

# Insights in Tuberous Sclerosis Complex from Novel Diffusion-Weighted Imaging Models

Jurriaan M. Peters<sup>1,2,\*</sup>; Maxime Taquet<sup>2\*</sup>; Benoit Scherrer<sup>2</sup>; Jolene M. Singh<sup>2</sup>; Anna K. Prohl<sup>1</sup>; Sanjay P. Prabhu<sup>2</sup>; Mustafa Sahin<sup>1</sup>; Simon K. Warfield<sup>2</sup>

\*These authors contributed equally

<sup>1</sup>Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital & Harvard Medical School, Boston, MA, USA

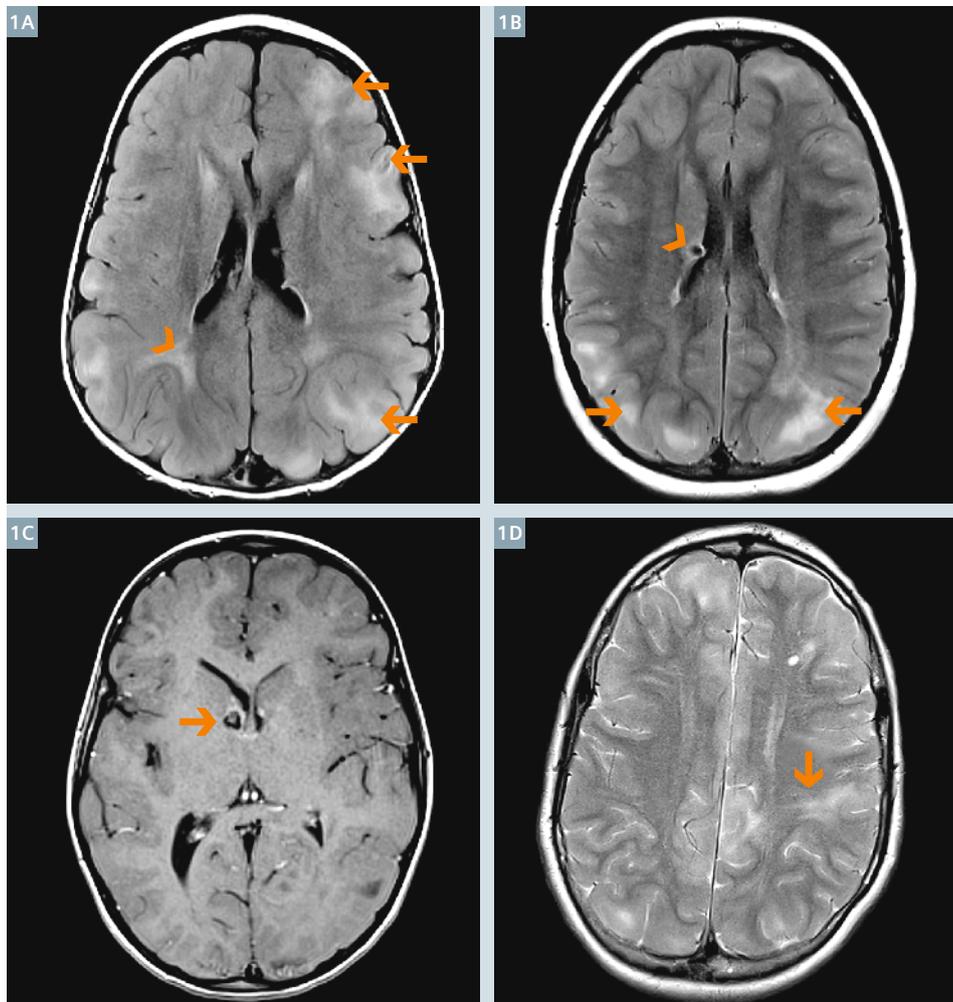
<sup>2</sup>Computational Radiology Laboratory, Department of Radiology, Boston Children's Hospital & Harvard Medical School, Boston, MA, USA

## Background

Tuberous Sclerosis Complex (TSC) is a genetic neurocutaneous syndrome with an incidence of about 1:6000, and more than one million people affected worldwide. It is associated with significant comorbidity as benign

lesions called hamartomas can develop in multiple organ systems including the kidneys, lungs, heart, brain and eyes. Neurologically, the presentation of TSC is highly variable, and manifests with intellectual disability,

behavioral problems, autism spectrum disorder, and often-intractable epilepsy [1]. These symptoms are particularly burdensome as they frequently occur early in life, and impact development and long-term neurological outcome.



**1**  
**Conventional MR imaging findings in Tuberous Sclerosis Complex.** All images are in the axial plane. **(1A)** Fluid-Attenuation Inversion Recovery (FLAIR) image reveals multiple hyperintense subcortical tubers (arrows). Some follow the gyral pattern (arrowhead). **(1B)** FLAIR image with posterior tubers (arrows) and a subependymal nodule (SEN; arrowhead). **(1C)** T1-weighted MPRAGE image with gadolinium contrast reveals a partially enhancing subependymal giant cell astrocytoma (SEGA) close to the foramen of Monro, posing a hydrocephalus risk. **(1D)** FLAIR image with linear T2-hyperintensities traveling from cortex towards the ventricle, reflecting radial migration lines (RML; arrow).

