Increased motor cortex white matter volume predicts motor impairment in autism

Stewart H. Mostofsky,1,2,3 Melanie P. Burgess1 and Jennifer C. Gidley Larson1

1Kennedy Krieger Institute, 707 North Broadway, Baltimore, MD 21205, USA, Johns Hopkins School of Medicine, Departments of 2Neurology and 3Psychiatry, Baltimore, MD, USA

Correspondence to: Stewart H. Mostofsky, MD, Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205, USA E-mail: mostofsky@kennedykrieger.org

Careful consideration of motor impairments, such as those documented in autism, can afford valuable insights into the neurological basis of developmental disorders. Motor signs are highly quantifiable and reproducible and can serve as markers for deficits in parallel systems important for socialization and communication. Correlations of motor signs with anatomic MRI (aMRI) measures therefore offer an important means of investigating brain abnormalities contributing to autism. Prior aMRI studies have revealed increased cerebral volume in young children with autism, particularly in ‘outer zone’ radiate white matter; however functional correlates of these findings have not been reported. In this study, we examined whether radiate white matter within the primary motor cortex would predict impaired motor performance in children with autism. Subjects included children ages 8–12 years: 20 with autism, 36 typically developing (TD) controls and 20 clinical controls with attention-deficit/hyperactivity disorder (ADHD). Regional tissue volumes were measured using an automated tissue classification algorithm followed by a semi-automated parcellation method. Motor performance was assessed using the Physical and Neurologic Examination of Subtle Signs (PANESS), with higher scores indicating poorer performance. Independent linear regression analyses revealed that for TD controls there was a significant negative correlation between total PANESS score and primary motor cortex white matter volume in both the right and left hemispheres, such that increased white matter volume predicted improved motor skill. In contrast, children with autism showed a robust positive correlation between total PANESS score and left hemisphere primary motor and premotor white matter volumes, such that increased white matter volume predicted poorer motor skill. No significant correlations were found for ADHD. Multivariate regression analyses revealed that the correlation between PANESS score and left motor cortex white matter volume in children with autism significantly differed from those in both ADHD and TD children. The correlation in ADHD did not significantly differ from that in TD children. The findings for the first time demonstrate an association between increasing radiate white matter volume and functional impairment in children with autism, in this case basic motor skill impairment. The observed association, which appears specific to autism, may be representative of global patterns of brain abnormality that not only contribute to motor dysfunction in autism, but also deficits in socialization and communication that define the disorder.

Keywords: autism; white matter; imaging; motor; central coherence

Abbreviations: ADHD = attention deficit hyperactivity disorder; PANESS = Physical and Neurologic Examination of Subtle Signs; TD = typically developing


Introduction

Abnormalities on motor examination have often afforded valuable insights into developmental disorders of the brain (Denckla and Roeltgen, 1992). Such abnormalities have been well documented in individuals with autism (Gidley Larson and Mostofsky, 2006) and include difficulties with both basic motor control (Jansiewicz et al., 2006) and performance of complex motor skills and gestures (Rogers et al., 1996; Mostofsky et al., 2006). Increased insight into the brain mechanisms underlying autism can be gained...
from careful consideration of these motor signs. Motor signs can serve as markers for deficits in parallel brain systems important for control of socialization and communication; in a developmental disorder such as autism, procedural learning mechanisms important for acquisition of motor skills may also contribute to impaired development of social and communicative skills (Mostofsky et al., 2000; Ullman, 2004; Walenski et al., 2006). Measures of motor function are more quantifiable and reproducible than are measures of complex social behaviour. Examination of correlations between motor function and anatomic magnetic resonance imaging (aMRI) measures of brain structure therefore offers an important means of investigating brain abnormalities that contribute to the phenotypic features of autism.

Increased brain volume is the most consistent neuroimaging finding in children with autism, with prominent differences during early childhood that are no longer seen by adolescence (Courchesne et al., 2001; Carper et al., 2002; Hazlett et al., 2005). The increased volume has been principally attributed to larger white matter volumes, particularly in outer ‘radiate’ regions (Herbert et al., 2004).

