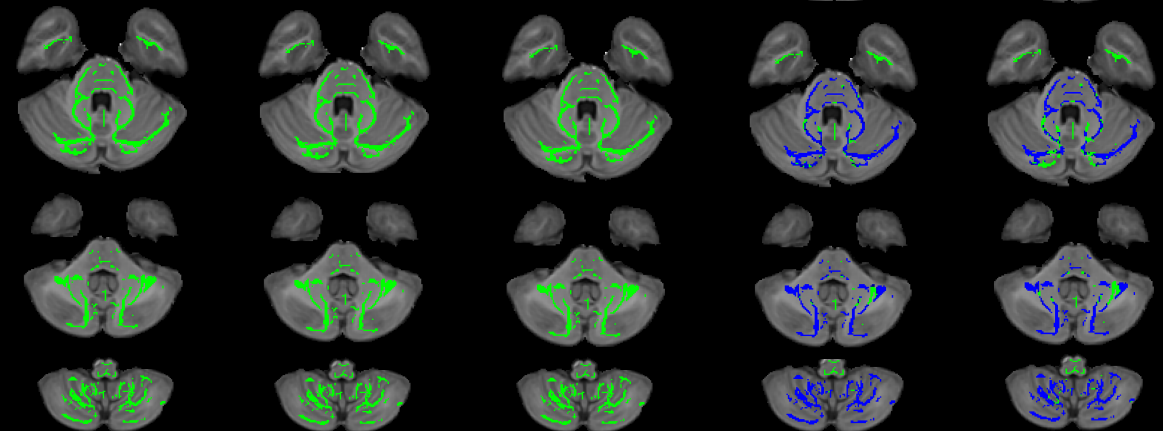
MD

T1-TBM
(global)D-TBM
(global)D-TBM
(local)

