Localization of white matter transverse relaxation time abnormalities in autism

Y. Gagnon[1], T. Devito[1], J. Hendry[1], N. Gelman[1], N. Rajakumar[2], P. Williamson[2], R. Nicolson[2], and D. Drost[1]

[1]Medical Biophysics, University of Western Ontario, Lawson Health Research Institute, London, Ontario, Canada, [2]Department of Psychiatry, University of Western Ontario, London, Ontario, Canada

Introduction: Autism is a developmental disorder characterized by social deficits, impaired communication, and restricted and repetitive patterns of behavior. Although there is strong evidence that autism is associated with abnormal brain development (1), the anatomical extent and timing of these neurobiological differences are unknown. One method to examine tissue abnormalities *in vivo* is quantitative transverse relaxation time (T2) imaging. T2 is influenced by the molecular environment and tissue properties, particularly tissue water content. In the first published study to use whole-brain T2 imaging in autism (2), we reported an increase in overall white matter T2 in children and adolescents with autism, suggesting an elevation in white matter tissue water. However, the white matter regions contributing to this increase are uncertain. That is, it is unclear if the increase in white matter T2 is increased globally or if there are certain white matter regions that contribute disproportionately to this increase. The purpose of this study was to localize the areas of increased T2 contributing to the reported global increase in white matter T2.

Methods: Twenty-one male patients with autism between the ages of 6 and 16 (mean: 9.4±3.2 years) and 20 male controls between ages 6 and 16 years (mean: 10.8±2.6 years) participated in this study. The diagnosis was made according to DSM-IV-TR criteria using the Autism Diagnostic Interview-Revised, the Autism Diagnostic Observation Schedule. All patients had non-verbal IQ's greater than 70. Control subjects were drawn from the local community and were assessed using the Schedule for Affective Disorders and Schizophrenia, Childhood Version to rule out psychiatric illnesses. The groups did not differ significantly in age, sex, race, full-scale IQ, or non-verbal intelligence. Patients did have a lower mean verbal IQ than controls (p=0.02). Consistent with previous studies, there was a significantly greater proportion of left-handed subjects in the patient group (7/21 vs. 0/23; p=0.003). 10 patients were medication-naïve at the time of their scan, while 3 others had discontinued their medication prior to the scan. The remaining patients were being treated with stimulants (n=5), antipsychotics (n=4), and antidepressants (n=1). 16 patients required sedation with oral midazolam in order to complete the scan.

Magnetic resonance imaging data were acquired on a 3T magnetic resonance scanner with a quadrature head coil. T2 data were acquired using a Gradient Echo Sampling of the Free Induction Decay and Echo (GESFIDE) sequence (TR=2800ms; matrix size=192x256; FOV=220mm; slice thickness=4mm with 1.5mm gaps for 22 slices; resolution=1.15x0.86x4mm; total scan time=9min) (3). Five gradient echoes were acquired prior to the 180º radio frequency (rf) pulse, with a first-echo time of 9 msec and an inter-echo spacing of 8.70 msec. Six gradient echoes were acquired after the 180º rf pulse, each spaced by 8.78 msec. The k-space data was then reconstructed into $R2^*$ and $R2^-$ maps by performing a voxel-by-voxel least-squares fit of the natural logarithm of the signal amplitude versus echo time. R2 maps (1/T2 maps) were calculated from $R2 = (R2^* + R2^-)/2$.

Using SPM2, each subject's T2 weighted image was spatially normalized to the adult T2 template (icmb-152, Montreal Neurological Institute) using a 12 parameter affine registration, followed by an iterative non-linear global registration to account for inter-subject low frequency shape differences (4). The calculated transformation parameters were then applied to the subject's respective R2 map, yielding a volume of R2 values approximating Talairach space. Masks for each region of interest (frontal, temporal, parietal, and occipital white matter) in standard space were generated using the Pickatlas toolbox for Matlab (Wake Forest University) (5). Mean T2 values for each region of interest were then calculated by multiplying the normalized R2 maps by these binary masks.

Group differences in lobar white matter T2 were investigated using a Repeated-Measures Analysis of Covariance. In the analysis, T2 was the dependent variable, diagnosis (autism or control) was the between-subjects factor, and region (frontal, temporal, parietal, and occipital lobe) and side (left and right) were the within-subjects factors. Significant main effects of diagnosis or higher order interactions involving diagnosis (p<.05), were examined for each region and side individually with Analyses of Covariance (ANCOVAs) to identify the region(s) that contributed to the significant main effect or interaction. Although age did not differ significantly between the groups, the age range in this study was wide. Given the changes in T2 described in childhood, we covaried the statistical analysis of T2 for age to reduce error variance and increase statistical power.

Results: Table 1 presents the mean T2 in each of the regions assessed. Repeated measures ANCOVA revealed a significant main effect of diagnosis and a significant group by side interaction. There were no other significant interactions involving diagnosis. Post-hoc analyses revealed that patients had an overall increase in white matter T2 (2.9%; p=0.02) as well as an increase in white matter T2 in the left hemisphere (3.3%; p=0.004). As there were no diagnosis by region interactions, indicating that there were no other significant asymmetries of T2, left and right hemisphere data were pooled for further analyses. Post-hoc analysis revealed that patients had a significant increase in frontal (3.0%; p=0.03) and parietal white matter (3.1%; p=0.003).

Table 1. Mean transverse relaxation times of lobar white matter regions in milliseconds

Region (white matter)	Autism	Control
Left frontal lobe	70.1 (2.5)	67.7 (2.5)
Right frontal lobe	69.2 (2.7)	67.2 (2.6)
Left occipital lobe	70.2 (3.0)	68.1 (2.4)
Right occipital lobe	71.0 (2.8)	69.3 (2.8)
Left parietal lobe	72.4 (2.6)	69.7 (2.1)
Right parietal lobe	71.9 (2.6)	70.1 (2.1)
Left temporal lobe	67.3 (3.0)	65.3 (2.8)
Right temporal lobe	67.7 (3.2)	66.6 (3.0)

All data presented as mean (SD).

Discussion: Patients in this study had an increase in left-sided white matter T2 as well as an increase in frontal and parietal white matter T2. The interpretation of the results of this study is limited by a small sample size, the absence of female subjects, the use of medication and sedation in some patients and the use of an adult template for the spatial normalization of images. These findings of increased white matter T2 in the frontal and parietal lobes are unlikely to be caused by differences in tissue iron content or cerebral blood flow volume. Instead, a probable source is increased water content in the white matter tissue. These observations complement previous findings of several other imaging modalities (volumetric, diffusion tensor imaging) of abnormal white matter structure and function in patients with autism, particularly in the frontal lobes. Furthermore, the increased left-sided white matter T2 is consistent with findings of abnormal brain lateralization in autism. Future work will focus on specifying the tissue origin of these local T2 differences in patients with autism.

References:

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