For the current study, we examined whether aMRI measures of radiate white matter volume within primary motor cortices would predict motor skill deficits in children with autism, hypothesizing that, for children with autism, increased white matter volume in the primary motor cortex would predict the degree of basic motor skill impairment. Furthermore, we hypothesized that this association would be specific to autism. We examined this by including: (i) a group of typically developing (TD) control children and (ii) a clinical control group of children with attention deficit/hyperactivity disorder (ADHD), a developmental disorder which, like autism, has been found to be associated with impairments in motor execution and control (Mostofsky et al., 2001, 2003; Klimkeit et al., 2005; Klein et al., 2006).

**Participants and methods**

**Subjects**

Subjects, ages 8–12 years, included 20 high-functioning children with autism (3 girls), 36 TD controls (10 girls) and 20 children (4 girls) with ADHD; children with ADHD were recruited as part of a separate ongoing study in our laboratory that also included neuroimaging and motor assessment. All participants had full-scale IQ (FSIQ) scores greater than 80, except one child with autism who had a FSIQ of 78 but a verbal IQ of 88, based on performance on the Wechsler Intellectual Scale for Children (WISC), 3rd edition (Wechsler, 1991), or the WISC, 4th edition (Wechsler, 2003). Participants were recruited from outpatient clinics at the Kennedy Krieger Institute, local area paediatricians, support groups for families of children with autism and/or ADHD (e.g. the Autism Society of America, Children and Adults with Attention-Deficit Hyperactivity Disorder), schools, social/service organizations (e.g. Boy and Girl Scouts of America) and from advertisements in the community (e.g. postings at libraries).

Children with autism met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. The diagnosis was confirmed using both the Autism Diagnostic Observation Schedule—Generic (ADOS-G) (Lord et al., 2000) and the Autism Diagnostic Interview—Revised (ADI-R) (Lord et al., 1994). Children with identifiable causes of autism (e.g. Fragile X syndrome) and known neurological disorders, including epilepsy, were excluded.

Children in the clinical control group met DSM-IV criteria for ADHD. The structured parent interview, Diagnostic Interview for Children and Adolescents—Fourth edition (DICA-IV) (Reich et al., 1997) and ADHD-specific and broad behaviour rating scales [Conners’ Parent Rating Scale—Revised (CPRS-R: Conners et al., 1998a) and Teacher Rating Scale—Revised (CRS-R: Conners et al., 1998b)] were used to confirm ADHD diagnosis.

The CPRS-R and DSM-IV criteria were also used to evaluate ADHD subtype, with 8 children (one girl) meeting criteria for the predominantly inattentive subtype and 12 (three girls) meeting criteria for the combined subtype. Children meeting criteria for other psychiatric diagnoses based on the DICA-IV, other than Oppositional Defiant Disorder (ODD) and simple phobia, were excluded from this study. ODD was present in eight of the subjects and simple phobia was present in two, including one subject with both. Children with identified neurological disorders, including epilepsy and tic disorders, were also excluded from participation. In addition, none of the children with ADHD had a history of speech/language disorder or a Reading Disability, and all had a basic reading standard score of 85 (16th percentile) or higher on the Word Reading subtest from the Wechsler Individual Achievement Test, First Edition (WIAT; Wechsler, 1992) or Second Edition (WIAT–II; Wechsler, 2002). Children with ADHD taking longer-acting medications (i.e. other than stimulants) were excluded from the study. For children taking stimulant medication, parents were requested to withhold medication on the day of and the day prior to testing.

Subjects in the typically developing control group were free of any neurological, developmental or psychiatric disorders based on responses from the DICA-IV. None of the controls had a history of academic problems requiring school-based intervention services or history of defined primary reading or language-based learning disability and all had a basic reading standard score of 85 (16th percentile) or higher on the Word Reading subtest from either the WIAT or WIAT–II.

Written assent was obtained from all participating children and written consent was obtained from a parent/guardian under approval from the Johns Hopkins Medical Institutional Review Board.

