Towards A Diffusion Biomarker of Autism

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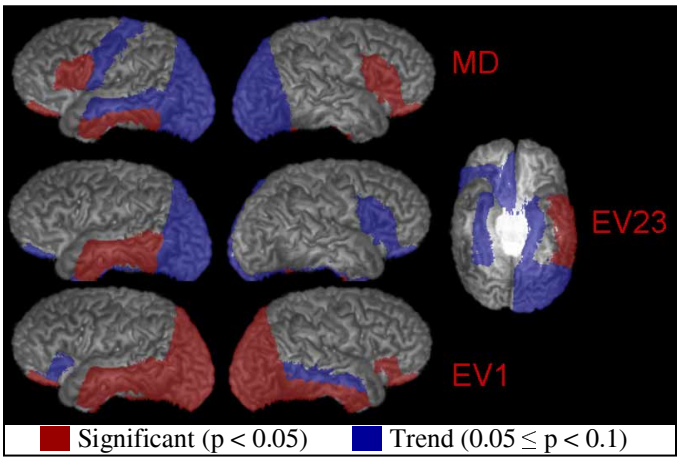
Introduction: Autism is a neurodevelopmental disorder characterized by atypical social and communicative behavior. To date, both the origin and physiology of autism remain unknown. Recently, Yoshiura (1) reported diffusion abnormalities of white matter directly underlying the cortex in a group of patients with Alzheimer's disease (AD). They mapped these abnormalities onto the cortex and found a pattern consistent with behavioral deficits in AD. Here we report an extension of Yoshiura's 2-D method to three dimensions and its application to autism.

Methods: This study included eight high functioning adult individuals with autism spectrum disorder (six male and two female, mean age 28.4, SD 7.3) confirmed by DSM-IV criteria. Subjects with full WASI (Wechsler Abbreviated Scale of Intelligence) IQ scores ≥ 70 and no known major medical, genetic, or psychiatric condition were chosen to participate in the study. All eight control subjects were age and sex matched, in good physical condition, and had no history of psychiatric, neurological or developmental disorder.

MR images were obtained using a Siemens Allegra 3.0 T head-only scanner. High-resolution structural T_1-weighted images were obtained using a gradient echo pulse sequence (Siemens MPRAGE). A double spin-echo, echo-planar pulse sequence was used for the diffusion weighted images. Diffusion images were acquired with 60 gradient directions ($b = 1000$ s/mm^2). All scans were run in triplicate. From these images, mean diffusivity (MD), fractional anisotropy (FA), principal diffusivity (first eigenvalue; EV1), and perpendicular diffusivity (average of second and third eigenvalues; EV23) maps were constructed. Images were then segmented into GM, WM, and CSF. Central GM regions, cerebellum, and neck were manually removed from the images. An in-house Matlab script was used to assign subcortical white matter MD values to the nearest gray matter voxels. This algorithm first finds the nearest WM voxel for each GM voxel by searching within a spherical window of radius 9 mm around the GM voxel. Next, a spherical window of radius 3 mm is placed around the chosen WM voxel to find the minimum MD value in this neighborhood. This step reduces the chance that a CSF-contaminated voxel is chosen. The minimum MD value is the final subcortical WM MD value assigned to each GM voxel. The same subcortical WM voxels, chosen on the basis of minimum MD in the aforementioned method, were also used to construct cortical FA maps, EV1 maps, and EV23 maps. The cortex of each subject was then divided into 36 anatomical areas using Mindboggle (2). A paired t-test was subsequently performed to assess the significance of median MD/FA/EV1/EV23 value differences per label in controls versus autistics.

Results: Cortical areas showing a significant ($p<0.05$) difference in subcortical MD are right and left inferior frontal, right orbital frontal, and left inferior temporal; in all areas, MD is increased in the autistic group. An overall significant increase in subcortical EV23 in the autistic group is seen in left middle temporal and left inferior temporal. An overall significant increase in subcortical EV1 in the autistic group is seen in right orbital frontal, right and left occipital, left middle temporal, and right and left inferior temporal. (See Figure). No significant differences in FA were observed.



Cortical areas showing increased diffusion values in the autistic group

Discussion The physiological basis for increased mean diffusivity in white matter is unclear. A simultaneous increase in T2, if present, would point towards higher water content and possibly decreased cell density; notable in this context is also that FA is not (or not strongly) affected. However, the measured MD differences, in themselves, can serve as biomarkers and classifiers in the automated diagnosis and classification of autism.

References:

1. Yoshiura et-al. MRM. 54:455-459 (2005).
2. Klein et-al. NeuroImage. 24:261-280 (2005).