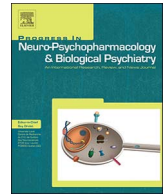




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Investigation of superior longitudinal fasciculus fiber complexity in recent onset psychosis



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ABSTRACT

Background: Standard diffusion tensor imaging measures (e.g., fractional anisotropy; FA) are difficult to interpret in brain regions with crossing white-matter (WM) fibers. Diffusion spectrum imaging (DSI) can be used to resolve fiber crossing, but has been difficult to implement in studies of patients with psychosis given long scan times.

Methods: We used four fold accelerated compressed sensing to accelerate DSI acquisition to investigate the superior longitudinal fasciculus (SLF) in 27 (20M/7F) patients with recent onset psychosis and 23 (11M/12F) healthy volunteers. Dependent measures included the number of crossing fiber directions, multi directional anisotropy (MDA), which is a measure sensitive to the anisotropy of the underlying water diffusion in regions of crossing fibers, generalized FA (GFA) computed from the orientation distribution function, FA and tract volume.

Results: Patients demonstrated a greater number of crossing WM fibers, lower MDA, GFA and FA in the left SLF compared to healthy volunteers. Patients also demonstrated a reversal in the normal (R > L) asymmetry of crossing fiber directions in the SLF and a lack of normal (L > R) asymmetry in MDA, GFA and FA compared to healthy volunteers. Lower GFA correlated significantly ($p < 0.05$) with worse overall neuropsychological functioning; posthoc tests revealed significant effects with verbal functioning and processing speed.

Conclusions: Our findings provide the first in vivo evidence for abnormal crossing fibers within the SLF among individuals with psychosis and their functional correlates. A reversal in the normal pattern of WM asymmetry of crossing fibers in patients may be consistent with an aberrant neurodevelopmental process.

1. Introduction

Magnetic resonance (MR) imaging studies have identified white-matter connectivity deficits in the neurobiology of psychosis, including individuals with schizophrenia (Voineskos, 2015) and bipolar disorder (Bellani et al., 2016; Mahon et al., 2009). The first generation of diffusion tensor imaging (DTI) studies used voxelwise and region of interest approaches to investigate white-matter microstructure in patients with psychosis and demonstrated that abnormalities are present early in

the course of illness and prior to extensive pharmacologic intervention (Sun et al., 2015; Szeszko et al., 2005; Szeszko et al., 2008). Subsequent studies used tractography to identify abnormalities within specific white-matter bundles among individuals at risk for (Cho et al., 2016) and experiencing (Cho et al., 2016; Kikinis et al., 2015) a first episode of psychosis. Moreover, white-matter abnormalities in schizophrenia have been linked with poor treatment response (Reis Marques et al., 2014) and negative symptoms (Voineskos et al., 2013), thus making them a potentially important target for treatment intervention.

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The proportion of white-matter voxels containing crossing white-matter fibers has been estimated to be approximately 63% using automatic relevance determination and 90% using constrained spherical deconvolution, thus exceeding prior estimates (Jeurissen et al., 2013). Automatic relevance determination (Behrens et al., 2007) is a selection technique that utilizes a complex model to fit the data ensuring that parameters not supported by the model contribute minimal overall effect. This stands in contrast to other model selection techniques that fit different models to the data separately and compare them through measures reflecting data fit and complexity. In spherical deconvolution (Tournier et al., 2004; Tournier et al., 2007) fiber orientation can be assessed from high angular resolution diffusion imaging without any need for assumptions regarding the number of fiber orientations that may be present within a given voxel. This signal is expressed as a convolution over a sphere to yield a response function along with a concomitant orientation distribution function (ODF), thus allowing the fiber orientation distribution to be resolved using deconvolution.

Although the commonly used DTI model can perform well in regions consisting of a single fiber direction, this approach cannot resolve fiber tracts aligned along different axes (Farquharson et al., 2013). FA, measured through DTI, does not provide an accurate representation of the underlying white-matter microstructure in regions of crossing white-matter fibers, making both interpretation of findings and tractography inaccurate. The challenge of considering fiber crossing in image processing can be overcome using several approaches. For example, Rathi et al. (2011) used unscented Kalman filter tractography with a two tensor model and reported that 20 patients with first episode schizophrenia had at least one significantly different diffusion measure in 740 among 1254 fiber bundles compared to 20 healthy controls. In addition, the field has moved toward the application of techniques that provide high angular resolution such as diffusion spectrum imaging (Wedeen et al., 2012) to provide information regarding the constituent fibers and enable resolution of crossing fibers. More specifically, in contrast to DTI q-space, which provides angular coverage along a sphere, DSI samples q-space on a uniformly-spaced Cartesian grid (Fig. 1 illustrates the differences in these approaches). The additional q-space samples in DSI allow for the calculation of the diffusion probability distribution function (PDF). The angular component of the PDF

is the orientation distribution function (ODF). Multiple fiber directions can be resolved by identifying peaks and troughs of the ODF. Using diffusion spectrum imaging (DSI) Griffa et al. (2015) reported that connectivity strength within an affected core of brain regions, quantified using both generalized fractional anisotropy (GFA) and the apparent diffusion coefficient, was abnormal in 15 patients with schizophrenia compared to healthy volunteers. Wu et al. (2014) identified lower white-matter microstructural integrity involving dorsal and ventral tracts assessed using DSI and concomitant lower functional lateralization of the dorsal pathway in 18 patients with schizophrenia compared to 18 matched healthy volunteers.

