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Motor Circuit Anatomy in Children with Autism Spectrum Disorder With or Without Attention Deficit Hyperactivity Disorder

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Abstract

This study examined the morphology of frontal-parietal regions relevant to motor functions in children with autism spectrum disorder (ASD) with or without attention deficit hyperactivity disorder (ADHD). We also explored its associations with autism severity and motor skills, and the impact of comorbid ADHD on these associations. Participants included 126 school-age children: 30 had ASD only, 33 had ASD with ADHD, and 63 were typically developing. High resolution 3T MPRAGE images were acquired to examine the cortical morphology (gray matter volume, GMV, surface area, SA, and cortical thickness, CT) in three regions of interest (ROI): precentral gyrus (M1), postcentral gyrus (S1), and inferior parietal cortex (IPC). Children with ASD showed abnormal increases in GMV and SA in all three ROIs: (a) increased GMV in S1 bilaterally and in right M1 was specific to children with ASD without ADHD; (b) all children with ASD (with or without ADHD) showed increases in the left IPC SA. Furthermore, on measures of motor function, impaired praxis was associated with increased GMV in right S1 in the ASD group with ADHD. Children with ASD with ADHD showed a positive relationship between bilateral S1 GMV and manual dexterity, whereas children with ASD without ADHD showed a negative relationship. Our findings suggest that (a) ASD is associated with abnormal morphology of cortical circuits crucial to motor control and learning; (b) anomalous overgrowth of these regions, particularly S1, may contribute to impaired motor skill development, and (c) functional and morphological differences are apparent between children with ASD with or without ADHD.

Keywords

structural MRI; motor circuit; autism spectrum disorder; attention deficit hyperactivity disorder

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Introduction

Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorder with an estimated prevalence of 1 in 68 children [Centers for Disease Control and Prevention, CDC, 2014]. In addition to the core diagnostic features of deficits in social communication, and restricted and repetitive behaviors, children with ASD often present with motor abnormalities [Kanner 1968; Ghaziuddin & Butler, 1998; Miyahara et al., 1997; Szatmari, Archer, Fisman, Streiner, & Wilson, 1995; Vilensky, Damasio, & Maurer, 1981]. Prior studies of ASD have revealed abnormalities in both basic and postural motor control [Freitag, Kleser, Schneider, & von Gontard, 2007; Jansiewicz et al., 2006; Minshew, Sung, Jones, & Furman, 2004], and in imitation and execution of skilled or learned motor actions [Dziuk et al., 2007]. Impaired ability to perform skilled gestures on praxis examination (i.e., developmental dyspraxia), has been reported in children with ASD [Dowell, Mahone, & Mostofsky, 2009; Dziuk et al., 2007; MacNeil & Mostofsky, 2012; Mostofsky et al., 2006] and is hypothesized to be secondary to abnormalities of procedural/sequential learning mechanisms that lead to the formation of internal action models that guide the execution of learned skilled/complex motor actions [Dowell et al., 2009; Mostofsky & Ewen, 2011]. Motor system dysfunction may be recognized earlier in ASD than core diagnostic features such as communication deficits, thus may help with early intervention [Bhat, Galloway, & Landa, 2012]. Furthermore, the study of motor dysfunction may offer a potentially reliable and quantifiable way to elucidate the neural basis of altered developmental trajectories and the associated impairments in children with ASD.

Neuroimaging studies of developmental trajectories have delineated a pattern of anomalous brain development in children with ASD: an early rapid and pervasive increase in brain size in infancy and toddlerhood [Aylward, Minshew, Field, Sparks, & Singh, 2002; Carper, Moses, Tigue, & Courchesne, 2002; Courchesne, Campbell, & Solso, 2011; Hazlett et al., 2005; Herbert et al., 2004] followed by arrested development in later childhood and a potential decline in preadolescence into adulthood [Courchesne et al., 2007; Courchesne, Campbell, & Solso, 2011]. Regional variations (primarily increases) have been reported in ASD in gray matter (GM) and white matter (WM) in prefrontal cortices [Knaus, Tager-Flusberg, & Foundas, 2012], sensorimotor cortices [Herbert et al., 2003; Mostofsky, Burgess, & Gidley Larson, 2007; Rojas et al., 2006], temporal and posterior parietal regions [Ecker et al., 2013; Palmen et al., 2005], and subcortical structures including the basal ganglia [Estes et al., 2011; Qiu, Adler, Crocetti, Miller, & Mostofsky, 2010], and the cerebellum [Allen & Courchesne, 2003; Fatemi et al., 2012]. These regional increases in cortical volumes have been associated with a number of impairments, including those in motor control [Mostofsky et al., 2007].

In concert with aberrant cortical maturation in ASD, motor impairments may be associated with anomalous development within a frontal-parietal network crucial to sensorimotor control and learning, comprising primary motor (M1) and primary somatosensory (S1) cortices, as well as premotor cortex (PMC) and inferior parietal cortex (IPC). The perception-action coupling process subserved by this network involves communication of proprioceptive and haptic information from the afferent pathways to S1; which, in turn, is interconnected with motor and parietal association areas, in particular the IPC. The IPC,

which is also central to the mirror neuron system responsible for imitation, is involved in encoding spatio-temporal representations of movement; these representations are then trans-coded into action sequences in the PMC, needed for guidance of a motor command within M1. This process underlies the formation of internal action models which are maintained within a network of reciprocal connections between the PMC and IPC. These internal action models are important for guiding the execution of a wide array of behaviors ranging from simple motor actions (e.g., reaching and grasping) to complex motor/behavioral skills such as those used during social communication; they are also necessary to understanding the meaning of these actions as performed by others. This network is thereby central to learning movement patterns crucial to motor as well as social communicative skills. Consistent with this construct, several studies have suggested that dysfunction within this frontal-parietal network may be salient to ASD, contributing to autism-associated impairments in development of a range of skills, motor as well as social-communicative [above is reviewed at length in Mostofsky & Ewen, 2011].

Psychiatric comorbidity is frequent in ASD and the presence of these comorbidities may be relevant to abnormalities in sensorimotor development. In particular, attention deficit hyperactivity disorder (ADHD) is highly comorbid with ASD, with reported rates of 16–78% [Hanson et al., 2013; Murray, 2010]. ADHD itself is also associated with abnormalities in motor development such as slower and variable response latencies [Leth-Steensen, Elbaz, & Douglas, 2000], excessive motor overflow [Denckla & Rudel, 1978], and reduced response inhibition that may reflect immature motor circuitry [Cole, Mostofsky, Larson, Denckla, & Mahone, 2008; Gillberg, 2003; Moll, Heinrich, Trott, Wirth, & Rothenberger, 2000; Mostofsky, Newschaffer, & Denckla, 2003; Vaidya & Stollstorff, 2008; Wodka et al., 2007]. While studies directly comparing children with ASD and children with ADHD have revealed similar degrees of impairment in basic motor control, dyspraxia appears to be more specific to ASD compared to ADHD [Dewey, Cantell, & Crawford, 2007; MacNeil & Mostofsky, 2012]. Children with ADHD have been shown to have deficits in the execution of motor control as compared to children with ASD who specifically show deficits in motor learning [Gidley Larson & Mostofsky, 2008].

Unlike ASD, children with ADHD (without ASD) show cortical maturation that may be delayed by several years compared to typically developing (TD) children; however, typical cortical volumes may be attained by late adolescence or early adulthood [Shaw et al., 2007]. Neuroimaging studies of children with ADHD have revealed thinner cortices and smaller brain volumes when compared to TD children [Carmona et al., 2005; Shaw et al., 2007; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009], especially in prefrontal and premotor regions [Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002]. These regional changes have also been associated with impaired motor control and response control [Mostofsky & Simmonds, 2008; Suskauer et al., 2008]. Although, ASD and ADHD have a phenotypic overlap [Reiersen & Todd, 2008; Sinzig, Walter, & Doepfner, 2009; Stam, Schothorst, Vorstman, & Staal, 2009], it is unclear how the presence of comorbid ADHD may affect the brain development of children with ASD. Despite the high rates of comorbidity and divergent cortical development, there has been limited investigation of the relationship between the two—in one recent study [O'Dwyer et al., 2014], ASD symptoms were significantly elevated in ADHD subjects (without ASD) relative to both controls and

unaffected siblings; furthermore, increasing ASD score was associated with greater GM volume. To our knowledge, there is no current neuroimaging study that has examined the brain development in children with ASD with or without ADHD.