The correlation between genotype and phenotype is limited, and on an individual level does not allow for predicting neurological prognosis. Clinical determinants of neurological and cognitive outcome are the presence of seizures in early life (specifically, infantile spasms), age at onset and severity of epilepsy [2, 3]. While there is emerging evidence that seizure control in early life may lead to better neurological outcome [4, 5], there are no clinical or genetic early predictors of neurological outcome.

Neuroimaging reveals several abnormalities, and brain imaging\*\* is routinely used for both diagnosis and monitoring of the disorder (Fig. 1). Tubers are juxtacortical cerebral and cerebellar hamartomas, which consist of abnormally differentiated and migrated cells. Subependymal nodules (SEN) line the ventricular ependyma, and when larger than 1 cm are referred to as subependymal giant cell astrocytoma (SEGA). Finally, radial migration lines (RML) represent gliosis and aberrant centrifugal migration of glia and neurons en route to the cortex. Quantification (and perhaps localization) of each of these lesions reflects to some extent the cerebral burden of the disease [6], but the correlation with overall outcome is not sufficient on an individual level to prognosticate. In short, there is no robust imaging biomarker for reliably predicting neurological outcome in TSC patients. And, conventional MRI cannot be used for early institution or monitoring of therapeutic interventions regarding autism spectrum disorder, epilepsy and cognitive impairment related to TSC.

Diffusion Tensor Imaging (DTI) offers the possibility of a putative biomarker for neurological outcome in TSC, essentially through modeling the underlying microstructural neuropathology of TSC. In this article, we will review DTI and the TSC phenotype, the limitations of the single tensor model, and the promise of novel diffusion acquisition and modeling techniques. The basics of diffusion-weighted imaging and detailed conventional imaging and clinical aspects of tuberous sclerosis complex can be found in a prior review by this group [7].

## Aberrant neural connectivity in TSC

The TSC1 and TSC2 genes encode the proteins TSC1 (hamartin) and TSC2 (tuberin), respectively. TSC1 and TSC2 form a heterodimer, and regulate the mammalian target of rapamycin (mTOR), to form a protein complex responsible for protein synthesis, cell proliferation, and cell size regulation. In patients with TSC, the inhibition of the mTOR signaling pathway fails and uncontrolled growth occurs on multiple cellular levels [1].

Several rodent models of TSC exist, and are reviewed elsewhere [8]. Of importance, while none of the rodent models is able to replicate SEN, SEGA, RML or tubers, phenotypically they can have cognitive impairment and deficiencies in learning, behavioral and social deficits, seizures and early mortality. This suggests a role for non-tuber pathology in the pathogenesis of neurological symptoms in TSC, and the structural correlate of neurological deficits in animal models of TSC may lie in the microstructural neuroanatomy. Indeed, microstructurally, TSC knockout mice have been shown to have deficits in myelination, and in neuronal connectivity – specifically neuronal polarity, axon formation and guidance [9-11].

Indirectly, several lines of evidence suggest a similar abnormal neural connectivity in human patients with TSC. Cytoarchitectural abnormalities have been reported throughout the cerebral cortex, outside of the classic lesions, suggesting widespread microstructural pathology [12]. Through the use of depth electrodes in patients with TSC undergoing epilepsy surgery, epileptic activity adjacent to the conventionally described tubers has been found [13, 14]. Anecdotally, TSC patients without tubers can have epilepsy and conversely, patients with tuber pathology can have (near-) normal intelligence. Finally, in non-syndromic (idiopathic) autism, decreased cortico-cortical connectivity has been described using various conventional, diffusion and functional imaging modalities [15]. The high prevalence of (syndromic) autism in TSC may also reflect abnormal neuro-

nal connectivity, which would be consistent with the current view of autism as a disconnection syndrome [15, 16].

## Diffusion tensor imaging

The first reports of abnormal diffusion in TSC, starting in 2001, focused on tubers, which appear as areas of decreased FA and increased MD, consistent with pathological findings of poorly organized collections of dysplastic and abnormally enlarged cells [17]. While tubers appear discrete and well-delineated on fluid attenuation inversion recovery (FLAIR), diffusion imaging revealed an abnormal *perituber* white matter and a more gradual transition to the white matter, suggesting that pathology is more widespread than the tubers alone. Moreover, even the white matter only *appears* normal, as a growing body of work describes increased MD and decreased FA, compared to controls, in the conventionally normal appearing white matter (NAWM) – summarized in [18]. Thus, diffusion tensor imaging supports diffusely present deficits in migration, myelination and differentiation beyond tuber and perituber regions.

Both in imaging and in pathological studies patches of truly normal white matter have been described, resulting in a scientific debate about whether abnormalities in connectivity are omnipresent (TSC as a connectopathy) or multifocal (TSC as a cortical dysplasia syndrome) [6]. Different imaging parameters and analysis techniques have hampered comparison across different institutions, but now a large, NIH-funded multicenter Autism Center of Excellence (ACE) study is acquiring prospective imaging and neuropsychological data in a goal sample of 150 patients with TSC in 5 US centers (clinicaltrials.gov: NCT01780441).

\*\*Siemens disclaimer: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.



**2** Example of the relationship between diffusion measures and neurological phenotype in Tuberous Sclerosis Complex. Three-dimensional projections of the corpus callosum are superimposed on sagittal T1-weighted MPRAGE images in three 5-year-old subjects: control (2A) FA 0.53; tuberous sclerosis without autism (2B) FA 0.54; tuberous sclerosis with autism (2C) FA 0.34. Images adapted from [18].