**Motor skill assessment**

Basic motor skills were assessed using a standardized motor examination for children, the Physical and Neurologic Examination of Subtle Signs (PANESS) (Denckla, 1985). This examination has been used to demonstrate basic motor skill impairments in both children with ADHD (Mostofsky et al., 2003) and children with autism (Mandelbaum et al., 2006; Jansiewicz et al., 2006), and a regression model including PANESS variables was found to offer a high level of discrimination in distinguishing boys with autism from controls (Jansiewicz et al., 2006).
Imaging methods
Fast field echo (FFE) MRI sequences were acquired on a 1.5 Tesla Philips Gyroscan NT Intera with the following parameters: TR = 35 ms, TE = 6 ms, flip angle = 45°, 256 × 256, FOV = 240 mm, slice thickness = 1.5 mm. Images were analysed in BrainImage using a fuzzy tissue segmentation algorithm (Reiss et al., 1998) and a semi-automated parcellation method for which a revised Talairach stereotaxic grid specific for measurement in paediatric groups was used to subdivide the cerebrum into lobar and subcortical regions; the frontal lobe was then further subdivided into functionally relevant regions, including the primary motor cortex defined by the precentral gyrus (see Mostofsky et al., 2002 for a more detailed description).

Statistical methods
Analysis of Variance (ANOVA) was used to examine for group differences in sample characteristics, including FSIQ, age, total PANESS score, total brain volume (TBV) and motor cortex white matter volume. Chi-square analyses were used to examine for group differences in handedness and gender.

Independent linear regression analyses were used to examine for correlations between motor cortex white matter volume and total PANESS score in each diagnostic group; these analyses were conducted both with and without controlling for FSIQ and TBV. Following this, a multivariate regression model was used to examine for an interaction effect of diagnosis and primary motor cortex white matter volume on total PANESS score. The approach allowed us to first test our hypotheses that, for children with autism, increased white matter volume in the primary motor cortex would predict the degree of basic motor skill impairment and subsequent to that, test whether this association would significantly differ from that observed in either TD controls or children with ADHD.

Results
Sample characteristics
The groups did not differ significantly in age (P = 0.7). There was a significant group effect for FSIQ (P = 0.0001). Post hoc analyses revealed that TD controls showed significantly higher FSIQ than both children with autism (P < 0.0001) and children with ADHD (P = 0.002); there was no significant difference in FSIQ between children with autism and children with ADHD (P = 0.4). Chi-square analyses did not reveal any group differences in handedness or gender. (See Table 1 for summary of sample characteristics.)

There was a significant effect of diagnosis on total PANESS score (P < 0.0001). Post hoc analyses were consistent with published findings (Jansiewicz et al., 2006), revealing that children with autism show basic motor skill impairment, with significantly higher total PANESS scores than TD controls (P < 0.0001). Children with autism also showed significantly higher total PANESS scores than children with ADHD (P = 0.001). Children with ADHD showed higher total PANESS scores than TD controls at a level that trended toward significance (P = 0.08).

There were no significant group differences in TBV (P = 0.6) or in primary motor cortex (total, left and right) white or gray matter volumes, which is consistent with previously reported total brain and precentral gyrus findings in children with autism in this age range (Courchesne et al., 2001; Herbert et al., 2004).

Analyses of correlations between motor cortex white matter volume and PANESS score
Independent linear regression analyses revealed that for children with autism there was a positive correlation between total PANESS score (with higher score indicating poorer performance) and left primary motor cortex white matter volume (R² = 0.60, P < 0.0001), such that increased white matter volume predicted poorer motor skill (Fig. 1A). Based on the regression, it was estimated that for every cubic centimetre increase in left motor cortex white matter volume, there was a 5-point increase in total PANESS score. No significant correlation was seen with right primary motor cortex white matter volume.