The use of techniques that can resolve crossing white-matter fibers such as DSI can provide complementary measures to traditional DTI and is better suited for tracking white-matter bundles in the brain (Wedeen et al., 2005). The main drawback of DSI, however, is the long scan time making it difficult to implement in clinical practice. Accelerated acquisition of DSI may be accomplished, however, by leveraging the sparsity of diffusion data in a suitable transform domain (Khare et al., 2012; Menzel et al., 2011). This acceleration uses compressed sensing (Candès, 2006) which has become more widely adopted in MR imaging research (Lustig et al., 2007). The purpose of applying compressed sensing to DSI is to exploit the inherent sparsity of the diffusion propagator in a suitable transform domain (e.g. wavelets) by first randomly under sampling the diffusion encoding space, and then using the under sampled pattern to reconstruct missing data points.

A potentially important measure that can be derived from DSI includes the number of crossing fiber bundles within a white-matter tract by identifying the peaks and troughs of the ODF. In addition, similar to FA, GFA ranges from 0 to 1 (denoting zero to maximal anisotropy), but normalizes the angular variability within the diffusion ODF to quantify the angular dependence of diffusion mobility, thus deriving a measure that is generalized from more than three eigenvalues of the DTI model (Glenn et al., 2015). More specifically, a major drawback of the tensor model is that it cannot represent non-Gaussian PDFs, which are more likely to represent water diffusion properties in the brain. Therefore, an advantage of GFA compared to FA is that it provides a more appropriate estimate of anisotropy from the computed ODF to provide a potentially more valid estimate of water diffusion properties in white matter (Tuch

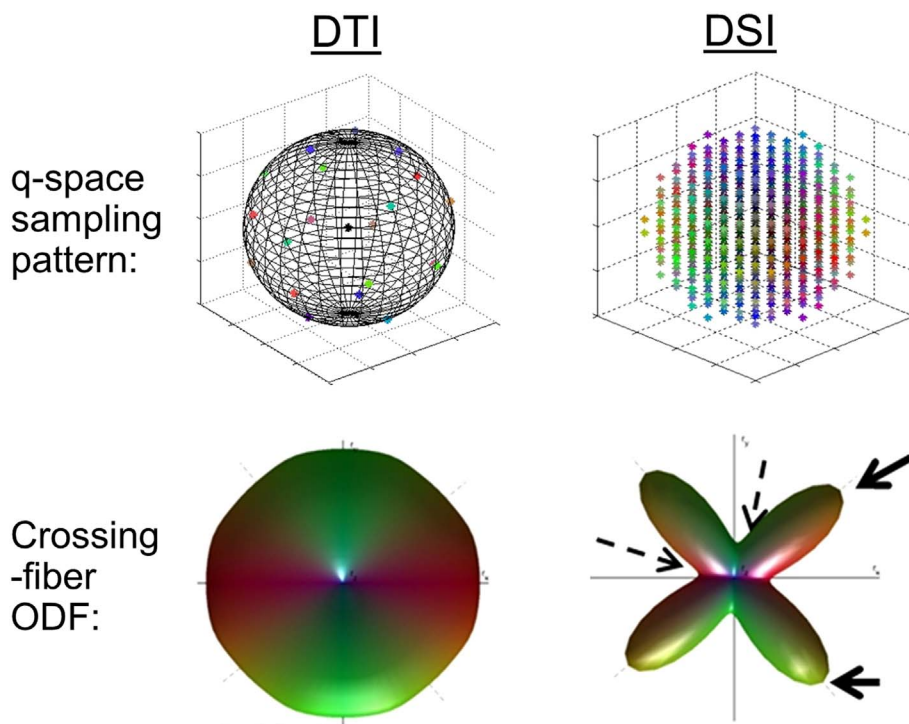


Fig. 1. Illustration of differences between diffusion tensor imaging and diffusion spectrum imaging (DSI), regarding its diffusion-space sampling (q-space) and orientation distribution function (ODF).

Note: In DTI, q-space is sampled on a spherical shell, whereas in DSI q-space is sampled on a Cartesian grid bounded by a spherical surface of given maximum b-value (typically much larger than usual b-values employed in DTI). In a simulation of a 90-degree, equal crossing fibers, DTI is unable to resolve the two directions, whereas the added samples in DSI allow for the computed ODF to resolve the two directions. The solid and dashed arrows point to the peaks and troughs of the ODF that are used to resolve diffusion directionalities.

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