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Gray matter abnormalities in autism spectrum disorder revealed by T2 relaxation

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Abstract—Objective: To perform quantitative T2 relaxation measurements to evaluate cerebral water content in children with autism. **Methods:** Sixty 2- to 4-year-old children with autism spectrum disorder (ASD), 16 age-matched children with idiopathic developmental delay (DD), and 10 children with typical development (TD) were scanned on a 1.5 T GE MRI scanner to obtain dual-echo fast spin echo images (2.5 mm thick, 0-mm gap). Images were segmented into gray and white matter and used to mask regions of interest for calculating T2 for each tissue type. Analysis of variance, covarying for age and sex, was used to compare T2 between groups, and correlations were used to compare T2 to IQ measures. **Results:** Children with ASD had prolonged cortical gray matter T2, but white matter T2 was not significantly different, compared with the children with TD. T2 was prolonged in cortical gray matter and white matter in children with DD compared with children with ASD or TD. Significant interactions between T2 measures and IQ were not observed. **Conclusions:** Prolonged gray and white matter T2 in the children with developmental delay likely represents a delay in neuronal development and maturation. Prolonged T2 in gray matter, but not white matter, observed in children with autism spectrum disorder may signify abnormal developmental processes specific to autism.

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Autism spectrum disorder (ASD) is a behavioral syndrome typically diagnosed during early childhood and characterized by language and communication deficiencies, social deficits, and repetitive behavior.^{1,2} Prior MRI volumetric studies have observed increased overall brain volume, as well as for specific subregions, though the differential distribution of this apparent increase in cerebral white and gray matter and subcortical volumes has been variable. Because increased brain volume is more consistently reported in pre-school-aged children with ASD^{3–5} than in adolescents and adults,^{6,7} and from observations of normal head circumference at birth, cerebral enlargement has been hypothesized to reflect accelerated brain maturation or an overgrowth early in the course of ASD.^{8,9}

Assessment of quantitative T2 relaxation has been used to characterize the temporal progression of brain maturation.^{10–12} In consideration of this work, we quantitatively assessed cerebral white matter and cortical gray matter T2 relaxation in children with ASD compared with age-matched populations of children with typical development (TD) or developmental delay (DD). These children comprised an expanded sample of 3- to 4-year-old children whose T1 volumetric imaging data have been previously re-

ported to show cerebral enlargement in the children with ASD compared with both of the other diagnostic groups.³ We hypothesized that if this enlarged cerebral volume was due to accelerated normal brain growth, gray and white matter T2 in the children with ASD would be decreased relative to the children with TD, reflecting a more advanced stage of brain maturation. In contrast, the children with DD would be expected to demonstrate prolonged T2 relaxation in conjunction with delayed brain development.

Methods. Methodologic details of recruitment and clinical evaluation of subjects in this study have been previously described.³

Subjects. Three groups of children composed the study cohort: 1) 60 children with ASD (48 boys, 12 girls; mean age 41.6 ± 10.9 SD months, range 21 to 54 months), 2) 16 children with DD (7 boys, 9 girls, mean age 44.8 ± 9.0 SD months, range 25 to 58 months), and 3) 10 children with TD (8 boys, 2 girls, mean age 36.9 ± 11.6 SD months, range 20 to 50 months). Children with previously reported T1-weighted imaging data³ were excluded from this study if the T2/proton density (PD) imaging sequence was not successfully acquired owing to the length of the exam ($n = 9$) or if the images were not usable due to artifacts ($n = 2$).

Participants were recruited from local parent advocacy groups, public schools, the Department of Developmental Disabilities, clinics, hospitals, and the University of Washington Infant and Child Subject Pool. Written parental/guardian informed consent to participate in the study, approved by the University of Washington Internal Review Board, was obtained for each child. Children in the ASD and DD groups exhibited significant DD as

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demonstrated on standardized tests of intellectual and adaptive abilities, and their DD could not be attributed to known genetic abnormalities (e.g., fragile X syndrome, Norrie syndrome, neurofibromatosis, tuberous sclerosis, phenylketonuria, Down syndrome), prenatal or postnatal brain trauma, or another defined disease. Each of these children was evaluated at a multidisciplinary research center where the children with ASD or DD were diagnosed or had their original diagnosis confirmed.