To investigate the motor circuit in ASD, the main objectives of this study were: (1) to examine the motor circuit anatomy in the frontal-parietal regions of interest (ROIs) known to be relevant to motor skill development: precentral gyrus (roughly corresponding to M1) and postcentral gyrus (roughly corresponding to S1), and the IPC; (2) to explore anatomical associations with severity of autistic features as well as motor skills in children with ASD; (3) to explore the effect of comorbid ADHD on these associations of ASD. We hypothesized increased surface area (SA) and GM volume (GMV) of sensorimotor regions in children with ASD, and that these increases will be associated with impairments in basic motor control and praxis, as well as core social communicative features of autism.

Methods

Subjects

A total of 126 children participated in the study, ages 8–12 years (mean age=10.4±1.4 years). Sixty-three were TD (9F; 52 right handed, 7 left handed, 4 mixed handed) children. Sixty-three children (9F; 52 right handed, 6 left handed, 5 mixed handed), had ASD; of these 33 had comorbid ADHD (ASD+ADHD; 4F; 27 right handed, 3 left handed, 3 mixed handed) and 30 did not have comorbid ADHD (ASD-only; 5F; 25 right handed, 3 left handed, 2 mixed handed). Sources of recruitment included advertisements posted in the community, local pediatricians' and psychologists' offices, local schools, and social service organizations and chapters of the Autism Society of America, the Interactive Autism Network database, outpatient clinics at Kennedy Krieger Institute, and word of mouth. This study was approved by the Johns Hopkins Medical Institutional Review Board. Written consent was obtained from a parent/guardian and assent was obtained from the participating child.

Psychopathology was assessed using the Diagnostic Interview for Children and Adolescents-IV, Parent version (DICA-IV) [Reich, Welner, & Herjanic, 1997]. The DICA-IV is a well-established semistructured measure for ascertaining DSM-IV psychiatric disorders in children and adolescents. It has strong psychometric properties and can measure current and past psychiatric diagnoses [Reich et al., 1997] None of the children had intellectual disability (ID), a seizure or other neurological disorder, any severe chronic medical disorder, a diagnosed genetic disorder, or a psychotic disorder. In the TD group, additional exclusions were any psychiatric disorder (except specific or social phobia), a speech and language disorder, and to preclude broader autism phenotype effects [Piven, Palmer, Jacobi, Childress, & Arndt, 1997], a family history of first-degree relatives with ASD.

Intellectual ability was assessed by the Wechsler Intellectual Scale for Children 4th edition, WISC-IV [Wechsler, 2003]. All TD subjects and 58 out of the 63 ASD subjects had a Full Scale IQ (FSIQ) ≥ 80. Two ASD-only and three ASD+ADHD subjects with a FSIQ below 80 were also included, as they had a Perceptual Reasoning Index (PRI) score of 85 or greater on WISC-IV. PRI is a measure of the nonverbal abilities, which are an area of strength for

children with ASD and may be a better measure of their cognitive abilities. This is in line with recommendations to individualize the measures best suited for the participants to get an accurate estimate of their cognitive abilities [Mottron, 2004]. One ASD-only subject completed only the PRI and Verbal Comprehension Index (VCI) sections of the WISC-IV; therefore, the full scale IQ was not calculated. Yet a comparable score, Wechsler General Ability Index (based off the VCI and PRI) was scored at 128; the subject was therefore included in the study.

ASD Diagnosis

Diagnosis of ASD was based on DSM-IV criteria (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000) and confirmed using the Autism Diagnostic Interview—Revised (ADI-R) [Lord, Rutter, & Le Couteur, 1994] and the Autism Diagnostic Observation Schedule—Generic (ADOS-G) [Lord et al., 2000] module 3, administered by a master's level or higher research reliable psychologists. All participants met criteria for ASD based on the ADOS-G or ADI-R and the clinical impression of a child neurologist with extensive experience in autism diagnosis (S.H.M.). Two families did not complete the ADI-R; their inclusion in the ASD group was solely based on the ADOS-G and clinical impression.

Four subjects (one ASD-only, three ASD+ADHD) completed the more recent Autism Diagnostic Observation Schedule—Second Edition (ADOS-2) [Lord et al., 2012] instead of the ADOS-G. To create comparable ADOS total scores, two categories from the ADOS-G (1: insight part of the Social Interaction subscore and 2: compulsions part of the Stereotyped and Restricted Behaviors subscore) were also assessed in these four subjects. Additionally, amount of reciprocal social communication (part of the Social Affect subscore) in the ADOS-2 was not included in the calculation of the ADOS total score. The ADOS total score was then recalculated to match the ADOS-G total score.

ADHD Diagnosis

Comorbid diagnosis of ADHD was based on DSM-IV criteria using DICA-IV [Reich et al., 1997]. Further, ADHD-specific standardized rating scales commonly used in clinical and research settings were also administered to assess for ADHD symptoms. These included the Conners' Parent and Teacher Rating Scales-Revised, Long Version (CPRS-R and CTRS-R) [Conners, Sitarenios, Parker, & Epstein, 1998] and the ADHD Rating Scale-IV, home and school versions (ADHD-RS) [DuPaul, Power, Anastopoulos, & Reid, 1998]. A comorbid ADHD diagnosis was confirmed by the following criteria: (1) an ADHD diagnosis on the DICA-IV and (2) a *T*-score of 60 or higher on scale L (DSMIV: inattentive) and/or M (DSM-IV: hyperactive-impulsive) on the CPRS-R:L or CTRS-R:L, when available, or a score of 2 or 3 on at least 6/9 items on the Inattentive and/or Hyperactivity/Impulsivity scales of the ADHD-RS. Final confirmation was based on clinical judgment of the investigators. In the ASD+ADHD group, 23 subjects met criteria for Combined Type (2F), 3 subjects met criteria for Hyperactive-Impulsive Type (1F), and 7 met criteria for Inattentive Type (1F).

Psychiatric Comorbidity and Psychotropic Medications

Presence of other comorbid psychiatric disorders was also assessed using the DICA-IV. Of the 63 subjects in the ASD group (ASD-only and ASD+ADHD), 23 met criteria for oppositional defiant disorder, 5 for generalized anxiety disorder, 16 for specific or social phobia, and 4 for obsessive-compulsive disorder. Five subjects met criteria for a past episode of major depressive disorder. None met for somatization, hypomania/mania, or psychosis currently or in the past. None, except two TD subjects had any psychiatric diagnosis: one met for simple phobia (being alone), the other had specific phobias (spiders, the dark, and thunderstorms). These subjects were included in the TD group as the phobias were circumscribed and they were not thought to have a severe anxiety disorder.

Subjects in the ASD-only and ASD+ADHD groups on prescribed psychotropic medications at the time of assessment, were as follows: stimulant medications (methylphenidate, dexmethylphenidate, amphetamine salts): 18 ASD whole group (3 ASD-only, 15 ASD +ADHD), antidepressants (fluoxetine, sertraline, citalopram, escitalopram, and bupropion): 13 ASD whole group (7 ASD only, 6 ASD+ADHD), antipsychotics (only risperidone): 3 ASD whole group (2 ASD-only and 1 ASD+ADHD), alpha agonists (only clonidine): 1 ASD-only, and others (atomoxetine: 2 ASD whole group, 1 ASD-only, and 1 ASD+ADHD; Lithium: 1 ASD-only). None were on anticonvulsants or benzodiazepines. None of the TD subjects were on prescribed psychotropic medications. To avoid effects on cognitive and behavioral measures, stimulant medications were discontinued the day prior to and the day of testing. Participants were, however, allowed to continue treatment with other psychotropic medications that would normally require a longer washout period, for both ethical and practical reasons.

Motor Assessment

Basic motor control was assessed using the Movement Assessment Battery for Children—Second Edition (MABC-2) [Henderson, Sugden, & Barnett, 2007]. MABC-2 is a widely used measure to identify and describe motor impairments in children 3–17 years of age. It is composed of two parts: the Performance Test and The Checklist. The Performance Test further includes series of fine and gross motor tasks in three categories—manual dexterity (three items), aiming and catching (two items), and balance (three items). Items from each component are scored and then transformed into standard scores. The Checklist is a parent/other adult rating of motor competence on a 30-item scale (see Brown & Lalor, [2009] for further details). Only the Performance Test was used in the study. Eighty participants (40 TD, 6F; 20 ASD-only, 4F; 20 ASD+ADHD, 2F) completed the Performance Test. The ASD subgroups were matched on age, PRI (WISC-IV), socioeconomic status (SES), and handedness.