Early studies were limited by small sample size, poor magnet strength, or few diffusion directions, and were able to make comparisons between TSC patients and controls only in certain 2D defined areas of interest. Our group was the first to study a population sufficiently large enough to allow for correlation with neurological phenotype [18]. Using a 3T magnet, and 35 diffusion directions, with a stochastic tractography algorithm developed in-house, we analyzed 40 patients with TSC and 29 age-matched controls. The corpus callosum was analyzed, as it represents a major white matter tract and has been implicated in autism. To include all tracts of the 3-dimensional white matter structure, we introduced a novel analysis method<sup>§</sup> that adjusts for partial volume averaging in the calculation of DTI measures. On a group level, patients with TSC and autism had a higher MD and lower FA in the corpus callosum, as compared to patients with TSC without autism and as compared to controls (Fig. 2). This difference was seen early in the course of the developmental trajectory of white matter maturation. An extension of this work revealed that language pathways also differ in TSC patients with autism [19].

The relation between aberrant connectivity and the neurological and behavioral phenotype of TSC has also been demonstrated with other modalities. A globally reduced EEG connectivity was found in 42 patients with TSC, and network analysis showed an increased resilience to network disruption in patients with TSC and autism. The same was found in autism without TSC, suggesting a common mechanism, or at least validating the use of TSC as a model for autism spectrum disorders [20].

Epilepsy is refractory in over a third of patients with TSC, and infantile spasms or early onset refractory seizures may predict poor neurological outcome in TSC. In TSC, epileptogenic tubers have an increased MD and decreased FA as compared to silent tubers [21]. Whether this diffusion change is secondary to focal seizures (excitotoxic edema, axonal injury, maladaptive developmental changes, etc.) or represents the primary deficit in microstructural organization responsible for increased epileptogenicity is not yet clear. A relationship has been described between poorly controlled epilepsy and the predominance of poorly organized tubers. The study based tuber classification on conventional imaging findings, but an additional analysis

of ADC values of the dominant tuber type was also performed. This showed differences in ADC values of the dominant tubers between the three epilepsy severity subgroups [22]. The prospective collection of serial imaging and EEG recordings combined with epilepsy and neuropsychological variables (ACE/P20-study) will provide an opportunity to further elucidate the relation between EEG markers, DTI measures and clinical epilepsy (clinicaltrials.gov: NCT01780441; NCT01767779).

Finally, everolimus and sirolimus are pharmacological inhibitors of the mTOR pathway, and almost directly target the molecular deficit of TSC. These drugs have demonstrated efficacy for multiple complications of TSC related lesions, including pulmonary lymphangioleiomyomatosis [23], renal angiomyolipoma [24], and SEGAs [25]. The imaging data from the SEGA study revealed a compelling improvement of NAWM in patients treated with mTOR inhibitors [26]. Preclinical data, case reports, and secondary outcome measures regarding seizures, cognition and behavior suggested beneficial effects of mTOR inhibitors, and have led to prospective, randomized, double blind and placebo controlled trials of the use of these drugs to improve epilepsy (EXIST-II and III) and neurocog-

<sup>§</sup> WIP, the product is currently under development and is not for sale in the US and other countries. Its future availability cannot be ensured.

niton (NCT01289912). Given the relation between NAWM integrity and autism, and the report of improved NAWM DTI measures with the use of mTOR inhibitors, DTI can be considered a candidate biomarker in TSC. It will be critical to investigate whether DTI measures parallel the anticipated clinical changes in the abovementioned trials. If DTI indeed becomes a robust and biologically plausible biomarker, it will facilitate future trials through early patient stratification and quantitative assessment of treatment response.

### Limitations of the single tensor model

The diffusion tensor model relies on the assumption that the water molecules in one voxel all follow the same diffusion process, and are equally constrained by the brain tissues. Each voxel, however, is subjected to the presence of heterogeneous fascicle orientations and partial volumes of different tissues [27]. In this section, we discuss these fundamental limitations of the diffusion tensor model to represent the brain microstructure.

**Heterogeneous Fascicle Orientations**  
The DTI model assumes that, at each voxel, the diffusion is Gaussian with either no preferential direction (isotropic diffusion) or one preferential direction. This assumption is reasonable only when all axons in the voxel are aligned together and contained in one fascicle with a specific orientation. However, owing to the presence of complex fascicle organizations, heterogeneous fascicle orientations can be present in one voxel. In the corona radiata, for instance, corticospinal tracts (vertical tracts connecting the cortex to the spinal cord) cross fascicles of the corpus callosum (horizontal tracts connecting the left and right hemispheres) and the superior longitudinal fasciculus [27]. Recent studies estimate the prevalence of those heterogeneities to range between 60% and 90% of voxels in the white matter at typical DWI resolution [28]. When fascicles are crossing, interpretation of the DTI-based measures (MD and FA) is unreliable [29]. For instance, in the presence of two crossing fascicles, a single overly wide tensor would be estimated resulting in decreased FA. This

decreased FA is not related to a property of the fascicle and, if interpreted this way and without knowledge of the underlying neuroanatomy, may incorrectly lead to the assumption that the myelination or microstructure is altered for that fascicle [30].

