1. DTI Data Acquisition and Pre-processing:

High resolution T1-weighted magnetic resonance images (MRI) were acquired with a GE SIGNA 3-Tesla scanner with a quadrature head coil with 256 X 256 mm field of view and 124 axial sections. The voxel dimensions are 0.937 X 0.937 X 1.200 mm. T2-weighted images were used to smooth out inhomogeneities in the inversion recovery-prepared images using FSL (www.fmrib.ox.ac.uk/fsl). The Autism Diagnostic Interview-Revised ([27]) was used for diagnoses by trained researchers K.M. Dalton and B.M. Nacewicz ([26]). Diffusion weighted images were acquired in 12 non-collinear diffusion encoding directions with diffusion weighting factor (b=0) 1000 s/mm^2 in addition to a single reference image. The voxel resolution for the DTI data is 256 X 256 X 39 mm and voxel dimensions are 0.9375 X 0.9375 X 3.0 mm.

Eddy current related distortion and head motion of each data set were corrected using AIR and distortions from field inhomogeneities were corrected using custom software algorithms based on [1]. The six tensor elements were calculated using non-linear fitting methods available in CAMINO [3,4,5]. Finally, the resulting tensor volumes were resampled to a voxel space of 128 X 128 X 64 with voxel dimensions equal to 1.5mm X 1.75mm X 2.25mm. The resampled volume, with axial dimension equal to a power of 2, is better suited for registration algorithms that require the construction of standard multi-resolution image pyramids.

The DTI data from 31 subjects were used in this study:
1) 17 subjects with high functioning autism spectrum disorders.
2) 14 control subjects matched for age, handedness, IQ, and head size.

A population-specific tensor template was constructed from all 31 subjects using an iterative strategy similar to the one described in [7,8]. An initial template was computed as an average of the original subject diffusion tensor images. The template was then iteratively refined by repeating the following procedure: register the subjects to the template, and then compute a refined template for the next iteration as an average of the normalized images. This procedure was repeated until the change between templates from consecutive iterations became sufficiently small. During each iteration, the diffusion tensor images were registered to the respective template estimate using the tensor registration algorithm described later in the section. The FA template was taken as the FA map derived from the tensor template and it is illustrated in Fig. 1.
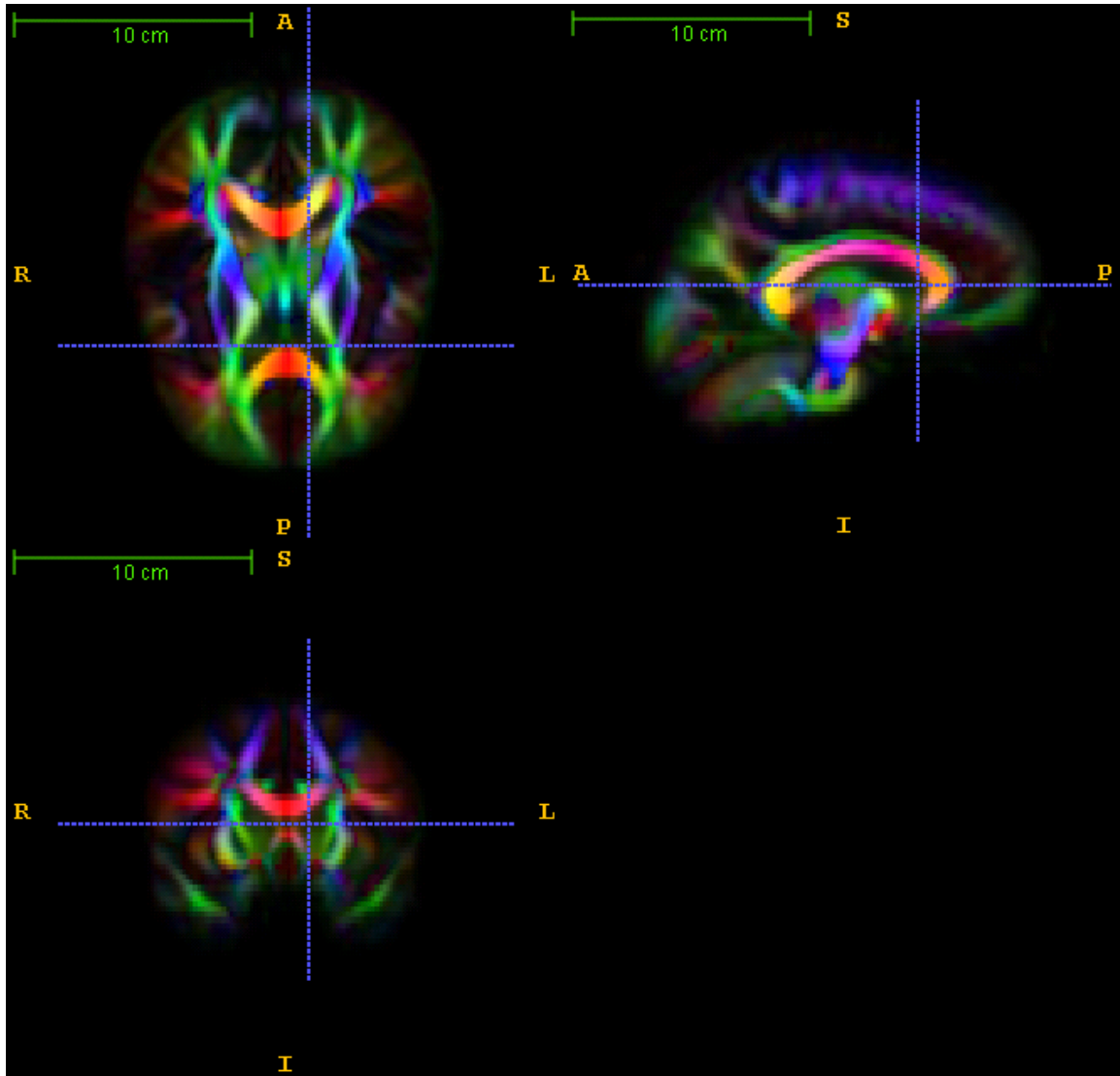
Fig. 1. FA-weighted RGB-encoded principle diffusion direction map of the population specific template obtained after 6 iterations of diffeomorphic registration.