Results

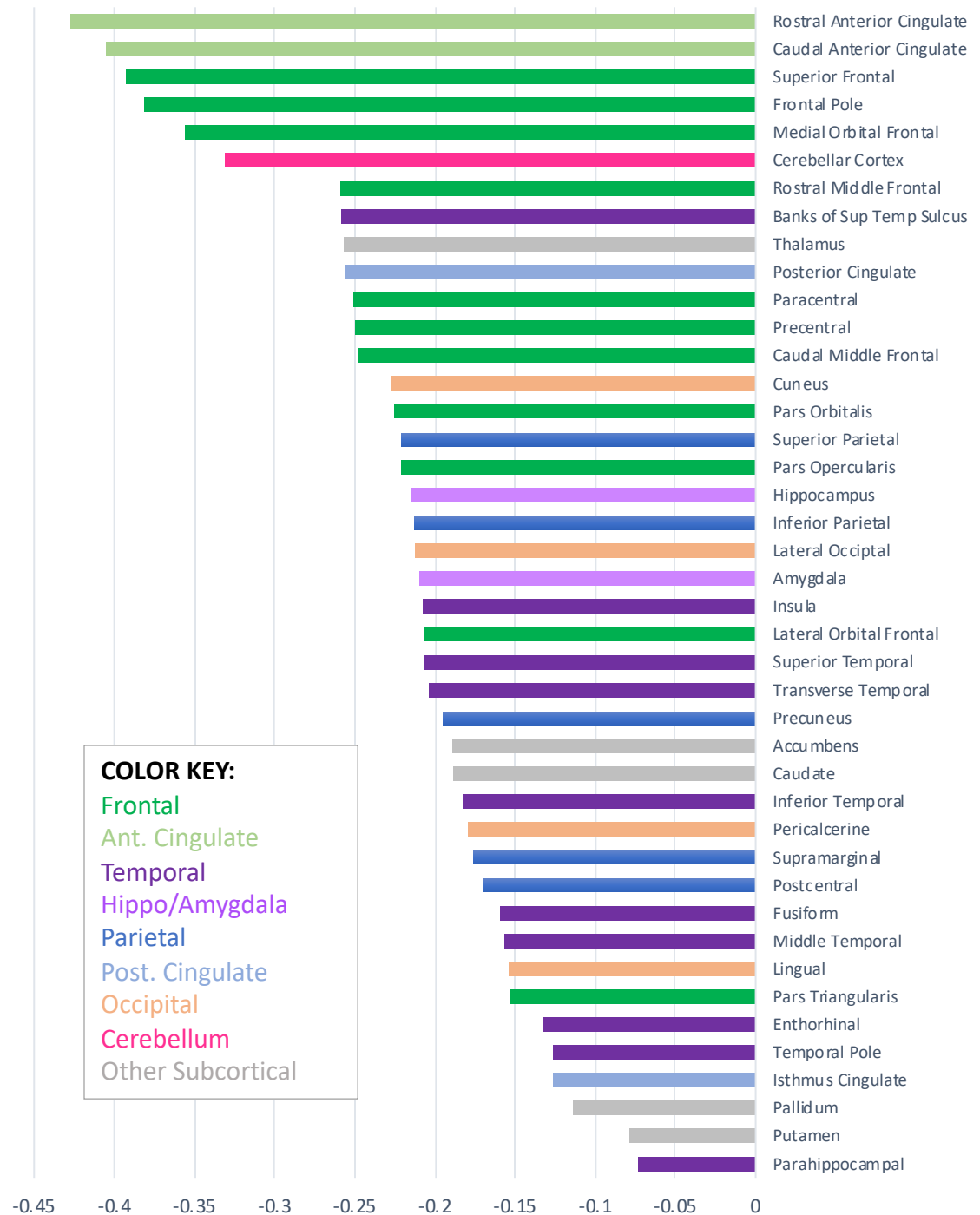


TBSS

Statistical
Analysis $(p < 0.01)$ Blue pt lower
than ctRed pt higher
than ct

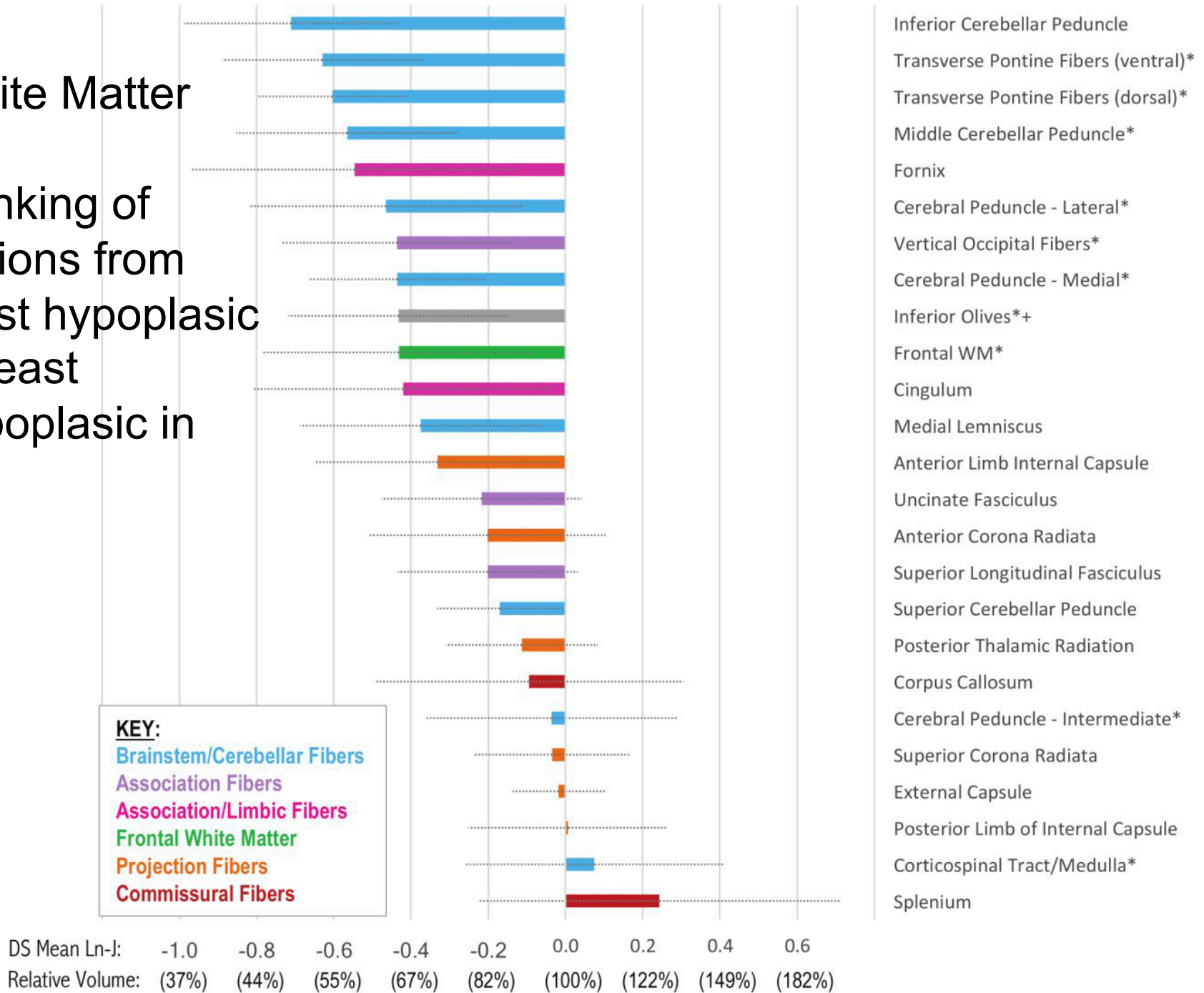
Gray Matter

Ranking of regions from most hypoplastic to least hypoplastic in DS



White Matter

Ranking of regions from most hypoplastic to least hypoplastic in DS



KEY:
 Brainstem/Cerebellar Fibers
 Association Fibers
 Association/Limbic Fibers
 Frontal White Matter
 Projection Fibers
 Commissural Fibers

DS Mean Ln-J: -1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2 0.4 0.6
 Relative Volume: (37%) (44%) (55%) (67%) (82%) (100%) (122%) (149%) (182%)

Application to Moebius Syndrome

DTBM identifies atrophy of the Medial Longitudinal Fasciculus as a hallmark feature of Moebius Syndrome

DTBM results allows 100% classification accuracy in differentiating Moebius patients from controls and Congenital Facial Palsy patients

What is Moebius syndrome?