#### *Partial Volume Effect*

Voxels that are at the interface between different tissues (gray and white matter), between adjacent fiber bundles or between a tissue and cerebrospinal fluid (CSF) suffer another problem called *partial voluming*. The diffusion signal arising from protons in the different compartments (CSF, gray or white matter) will be averaged into a single value that is observed in DWI. Because DTI assumes that the diffusion of water molecules is either purely unrestricted or purely restricted within a single fascicle in the voxel, influences of different compartments will confound, resulting in an inflated tensor with a lower FA [31]. As with heterogeneous fascicle orientations, this decreased FA may be misleadingly interpreted as altered myelin.

Even in voxels that are not at the interface between tissues, some fraction of the water molecules will diffuse in the extra-axonal space (either within other cells or in the extracellular lattice). Their diffusion process is different from the diffusion within axons and results in a different diffusion signal. The partial volume effect therefore also applies within a fascicle, between molecules inside and outside axons [32]. The partial volume effect is essentially a resolution limitation.

### Multi-fascicle models

The problems related to heterogeneous fascicle orientations and partial voluming of other tissues may naturally be solved by providing different representations of the signal arising from water molecules in different compartments [31]. Such a representation is the gist of multi-fascicle

models. Multi-fascicle models focus on modeling the signal arising from each important compartment. In particular, the diffusion signal is modeled as a mixture of sources of isotropic diffusion, and sources of diffusion in each fascicle, that are identified, modeled and parameterized. We have utilized a multi-fascicle model in which isotropic diffusion of extra-axonal water is modeled with one or more isotropic diffusion tensors (that is, diffusion tensors in which diffusion is the same in all directions), and one or more potentially anisotropic tensors (with anisotropy determined by the imaging data), modeling restricted and hindered diffusion associated with each fascicle.

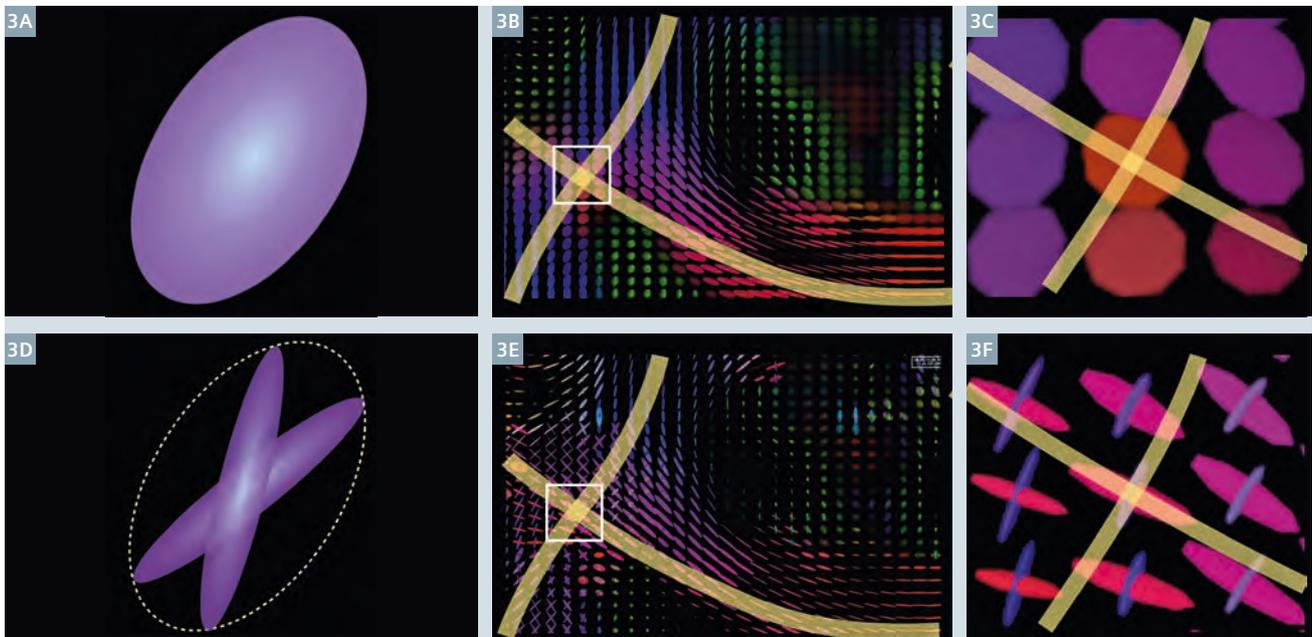
Figure 3 illustrates the resolution of two crossing tracts with the single tensor model and a multi-fascicle model.