A version of the Florida Apraxia Battery [Rothi et al., 1997], modified for children [Mostofsky et al., 2006], was used to assess ability to perform skilled gestures (Praxis). Children had to perform skilled gestures in the response to three different standardized verbal prompts: verbal command (gesture to command, GTC), imitation of the examiner performing the gesture (gesture to imitation, GTI), and actual tool use in response to the tool being placed on the table (gesture with tool use, GTU). Each subject's examination was

video recorded and later scored independently by two raters, both blinded to diagnosis. There were 25 GTC items, 34 GTI items, and 17 GTU items that were each evaluated for the occurrence of errors (See Dowell et al., [2009] for a detailed summary of errors). Inter-rater reliability of at least 80% was achieved for each subject. Average total errors were used to assess praxis performance. (For comprehensive descriptions of the modified praxis examination, scoring methodology, and reliability data, references Mostofsky et al., [2006] and Dziuk et al., [2007].)

MRI Image Acquisition and Processing

Before each scanning session, all participants underwent a practice (mock scan) session to acquaint them with the scanner and the scanning environment. The practice session consisted of an abridged version of the actual scanning protocol (sliding into the scanner, wearing ear plugs, hearing loud magnetic resonance imaging (MRI) scanner noises, and being alone in the scanner for 10 min). An instructor trained the child until he/she was willing to be alone in the mock scanner room and lie still comfortably.

All scanning was completed using a 3.0T Philips GyroscanNT scanner. High resolution magnetization prepared rapid acquisition by gradient echo (MPRAGE) images (Slice thickness=1.0mm; FOV=26cm; Matrix size: 256×256) were acquired on all subjects used for anatomical segmentation. Cortical reconstruction and volumetric segmentation was performed with the Free-Surfer image analysis suite, (available at http://surfer.nmr.mgh.harvard.edu/); the technical details of these procedures are available in prior publications: Fischl, Sereno, & Dale [1999] and Dale, Fischl, & Sereno [1999]. Free-Surfer morphometric procedures have good test-retest reliability across scanner manufacturers and across field strengths. Atlas-based ROIs and total cerebral volume measurements were obtained using FreeSurfer [Fischl et al., 2004]. The Desikan Killiany (DK) atlas was used to extract the cortical measures of interest [Desikan et al., 2006]. Three ROIs associated with the motor circuitry that involves the frontal-parietal networks were chosen for the regional measurements. These included the precentral gyrus (roughly, M1), the postcentral gyrus (roughly, S1), and the IPC bilaterally. The DK atlas does not include a PMC ROI but rather includes large anatomically defined frontal lobe ROIs that combine multiple functional subregions, therefore, a PMC ROI was not included in this analysis. Cortical thickness (CT), GMV, and SA were extracted using FreeSurfer and were used as measures of cortical morphometry in these regions.

Statistical Analysis

Separate MANCOVAs for GMV, SA, and CT were used to examine the effect of diagnosis (TD, ASD-only, and ASD+ADHD) across the three motor control ROIs (M1, S1, and IPC) while controlling for age and total brain volume (TBV). Age and TBV were used as covariates due to established findings on age dependent changes in brain volume and increased brain volume in children with autism in this age range. Given findings of left hemispheric abnormalities in autism, ROIs were also divided by hemisphere to explore any laterality of the findings [Dziuk et al., 2007; Escalante-Mead, Minshew, & Sweeney, 2003a; Kleinhans et al., 2008; Mostofsky et al., 2006]. Planned post hoc comparisons included TD vs. ASD-only, TD vs. ASD+ADHD, and ASD-only vs. ASD+ADHD. Pearson correlations

were used to better understand the behavioral significance of differences observed in cortical morphology. Motor relevant ROIs that showed diagnostic differences unique to the ASD-only group (S1 GMV only) were used in the correlation analysis with motor control and symptom severity. In line with the goal of the study, correlations were limited to the ASD-only and ASD+ADHD group to investigate the association between motor-relevant ROIs and behavior in autism. A regression analysis was conducted to test the association between ROIs with significant group effects and ADOS-total score, with Akaike information criterion (AIC) used to test quadratic vs. linear fit. Due to the exploratory goal of the correlation analysis, we did not correct for multiple comparisons. IBM SPSS Statistical Version 20 (IBM, Chicago) was used for the statistical analyses.

Results

Demographic Information and Other Characteristics

Please see Table 1 for details. There were no significant group differences in age, gender, racial composition, SES, handedness, and PRI on WISC-IV.

ROI Analysis

The GMV MANCOVA (P=0.023) and the SA MANCOVA (P=0.005) revealed a significant overall effect of diagnosis (ASD > TD). Region-wise, a significant effect of diagnosis was noted on some of the ROIs (ASD > TD). For **GMV** MANCOVAs, this included only the *right M1* (P=0.023), and *left S1* (P=0.007). A marginal effect of diagnosis was noted on *left IPC* (P=0.066). The rest of the regions (left M1: P=0.147; right S1: P=0.114; and right IPC: P=0.520) did not show a significant effect of diagnosis on GMV.

For **SA** MANCOVAs, a significant effect of diagnosis (ASD>TD) was noted on the *right M1* (P=0.015), the *left M1* (P=0.038), and the *left IPC* (P=0.005). A marginal effect of diagnosis was noted on the *left S1* (P=0.067) only. The rest of the regions (right S1: P=0.51; and right IPC: P=0.132), did not reveal a significant effect of diagnosis.

The **CT** MANCOVA did not show a significant effect of diagnosis, (P=0.106). There was, in addition, no significant effect of diagnosis on CT in any of the ROIs (left M1: P=0.366; right M1: P=0.441; left S1: P=0.440; right S1: P=0.101; left IPC: P=0.106; and right IPC: P=0.147).

Further region-wise results for the GMV and SA are as below; also see Figure 1; Post hoc Analysis.

Table 2 summarizes the post hoc analysis findings. Planned post hoc analyses revealed the following:

a. Precentral Gyrus—For **GMV**, TD vs. ASD-only contrast (ASD-only> TD; P=0.007) and the ASD-only vs. ASD+ADHD contrast (ASD-only>ASD+ADHD; P=0.048) were both significant for *right M1*. A marginally significant effect of diagnosis was observed in *left M1* (ASD+ADHD>TD; P=0.066). No other comparisons were significant (P > 0.21).

For **SA**, the TD vs. ASD-only contrast was significant for *right M1* (ASD-only>TD; P=0.011), while TD vs. ASD+ADHD contrast was significant for *left M1* (ASD +ADHD>TD; P=0.004). No other comparisons were significant (P>0.16).

b. Postcentral Gyrus—For **GMV**, TD vs. ASD-only contrast (ASD-only> TD; P=0.004) and the ASD-only vs. ASD+ADHD contrast (ASD-only>ASD+ADHD; P=0.007) were both significant for *left S1*. A marginal effect of diagnosis, which was similar to left S1 GMV results, was apparent for *right S1* GMV (ASD-only>TD; P=0.056; ASD-only> ASD +ADHD; P=0.072). No other comparisons were significant (P > 0.8).

For **SA**, TD vs. ASD-only contrast was significant for *left S1* (ASD-only>TD; P=0.028), while ASD-only vs. ASD+ADHD contrast was marginally significant for *left S1* (ASD-only>ASD+ADHD; P=0.058). No other comparisons were significant (P>0.33).

c. Inferior Parietal Cortex—For **GMV**, the TD vs. ASD+ADHD contrast was significant only for the left IPC, (ASD+ADHD>TD; P=0.032). No other comparisons were significant (P>0.11).

For **SA**, the TD vs. ASD-only (ASD-only>TD; P=0.032) and the TD vs. ASD+ADHD (ASD+ADHD>TD; P=0.002) contrasts were both significant for *left IPC*. TD vs. ASD-only (ASD-only>TD; P=0.047) contrast was significant for the *right IPC*. No other comparisons were significant (P>0.32).

Association of GMVs With Basic Motor Control and Praxis—In line with the aim of this study, to understand brain-behavior associations for motor impairment particular to ASD and ASD+ADHD, we investigated the association between motor control and the ASD-only specific finding that emerged from the 3-groups analyses: *increased S1 GMV*. Pearson correlations were used to test for associations between S1 GMV and motor control using the MABC-2 and Praxis. Although right S1 GMV showed marginally significant differences, left and right S1 were combined into a single ROI when testing the association between S1 GMV and MABC-2's manual dexterity score due to the mixed-handed nature of the groups as well as the similarity in the diagnostic effects seen in left and right S1 GMV.