Moebius syndrome is a nonprogressive craniofacial/neurological disorder that involves primarily the facial abducens nerve. Individuals with Moebius syndrome cannot smile or frown, and do not have lateral eye movements. (From <http://moebiussyndrome.org>)

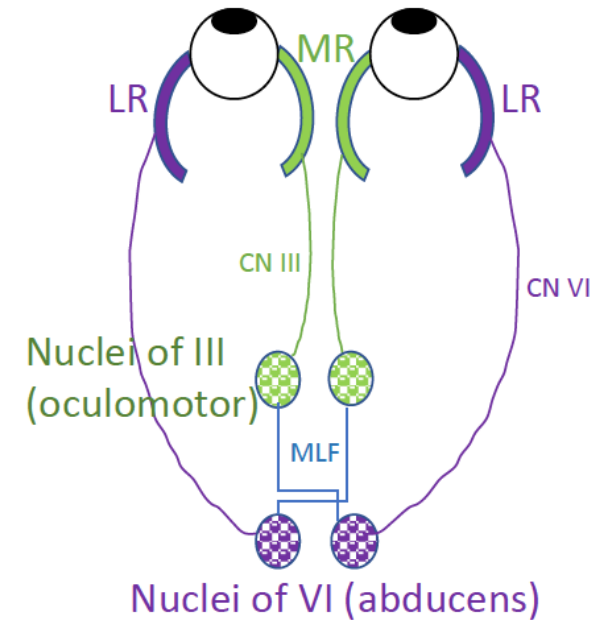
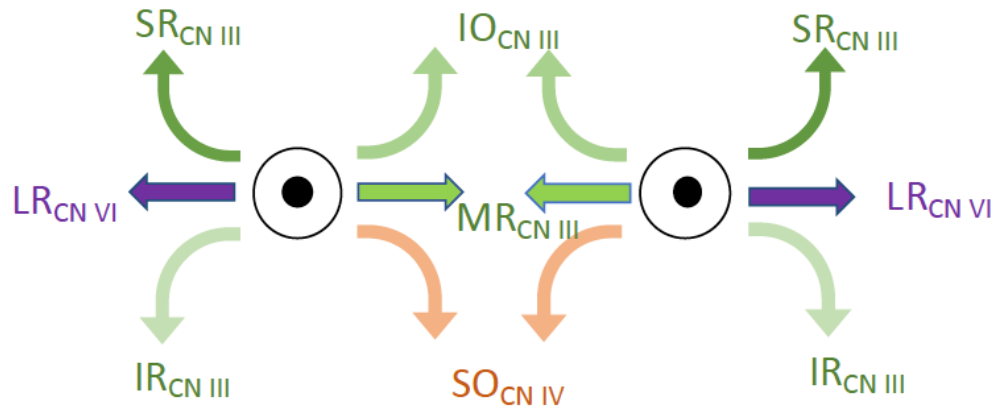