A diagnosis of ASD was based on the Autism Diagnostic Interview-Revised (ADI-R)¹⁴ and the Autism Diagnostic Observation Schedule-Generic (ADOS-G).¹⁵ In addition, clinical evaluation by an experienced clinician confirmed the diagnosis. Children meeting strict criteria for a diagnosis of Asperger syndrome were excluded from the study. The ADOS-G was administered to the children with DD or TD. These children did not meet criteria for ASD based on the ADOS-G or by a clinical evaluation, nor did they show elevated symptoms of autism on these measures. Affected children were studied soon after a clinical diagnosis was established, and none was under treatment with either medication or cognitive behavioral intervention. TD subjects were included if they scored within 1 SD of normal on the Vineland Adaptive Behavior Scales.¹⁶ No history of language, social, motor, cognitive delay, speech therapy, psychiatric disturbances, or learning problems was present in the TD sample. Subjects from all diagnostic groups were excluded from participation if there was a history of seizures, cerebral vascular disease, severe sensory or motor impairments (deaf/blind), significant pulmonary disease, unstable cardiovascular status, major physical abnormalities, documented pre- or postnatal head trauma, metal implants such as prostheses, or if they were regularly taking psychoactive medication.

For children with ASD or DD, verbal and nonverbal IQ scores were assessed using the Mullen Scales of Early Learning,¹⁷ a well-validated, normalized measure of language, visual spatial, and motor abilities. A composite ratio IQ was calculated by taking the age-equivalent score divided by the child's chronologic age (Mullen group means: ASD = 58.6 ± 19.4 SD, DD = 58.9 ± 14.7 SD).

MRI. Children with ASD or DD younger than 36 months (n = 18) were sedated with chloral hydrate (100 mg/kg, 2 g maximum, administered approximately 30 to 90 minutes prior to scanning). Children with ASD or DD, age 36 months or older (n = 58), were sedated with propofol (180 to 220 µg/kg per minute).¹⁸ Children with TD were scanned late at night while asleep. Some children with TD were sedated on an optional basis with parentally administered diphenhydramine hydrochloride (n = 4, 25 mg PO) if the child had previously experienced sedation when given this agent.

Axial PD and T2-weighted MR images were acquired from a 1.5 T GE Signa (GE, Milwaukee, WI) using a fast spin echo sequence (echo train length = 8, [effective] echo time = 13/91 milliseconds, repetition time = 2,000 milliseconds, field of view = 22 cm, 256 × 160 matrix, and 2.5-mm slice thickness, 0 mm gap). Each MRI was clinically evaluated by a board-certified pediatric neuroradiologist. None of the children exhibited gross anatomic abnormalities with the exception of one child with DD who was excluded from the analyses.

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/CSF contrast. Added and subtracted images were corrected for radiofrequency (RF) inhomogeneity using homomorphic filtering.¹⁹ The process involved taking the log of each added image and subtracting from it the log of the estimate of the RF bias. The result was exponentiated to produce the restored image. The RF bias was estimated from the PD image using a normalized convolution that takes into account only the regions containing tissue. This was accomplished by masking out any background noise and then separately low-pass filtering the masked tissue image and the mask itself. The filtered mask was divided into the filtered masked tissue image to produce an image containing the estimate of the inhomogeneity.