### CuBe and SPHERE (CUSP) imaging

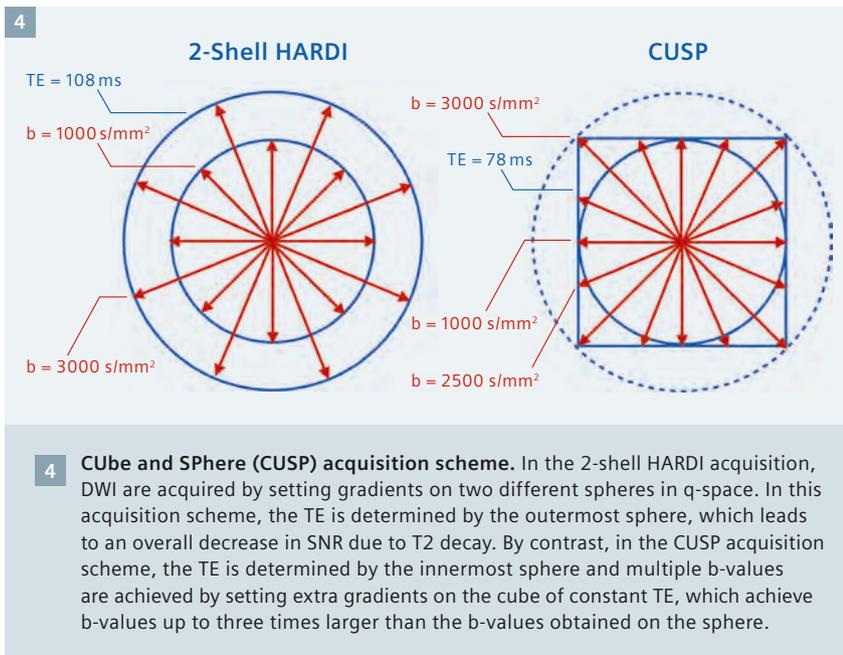
The estimation of a multi-fascicle model from diffusion-weighted imaging poses additional challenges. When only DWI at a single non-zero b-value are available, the problem of estimating a multi-fascicle model is mathematically ill-posed [31, 33]. This means that an infinite number of models are equally compatible with the DWI measurements and none of these equivalent models can reliably be selected.

To reliably estimate a multi-fascicle model, diffusion-weighted imaging must be acquired at multiple different non-zero b-values to disambiguate the overlapping diffusion decay curves of each compartment. A popular acquisition to do so has been the multi-shell HARDI, which provides uniform angular coverage in q-space. A multi-shell HARDI, however, requires setting the nominal b-value to the largest imaged b-value, leading to a long duration echo time (TE) and therefore a low SNR due to T2 relaxation.

By contrast, Cube and Sphere (CUSP) imaging combines both spherical and cubic sampling in q-space, leading to a large number of non-zero b-values with short TE, high SNR and