The ASD-only group showed a significant negative relationship between bilateral S1 GMV and the manual dexterity MABC-2 subscore (Fig. 2; r=−0.520, P=0.032); no other correlations were significant. In contrast, the ASD+ADHD group showed a significant positive relationship between bilateral S1 GMV and the manual dexterity subscore on the MABC-2 (r=0.40, P=0.036); none of the other scores were significant.

The ASD+ADHD group showed a significant correlation between right S1 GMV and Praxis total score (r=−0.370, P=0.044); no relationship was observed for left S1 GMV (r=−0.156, P=0.41). Follow-up analyses in the ASD+ADHD group using the Praxis subscores revealed a similar trend across all subscores; GTC (r=−0.343, P=0.055), GTI (r=−0.334, P=0.071), and GTU (r=−0.359, P=0.051). The ASD-only group did not show a significant association between the Praxis total score and left or right S1 (P>0.3), therefore a follow-up analysis on S1 GMV associations with Praxis subscores was not conducted.

Association of Brain Volumes With Symptom Severity—The ASD-only group also showed a U-shaped/parabolic relationship (Fig. 3) between left S1 GMV and ADOS total score, such that increasing ADOS scores were associated with deviations from the TD mean GMV in the left S1 (r=0.503, P=0.022). A quadratic fit was a better fit for the data (quadratic fit AIC=76.31, linear fit AIC=79.83). This approach is in line with other studies of complex brain development where there may be a variation, for example, in CT with age [Shaw et al., 2008]. The ASD+ADHD group did not show a significant relationship, linear or quadratic, between the post-central gyrus and ADOS total score.

Discussion

Consistent with previous studies and our hypothesis, we found significant increases in cortical GMV and SA across frontal-parietal regions comprising a network crucial to motor control and learning (M1, S1, and IPC) in children with ASD as compared to TD children. Furthermore, to our knowledge, this was the first study to have examined the effects of comorbid ADHD upon the morphology of this network in ASD. Increased GMV and SA in left S1 were found to be specific to ASD children without comorbid ADHD, whereas increased GMV and SA in the left IPC were seen in children with ASD irrespective of the presence of comorbid ADHD. For M1, the presence of comorbid ADHD impacted the laterality of the findings, such that children with ASD without comorbid ADHD showed increased GMV and SA in the right M1, while those with ASD and comorbid ADHD had increased GMV and SA in the left hemisphere. Further details of the findings are discussed below.

Cortical Metrics

While GMV and SA were consistently larger in children with ASD, surprisingly, we did not observe any differences in CT. Prior studies [reviewed in Shaw et al., 2011] examining CT in ASD have reported conflicting findings, with some revealing no differences in CT [Ecker et al., 2013; Raznahan et al., 2010], some revealing increased CT, [Hardan, Muddasani, Vemulapalli, Keshavan, & Minshew, 2006] and others revealing decreased CT [Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Hardan, Libove, Keshavan, Melhem, & Minshew, 2009]. The discrepancies in CT findings might be due to age, with older adolescents and adults showing a decline in CT, and the regions studied [Wallace, Dankner, Kenworthy, Giedd, & Martin, 2010]. Increases in cortical SA in ASD have been suggested to be associated with increased gyrification [Courchesne, Campbell, & Solso, 2011; Hardan, Jou, Keshavan, Varma, & Minshew, 2004] as well as increased underlying WM volume [Hardan et al., 2004; Zikopoulos & Barbas, 2010], which may reflect distinct genetic and epigenetic processes as compared to CT [Winkler et al., 2010]. SA is thought to reflect the number of ontogenetic columns in a cortical region during neuronal migration in early brain development; CT, on the other hand, may be a reflection of the number of cells within a column [Rakic, 1988]. Although, cortical volume depends upon both SA and CT (cortical volume=SA×CT), SA expansion is the principal driving factor in cortical volume after 2 years of age in children, with 97% of adult CT attained by 2 years of age as compared to 69% of that for SA [Lyall et al., 2014]. By 8–12 years of age, both TD and ASD children have reached peak CT and show signs of cortical thinning whereas SA continues to increase

into adolescence [Ecker et al., 2013; Shaw et al., 2012]. Our CT findings may, thus, be a reflection of the age of the participants who may have attained peak CT, before thinning in adolescence, while the SA may still be on the increase.

Precentral Gyrus

Children with ASD (i.e., both with and without ADHD) showed increased M1 GMV and SA. This finding is consistent with other studies [Ecker et al., 2013] that have found similar increases in M1 in ASD. The findings are also in line with previous evidence of autism-associated functional disorganization of M1, including atypical functional connectivity patterns [Nebel, Eloyan, Barber, & Mostofsky, 2014; Nebel, et al., 2014], as well as an anomalous association between increased M1 WM volume and impairments in basic motor control [Mostofsky et al., 2007]. Additionally, given the extensive cortical and subcortical connections (as with cerebellum and basal ganglia), this disorganization of the M1 may affect modulation of voluntary action as well as repetitive behaviors and other complex motor abnormalities (such as involving a dysfunction of the fronto-cerebello-thalamo-frontal network) [Nobile et al., 2011].

There was a laterality effect of comorbid ADHD on the M1 findings. For children with ASD without ADHD, increases in M1 GMV and SA were localized to the right hemisphere, in contrast to ASD children with comorbid ADHD who showed increases in SA only in the left hemisphere. This finding highlights the need to carefully investigate ADHD symptoms in children with ASD, particularly, in light of previous reports of disproportionate left sided GMV enlargement in ASD [Hazlett et al., 2005]; the results in this study may accord with abnormal brain lateralization and atypical cerebral dominance reported in ASD [Dawson, Warrenburg, & Fuller, 1982; Escalante-Mead et al., 2003a; Escalante-Mead, Minshew, & Sweeney, 2003b]. Such lateralized abnormalities may affect interhemispheric communication as well as normal hemispheric specialization of their functions. Thus, more significant right hemispheric cortical volume increases, implying greater dysfunction, may cause greater visuospatial processing abnormalities such as lack of awareness of peripersonal space, as well as dysprosody and limited affective tone in communication [McKelvey, Lambert, Mottron, & Shevell, 1995; Ozonoff & Miller, 1996]. Greater left hemispheric increases, on the other hand, may imply greater motor skill abnormalities—in basic motor skills, execution of motor actions as well as in praxis, and via parallel connections involving prefrontal lobe, abnormalities in language, socialization and Theory of Mind [reviewed in Mostofsky and Ewen, 2011]. Future investigations may shed more light on the possible functional consequences of comorbid disorders (including ADHD) on such laterality differences in children with ASD.

Inferior Parietal Cortex

This is the first study, to our knowledge, to specifically examine for autism-associated abnormalities in IPC structure. This, despite the well-established role of the IPC in motor imitation and praxis, both of which have been consistently found to be impaired in children with ASD [Bernier, Dawson, Webb, & Murias, 2007; Dewey et al., 2007; Dowell et al., 2009; Dziuk et al., 2007; Jones & Prior, 1985; MacNeil & Mostofsky, 2012; Mostofsky et al., 2006; Rogers, Bennetto, McEvoy, & Pennington, 1996; Stieglitz Ham et al., 2011;

Vanvuchelen, Roeyers, & De Weerdt, 2007; Vivanti, Nadig, Ozonoff, & Rogers, 2008]. The IPC is identified as a core node in the mirror-neuron system, important for motor imitation, but is more generally understood to be fundamental to the visuomotor processing stream necessary to translating visual inputs into motor outputs [Cisek & Kalaska, 2010; Mostofsky & Ewen, 2011]; it is thereby crucial to development of a wide range of visuomotor skills. Our finding of IPC abnormality that was localized to the left hemisphere, in both ASD groups, is thereby consistent not only with impaired praxis and imitation in autism, but also with reported difficulty with adjusting reach-to-grasp movements in response to visual input [Fabbri-Destro, Cattaneo, Boria, & Rizzolatti, 2009] along with a tendency to discount visual input when learning novel movement patterns [Haswell, Izawa, Dowell, Mostofsky, & Shadmehr, 2009; Izawa et al., 2012].