2. DTI Spatial Normalization:

Spatial normalization of diffusion tensor images plays a key role in voxel-based analysis of white matter (WM) group differences. The quality of spatial normalization determines the extent to which the shared anatomy, in this case WM tracts, are aligned. Therefore, it has direct impact on the successful removal of shape confounds and consequently on the validity, specificity, and sensitivity of the subsequent statistical inferences of group differences. Currently, the large majority of clinical studies have chosen to employ the spatial normalization approach of aligning the diffusion tensor images using low-dimensional image registration algorithms via their corresponding structural images, i.e., T1- or T2-weighted images [9,10,11,12,13,14,15], or via their fractional anisotropy (FA)

images [16]. This normalization strategy allows researchers to take advantage of available registration tools, with the nonlinear normalization algorithm within SPM2 [17] being the most commonly used. However, the limited spatial normalization quality of low-dimensional approaches has made the interpretation of their findings challenging, as discussed in [18]. The registration algorithms underlying the low dimensional approaches use low-dimensional representations of spatial transformation that can not adequately model the complex brain morphological differences often seen across subjects. Inadequate normalization with low-dimensional approaches can result in insufficient removal of shape differences which in turn can confound FA differences in a complex manner, and that utilizing high-dimensional normalization can both significantly minimize the confounding effect of shape differences to FA differences and provide a more complete description of WM differences in terms of both size and tissue architecture differences [7]. Further high-dimensional approaches, by leveraging full tensor features instead of tensor-derived indices, can further improve the alignment of WM tracts (see for e.g. Fig. 2). Spatial normalization strategies based on high-dimensional registration methods have so far found few clinical applications in WM studies, with the Park et al. analysis of WM asymmetry [19] being one notable exception.
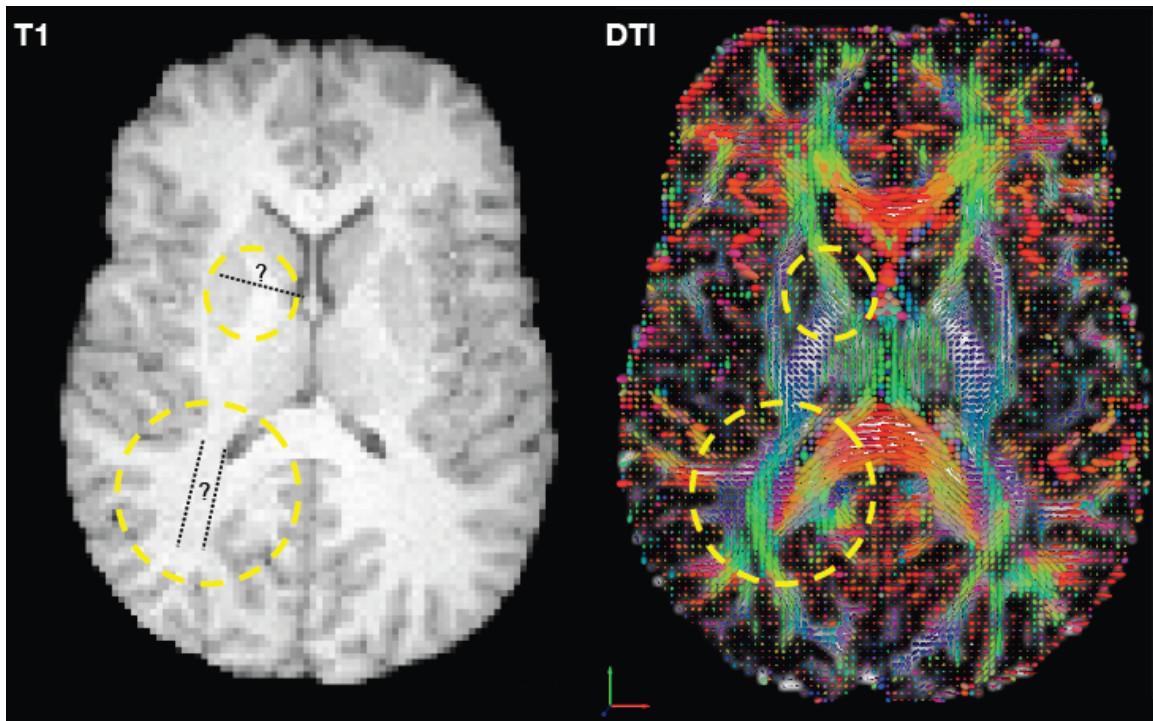