Each of the added and subtracted images was classified using a k-means algorithm to delineate 1) gray and white matter from the added image and 2) brain tissue and CSF from the subtracted image. Binary images of segmented gray matter and of CSF were combined using Boolean (logical) operators to exclude areas of CSF that could otherwise falsely elevate T2 in the gray matter

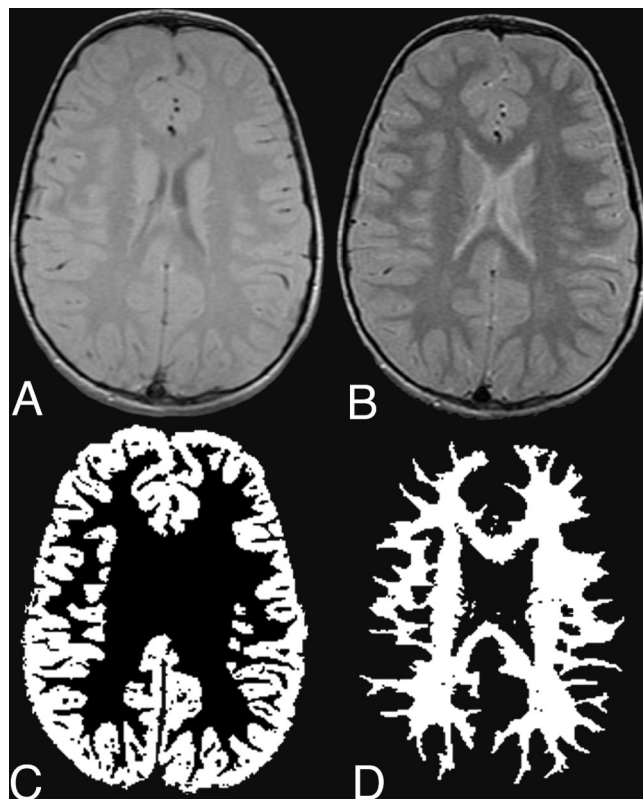


Figure 1. (A) Proton density image; (B) T2-weighted image; (C) segmentation of cortical gray matter; (D) segmentation of white matter.

measurement.²⁰ Likewise, binary images of segmented white matter and of CSF were logically combined to exclude ventricular CSF. Subcortical structures were edited out manually. Characteristic segmentation of gray matter and white matter is demonstrated in figure 1. T2 was calculated on a pixel-by-pixel basis from the raw, uncorrected MR images using a singular value decomposition routine in IDL (v. 6.0; Research Systems, Boulder, CO). Average T2 values for each tissue type were calculated from the area corresponding to their respective gray matter and white matter masks. An example of a calculated T2 map is shown in figure 2A with corresponding histograms in figure 2B, showing characteristic T2 distributions in each tissue type.

Statistical analysis was performed using SPSS (v 11.0 for the Macintosh; Chicago, IL) using a one-way analysis of covariance, controlling for age and sex contributions, among main diagnostic groups (ASD, DD, and TD) to compare average T2 in gray and white matter. Cerebral volume, when used as an exploratory covariate, was not significant in any of the models and was therefore excluded. For main analyses reaching significance, posthoc testing was performed (Tukey). Because many individuals with ASD (approximately 70%) have mental retardation in addition to core autism features, comparing these children with a group of age-

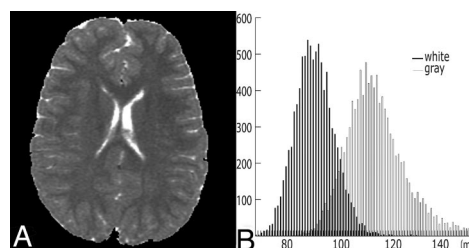


Figure 2. (A) Calculated T2 map; (B) histograms of characteristic T2 distributions for regions corresponding to each of the binary masks.