Post-Central Gyrus

In contrast to differences observed in the IPC, increases in S1 GMV and SA were specific to ASD children without comorbid ADHD. S1, is crucial to representation of haptic and proprioceptive feedback, receiving sensory information via afferent pathways. Consistent with these findings, recent research has revealed that children with ASD show differences in tactile discrimination [Blanche, Reinoso, Chang, & Bodison, 2012; Tomchek & Dunn, 2007], and an atypical over-reliance on proprioceptive, instead of visual, feedback when learning a novel movement pattern [Haswell et al., 2009; Izawa et al., 2012].

Post-Central Gyrus Volume, Autism Severity, and Motor Functions

Our examination of brain-behavior correlations revealed that left S1 volume was associated with autism symptom severity. ADOS total score was observed to have a quadratic relationship with S1 GMV (Fig. 3), such that the GMVs closer to the TD mean (10,980mm^3; SD 1316) were associated with lower symptom severity; this association was specific to the left S1 in ASD children without comorbid ADHD. Although overall, this group's GMV was significantly larger than the TD group's, there were some subjects with a GMV lower than the TD group's mean; the total ADOS scores for these children (with lower than TD GMV) were similar to those with GMV greater than TD group mean. Thus, it may be inferred that variation from the TD mean in S1 GMV, especially in the left hemisphere, may be associated with severity of core deficits of ASD; these may also reflect the left hemispheric dysfunction that has been associated with both impairments in language [Escalante-Mead et al., 2003a, 2003b] and praxis [Dziuk et al., 2007; Kleinhans et al., 2008; Mostofsky et al., 2006] in children with ASD. It follows that increased left S1 GMV may be associated with an over-representation of proprioceptive information during motor learning, with resulting impairments in acquisition of skilled behaviors (dyspraxia) crucial to motor, as well as social-communicative functions.

Our examinations of motor control associations with S1 GMV revealed difference between the ASD groups. In the ASD with ADHD group, impaired praxis was associated with increased right S1 GMV; no association was observed in the ASD group without ADHD. In contrast, both ASD groups showed a significant yet divergent association between bilateral S1 GMV and manual dexterity. For children with ASD-only, larger S1 GMV was associated with poorer motor dexterity, again suggesting that autism-associated overgrowth within S1

may contribute to impaired motor development. In contrast, for children with ASD with ADHD, larger S1 GMV was associated with better motor dexterity, raising the question whether, in the context of comorbid ADHD, impaired basic motor control may be associated with merely delayed cortical maturation with limited cortical disorganization as has been reported in children with ADHD only [Shaw et al., 2007; Vaidya & Stollstorff, 2008].

Effects of Comorbid ADHD

As discussed above, the effects of comorbid ADHD on the motor circuit in children with ASD are, varied. S1, in particular, showed the greatest effect of comorbid ADHD both upon the morphology and in associations with measures of motor control and symptom severity. One could posit a potentially "protective" effect of co-occurrence of ADHD in children with ASD (in other words, the delayed cortical maturation in ADHD may moderate the effect of greater cortical disorganization in ASD). Conversely, given the remarkable neurogenetic and clinical heterogeneity of autism, it may be more likely that ASD with comorbid ADHD may signify an independent neuroendophenotype as has been proposed in several studies [Reiersen & Todorov, 2011; Sinzig et al., 2009; Smalley et al., 2002]. That the Connors scale total T-scores (Table 1) are not notably different in children with ASD with ADHD (70) as compared to children with ASD only (64) also appears consistent with this possibility. Approaches such as imaging genomics focused on neurodevelopmental endophenotypes may potentially shed more light upon such findings in the future.

Our study adds to the ever-increasing evidence for abnormal brain developmental trajectories in children with ASD and the effect of a common psychiatric comorbidity. This study has a moderately large cohort size, although, even larger cohorts of the specific subgroups, would be needed to confirm these findings. The use of gold standard diagnostic instruments for ASD diagnosis, and standardized measures for confirming diagnoses of ADHD and assessment of basic and more complex motor control are strengths of the study. Further, we focused on the anatomy of a particular circuit rather than the whole brain, to correlate the neuroimaging findings with a measurable clinical effect, i.e., motor functioning, which has a well-defined neural circuit; thus, our findings have implications at the anatomical/neuropathological, neural circuits, and clinical/behavioral levels.

Like other similar studies, the subjects are all high functioning with FSIQ in at least the average range; therefore, this data may not be directly applicable to lower functioning children in the intellectually disabled range. Additionally, the ROI approach, while useful for addressing specific brain-behavior hypotheses, may also limit the specificity of our findings, with more localized changes obscured within the regional analyses. Future voxel-based analyses may help further shed light on more localized changes. The study is also limited in not including PMC due to the absence of a functionally defined region in the DK atlas, thus allowing for a partial investigation into the frontal-parietal network crucial for sensorimotor control; the use of other atlases with well-defined premotor region [such as the Ranta frontal atlas; Ranta et al., 2014] may allow for investigation of PMC. Furthermore, our data captures a limited age range of preadolescents between the ages of 8–12 years, thus limiting generalization to all ages; conversely, this may also be a strength, from the perspective of capturing findings in specific developmental age groups.

In essence, the effect of ADHD on cortical development, particularly motor circuits, is still not fully understood and deserves more research in order to understand the variability within the ASD diagnosis. Whether ASD and ADHD are phenomenologically co-occurring heterotypic psychiatric disorders [Angold, Costello, & Erkanli, 1999]; as is frequently assumed in ASD comorbidity studies [Matson & Nebel-Schwalm, 2007], with separate etiopathophysiological pathways or if there is a unique endophenotype, characterized by features of both ASD and ADHD [Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008], remains an area of ongoing and future research.

Conclusions

Consistent with our hypothesis, we found that school-age children with ASD showed abnormal morphology of cortical regions crucial to motor control and learning, with increases in both GMV and SA. Furthermore, the presence of comorbid ADHD impacted regional cortical morphology within these frontal-parietal regions. While regional increases in the IPC GMV (ASD>TD) were observed in children with ASD regardless of the co-occurrence of ADHD, this was not the case for S1 in which increases in GMV were specific to children with ASD-only. This increase in S1 GMV was particularly relevant to altered motor function in children with ASD. Increased S1 GMV was associated with impaired praxis, but better manual dexterity in children with ASD with ADHD. The findings thereby suggest that ASD is associated with altered development of cortical circuits crucial to motor control and learning and that anomalous overgrowth of these regions, particularly S1, may contribute to impaired motor skill development. These structural and functional differences suggest that the presence of comorbid ADHD in children with ASD may possibly be an independent neuroendophenotype.

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References

Allen G, Courchesne E. Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: An fMRI study of autism. The American Journal of Psychiatry. 2003; 160:262–273. [PubMed: 12562572]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4). 2000; text rev. doi: 10.1176/appi.books.9780890423349

Angold A, Costello EJ, Erkanli A. Comorbidity. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 1999; 40:57–87.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. Neurology. 2002; 59:175–183. [PubMed: 12136053]

Bernier R, Dawson G, Webb S, Murias M. EEG mu rhythm and imitation impairments in individuals with autism spectrum disorder. Brain and Cognition. 2007; 64:228–237. DOI: 10.1016/j.bandc.2007.03.004 [PubMed: 17451856]

Bhat AN, Galloway JC, Landa RJ. Relation between early motor delay and later communication delay in infants at risk for autism. Infant Behavior & Development. 2012; 35:838–846. DOI: 10.1016/j.infbeh.2012.07.019 [PubMed: 22982285]

Blanche EI, Reinoso G, Chang MC, Bodison S. Proprioceptive processing difficulties among children with autism spectrum disorders and developmental disabilities. The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association. 2012; 66:621–624. DOI: 10.5014/ajot.2012.004234 [PubMed: 22917129]

Brown T, Lalor A. The movement assessment battery for children--Second edition (MABC-2): A review and critique. Physical & Occupational Therapy in Pediatrics. 2009; 29:86–103. DOI: 10.1080/01942630802574908 [PubMed: 19197761]

Carmona S, Vilarroya O, Bielsa A, Trèmols V, Soliva JC, Rovira M, et al. Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. Neuroscience Letters. 2005; 389:88–93. DOI: 10.1016/j.neulet.2005.07.020 [PubMed: 16129560]

Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: Early hyperplasia and abnormal age effects. NeuroImage. 2002; 16:1038–1051. [PubMed: 12202091]