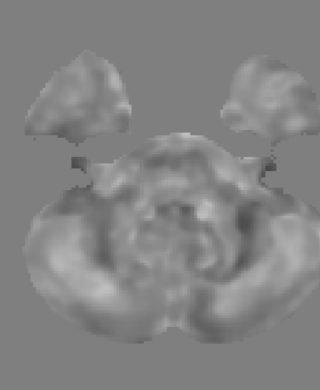
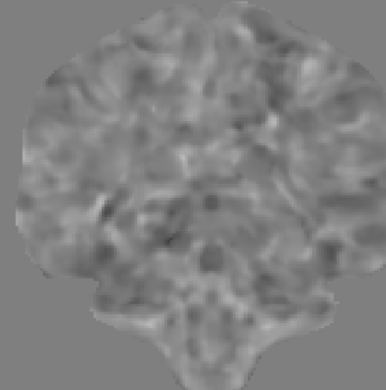
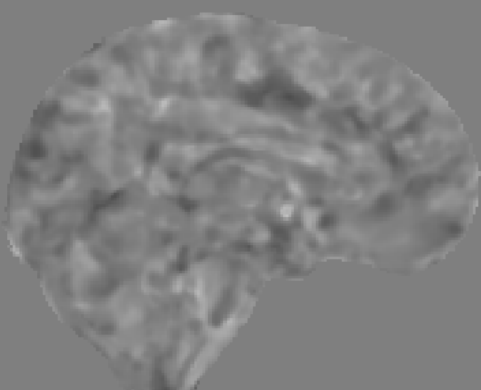
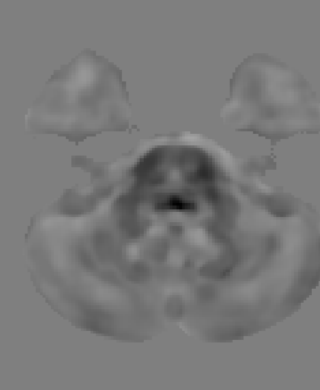
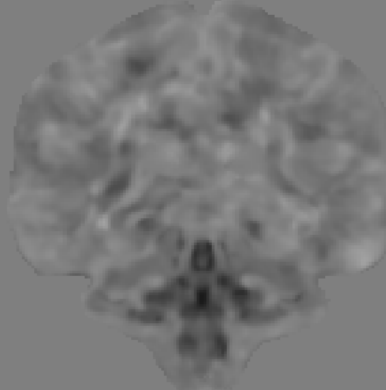
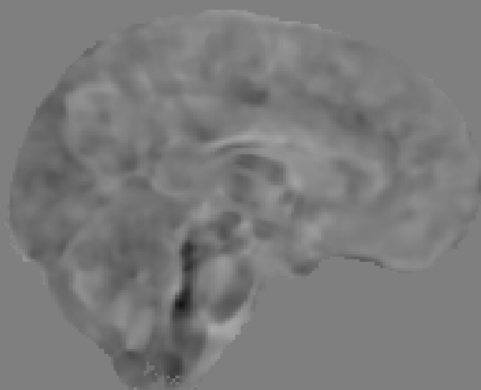
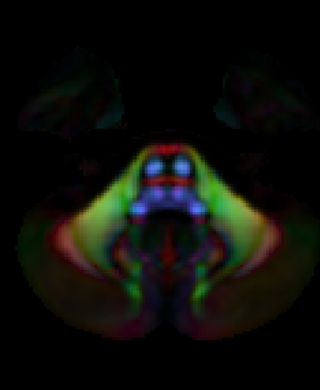
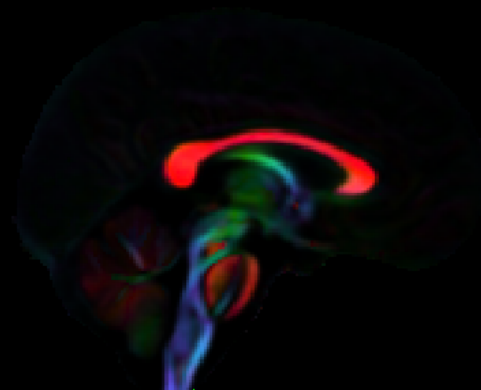
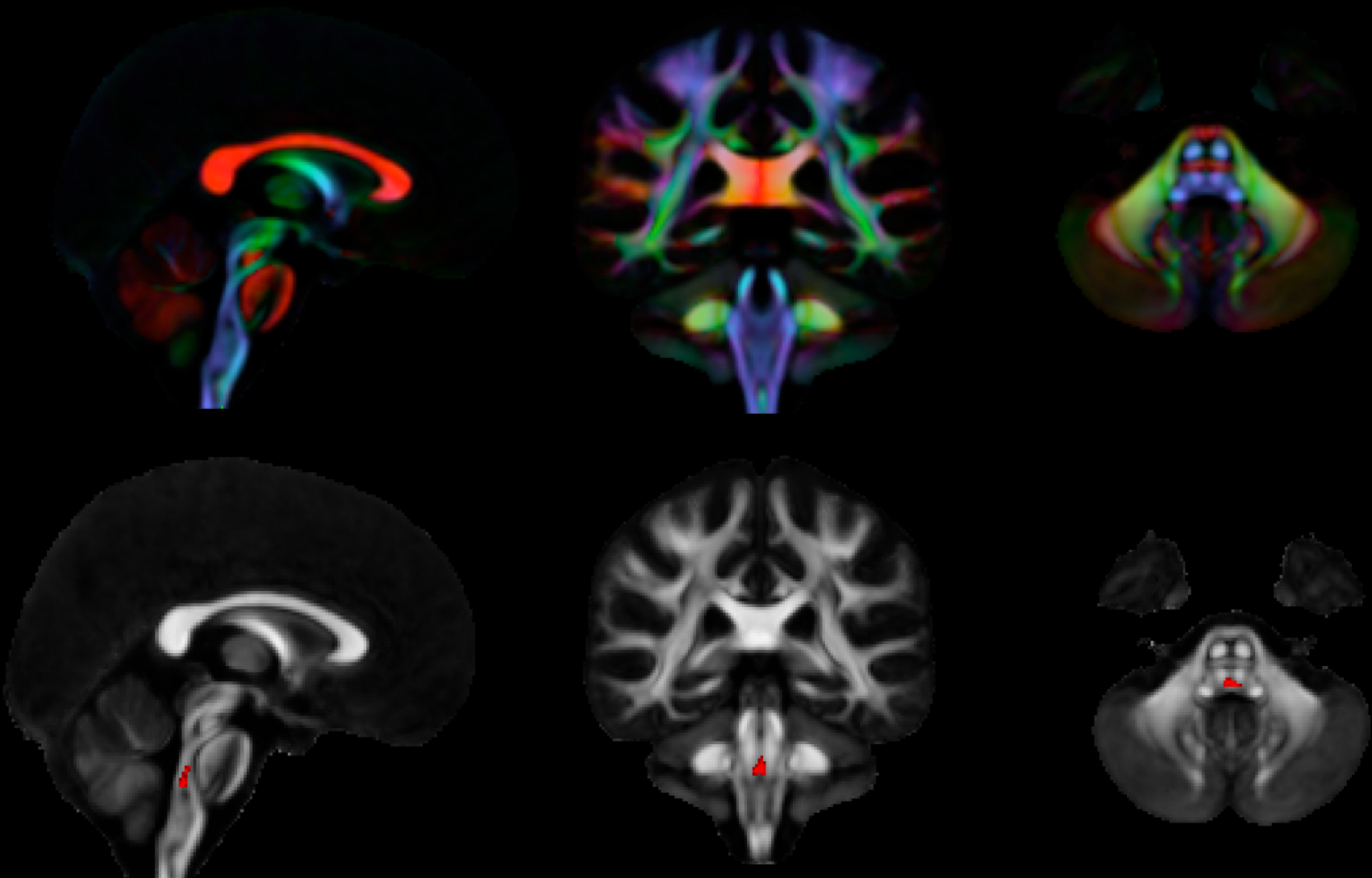


