

# Investigating transverse relaxation time abnormalities in autism

Y. Gagnon<sup>1,2</sup>, N. Rajakumar<sup>3</sup>, N. Gelman<sup>1,2</sup>, P. Williamson<sup>3</sup>, D. Drost<sup>1,2</sup>, J. Théberge<sup>1,2</sup>, and R. Nicolson<sup>3</sup>

<sup>1</sup>Imaging, Lawson Health Research Institute, London, Ontario, Canada, <sup>2</sup>Medical Biophysics, University of Western Ontario, London, Ontario, Canada, <sup>3</sup>Psychiatry, University of Western Ontario

**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. A follow-up study found that the frontal and parietal lobes had disproportionately increased T2 in this sample (3). This pattern of increased T2 parallels that of increased white matter volume of many volumetric studies in autism. A recent volumetric study has further characterized volume abnormalities in autism using a white matter parcellation scheme anatomically relevant to brain development by radially parcelling white matter into radiate and inner zones and appropriate sub-compartments(4). The purpose of the current study was to investigate T2 differences in patients with autism by following a similar parcellation scheme to determine if the spatial pattern of T2 abnormalities remained similar to that of volumetric studies.

**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 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). Ten 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). Sixteen 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)(5) 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). Five gradient echoes were acquired prior to the 180° 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 180° 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 SPM5, each subject's T2 weighted image was spatially normalized to the adult T2 template (icmb-T2, Laboratory of Neuro Imaging, University of California, Los Angeles) using a 12 parameter affine registration, followed by an iterative non-linear global registration to account for inter-subject low frequency shape differences (6). The calculated transformation parameters were then applied to the subject's respective R2 map, yielding a volume of R2 values approximating Talairach space. White matter probability maps were constructed for each subject using a routine offered in SPM5 and were converted to binary masks using a threshold value of 0.90 to eliminate gray matter voxels for each region of interest (superficial white matter, radiate white matter and deep/bridging white matter) in standard space were generated using the Pickatlas toolbox for Matlab (Wake Forest University)(7) and the DTI-81 white matter atlas(cite). Mean T2 values for each region of interest were then calculated by multiplying the normalized R2 maps by these binary masks.

Group differences in 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 white matter region and side were the within-subjects factors. 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:** Repeated measures analysis of covariance revealed a significant main effect of diagnosis. Post hoc analyses revealed that mean T2 values were significantly increased in the radiate and bridging compartments (p<0.05) but not in the sagittal compartment (Table 1)

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

White Matter Region	Autism	Control
Radiate	66.7 (2.0)	64.9 (2.3)
Sagittal	66.0 (2.0)	64.8 (2.2)
Bridging	63.7 (2.5)	61.5 (2.6)

All data presented as mean(SD).

**Discussion:** This study has some limitations such as patient use of medication and image registration confounds. T2 differences can be caused by differences in cerebral blood flow and brain iron content, but our investigation of T2' (a related MRI parameter) suggests against this possibility. Instead, we suggest that the cause could be increased water content in white matter tissue, pathophysiological differences affecting the relaxation time, or both. This study complements other studies of white matter abnormalities in autism (structural, volumetric, and diffusion tensor imaging). Although a significant difference was only expected in the radiate WM based on a volumetric study by Herbert et al., the significant differences in the bridging compartment may be related to reports of reduced corpus callosum size in autism. Future work will attempt to identify abnormalities in specific tissue components of white matter (e.g., myelin) that may contribute to the local T2 differences reported here.

## References:

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