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Reduced Central White Matter Volume in Autism: Implications for Long-Range Connectivity

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Abstract

Cortical and central white matter (WM) volumes were measured to assess short- and long-range connectivity in autism, respectively. Subjects included 23 boys with autism and 23 matched controls, all without intellectual disability. Magnetic resonance imaging data obtained at 1.5-T were analyzed using BRAINS2 software. Central WM volume was quantified by subtracting cortical from supratentorial WM volumes. Reduced central WM volume was observed in the autism group. IQ was higher in controls with no observed correlations between WM volumes and IQ. This preliminary evidence of reduced central WM volume in autism suggests abnormal long-range connectivity.

Keywords

autism; brain; child and adolescent psychiatry; magnetic resonance imaging

INTRODUCTION

The neurobiology of autism remains unclear despite a rapidly growing body of research literature. Advances in neuroimaging methodologies examining brain–behavior relationships and their applications to the study of autism have provided considerable evidence supporting the aberrant connectivity hypothesis.1 Alterations of short- and long-distance corticocortical connectivity have been suggested.2

Structural magnetic resonance imaging (MRI) studies have provided indirect support to this hypothesis; however, abnormal connectivity has mainly been inferred by diffusion abnormalities3 and volumetric abnormalities of white matter (WM)4 or large structures, such as the corpus callosum.5 Attempts have also been made to specifically estimate short-

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and long-range connections. Hardan and colleagues compared gyral and sulcal thickness as indices of short-and long-range connections, respectively.6 They found an overall increase in cortical thickness in boys with autism, suggesting abnormal cortical connectivity. Herbert and colleagues reported increased WM volume in outer zone regions in boys with autism, suggesting an overabundance of short-range connections.7 While these studies suggest aberrant connectivity in autism, confirmatory studies have been limited.

The purpose of this study was to test the aforementioned connectivity hypothesis using magnetic resonance morphometric techniques to indirectly estimate short- and long-range fiber populations. We hypothesized that there would be an increase in cortical WM and a decrease in central WM, suggesting aberrant short- and long-range connectivity, respectively.

METHODS

Participants included 46 boys: 23 with autism and 23 typically developing controls. There was no significant difference in age (autism = 10.7 ± 1.6 years, control = 10.5 ± 1.3 years, $t = 0.391$, d.f. = 44, $p = 0.698$). Autism subjects met the following criteria: (i) diagnosis through clinical evaluation, Autism Diagnostic Interview-Revised (ADI-R),8 and Autism Diagnostic Observation Schedule (ADOS);9 and (ii) absence of medical/neurological disorders. Control subjects consisted of healthy individuals without intellectual disability and were evaluated by interviews, questionnaires, and observation. The Wechsler Intelligence Scale for Children was administered to measure full-scale IQ (FSIQ). The Hollingshead method was used to assess socioeconomic status. While there was no significant difference in socioeconomic status (autism = 4.5 ± 0.6, control = 4.4 ± 0.6, $t = 0.508$, d.f. = 42, $p = 0.614$), FSIQ was significantly higher in controls (autism = 95 ± 20, control = 116 ± 13, $t = -4.285$, d.f. = 44, $p < 0.001$). The institutional review board approved the methodology of this study. All subjects provided verbal assent and their legal guardians provided written informed consent.

MRI scans were acquired using a 1.5-T General Electric Signa MR Scanner (Milwaukee, WI, USA). Final images were generated using T1-, T2-, and proton density (PD)-weighted images. The T1-weighted SPGR sequence was acquired using the following parameters: slice thickness = 1.5 mm, slice number = 124, echo time (TE) = 5 ms, repetition time (TR) = 24 ms, flip angle = 40°, number of excitations (NEX) = 2, field of view (FOV) = 26 cm, and matrix = 256 × 192. PD-and T2-weighted images were obtained using the following parameters: slice thickness = 5 mm, TE = 96 ms for T2 and 36 ms for PD, TR = 3000 ms, NEX = 1, FOV = 26 cm, and matrix = 256 × 192 with an echo train length = 8. Images were obtained in the coronal plane.

Image processing and analysis was performed using the BRAINS2 software package (University of Iowa, Iowa City, IA, USA).10 Six brain-limiting points were identified to normalize the image data to standard Talairach space. The voxels representing gray matter, WM, and cerebrospinal fluid were identified using a segmentation algorithm applied to the T1-, T2-, and PD-weighted images.11 Measurements were performed using masks as generated by a neural network and corrected by manual tracing (intraclass correlation > 0.9). Analogous to the study performed by Herbert and colleagues,7 short- and long-range connectivity were operationalized by cortical and central WM volumes, respectively. Notably, central WM is an amalgamation of many different fiber types, including association, projection, and commissural fibers.12 Central WM volume was quantified by subtracting cortical WM volume from supratentorial WM volume. Total brain volume (TBV) included the cerebrum, cerebellum, and brainstem.