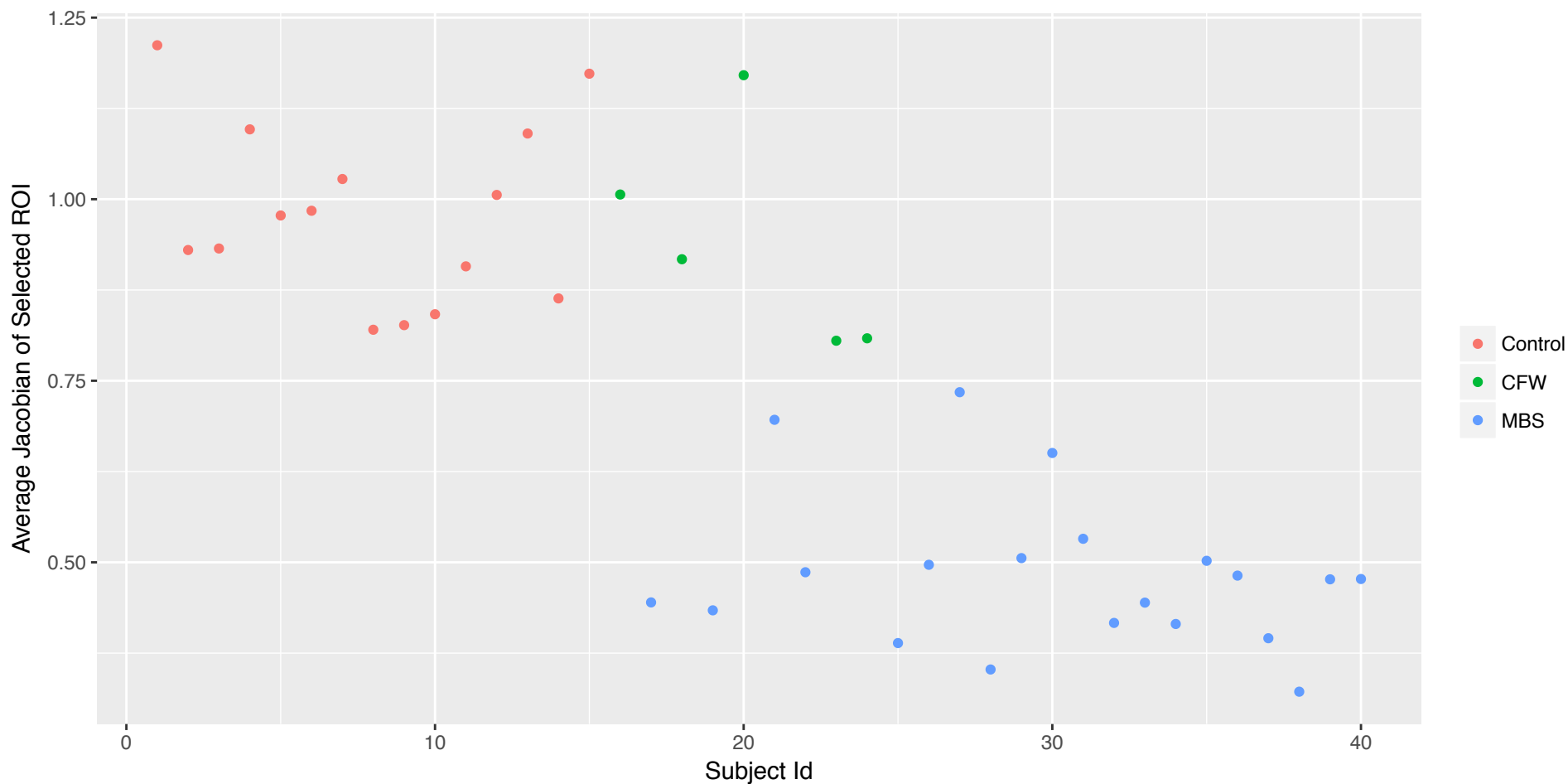
Figure 4: Left: schematic diagram of muscles and cranial nerves involved in eye movement, SR: superior rectus, IO: inferior rectus, LR: lateral rectus, IR: inferior rectus, SO: superior oblique, MR: medial rectus. Right: schematic diagram of cranial nerves and muscles involved in conjugate horizontal gaze. Motor neurons of CN VI project ipsilaterally to LR to abduct the eye, whereas the interneurons cross the midline via medial longitudinal fasciculus (MLF) and project contralaterally to MR to adduct the eye.