Mean Cortical Gray Matter T2

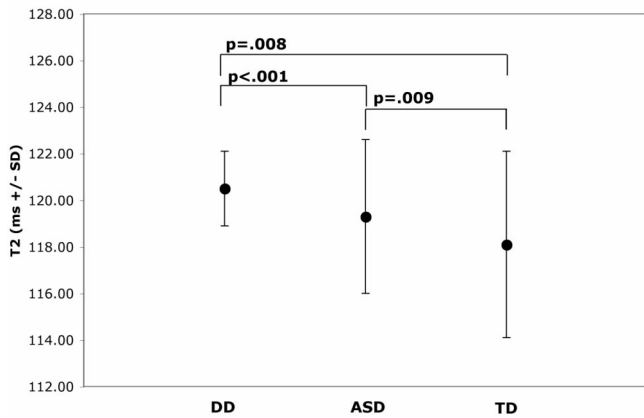


Figure 3. Age-adjusted mean T2 of cortical gray matter for each group of children showing significantly prolonged values in children with autism spectrum disorder (ASD) and children with developmental delay (DD) with respect to each other and each with respect to children with typical development (TD).

matched children with DD was anticipated to have utility for evaluating shared or distinct biologic features. To evaluate relationships between T2 and IQ, partial correlations were carried out separately for each of the affected (ASD and DD) groups. For these correlation analyses, age was entered as a covariate.

Results. The age ranges in months between diagnostic groups were not different ($F[1,83] = 1.8, p = 0.172$). Group differences in sex were shown ($\chi^2 = 21.6, df = 1, p < 0.001$), resulting from a greater proportion of males in the ASD (80%) compared with the DD (44%) ($\chi^2 = 0.3, df = 1, p = 0.617$) and TD (80%) ($\chi^2 = 3.6, df = 1, p = 0.058$) groups.

Group differences were present in gray matter T2 ($F[2,83] = 8.6, p < 0.001$), with age as a significant covariate within the model ($F[1,83] = 188.9, p < 0.001$). Sex was also significant at the trend level within the model ($F[1,83] = 3.9, p = 0.053$). Posthoc analyses revealed differences comparing the children with ASD and TD (1.0%; $p = 0.009$), the children with ASD and DD (-1.0%; $p < 0.001$), and the children with DD and TD (2.0%; $p = 0.008$). As displayed in figure 3, estimated marginal means and SD were as follows: ASD = 119.3 ± 1.6 SD milliseconds, DD = 120.5 ± 3.3 SD milliseconds, TD = 118.1 ± 4.0 SD milliseconds.

Group differences were present in white matter T2 ($F[2,83] = 6.2, p = 0.003$) with age as a significant covariate within the model ($F[1,83] = 95.7, p < 0.001$). Effects of sex were significant at the trend level within the model ($F[1,83] = 3.5, p = 0.067$). Posthoc analyses revealed differences comparing the children with ASD and DD (-1.5%; $p = 0.002$) and the DD and TD children (2.1%; $p = 0.003$), but there were no significant differences comparing the children with ASD and TD (0.6%; $p = 0.359$). As displayed in figure 4, estimated marginal means and SD were as follows: ASD = 101.6 ± 2.0 SD milliseconds, DD = 103.1 ± 4.0 SD milliseconds, TD = 101.0 ± 4.9 SD milliseconds.

Gray matter T2 relaxation did not correlate with any of the IQ scales for either the ASD (composite, $r = 0.429, p = 0.171$; verbal, $r = 0.414, p = 0.204$; and nonverbal, $r =$

Mean Cerebral White Matter T2

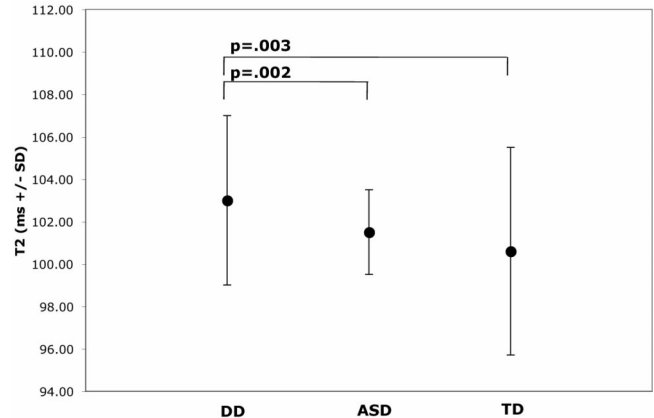


Figure 4. Age-adjusted mean T2 of cerebral white matter for each group of children showing significantly prolonged values for children with developmental delay (DD) compared with children with autism spectrum disorder (ASD) and typical development (TD).