Statistical analyses were carried out using SPSS (SPSS, Chicago, IL, USA). Measures were compared using Student's t-test ($p < 0.05$, two-tailed). Pearson's correlation was implemented to examine potential relationships between WM volumes and FSIQ ($p < 0.05$, two-tailed).

RESULTS

Reduced central WM volume was observed in the autism group; however, there was no significant difference in cortical WM (Table 1). There were no significant differences in total gray matter, total WM, and TBV (Table 1). There were also no significant correlations between regional WM volumes (cortical and central) and FSIQ in both groups (autism: $r_{cortical,\ FSIQ} = 0.140$, $p = 0.525$; $r_{central,\ FSIQ} = 0.069$, $p = 0.753$; control: $r_{cortical,\ FSIQ} = -0.213$, $p = 0.330$; $r_{central,\ FSIQ} = 0.259$, $p = 0.233$).

DISCUSSION

This study provides preliminary evidence of reduced central WM volume and normal cortical WM volume in a sample of youth with autism. Implied in these findings is a reduction in long-range connectivity without significant differences in short-range connectivity. Notably, central WM consists of association, projection, and commissural fibers.12 While structural MRI studies specifically assessing association and projection fibers are limited, there is a large body of evidence suggesting abnormalities in commissural fibers, namely the corpus callosum. Therefore, the reported reduction of central WM volume is consistent with a recent meta-analysis confirming decreased corpus callosum size in autism.5 Overall, these results are concordant with the growing body of evidence converging on theories of aberrant brain connectivity in autism.1

These results differ from those reported by Herbert and colleagues who observed alterations in superficial (cortical) but not deep (central) WM volume.7 Important differences in methodology may contribute to this inconsistency with the most notable being how WM was parcellated to assess short- and long-range connections. Looking at volumes for cortical and central WM in the autism group, cortical WM is higher and central WM is lower in the current study when compared to the Herbert study. This suggests that the cortical–central boundary lies deeper in the brain in the current study. Moreover, the current study consists of 23 individuals with autism and 23 controls (N = 46) with diagnosis based on the ADI-R8 and ADOS.9 The study reported by Herbert and colleagues consists of 13 individuals with autism and 14 controls (N = 27) with diagnosis based on the Autistic Disorder Interview Checklist.

Findings reported in this study must be interpreted in the context of multiple methodological limitations. The two groups were not matched on FSIQ; however, there are no significant correlations between the WM volumes and FSIQ, making it less likely that group differences in central WM volumes are due to FSIQ. Moreover, it remains an open question whether matching for IQ is necessary in autism-related research.13 Additionally, accuracy and validity of the WM parcellation have not been confirmed by post-mortem studies. Furthermore, abnormalities in connectivity could not be confirmed by other imaging modalities. Also, the Talairach system was used for normalization of pediatric brains, though this practice is generally more problematic when accuracy is critical, such as describing coordinates of functional MRI activations.14 Finally, clinical significance of the findings is unclear because imaging findings are not linked to behavioral data.

In summary, this study provides preliminary evidence of reduced central WM volume. This finding supports a theory of aberrant long-range with possible sparing of short-range

corticocortical connectivity in autism. However, abnormal gyral cortical thickness suggests that even short-range connections are affected in autism.6 Future studies applying multimodal imaging techniques, such as high-resolution structural MRI, functional MRI, and diffusion tensor imaging, would be helpful in more accurately characterizing the aberrant connectivity believed to underlie this severe developmental disorder.

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Table 1

Differences in brain volumes between autism and control groups

	Autism		Control		Student's t-test	
	n = 23		n = 23		d.f. = 44	
	Mean	SD	Mean	SD	T	p
Central White Matter	36.7	4.6	39.2	3.4	−2.079	0.043*
Cortical White Matter	368.4	34.8	383.1	34.2	−1.446	0.155
Supratentorial White Matter	405.2	36.1	422.3	36.3	−1.610	0.115
Total Gray Matter	867.4	83.7	856.9	67.0	0.470	0.641
Total White Matter	479.9	42.4	493.2	47.0	−1.005	0.321
Total Brain Volume	1347.4	119.4	1350.1	102.9	−0.084	0.934

Volumes expressed in cubic centimeters

*statistically significant, p <0.05 (two-tailed)