Voxelwise significant differences ($p < 0.01$) on DTBM
(In red on FA map: local Det Jacobian lower in Moebius than in Controls)



High sensitivity and specificity in differentiating Moebius Subjects (MBS) from both Controls and Congenital Facial Weakness (CFW) subjects



Conclusions

DTBM is a promising tool to complement conventional analysis of diffusion MRI for neurological applications. It has great potential for personalized medicine. It requires “good data” not necessarily “big data”.

Practical consideration

Prospective diffusion MRI studies should be designed with blip-up blip-down acquisitions including also the DWIs

Special thanks !

M. Okan Irfanoglu NIBIB

Neda Sadeghi NIBIB

Amritha Nayak NIBIB

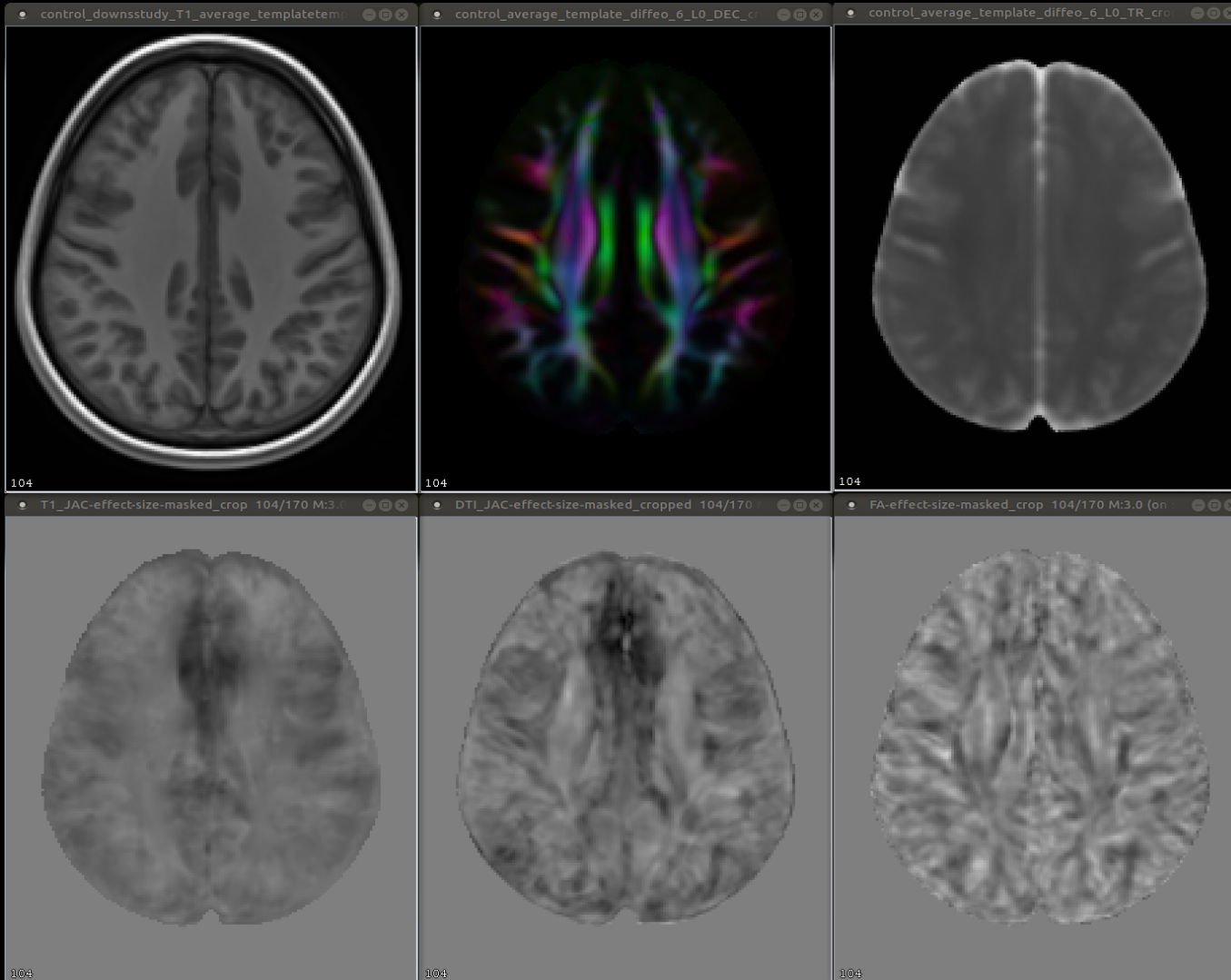
Nancy Reitano Lee Drexel U

Irini Manoli NHGRI

T1 average study template

DEC map

Trace (D) map



Effect Size log J map T1

Effect size log J map DTI

Effect size log J map FA

-3

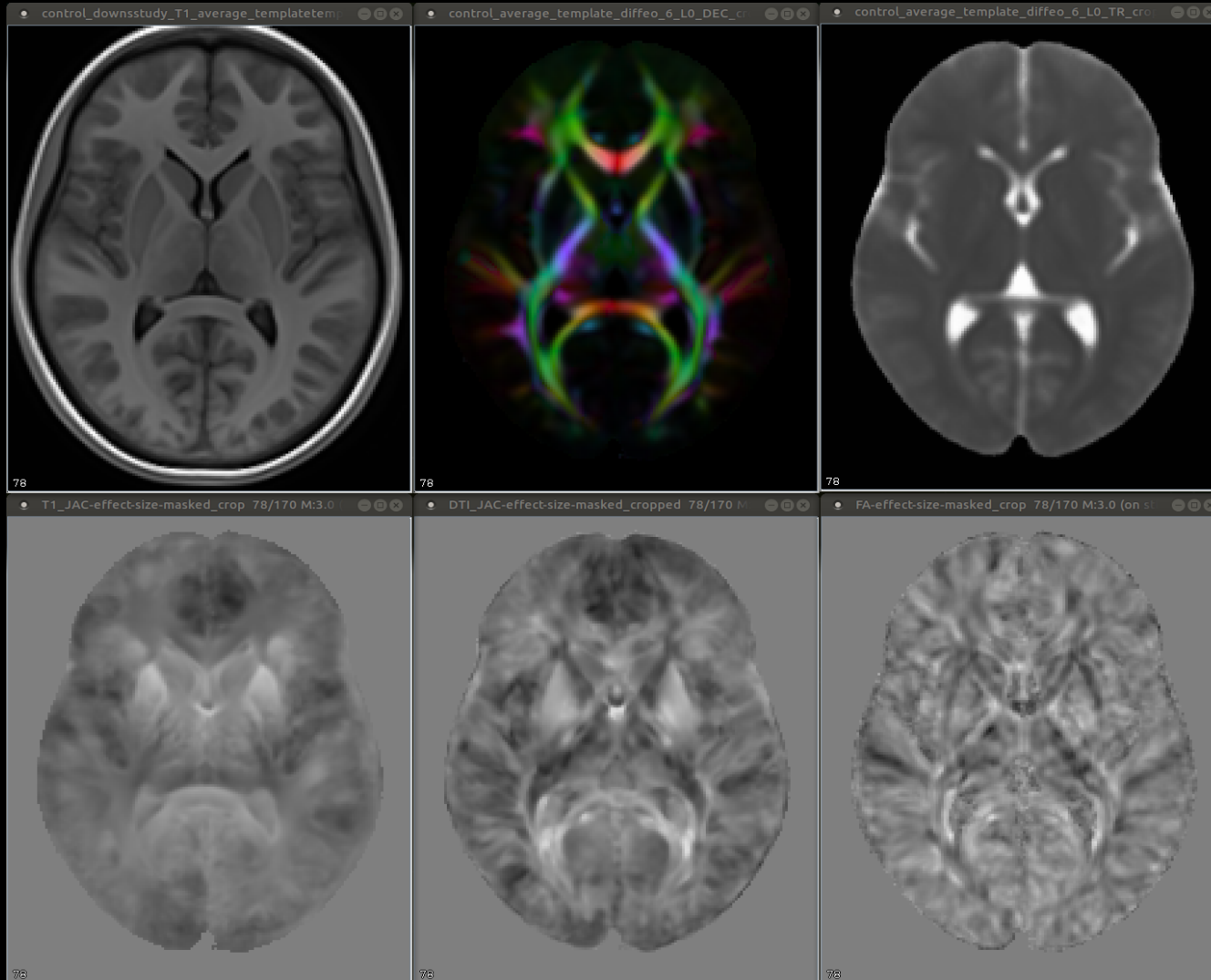


3

T1 average study template

DEC map

Trace (D) map



Effect Size log J map T1

Effect size log J map DTI

Effect size log J map FA

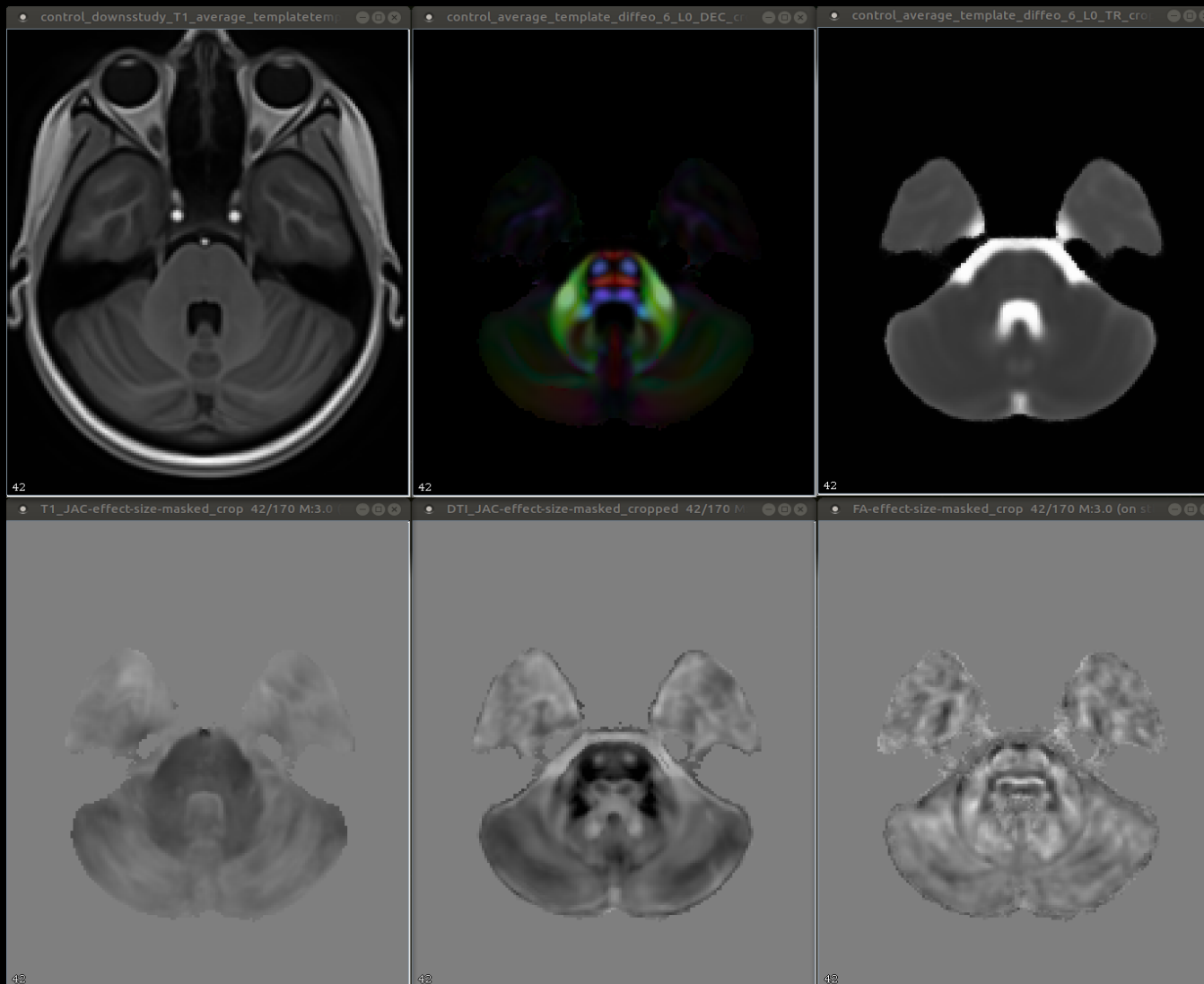
-3

3

T1 average study template

DEC map

Trace (D) map



Effect Size log J map T1

Effect size log J map DTI

Effect size log J map FA

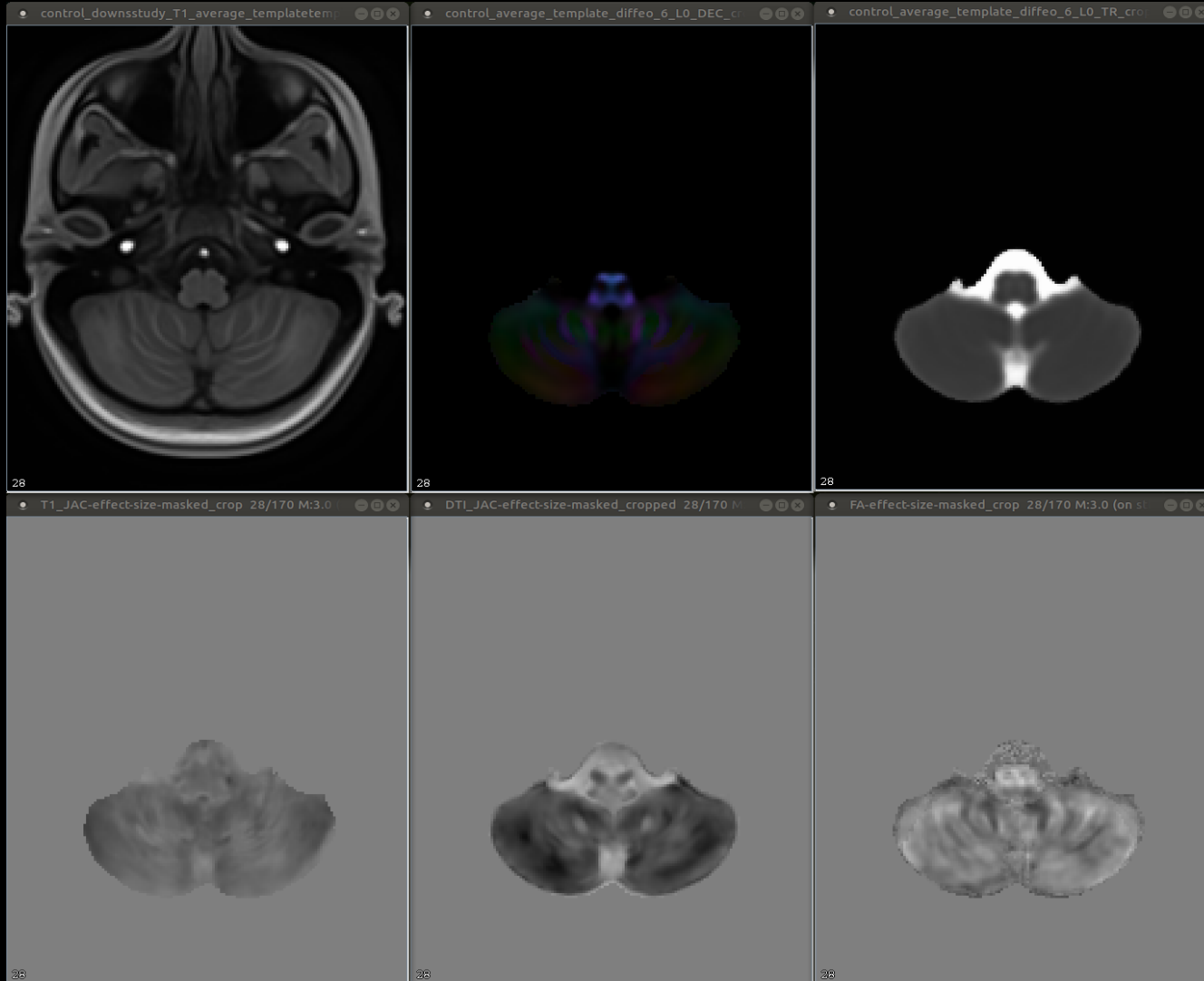
-3

3

T1 average study template

DEC map

Trace (D) map



Effect Size log J map T1

Effect size log J map DTI

