

Cerebral Gray and White Matter T2 in Autism Spectrum Disorder

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Introduction

Autism Spectrum Disorder (ASD) is a clinically defined syndrome characterized by language and communication deficiencies, social deficits, and repetitive behavior. Diagnosis can be established as early as eighteen months, but typically by around three to four years of age. Morphometric studies increasingly focus on elucidating the underlying pathogenesis of the disorder. Magnetic resonance imaging volumetric studies have reported larger brain volumes in individuals with ASD. It has been suggested that this brain enlargement is due to accelerated growth, or overgrowth, that occurs post-natally and extends through the first several years of life, but which plateaus by about five years of age.¹ Many studies have employed T2 relaxation measurements to characterize the normal progression of brain growth and development. As the brain matures, T2 decreases due to a general decrease in water that occurs as myelin structure and lipids increase and as neuron synapses and dendritic processes develop. To address whether there is abnormal cerebral T2 relaxation in autism, we measured quantitative cortical gray matter and white matter T2 in a sample of 2-4 year old children with autism, compared to age matched children with non-specific developmental delay, and children having typical development.

Methods

Subjects. Three groups of subjects were examined: children with ASD (N=60, mean age=41.6±10.9 months; 48 males, 12 females), idiopathic developmental delay (DD)(N=16, mean age=44.8±9.0, males; 7 males, 9 females), and typical development (TD)(N=10, mean age=36.9±11.6 months; 8 males, 2 females). This analysis comprises a subgroup of 2-4 year old children studied at the UW as part of an ongoing longitudinal investigation.

MRI. Children with ASD and DD, who were greater than 36 months of age, underwent imaging during continuous IV infusion of Propofol at 180 to 220 µg/kg per minute. Affected children younger than 36 months of age were given chloral hydrate (100mg/kg, 2g maximum), between 30-90 minutes prior to scanning. TD children were scanned late at night while asleep.

Axial proton density (PD) and T2-weighted images were acquired from a GE Signa 1.5T (GE, Milwaukee, WI) (TE=13/91 ms, TR=2000ms, FOV = 22cm, 256 x 160 matrix, 2.5mm slice thickness, 0mm gap). These images were then segmented to generate masks used to derive two point T2 calculations from either gray matter or white matter. The PD and T2 images were added together to produce an image with enhanced gray/white contrast. The T2-weighted images were then subtracted from the PD images to produce an image with enhanced tissue/cerebrospinal fluid (CSF) contrast. Added and subtracted images were corrected for RF inhomogeneity using homomorphic filtering.² The process involved taking the log of each image and subtracting from it the log of the estimate of the RF bias. The result was exponentiated to produce the restored image. Each of the added and subtracted images was then classified using a k-means algorithm to delineate a) gray and white matter from the added image, and b) brain tissue and CSF from the subtracted image. Binaries of segmented gray matter and of CSF were combined with BOOLEAN operators to exclude areas of CSF that could otherwise falsely elevate T2 in the gray matter measurement. Subcortical structures were edited out manually. T2 was calculated on a pixel by pixel basis from the resulting binaries using a singular value decomposition routine in IDL (Research Systems Inc, Boulder, Colorado). Statistical analysis was carried out using SPSS (Mac OS v 11.0, Chicago, Illinois), applying ANCOVA with age and gender as covariates, and Tukey post-hoc testing.

Results

For the entire brain, T2 values were significantly different between diagnostic groups for both measures of gray matter and white matter (F(2,83)=8.56, p=.001; white F(2,83)=6.19, p=.003). Post-hoc testing for cortical gray matter revealed significant prolongation of T2 within the DD sample compared to all other groups (DD-ASD p<.001, DD-TD p=.008), and between the ASD children and the TD children (p=.009). Cerebral white matter T2 of the whole brain echoed the direction of the gray matter results observed for the DD sample (DD-ASD p=.002, DD-TD p=.003), however, no white matter differences between the ASD and TD children were observed. Mean T2 values for each group of children are graphically displayed in Figures 1 and 2.

Discussion

Gray matter and white matter T2 decrease as the brain develops and water content decreases, largely a result of myelination and increased lipid content in white matter, and structural differentiation in gray matter. Significantly higher T2 in the DD children likely reflects a delay in the natural time course of brain development. On the other hand, prolonged T2 in the ASD children compared to the TD group, with no statistically significant T2 elevation in the white matter, suggests that developmental mechanisms occur in autism that differ from maturational delay.

Decreased serotonergic activity involved in regulating neuronal terminals and synaptogenesis has been reported in autism.³ This finding, in addition to reports of lower cell packing density in increased numbers of cortical minicolumns⁴, suggest that in autism there may be greater interstitial space in gray matter which would provide a biological environment with prolonged water T2. Accumulated observations in autism that support autoimmune activity in cerebral cortex⁵ are also consistent with prolonged T2, and may provide a plausible explanation for our results. As this analysis reflects a single time point of a longitudinal investigation, it is conceivable that change in T2 values over time may provide additional information to help understand brain maturation and cellular features that are altered in autism.

References

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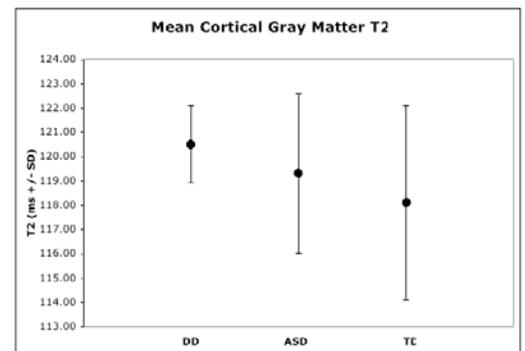


Figure 1 Estimated marginal means for gray matter T2

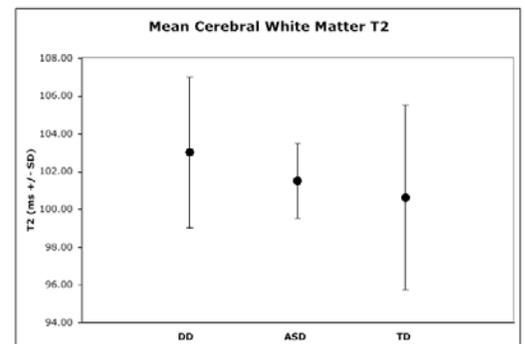


Figure 2 Estimated marginal means for white matter T2