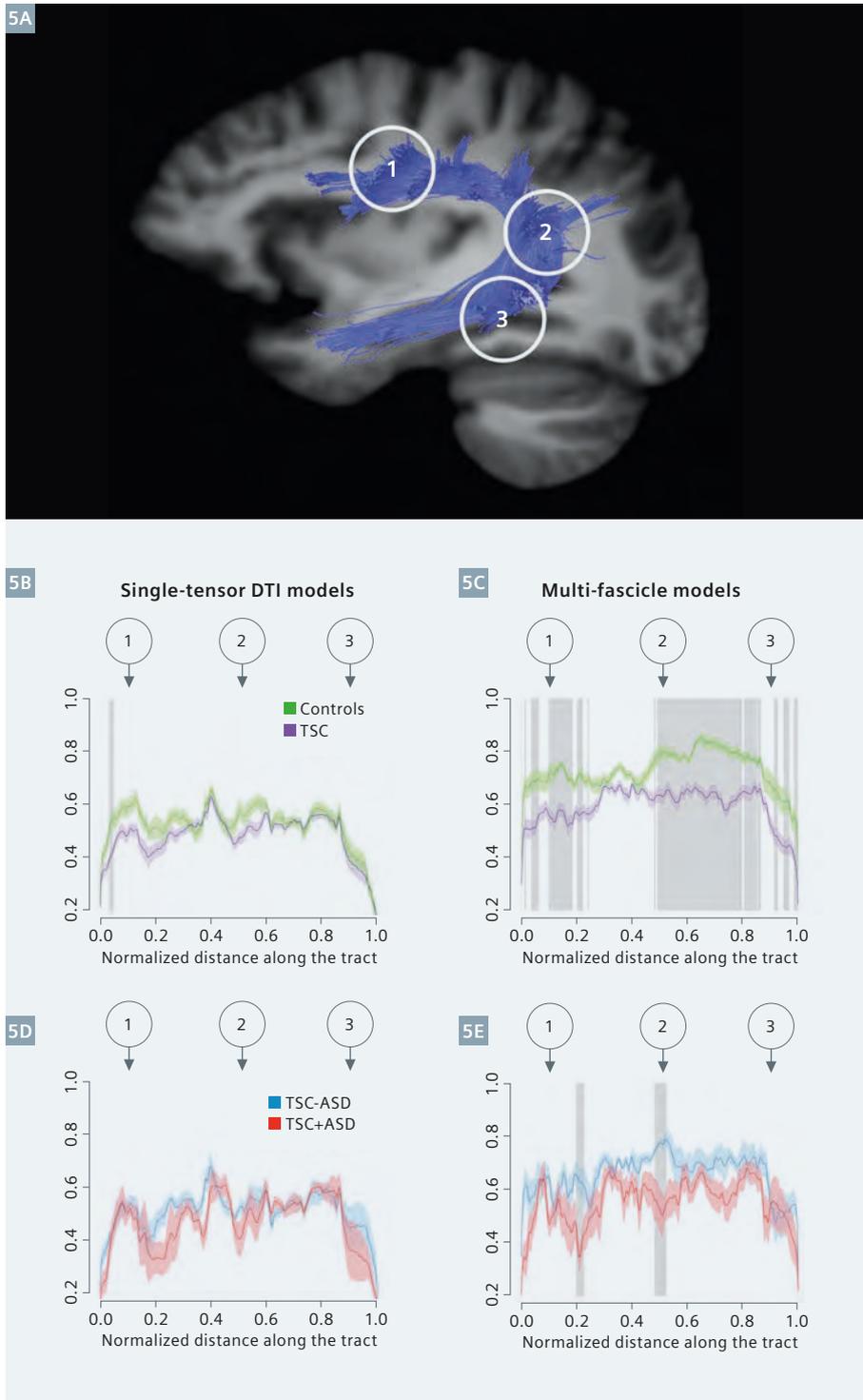


**3** Illustration of crossing fibers in the single tensor DTI model and in a multiple fascicle model. (3A–C) The diffusion tensor imaging (DTI) model assumes that at most one fascicle is present within each voxel. This assumption does not hold in regions where fascicles cross, such as (3B) the corona radiata. In those regions, the DTI model results in abnormally inflated tensors that conflates the signal from each fascicle, resulting in an artificially lower fractional anisotropy that may lead to misinterpretations. In contrast, (3D–F) multi-fascicle models provide a separate representation for the signal arising from each fascicle and are, therefore, able to characterize and resolve regions with crossing fascicles. Modified from [7], with permission.



**4** Cube and Sphere (CUSP) acquisition scheme. In the 2-shell HARDI acquisition, DWI are acquired by setting gradients on two different spheres in q-space. In this acquisition scheme, the TE is determined by the outermost sphere, which leads to an overall decrease in SNR due to T2 decay. By contrast, in the CUSP acquisition scheme, the TE is determined by the innermost sphere and multiple b-values are achieved by setting extra gradients on the cube of constant TE, which achieve b-values up to three times larger than the b-values obtained on the sphere.

high angular coverage [31]. CUSP is based on the modification of a 2-shell HARDI. In contrast to a multi-shell HARDI, the pulse duration and separation,  $\delta$  and  $\Delta$ , of the PGSE sequence are fixed to achieve the b-value of the inner shell, which requires a shorter TE and provides a significant SNR boost. The gradients of the outer shell are reduced in strength to lie on the cube enclosing the inner shell. This cube is a cube of constant TE in q-space. Since the b-value is proportional to the squared norm of the encoding gradient and since gradients in the corner of the cube have a squared norm three times that of the gradient lying on the sphere, images with b-value up to three times the original (nominal) b-values can be achieved in CUSP, without modifying the TE (Fig. 4), and therefore without any cost in SNR.



5

### Improved detection of group differences with the multi-fascicle model.

(5A) The dorsal language network is thought to connect Broca's area in the frontal lobe, Geschwind's territory and Wernicke's area in the posterior temporo-parietal areas. Streamlines were selected based on passing through certain regions of interest (inclusion regions-of-interest (ROIs)), and excluded when passing through other regions (exclusion ROIs) using a method that has been previously validated for perisylvian language areas [36]. Rather than gray matter areas to define endpoints, we defined 3 regions in the white matter adjacent to Broca's, Wernicke's and Geschwind's territory as described in our earlier work [19].

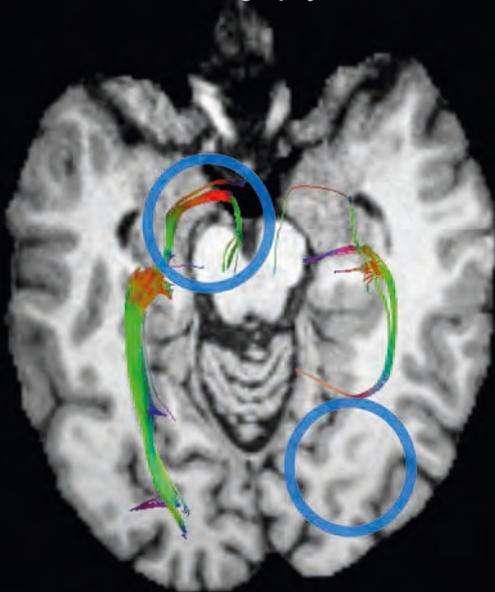
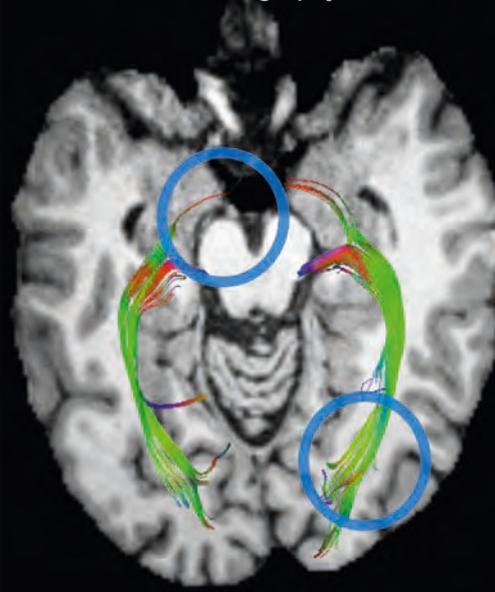
(5B–D) Fascicle-based spatial statistics (FBSS) of multi-fascicle models reveal local differences in the fascicle properties that single tensor DTI cannot. Curves show the mean FA along the median tract of the dorsal language circuit in each group. Shaded areas along the curves represent two standard errors. Grey rectangles indicate regions where the FA is significantly different between the groups. The top row investigates differences between patients with tuberous sclerosis complex (TSC) and healthy controls. The bottom row further investigates differences between TSC patients with (TSC+ASD) and without autism (TSC-ASD).