In contrast, for TD controls there was a significant negative correlation between total PANESS score and primary motor cortex white matter volume in the right (R² = 0.13, P = 0.03) and left hemispheres (R² = 0.15, P = 0.02), such that increased white matter volume

Table 1 Results from ANOVA for all groups

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Autism (n = 20)</th>
<th>TD children (n = 36)</th>
<th>ADHD (n = 20)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>10.3 (1.7)</td>
<td>10.5 (1.3)</td>
<td>10.7 (1.3)</td>
<td>F(2,75) = 0.34, P = 0.71</td>
</tr>
<tr>
<td><strong>FSIQ</strong></td>
<td>104.1 (17.8)</td>
<td>120.2 (11.4)</td>
<td>108.0 (13.5)</td>
<td>F(2,75) = 10.2, P = 0.0001*</td>
</tr>
<tr>
<td><strong>Total PANESS score</strong></td>
<td>33.4 (12.1)</td>
<td>176 (8.0)</td>
<td>22.5 (11.5)</td>
<td>F(2,75) = 15.5, P &lt; 0.0001**</td>
</tr>
<tr>
<td><strong>Total brain volume (cm³)</strong></td>
<td>1341.3 (96.9)</td>
<td>1352.2 (1070)</td>
<td>1321.9 (85.6)</td>
<td>F(2,75) = 0.60, P = 0.55</td>
</tr>
<tr>
<td><strong>Motor white volume (cm³)</strong></td>
<td>210 (2.7)</td>
<td>216 (3.5)</td>
<td>20.3 (2.7)</td>
<td>F(2,75) = 1.2, P = 0.31</td>
</tr>
</tbody>
</table>

*Significant differences between Autism and TD Controls (P < 0.0001), ADHD and TD controls (P = 0.002).
**Significant differences between Autism and TD Controls (P < 0.0001), Autism and ADHD (P = 0.001).
predicted better motor skill (Fig. 1B). Based on the regressions, it was estimated that for every cubic centimetre increase in either right or left motor cortex white matter volume, there was a 1.5 point decrease in total PANESS score.

Similar to TD controls, children with ADHD showed a negative correlation between total PANESS score and both left hemisphere ($R^2 = 0.07, P = 0.3$) primary motor cortex white matter volumes, although neither of these correlations was statistically significant. Based on the regressions, it was estimated that for every cubic centimetre increase in either right or left motor cortex white matter volume there was a 2 point decrease in total PANESS score.

After covarying for FSIQ and TBV, the findings in both children with autism and TD controls remained significant, with correlations that were more robust. For children with autism there remained a significant positive correlation between total PANESS score and left hemisphere white matter volume ($R^2 = 0.72, P = 0.0001$). For TD controls, there remained a significant negative correlation between total PANESS score and primary motor cortex white matter volume in both the right ($R^2 = 0.30, P = 0.007$) and left ($R^2 = 0.23, P = 0.04$) hemispheres. Correlations in children with ADHD remained insignificant after controlling for FSIQ and TBV.

Multivariate regression analyses including all three groups of subjects (autism, ADHD and TD) revealed a significant effect of diagnosis on the correlation between total PANESS score and left motor cortex white matter volume ($P < 0.0001$). Separate two-group contrasts revealed that the correlation between total PANESS score and left motor cortex white matter volume in children with autism significantly differed from that in TD children ($P < 0.0001$) and that in children with ADHD ($P = 0.001$). The correlation in TD children and that in children with ADHD did not significantly differ.

**Analyses of correlations of other frontal regional white matter volumes with PANESS score**

To determine whether the findings were specific to the primary motor cortex, we examined correlations of PANESS scores with other frontal cortical regions, including prefrontal, premotor and anterior cingulate. For children with autism, a significant positive correlation was also observed between total PANESS score and left premotor white matter volume ($R^2 = 0.29, P = 0.02$) and this remained significant after controlling for FSIQ and TBV ($R^2 = 0.42, P = 0.05$); no correlations were seen for right premotor, or either hemisphere prefrontal or anterior cingulate volumes. For TD children and children with ADHD there were no significant correlations between PANESS scores and white matter volumes in any of the premotor, prefrontal or anterior cingulate regions.

**Discussion**

Consistent with our hypothesis, increased left motor and premotor white matter volumes were strong predictors of poor motor function in children with autism. The findings are in direct contrast to those seen in TD children, in whom increased white matter volume in both left and right motor cortex was associated with improved motor skills. The strength of these observations is evidenced by the fact that the correlations were significant both with and without covarying for FSIQ and TBV.