Effect size log J map FA

-3



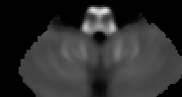
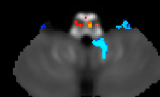
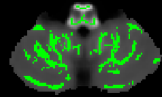
3

TBSS
FA

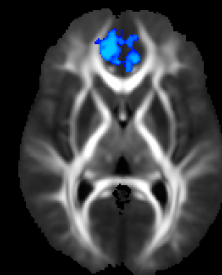
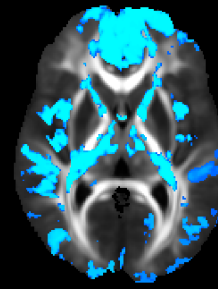
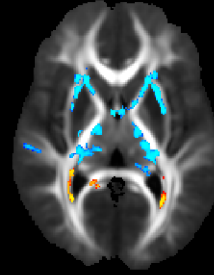
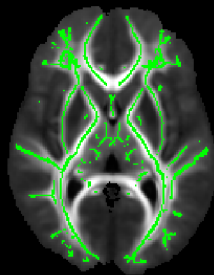
Whole brain
TFCE FA

Log J DTI

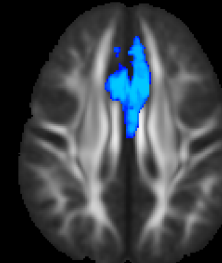
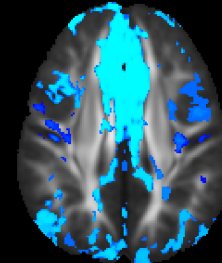
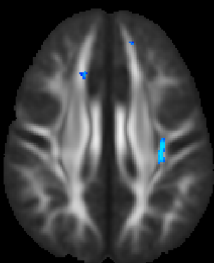
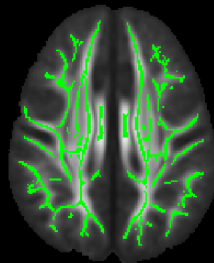
Log J T1



Mean FA
skeleton



Controls significantly
higher than patients
at $p < 0.01$



Patients significantly
higher than controls
fat $p < 0.01$

Log J: Log of the determinant of the
jacobian