Fig. 2. Tensor based registration can leverage rich discriminating features especially in the white matter of the brain where structural imaging is ambiguous. Encircled areas show some example areas in the white matter where DTI offers richer description for registration.

The state-of-the-art diffusion tensor image registration algorithm presented in [7] was used for spatial normalization of the subjects. There are two steps:

1) Initial Alignment: The diffusion tensor images were first affinely aligned to the template. The tensor images after the affine alignment were provided as the input to the tensor registration algorithm.

2) Tensor Normalization: The algorithm leverages full tensor-based similarity metrics while optimizing tensor orientation explicitly. It approximates smooth transformations using a dense piecewise affine parameterization which is sufficient when the required deformations are not large. They used the tensor metric that measures the L^2 distance between the anisotropic parts of the apparent diffusion profiles associated with the diffusion tensors, as described in [20]. Under this metric, the distance between two diffusion tensors D_1 and D_2 is equal to

$$\sqrt{\frac{8\pi}{15}\left(\left\|D_1 - D_2\right\|_C^2 - \frac{1}{3}Tr^2\left(D_1 - D_2\right)\right)}$$

where $\left\|D_1 - D_2\right\|_C$ is the Euclidean distance between the two tensors and equal to $\sqrt{Tr\left(\left(D_1 - D_2\right)^2\right)}$.

3. Tractography:

Tractography is performed in the normalized space by using the thresholded FA map of the population template. Since the tractography is performed using the normalized seed file the fiber bundles across the subjects have same starting points. Streamline tractography based on TENsor Deflection ([29]) has been used to generate the fiber tracts. The implementation in CAMINO was used for the purpose. Sample tractography results for two subjects can be seen in Fig. 3.
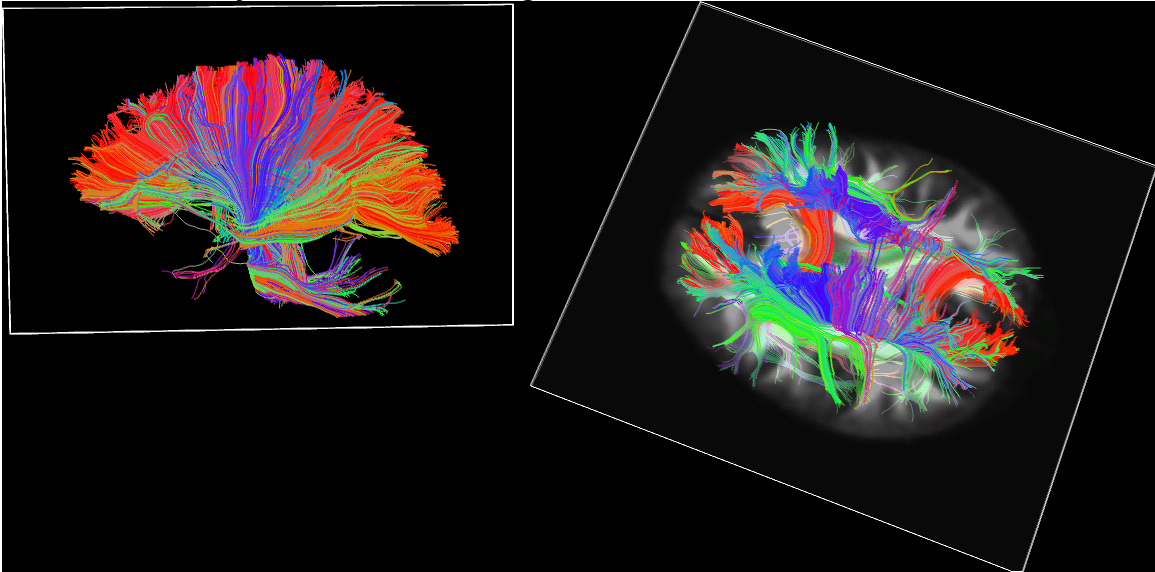

Fig. 3. Sample tractography results in normalized space for two different subjects in different views. On the right. The tracts are overlaid on axial view of the FA of template.