## Analyzing multi-fascicle models

Multi-fascicle models provide a variety of information about the brain microstructure. Each of the tensors representing a fascicle can be analyzed along a particular fascicle of interest using

Fascicle-Based Spatial Statistics (FBSS) [34], enabling the identification of abnormalities or group differences that pertain to a particular fascicle. The statistical power is increased, allowing the detection of differences not visible with the single-tensor model (Fig. 5).

Furthermore, the isotropic diffusion of water molecules in the extra-axonal space can be analyzed separately using Isotropic Diffusion Analysis (IDA) [34]. The latter method enables the detection of an excess in the volume of water molecules that are freely diffusing, which is thought to indicate

DTI  
TractographyMulti-Fascicle Model  
Tractography

- 6** DTI tractography and multiple fascicle model of the geniculocalcarine tracts, using a common region-of-interest (ROI) schema. This white matter pathway links the lateral geniculate nucleus (LGN) of the thalamus to the occipital lobe via the stratum sagittale. The white matter adjacent to the LGN was used as a selection ROI [37]. DTI tractography (**6A**) produced asymmetric tracts, which failed to reach the occipital lobe in the left hemisphere (posterior blue circles). Additionally, the fibers in the LGN are in an area of crossing fibers, resulting in tracts that extend far forward of the expected termination site (anterior blue circles). Multi-fascicle model tractography (**6B**) exhibits several key improvements. The tracts appear symmetric and reach the occipital lobe in both hemispheres. Though fibers in the LGN still extend forward, there is a sizeable reduction in the number of spurious streamlines and a much smaller angle of deviation between these fibers and those terminating in the LGN.

the presence of edema or neuroinflammation [35].

Figure 6 shows how the application of multiple-fascicle models to tractography can lead to the improved identification of fascicles, consistent with known anatomy.

## Conclusions

Diffusion-weighted imaging allows for non-invasive probing of microstructural tissue properties, and may directly represent underlying neuropathology in tuberous sclerosis complex. Moreover, preliminary evidence suggests diffusion abnormalities in the normal appearing white matter (NAWM) correspond to the neurological phenotype in TSC. Changes in white matter diffusion have been reported in patients treated with mTOR inhibitors [26], but whether such changes parallel clinical improvements in cognition, autism and epilepsy requires further study.

Single tensor models are limited by partial volume effects and cannot resolve crossing fibers. Multi-fascicle models address these limitations by modeling isotropic and anisotropic diffusion sources arising from each fascicle present at each voxel. However, single shell HARDI provides insufficient imaging data to identify the signal from each fascicle. More than two b-value diffusion images must be acquired in order to find all the parameters of a multi-fascicle model. CUSP imaging provides multiple non-zero b-values at high SNR. As the multiple-fascicle model better explains the diffusion signal, group differences can be more reliably detected and complex fiber streamlines modeled more accurately.

As white matter integrity in TSC may parallel neurological symptoms, and improves with treatment, the current developments in multiple fascicle models can further the potential for diffusion imaging to become a reliable biomarker in TSC.

## References

- 1 Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet*. 2008; 372(9639):657–668.
- 2 Jansen FE, Vincken KL, Algra A, et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. *Neurology*. 2008;70(12):916–923.
- 3 Numis AL, Major P, Montenegro MA, Muzykewicz DA, Pulsifer MB, Thiele EA. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. *Neurology*. 2011;76(11):981–987.
- 4 Jozwiak S, Kotulska K, Domanska-Pakiela D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2011;15(5):424–431.
- 5 Bombardieri R, Pinci M, Moavero R, Cerminara C, Curatolo P. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2010;14(2):146–149.
- 6 Van Eeghen AM, Teran LO, Johnson J, Pulsifer MB, Thiele EA, Caruso P. The neuro-anatomical phenotype of tuberous sclerosis complex: focus on radial migration lines. *Neuroradiology*. 2013;55(8):1007–14.