Cisek P, Kalaska JF. Neural mechanisms for interacting with a world full of action choices. Annual Review of Neuroscience. 2010; 33:269–298. DOI: 10.1146/annurev.neuro.051508.135409

Cole WR, Mostofsky SH, Larson JCG, Denckla MB, Mahone EM. Age-related changes in motor subtle signs among girls and boys with ADHD. Neurology. 2008; 71:1514–1520. DOI: 10.1212/01.wnl.0000334275.57734.5f [PubMed: 18981373]

Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. Journal of Abnormal Child Psychology. 1998; 26:257–268. [PubMed: 9700518]

Courchesne E, Campbell K, Solso S. Brain growth across the life span in autism: Age-specific changes in anatomical pathology. Brain Research. 2011; 1380:138–145. DOI: 10.1016/j.brainres.2010.09.101 [PubMed: 20920490]

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, et al. Mapping early brain development in autism. Neuron. 2007; 56:399–413. DOI: 10.1016/j.neuron.2007.10.016 [PubMed: 17964254]

Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage. 1999; 9:179–194. DOI: 10.1006/nimg.1998.0395 [PubMed: 9931268]

Dawson G, Warrenburg S, Fuller P. Cerebral lateralization in individuals diagnosed as autistic in early childhood. Brain and Language. 1982; 15:353–368. [PubMed: 7074350]

Denckla MB, Rudel RG. Anomalies of motor development in hyperactive boys. Annals of Neurology. 1978; 3:231–233. DOI: 10.1002/ana.410030308 [PubMed: 666263]

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage. 2006; 31:968–980. DOI: 10.1016/j.neuroimage.2006.01.021 [PubMed: 16530430]

Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, & Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years - Autism and developmental disabilities monitoring network, 11 sites, United States, 2010. Morbidity and Mortality Weekly Report Surveillance Summaries (Washington, DC: 2002). 2014; 63:1–21.

Dewey D, Cantell M, Crawford SG. Motor and gestural performance in children with autism spectrum disorders, developmental coordination disorder, and/or attention deficit hyperactivity disorder. Journal of the International Neuropsychological Society. 2007; 13(2):246–256. DOI: 10.1017/S1355617707070270 [PubMed: 17286882]

Dowell LR, Mahone EM, Mostofsky SH. Associations of postural knowledge and basic motor skill with dyspraxia in autism: Implication for abnormalities in distributed connectivity and motor learning. Neuropsychology. 2009; 23:563–570. DOI: 10.1037/a0015640 [PubMed: 19702410]

DuPaul, G., Power, T., Anastopoulos, A., Reid, R. ADHD rating scale-IV. New York: Guilford Press; 1998.

Dziuk MA, Gidley Larson JC, Apostu A, Mahone EM, Denckla MB, Mostofsky SH. Dyspraxia in autism: Association with motor, social, and communicative deficits. Developmental Medicine and

Child Neurology. 2007; 49:734–739. DOI: 10.1111/j.1469-8749.2007.00734.x [PubMed: 17880641]

Ecker C, Ginestet C, Feng Y, Johnston P, Lombardo MV, Lai MC, et al. Brain surface anatomy in adults with autism: The relationship between surface area, cortical thickness, and autistic symptoms. JAMA Psychiatry. 2013; 70:59–70. DOI: 10.1001/jamapsychiatry.2013.265 [PubMed: 23404046]

Escalante-Mead PR, Minshew NJ, Sweeney JA. Abnormal brain lateralization in high-functioning autism. Journal of Autism and Developmental Disorders. 2003a; 33:539–543. [PubMed: 14594334]

Escalante-Mead PR, Minshew NJ, Sweeney JA. Abnormal brain lateralization in high-functioning autism. Journal of Autism and Developmental Disorders. 2003b; 33:539–543. [PubMed: 14594334]

Estes A, Shaw DWW, Sparks BF, Friedman S, Giedd JN, Dawson G, et al. Basal ganglia morphometry and repetitive behavior in young children with autism spectrum disorder. Autism Research: Official Journal of the International Society for Autism Research. 2011; 4:212–220. DOI: 10.1002/aur.193 [PubMed: 21480545]

Fabbri-Destro M, Cattaneo L, Boria S, Rizzolatti G. Planning actions in autism. Experimental Brain Research. 2009; 192:521–525. DOI: 10.1007/s00221-008-1578-3 [PubMed: 18839160]

Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, et al. Consensus paper: Pathological role of the cerebellum in autism. Cerebellum (London, England). 2012; 11:777–807. DOI: 10.1007/s12311-012-0355-9

Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. NeuroImage. 1999; 9:195–207. DOI: 10.1006/nimg.1998.0396 [PubMed: 9931269]

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cerebral Cortex (New York, NY : 1991). 2004; 14:11–22.

Freitag CM, Kleser C, Schneider M, von Gontard A. Quantitative assessment of neuromotor function in adolescents with high functioning autism and Asperger Syndrome. Journal of Autism and Developmental Disorders. 2007; 37:948–959. DOI: 10.1007/s10803-006-0235-6 [PubMed: 17171541]

Ghaziuddin M, Butler E. Clumsiness in autism and Asperger syndrome: A further report. Journal of Intellectual Disability Research. 1998; 42(Pt 1):43–48. [PubMed: 9534114]

Gidley Larson JC, Mostofsky SH. Evidence that the pattern of visuomotor sequence learning is altered in children with autism. Autism Research. 2008; 1:341–353. DOI: 10.1002/aur.54 [PubMed: 19360689]

Gillberg C. Deficits in attention, motor control, and perception: A brief review. Archives of Disease in Childhood. 2003; 88:904–910. [PubMed: 14500312]

Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H. Anatomical differences in the mirror neuron system and social cognition network in autism. Cerebral Cortex (New York, NY: 1991). 2006; 16:1276–1282. DOI: 10.1093/cercor/bhj069

Hanson E, Cerban BM, Slater CM, Caccamo LM, Bacic J, Chan E. Brief report: Prevalence of attention deficit/hyperactivity disorder among individuals with an autism spectrum disorder. Journal of Autism and Developmental Disorders. 2013; 43:1459–1464. DOI: 10.1007/s10803-012-1677-7 [PubMed: 23065101]

Hardan AY, Jou RJ, Keshavan MS, Varma R, Minshew NJ. Increased frontal cortical folding in autism: A preliminary MRI study. Psychiatry Research. 2004; 131:263–268. DOI: 10.1016/j.pscychresns.2004.06.001 [PubMed: 15465295]

Hardan AY, Libove RA, Keshavan MS, Melhem NM, Minshew NJ. A preliminary longitudinal magnetic resonance imaging study of brain volume and cortical thickness in autism. Biological Psychiatry. 2009; 66:320–326. DOI: 10.1016/j.biopsych.2009.04.024 [PubMed: 19520362]

Hardan AY, Muddasani S, Vemulapalli M, Keshavan MS, Minshew NJ. An MRI study of increased cortical thickness in autism. The American Journal of Psychiatry. 2006; 163:1290–1292. DOI: 10.1176/appi.ajp.163.7.1290 [PubMed: 16816240]

Haswell CC, Izawa J, Dowell LR, Mostofsky SH, Shadmehr R. Representation of internal models of action in the autistic brain. Nature Neuroscience. 2009; 12:970–972. DOI: 10.1038/nn.2356 [PubMed: 19578379]

Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, et al. Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. Archives of General Psychiatry. 2005; 62:1366–1376. DOI: 10.1001/archpsyc.62.12.1366 [PubMed: 16330725]

Henderson, S., Sugden, D., Barnett, A. Psychological Corporation. London, England: Harcourt Assessment; 2007. Movement assessment battery for children - Second edition (Movement ABC-2).

