Evaluation of Frontal Lobe Gray Matter T2 in Autism Spectrum Disorder

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Introduction

Autism spectrum disorder (ASD) is a developmental disorder of unknown etiology that is characterized by unique abnormalities of behavior and social interactions. It has been hypothesized that accelerated brain growth occurs in autism between 1-4 years of age, during which time total brain size as well as many sub-structures exceed normal measurements. (1) Further, this period of accelerated growth may be followed by a period of relatively slow growth, such that by the age of 5 and onward, structural differences between autistic children and normal developing children are less consistently observed. While the precise cellular mechanisms underlying this altered maturational course remain unclear, histological investigations have suggested that increased neuronal density (2) or altered cortical cytoarchitecture (3) may underlie these volumetric changes. While reported brain structural abnormalities may vary by region, among the most affected areas are the frontal lobes. In children with developmental delay (DD), marked but distinct behavioral impairments are also found, although shared in severity with some general features of ASD, whereas cellular abnormalities are likely limited to delayed myelination. This study examined age matched children with ASD, children with DD, and typically developing (TD) children utilizing T2 relaxometry to assess frontal lobe gray matter at six years of age. Specifically, it was hypothesized that ASD children, though sharing features of delayed development with the DD sample, would observe markedly different T2 relaxation times at 6-7 years of age

Methods

Following parental informed consent, children with ASD (79.0±4.8mos, 15 males, 6 females) and children with DD (77.0±5.2mos, 5 males and 4 females) were anesthetized with propofol for MRI examinations. MRI exams were performed on TD children (76.6±3.4, 6 males and 3 females) late at night during sleep, without sedation. Fast spin echo images (thickness=2.5mm, FOV=22, TE=13/91ms, TR=2000ms) were acquired in the axial plane. Images were segmented as previously described to produce discrete areas of gray matter, white matter, and CSF. (4) The frontal lobe was delineated by drawing around the segmented gray matter (GM), manually cutting through the region defined by the most anterior point of the lateral ventricles (Figure 1). As per prior work (4), T2 was calculated on a pixel by pixel basis from the area underlying the frontal lobe GM defined by the segmentation for slices containing ventricles. Software for the T2 calculations was written in IDL (RSI Inc, Boulder, CO). To compare group behavioral burden, the GCASS, a standardized IQ measure, was compared between groups, covarying for age in months, using SPSS (Mac OS 10 version, Chicago, IL). A subset of TD subjects were tested on this measure. Average GM T2, calculated for each subject, was analyzed in a similar manner. For both analyses, post-hoc testing was performed when indicated by main effect results.

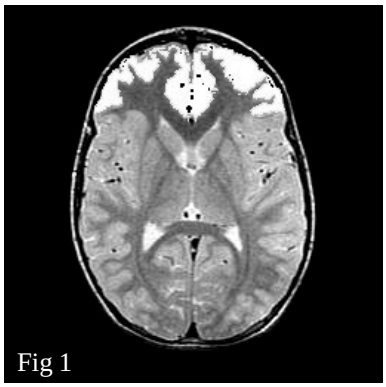

Fig 1

Results

Groups were significantly different on the GCASS ($F(2,32)=15.5$, $p<.001$). Age was at the trend level in this model ($F(1,32)=3.30$, $p=.08$). Post-hoc testing showed that both affected samples had similar behavioral impairment ($p=.46$) and both were dissimilar from the TD group (p's$<.001$) (Figure 2). For T2 measures, a significant between group effect was demonstrated ($F(3,39)=6.43$, $p=.001$), with age in months significant as a covariate ($F(1,39)=11.37$, $p=.002$). Post-hoc pairwise comparisons revealed that T2 was significantly elevated in children with DD compared to both the ASD and TD samples ($p=.004$ and $p=.030$, respectively). In contrast to behavioral differences, ASD children's T2 values were not different from TD children ($p=.40$) (Figure 3).

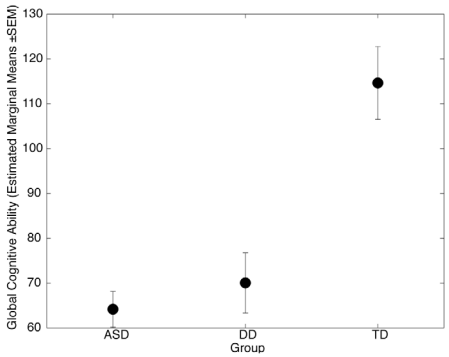

Fig 2

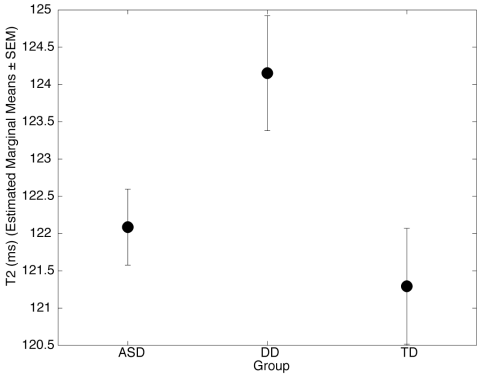

Fig 3

Discussion

Despite similar severity of behavioral deficits in the ASD and DD samples, GM T2 was only different in the DD sample at six years of age. Although speculative, it is possible that this T2 difference arises from processes associated with delayed myelination in the DD children. At six years of age, frontal lobe GM T2 is not dramatically altered in the ASD cohort compared to normally developing children. This may reflect the minicolumnar pathology (3) averaging across the frontal lobes, or the volume averaging of the smaller but less packed minicolumns in this combined intra- and extra-cellular measure. Ongoing analyses are focused on evaluating the regional heterogeneity of tissue T2 in these diagnostic samples, and applying these tools within a longitudinal study of autism and developmental delay being conducted at the University of Washington.

References

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