A Study of Underconnectivity in Autism using DTI: W-matrix Tractography

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Introduction

The gold standard diagnosis of autism involves time-consuming behavioral testing which requires special training to use. Children often wait many months for diagnosis. Recent neuroimaging evidence suggests that autism is associated with cortical underconnectivity, as demonstrated on measures of group means, with significant overlap between autistic and control populations. If underconnectivity can be accentuated such as to segregate the autistic population from controls, then one may diagnose autism earlier, and thus allow affected children to begin therapy earlier. Diffusion tensor tractography is a sensitive measure of structural connectivity. Conventional tractography involves choosing a seed voxel, calculating the most likely direction of diffusion from this seed voxel, proceeding in that direction until the next voxel is reached, and repeating this process until the streamline so generated terminates. Many such seed voxels are necessary to generate enough streamlines to construct an image of a white matter tract. In our approach, we also use seed voxels, but we allow streaming from each seed voxel to occur in every direction *simultaneously,* with a weight related to the probability of streaming in that direction. In this way, each seed voxel can give rise to a "flow" that can spread in all directions at once, and that can branch repeatedly. We hypothesize that allowing simultaneous multi-directional flow would generate a map that is more sensitive to disorders of connectivity. The algorithm we use to generate flow is a neural network model, chosen for its simplicity. We refer to our method as W-matrix tractography.

Theory

Given every pair of voxels *i* and *j*, a connection strength *W(i,j)* [Eqn 1] is constructed of three factors: (1) a measure of intravoxel structure derived from the fractional anisotropies of voxels *i* and *j*; (2) a measure of intervoxel structure based on the alignment of the principal diffusion tensor eigenvectors $\vec{e}$; and (3) a distance factor:

$W(i,j) = \left(FA(i) \cdot FA(j)\right)^k \cdot \left|\vec{e}(i) \cdot \vec{e}(i,j)\right|^q \cdot \left|\vec{e}(j) \cdot \vec{e}(i,j)\right|^q \cdot \exp\left(\frac{-d(i,j)}{L}\right)$ (Eqn 1), where $\vec{e}(i,j)$ is a unit vector between voxels *i* and *j*, *d(i,j)* is the distance between them, and *L* is the average voxel dimension. Note that all three factors have values between 0 and 1. A neural network simulation is then run, choosing a few seed voxels to "fire" at every time step, and taking *W(i,j)* as the probability that voxel *i* will fire in response to firing of voxel *j*. Voxel "firing" in our model does not represent real neural activity, but is simply a way to manifest the connection strength *W(i,j)*. The total probability that voxel *i* will fire at time *t*+1 is given by $A(i;t+1) = 1 - \prod_{j \neq i}\left(1 - W(i,j)F(j;t)\right)$, where $F(j;t) = 1$ signifies that voxel j fired at time *t*, and $F(j;t) = 0$ signifies that it did not. The simulation is continued until steady state is reached, and the fraction f of voxels that ever fire is monitored.

Methods

1. *Data acquisition*: DTI data of 43 autism and 34 normal subjects were acquired using a single-shot spin echo EPI sequence with diffusion-tensor encoding (12 directions, b=1000s/mm^2, identical slice locations, voxels = 2x2x2.5mm, 3 NEX, 23 cm FOV). Subjects were matched for age, handedness, IQ, and head size. Data were corrected for the eddy current and field inhomogeneity distortions using the *AIR* (http://bishopw.loni.ucla.edu/AIR5) and in-house field mapping software.

2. *Connection strengths W* : *W(i, j)* was calculated for every pair of voxels *i* and *j* using *k*=2, *q*= 0.125 in [Eqn 1]. 3 x 3 x 3 voxel neighborhoods were used for estimating the neighborhood voxels *j* in W (*i, j)*.

3. *Seeding*: 3x3x3 seed voxels at the splenium of each subject with FA > 0.3 were chosen to have an initial condition of F(seed voxels; 0) =1.

4. *Simulation*: a neural net simulation was carried out and stopped when it reached our stopping criterion which we take to be:

$\left(\sqrt{\sum_i \left((< A_t(i) >_t - < A_{t-1}(i) >_t\right)^2}\right) \Big/ \left(\sum_{i(A>0)} 1\right) < 10^{-3}$. On reaching the stopping criterion, we calculated f by counting the number of voxels that fired and dividing by the number of all white matter voxels. Also we calculated an $f_{0.95}$ when $< A_{plateau}(i) >_t$ was above of 0.95.

5. *Statistics*: the fraction $f_{0.95}$ and f were subjected to analysis of variance (ANOVA) and analysis of covariance (ANCOVA) comparing autistic subjects vs. controls and using age as a co-variate.

Results

Comparing autistic subjects vs. controls, connectivity was dramatically reduced for autistic subjects (Fig 1). Controlling for age, the ANCOVA for $f_{0.95}$ using all 77 subjects resulted in an F-value = 19.94 with p value of 3×10^{-11}. The ANOVA of f for the 16 subjects under age 10 led to an F value 19.64 with p value of 0.0006. In this younger population, there was only one false negative and no false positives (Fig 2). That is, the two populations almost segregate.

Discussion and Conclusions

Compared to a prior study using the same data [1], W-matrix tractography results in better group differentiation. With further tuning, it may be possible to segregate children with autism from non-autistic children.

Reference

[1] Alexander et al., 2007 NeuroImage vol. 34, pp. 61-73.

Fig 1. Examples of averaging firing rate maps. The top row shows maps from control children and the bottom is from autistic children. The first number under each map is the subject age, and the second number is the iteration number for each subject to reach our stopping criterion.

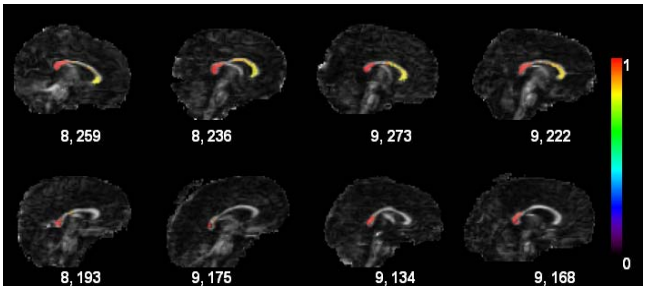

Fig 2. A mean/range plot of 10 autistics and 6 controls of age under 10.