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain: A Journal of Neurology. 2003; 126(Pt 5):1182–1192. [PubMed: 12690057]

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, et al. Localization of white matter volume increase in autism and developmental language disorder. Annals of Neurology. 2004; 55:530–540. DOI: 10.1002/ana.20032 [PubMed: 15048892]

Izawa J, Pekny SE, Marko MK, Haswell CC, Shadmehr R, Mostofsky SH. Motor learning relies on integrated sensory inputs in ADHD, but over-selectively on proprioception in autism spectrum conditions. Autism Research: Official Journal of the International Society for Autism Research. 2012; 5:124–136. DOI: 10.1002/aur.1222 [PubMed: 22359275]

Jansiewicz EM, Goldberg MC, Newschaffer CJ, Denckla MB, Landa R, Mostofsky SH. Motor signs distinguish children with high functioning autism and Asperger's syndrome from controls. Journal of Autism and Developmental Disorders. 2006; 36:613–621. DOI: 10.1007/s10803-006-0109-y [PubMed: 16609826]

Jones V, Prior M. Motor imitation abilities and neurological signs in autistic children. Journal of Autism and Developmental Disorders. 1985; 15:37–46. [PubMed: 3980428]

Kanner L. Autistic disturbances of affective contact. Acta Paedopsychiatrica. 1968; 35:100–136. [PubMed: 4880460]

Kleinhans NM, Richards T, Sterling L, Stegbauer KC, Mahurin R, Johnson LC, et al. Abnormal functional connectivity in autism spectrum disorders during face processing. Brain: A Journal of Neurology. 2008; 131(Pt 4):1000–1012. DOI: 10.1093/brain/awm334 [PubMed: 18234695]

Knaus TA, Tager-Flusberg H, Foundas AL. Sylvian fissure and parietal anatomy in children with autism spectrum disorder. Behavioural Neurology. 2012; 25:327–339. DOI: 10.3233/BEN-2012-110214 [PubMed: 22713374]

Leth-Steensen C, Elbaz ZK, Douglas VI. Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. Acta Psychologica. 2000; 104:167–190. [PubMed: 10900704]

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders. 2000; 30:205–223. [PubMed: 11055457]

Lord, C., Rutt, M., DiLavore, PC., Risi, S., Gotham, K., Bishop, SL. Autism diagnostic observation schedule, Second edition (ADOS-2) manual (Part I): Modules 1-4. Torrance, CA: Western Psychological Services; 2012.

Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders. 1994; 24:659–685. [PubMed: 7814313]

Lyall AE, Shi F, Geng X, Woolson S, Li G, Wang L, et al. Development of Regional Cortical Thickness and Surface Area in Early Childhood. Cerebral Cortex (New York, NY: 1991). 2014; doi: 10.1093/cercor/bhu027

MacNeil LK, Mostofsky SH. Specificity of dyspraxia in children with autism. Neuropsychology. 2012; 26:165–171. DOI: 10.1037/a0026955 [PubMed: 22288405]

Matson JL, Nebel-Schwalm MS. Comorbid psychopathology with autism spectrum disorder in children: An overview. Research in Developmental Disabilities. 2007; 28:341–352. DOI: 10.1016/j.ridd.2005.12.004 [PubMed: 16765022]

McKelvey JR, Lambert R, Mottron L, Shevell MI. Right-hemisphere dysfunction in Asperger's syndrome. Journal of Child Neurology. 1995; 10:310–314. [PubMed: 7594267]

Minshew NJ, Sung K, Jones BL, Furman JM. Underdevelopment of the postural control system in autism. Neurology. 2004; 63:2056–2061. [PubMed: 15596750]

Miyahara M, Tsujii M, Hori M, Nakanishi K, Kageyama H, Sugiyama T. Brief report: motor incoordination in children with Asperger syndrome and learning disabilities. Journal of Autism and Developmental Disorders. 1997; 27:595–603. [PubMed: 9403374]

Moll GH, Heinrich H, Trott G, Wirth S, Rothenberger A. Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. Neuroscience Letters. 2000; 284:121–125. [PubMed: 10771177]

Mostofsky SH, Burgess MP, Gidley Larson JC. Increased motor cortex white matter volume predicts motor impairment in autism. Brain. 2007; 130:2117–2122. DOI: 10.1093/brain/awm129 [PubMed: 17575280]

Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biological Psychiatry. 2002; 52:785–794. [PubMed: 12372650]

Mostofsky SH, Dubey P, Jerath VK, Jansiewicz EM, Goldberg MC, Denckla MB. Developmental dyspraxia is not limited to imitation in children with autism spectrum disorders. Journal of the International Neuropsychological Society. 2006; 12:314–326. [PubMed: 16903124]

Mostofsky SH, Ewen JB. Altered connectivity and action model formation in autism is autism. The Neuroscientist. 2011; 17:437–448. DOI: 10.1177/1073858410392381 [PubMed: 21467306]

Mostofsky SH, Newschaffer CJ, Denckla MB. Overflow movements predict impaired response inhibition in children with ADHD. Perceptual and Motor Skills. 2003; 97:1315–1331. [PubMed: 15002876]

Mostofsky SH, Simmonds DJ. Response inhibition and response selection: Two sides of the same coin. Journal of Cognitive Neuroscience. 2008; 20:751–761. DOI: 10.1162/jocn.2008.20500 [PubMed: 18201122]

Mottron L. Matching strategies in cognitive research with individuals with high-functioning autism: Current practices, instrument biases, and recommendations. Journal of Autism and Developmental Disorders. 2004; 34:19–27. [PubMed: 15098953]

Murray MJ. Attention-deficit/hyperactivity disorder in the context of autism spectrum disorders. Current Psychiatry Reports. 2010; 12:382–388. DOI: 10.1007/s11920-010-0145-3 [PubMed: 20694583]

Nebel MB, Eloyan A, Barber AD, Mostofsky SH. Precentral gyrus functional connectivity signatures of autism. Frontiers in Systems Neuroscience. 2014; 8:80.doi: 10.3389/fnsys.2014.00080 [PubMed: 24860442]

Nebel MB, Joel SE, Muschelli J, Barber AD, Caffo BS, Pekar JJ, et al. Disruption of functional organization within the primary motor cortex in children with autism. Human Brain Mapping. 2014; 35:567–580. DOI: 10.1002/hbm.22188 [PubMed: 23118015]

Nobile M, Perego P, Piccinini L, Mani E, Rossi A, Bellina M, et al. Further evidence of complex motor dysfunction in drug naive children with autism using automatic motion analysis of gait. Autism: The International Journal of Research and Practice. 2011; 15:263–283. DOI: 10.1177/1362361309356929 [PubMed: 21478224]

O'Dwyer L, Tanner C, van Dongen EV, Greven CU, Bralten J, Zwiers MP, et al. Brain volumetric correlates of autism spectrum disorder symptoms in attention deficit/hyperactivity disorder. PloS One. 2014; 9:e101130.doi: 10.1371/journal.pone.0101130 [PubMed: 24979066]

Ozonoff S, Miller JN. An exploration of right-hemisphere contributions to the pragmatic impairments of autism. Brain and Language. 1996; 52:411–434. DOI: 10.1006/brln.1996.0022 [PubMed: 8653388]

Palmen SJMC, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, et al. Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychological Medicine. 2005; 35:561–570. [PubMed: 15856726]

Piven J, Palmer P, Jacobi D, Childress D, Arndt S. Broader autism phenotype: Evidence from a family history study of multiple-incidence autism families. The American Journal of Psychiatry. 1997; 154:185–190. [PubMed: 9016266]

Qiu A, Adler M, Crocetti D, Miller MI, Mostofsky SH. Basal ganglia shapes predict social, communication, and motor dysfunctions in boys with autism spectrum disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2010; 49:539–551. 551.e1–4. DOI: 10.1016/j.jaac.2010.02.012 [PubMed: 20494264]

Rakic P. Defects of neuronal migration and the pathogenesis of cortical malformations. Progress in Brain Research. 1988; 73:15–37. [PubMed: 3047794]

Ranta ME, Chen M, Crocetti D, Prince JL, Subramaniam K, Fischl B, et al. Automated MRI parcellation of the frontal lobe. Human Brain Mapping. 2014; 35:2009–2026. DOI: 10.1002/hbm.22309 [PubMed: 23897577]

Raznahan A, Toro R, Daly E, Robertson D, Murphy C, Deeley Q, et al. Cortical anatomy in autism spectrum disorder: An in vivo MRI study on the effect of age. Cerebral Cortex (New York, NY: 1991). 2010; 20:1332–1340. DOI: 10.1093/cercor/bhp198

Reich, W., Welner, Z., Herjanic, B. The diagnostic interview for children and adolescents-IV. North Tonawanda: Multi-Health Systems; 1997.

Reiersen AM, Todd RD. Co-occurrence of ADHD and autism spectrum disorders: Phenomenology and treatment. Expert Review of Neurotherapeutics. 2008; 8:657–669. DOI: 10.1586/14737175.8.4.657 [PubMed: 18416666]

Reiersen AM, Todorov AA. Association between DRD4 genotype and autistic symptoms in DSM-IV ADHD. Journal of the Canadian Academy of Child and Adolescent Psychiatry (Journal de l'Académie Canadienne de Psychiatrie de L'enfant et de L'adolescent). 2011; 20:15–21.