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** Independent linear regression analyses, covaried for FSIQ and TBV, demonstrating (A) for children with autism there is a robust positive correlation between total PANESS score and left motor cortex white matter volume ($R^2 = 0.72, P = 0.0001$), such that increased white matter volume predicts poorer motor skill. (B) In contrast, for typically developing children there is a significant negative correlation between total PANESS score and left motor cortex white matter volume ($R^2 = 0.23, P = 0.04$), such that increased white matter volume predicts better motor skill.
There were no differences in precentral white matter volume between children with autism and TD children; this is consistent with previously published precentral white matter findings in this age range (Herbert et al., 2004) and the more general observation that increased white matter volume is seen in younger, but not older, children with autism (Courchesne et al., 2001). Myelination in the precentral gyrus reaches maturity around 6 years of age (Kimen et al., 1988). It may be that for children with autism, abnormal white matter development in the precentral cortex occurs at a young age, contributing to motor dysfunction; TD children instead show a more gradual increase in precentral white matter development associated with improvement in motor dexterity, so that by late childhood no differences in volume are observed. Examination of correlations between motor function and white matter volume in younger children would help to address this hypothesis.

The association of increased motor white matter volumes and poor motor function appears to be specific to autism. This association was not observed in the clinical control group of children with ADHD, another developmental disorder in which impairments in motor execution and control are a common finding (Mostofsky et al., 2001, 2003; Klimkeit et al., 2005; Klein et al., 2006). Furthermore, the correlation between motor skill performance and left motor cortex white matter volume in children with autism significantly differed both from that in TD children and that in children with ADHD. In contrast, the correlation in children with ADHD did not significantly differ from that in TD children. The population of children with ADHD in this study showed higher total PANESS scores than TD controls at a level that only trended toward significance. Further evidence for the specificity of the association of increased motor cortex white matter volume with motor skill impairment in autism could come from examining other populations of children with motor skill impairment in autism could come from examining other populations of children with motor difficulties, for instance those with Developmental Coordination Disorder, as well as children with features otherwise related to autism, such as those with specific language impairments.

The findings provide insight into the pathophysiology of autism. Autism has been found to be associated with enlarged cerebral white matter volume, particularly in outer radiate regions (Courchesne et al., 2001; Herbert et al., 2004). Consistent with these neuroimaging findings, post-mortem studies of individuals with autism reveal abnormalities in cortical minicolumns that reflect a bias towards shorter connecting fibers, which are localized to radiate white matter, at the expense of longer fibers connecting distant cortical and cortical-subcortical regions (Casanova et al., 2006). The current findings for the first time demonstrate an association between increasing radiate white matter volume and functional impairment, in this case basic motor skill impairment. The strength of the correlation in autism, beyond that observed with normal biological variation in TD controls, suggests that it may be a defining biological feature of the disorder.

The observed association between increased white matter volume and functional impairment may be representative of global patterns of brain abnormality that not only contribute to motor dysfunction in autism, but also to deficits in socialization and communication that define the disorder. Investigators have proposed that the pattern of impairments associated with autism, as well as some relative strengths in perceptual processing, are secondary to abnormalities in structural and functional connectivity (Minshew et al., 1997; Herbert et al., 2004; Happé and Frith, 2006). Overgrowth of localized cortical connections and undergrowth of more distant connections between cerebral cortical regions and with subcortical structures (Herbert et al., 2004; Happé and Frith, 2006) have been hypothesized to result in impaired complex information processing (Minshew et al., 1997) and ‘weak central coherence’ (Shah and Frith, 1993) and may also contribute to impaired motor sequence learning necessary for development of complex motor skills and social/communicative gestures (Mostofsky et al., 2000; Ullman, 2004; Gidley Larson and Mostofsky, 2006; Walsenski et al., 2006). The measure of precentral white matter volume used in the present study likely principally comprised localized connections; it corresponded to white matter within the precentral gyrus, with deep subcortical white matter explicitly excluded. The findings in the present study therefore appear to lend support to the notion that increasing volume of localized cortical connections contributes to functional impairment in children with autism.

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