0.417, $p = 0.195$) or DD samples (composite, $r = -0.255, p = 0.817$; verbal, $r = -0.362, p = 0.642$; nonverbal, $r = -0.032, p = 0.975$). White matter T2 relaxation also did not correlate with IQ measures for the children with ASD (composite, $r = 0.391, p = 0.255$; verbal, $r = 0.367, p = 0.318$; nonverbal, $r = 0.389, p = 0.262$) or children with DD (composite, $r = -0.332, p = 0.697$; verbal, $r = -0.164, p = 0.924$; nonverbal, $r = 0.423, p = 0.524$).

Discussion. We quantitatively assessed cerebral gray and white matter T2 relaxation in children with ASD vs children with DD or TD. Whole-brain cortical gray matter T2 was prolonged in the children with ASD, whereas whole-brain white matter T2 was not statistically different vs the children with TD. Children with DD demonstrated prolonged T2 in both cortical gray and white matter relative to children with either ASD or TD, an observation likely due to delayed neuronal structural growth and myelination. In the children with ASD, this evidence for gray matter T2 alterations is consistent with other reports also implicating gray matter abnormalities in ASD^{21,22} and with recent work demonstrating that regional decreases in chemical concentrations and increased chemical T2¹³ are largely specific to gray matter.²³ Although these combined observations support a pathologic gray matter process in ASD, there remains the possibility that white matter is progressively affected later in development. In support of this, a recent report, while observing regional gray matter T2 increases, found an overall preponderance of white matter T2 elevations in an older sample (9.2 ± 3.0 years) of individuals with autism.²⁴ Additional characterization of tissue alterations in relationship to developmental stage will be important to further address these findings.

Our T2 gray matter findings in the children with ASD, studied soon after clinical diagnosis was established, may reflect brain mechanisms involving neu-

roinflammation, which have been implicated in this disorder. Such processes are typically accompanied by edema and would result in increased T2 relaxation. For example, microglial activity and an elevation in cytokines have been reported for various cortical regions in association with autism.²⁵ Additionally, increases in glial fibrillary acidic protein have been found in frontal and parietal cortex, as well as cerebellum, which would also indicate inflammatory changes.²⁶ Thus, the presence of autoimmune markers, specifically identified for the cerebral cortex in autism, may provide a plausible mechanism for the prolongation of gray matter T2 observed in the ASD sample.

Other abnormal neurochemical and histologic processes early in the course of autism could produce an aberrant neuronal structural configuration and account for the differential gray matter T2 findings in the children with ASD. Deficits in the neuroregulatory protein Reelin implicate abnormal pathways for neuronal migration or synaptic plasticity.²⁷ Additionally, increased plasma levels of serotonin, reported in an estimated 30% of affected individuals with ASD, may lead to fewer serotonergic fibers, decreased numbers of serotonin terminals, and decreased synaptogenesis.²⁸ In the postnatal developing brain, decreased serotonin synthesis activity has also been linked to aberrations in cortical columnar development and connectivity.²⁹ Consistent with this are postmortem studies of autism that report higher numbers of cortical minicolumns, which are smaller in size but with greater intercellular dispersion.³⁰ Furthermore, cortical sulcal abnormalities have been observed in autism.³¹ Although it is not clear that children with ASD have a larger cortical surface area, these accumulated observations in autism converge toward a model that involves increased gray matter surface area having lower cell density per unit area. In that context, water protons would be less physically constrained in the gray matter, and there would be prolonged T2 relaxation, consistent with what was observed in the children with ASD.