- 7 Peters JM, Taquet M, Prohl AK, et al. Diffusion tensor imaging and related techniques in tuberous sclerosis complex: review and future directions. *Future Neurol.* 2013 Sep 28;8(5):583–597.
- 8 Tsai P, Sahin M. Mechanisms of neurocognitive dysfunction and therapeutic considerations in tuberous sclerosis complex. *Curr Opin Neurol.* 2011;24(2):106–113.
- 9 Meikle L, Talos DM, Onda H, et al. A mouse model of tuberous sclerosis: neuronal loss of Tsc1 causes dysplastic and ectopic neurons, reduced myelination, seizure activity, and limited survival. *J Neurosci.* 2007;27(21):5546–5558.
- 10 Nie D, Di Nardo A, Han JM, et al. Tsc2-Rheb signaling regulates EphA-mediated axon guidance. *Nat Neurosci.* 2010;13(2):163–172.
- 11 Choi YJ, Di Nardo A, Kramvis I, et al. Tuberous sclerosis complex proteins control axon formation. *Genes Dev.* 2008;22(18):2485–2495.
- 12 Marcotte L, Aronica E, Baybis M, Crino PB. Cytoarchitectural alterations are widespread in cerebral cortex in tuberous sclerosis complex. *Acta Neuropathol.* 2012;123(5):685–693.
- 13 Ma TS, Elliott RE, Ruppe V, et al. Electro corticographic evidence of perituberal cortex epileptogenicity in tuberous sclerosis complex. *J Neurosurg Pediatr.* 2012;10(5):376–382.
- 14 Major P, Rakowski S, Simon M V, et al. Are cortical tubers epileptogenic? Evidence from electrocorticography. *Epilepsia.* 2009;50(1):147–154.
- 15 Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Curr Opin Neurobiol.* 2007;17(1):103–111.
- 16 Minshew NJ, Williams DL. The new neurobiology of autism: cortex, connectivity, and neuronal organization. *Arch Neurol.* 2007;64(7):945–950.
- 17 Sener RN. Tuberous sclerosis: diffusion MRI findings in the brain. *Eur Radiol.* 2002;12(1):138–143.
- 18 Peters JM, Sahin M, Vogel-Farley VK, et al. Loss of white matter microstructural integrity is associated with adverse neurological outcome in tuberous sclerosis complex. *Acad Radiol.* 2012;19(1):17–25.
- 19 Lewis WW, Sahin M, Scherrer B, et al. Impaired Language Pathways in Tuberous Sclerosis Complex Patients with Autism Spectrum Disorders. *Cereb Cortex.* 2013;23(7):1526–32.
- 20 Peters JM, Taquet M, Vega C, et al. Brain functional networks in syndromic and non-syndromic autism: a graph theoretical study of EEG connectivity. *BMC Med.* 2013;11(1):54.
- 21 Jansen FE, Braun KP, van Nieuwenhuizen O, et al. Diffusion-weighted magnetic resonance imaging and identification of the epileptogenic tuber in patients with tuberous sclerosis. *Arch Neurol.* 2003;60(11):1580–1584.
- 22 Gallagher A, Grant EP, Madan N, Jarrett DY, Lyczkowski DA, Thiele EA. MRI findings reveal three different types of tubers in patients with tuberous sclerosis complex. *J Neurol.* 2010;257(8):1373–1381.
- 23 McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioliomyomatosis. *N Engl J Med.* 2011;364(17):1595–1606.
- 24 Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioliomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* 2013;381(9869):817–824.
- 25 Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med.* 2013;363(19):1801–1811.
- 26 Tillema JM, Leach JL, Krueger DA, Franz DN. Everolimus alters white matter diffusion in tuberous sclerosis complex. *Neurology.* 2012;78(8):526–531.
- 27 Tournier JD, Mori S, Leemans A. Diffusion tensor imaging and beyond. *Magn Reson Med.* 2011;65(6):1532–1556.
- 28 Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum Brain Mapp.* 2013;34(11):2747–66.
- 29 Vos SB, Jones DK, Jeurissen B, Viergever MA, Leemans A. The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. *Neuroimage.* 2011;59(3):2208–2216.
- 30 Douaud G, Jbabdi S, Behrens TEJ, et al. DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. *Neuroimage.* 2011;55(3):880–890.
- 31 Scherrer B, Warfield SK. Parametric representation of multiple white matter fascicles from cube and sphere diffusion MRI. *PLoS One.* 2012;7(11):e48232.
- 32 Scherrer B, Schwartzman A, Taquet M, et al. Characterizing the Distribution of Anisotropic Micro-structural Environments with Diffusion-weighted imaging (DIAMOND). *Proc 16<sup>th</sup> Int Conf Med Image Comput Assist Interv.* 2013. p. 518–526.
- 33 Taquet M, Scherrer B, Boumal N, Macq B, Warfield SK. Estimation of a Multi-Fascicle Model from Single B-Value Data with a Population-Informed Prior. *Med Image Comput Comput Interv MICCAI.* 2013.
- 34 Taquet M, Scherrer B, Commowick O, et al. A Mathematical Framework for the Registration and Analysis of Multi-Fascicle Models for Population Studies of the Brain Microstructure. *Med Imaging, IEEE Trans.* 2013, in press.
- 35 Pasternak O, Westin CF, Bouix S, et al. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. *J Neurosci.* 2012/12/01 ed. 2012;32(48):17365–17372.
- 36 Catani M, Jones DK, ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol.* 2005 Jan;57(1):8–16.
- 37 Benjamin CFA, Singh JM, Prabhu SP, Warfield SK. Optimization of tractography of the optic radiations. *Hum Brain Mapp.* 2014 Feb;35(2):683–697.



Jurriaan M. Peters, M.D.



Maxime Taquet, Ph.D.

## Contact

### Correspondence Tuberous Sclerosis Complex:

Jurriaan M. Peters, M.D.  
Division of Epilepsy  
and Clinical Neurophysiology  
Boston Children's Hospital  
300 Longwood Ave – Fegan9  
Boston, MA 02115  
USA  
Phone: +1 617 355 5606  
Fax: +1 617 730 0463  
jurriaan.peters@childrens.harvard.edu

### Correspondence image acquisition, multi-fascicle models:

Maxime Taquet, Ph.D.  
Computational Radiology Laboratory,  
Department of Radiology  
Boston Children's Hospital  
300 Longwood Ave – Main2  
Boston, MA 02115  
USA  
Phone: +1 857 218 5172  
Fax: +1 617 730 4644  
maxime.taquet@childrens.harvard.edu