A challenge in generalizing ASD results concerns the variable occurrence of mental retardation in association with the syndrome. Many of the children studied (67% of the ASD group and 79% of the DD group) demonstrated severe cognitive impairment based on a composite IQ score of less than 70. Specifically assessing potential relationships between T2 relaxation and mental retardation, no significant interactions with any of the IQ scales were observed, suggesting that global T2 measures may not be a specific marker for developmental processes underlying cognitive ability or behavioral performance.

MRI has played an important role in characterizing the course of a typically developing brain. On T1-weighted images at birth, unmyelinated white matter appears hypointense relative to gray matter, whereas white matter appears hyperintense relative to gray matter on a T2-weighted image. As the brain matures, cerebral water in white matter is replaced

by myelin and growing axonal diameter, while in gray matter water decreases owing to differentiating neuronal anatomy.³²⁻³⁴ Consequently, T1 and T2 relaxation times shorten, causing corresponding signal intensity changes. Relaxation times decrease dramatically in the first 6 months of life and continue to decline at a slower rate such that by age 18 months, the changes accompanying development have reversed the relative intensities of the tissue types and the gray/white tissue contrast is visually similar to what is observed in an adult. In general, T1-weighted images are more sensitive to developmental processes at birth through approximately 3 to 6 months; thereafter, maturational changes appear more prominent in T2-weighted images. T2 signal intensity changes have been used to track the course of brain development in healthy children and have provided evidence of delayed myelination in children with developmental delay.³⁵

Quantitative T2 relaxation measures reflect complex factors in the brain that are characterized by multiexponential components primarily comprising intra- and extracellular water, as well as myelin, when present. Multicompartmental analyses with precise measurements of T2 relaxivity require time-consuming acquisitions of images with many echoes. Even so, T2 estimates made from both conventional dual echo acquisitions and fast spin echo dual time points have been shown to provide robust data differentiating brain pathology in normal-appearing gray and white matter, with subtle relaxation differences (on the order of 2%) found to identify specific active disease processes.³⁶⁻³⁹ Mean values for estimated T2 relaxation times from our data ranged from 114 to 122 milliseconds for gray matter and from 95 to 105 milliseconds for white matter, consistent with other reports of T2 measurements acquired from a similar age range of children.¹⁰ Furthermore, the strong relationship between age and T2 measures observed from our data demonstrates the fidelity of these measurements to characterize the progression of brain maturation across this abbreviated window of development.

An important consideration for the interpretation of results from this study is the administration of propofol or chloral hydrate and added supplemental O₂, which conceivably could have confounding effects on T2.¹⁸ Basal metabolic processes may be affected by use of anesthesia,⁴⁰ which can influence relaxation through possible changes in regional cerebral blood flow and consequently variations in magnetic susceptibility.⁴¹ Although influences on T2 from these factors are difficult to rule out, the different results comparing children with ASD or DD, both studied under anesthesia, support the validity of these findings.

Findings from volumetric studies of ASD have led to an interest in better characterizing what has been postulated to be an early brain overgrowth in autism, with related reports of regional heterogeneity in gray and white matter volume and possible de-

creases in white matter connectivity.^{5,42-44} Our results do not address possible localized regions of brain, which may be specifically affected in autism, but are consistent with structural and metabolic differences found across widespread areas of cerebral cortex, which suggest altered gray matter cytoarchitecture or pathology. Although we did not include subcortical gray matter in this initial assessment of T2, future studies will probe subregions of neocortex and white matter, along with discrete nuclei (e.g., the hippocampus, amygdala, and thalamus), for which volumetric differences and functional differences have been reported.^{3,45} Additional investigation employing the use of long echo train studies, which would allow for multicompartmental analysis of T2 relaxation, or MR diffusion tensor imaging may also provide additional sensitivity and aid in further understanding gray and white matter microstructural differences in autism.

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