Rogers SJ, Bennetto L, McEvoy R, Pennington BF. Imitation and pantomime in high-functioning adolescents with autism spectrum disorders. Child Development. 1996; 67:2060–2073. [PubMed: 9022229]

Rojas DC, Peterson E, Winterrowd E, Reite ML, Rogers SJ, Tregellas JR. Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. BMC Psychiatry. 2006; 6:56.doi: 10.1186/1471-244X-6-56 [PubMed: 17166273]

Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2008; 49:535–542. DOI: 10.1111/j.1469-7610.2007.01857.x

Rothi, GLJ., Raymer, AM., Heilman, KM. Limb praxis assessment. In: Rothi, LJG., Heilman, KM., editors. Apraxia: the cognitive neuropsychology of action. Hove, UK: Psychology Press; 1997. p. 61-74.

Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the National Academy of Sciences. 2007; 104:19649–19654.

Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, et al. Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: Support for a dimensional view of attention deficit hyperactivity disorder. American Journal of Psychiatry. 2011; 168:143–151. [PubMed: 21159727]

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, et al. Neurodevelopmental trajectories of the human cerebral cortex. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2008; 28:3586–3594. DOI: 10.1523/JNEUROSCI.5309-07.2008 [PubMed: 18385317]

Shaw P, Malek M, Watson B, Sharp W, Evans A, Greenstein D. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. Biological Psychiatry. 2012; 72:191–197. DOI: 10.1016/j.biopsych.2012.01.031 [PubMed: 22418014]

Sinzig J, Walter D, Doepfner M. Attention deficit/hyperactivity disorder in children and adolescents with autism spectrum disorder: Symptom or syndrome? Journal of Attention Disorders. 2009; 13:117–126. DOI: 10.1177/1087054708326261 [PubMed: 19380514]

Smalley SL, Kustanovich V, Minassian SL, Stone JL, Ogdie MN, McGough JJ, et al. Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism.

American Journal of Human Genetics. 2002; 71:959–963. DOI: 10.1086/342732 [PubMed: 12187510]

Stam AJ, Schothorst PF, Vorstman JA, Staal WG. The genetic overlap of attention deficit hyperactivity disorder and autistic spectrum disorder. The Application of Clinical Genetics. 2009; 2:7–13. [PubMed: 23776346]

Stieglitz Ham H, Bartolo A, Corley M, Rajendran G, Szabo A, Swanson S. Exploring the relationship between gestural recognition and imitation: Evidence of dyspraxia in autism spectrum disorders. Journal of Autism and Developmental Disorders. 2011; 41:1–12. DOI: 10.1007/s10803-010-1011-1 [PubMed: 20407815]

Suskauer SJ, Simmonds DJ, Caffo BS, Denckla MB, Pekar JJ, Mostofsky SH. fMRI of intrasubject variability in ADHD: Anomalous premotor activity with prefrontal compensation. Journal of the American Academy of Child and Adolescent Psychiatry. 2008; 47:1141–1150. DOI: 10.1097/CHI.0b013e3181825b1f [PubMed: 18724253]

Szatmari P, Archer L, Fisman S, Streiner DL, Wilson F. Asperger's syndrome and autism: Differences in behavior, cognition, and adaptive functioning. Journal of the American Academy of Child and Adolescent Psychiatry. 1995; 34:1662–1671. DOI: 10.1097/00004583-199512000-00017 [PubMed: 8543538]

Tomchek SD, Dunn W. Sensory processing in children with and without autism: A comparative study using the short sensory profile. The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association. 2007; 61:190–200. [PubMed: 17436841]

Vaidya CJ, Stollstorff M. Cognitive neuroscience of attention deficit hyperactivity disorder: Current status and working hypotheses. Developmental Disabilities Research Reviews. 2008; 14:261–267. DOI: 10.1002/ddrr.40 [PubMed: 19072750]

Vanvuchelen M, Roeyers H, De Weerdt W. Nature of motor imitation problems in school-aged boys with autism: a motor or a cognitive problem? Autism: The International Journal of Research and Practice. 2007; 11:225–240. DOI: 10.1177/1362361307076846 [PubMed: 17478576]

Vilensky JA, Damasio AR, Maurer RG. Gait disturbances in patients with autistic behavior: A preliminary study. Archives of Neurology. 1981; 38:646–649. [PubMed: 7295109]

Vivanti G, Nadig A, Ozonoff S, Rogers SJ. What do children with autism attend to during imitation tasks? Journal of Experimental Child Psychology. 2008; 101:186–205. DOI: 10.1016/j.jecp.2008.04.008 [PubMed: 18582895]

Wallace GL, Dankner N, Kenworthy L, Giedd JN, Martin A. Age-related temporal and parietal cortical thinning in autism spectrum disorders. Brain: A Journal of Neurology. 2010; 133(Pt 12):3745–3754. DOI: 10.1093/brain/awq279 [PubMed: 20926367]

Wechsler, D. Wechsler intelligence scale for children—Forth edition (WISC-IV). San Antonio, TX: The Psychological Corporation; 2003.

Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. NeuroImage. 2010; 53:1135–1146. DOI: 10.1016/j.neuroimage.2009.12.028 [PubMed: 20006715]

Wodka EL, Mark Mahone E, Blankner JG, Gidley Larson JC, Fotedar S, Denckla MB, et al. Evidence that response inhibition is a primary deficit in ADHD. Journal of Clinical and Experimental Neuropsychology. 2007; 29:345–356. DOI: 10.1080/13803390600678046 [PubMed: 17497558]

Wolosin SM, Richardson ME, Hennessey JG, Denckla MB, Mostofsky SH. Abnormal cerebral cortex structure in children with ADHD. Human Brain Mapping. 2009; 30:175–184. DOI: 10.1002/hbm.20496 [PubMed: 17985349]

Zikopoulos B, Barbas H. Changes in prefrontal axons may disrupt the network in autism. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2010; 30:14595–14609. DOI: 10.1523/JNEUROSCI.2257-10.2010 [PubMed: 21048117]

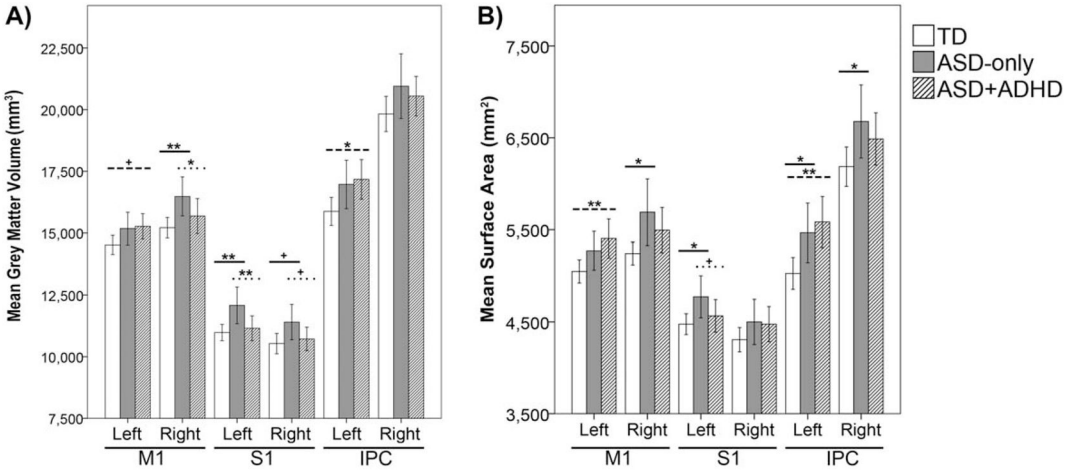

Figure 1.

Cortical metrics (a) mean gray matter volume, GMV (mm^3) and (b) mean surface area, SA (mm^2) plotted for the postcentral gryus, M1, and IPC for the TD (clear bars), ASD-only (solid bars), and ASD+ADHD (bars with crossed lines). GMV and SA in children with ASD were increased in all 3 motor circuit ROIs as compared to TD children. (Key: + $P < 0.1$; * $P < 0.05$; ** $P < 0.01$; solid lines: TD vs. ASD-only; large dashes: TD versus ASD+ADHD; small dashes: ASD-only versus ASD+ADHD).

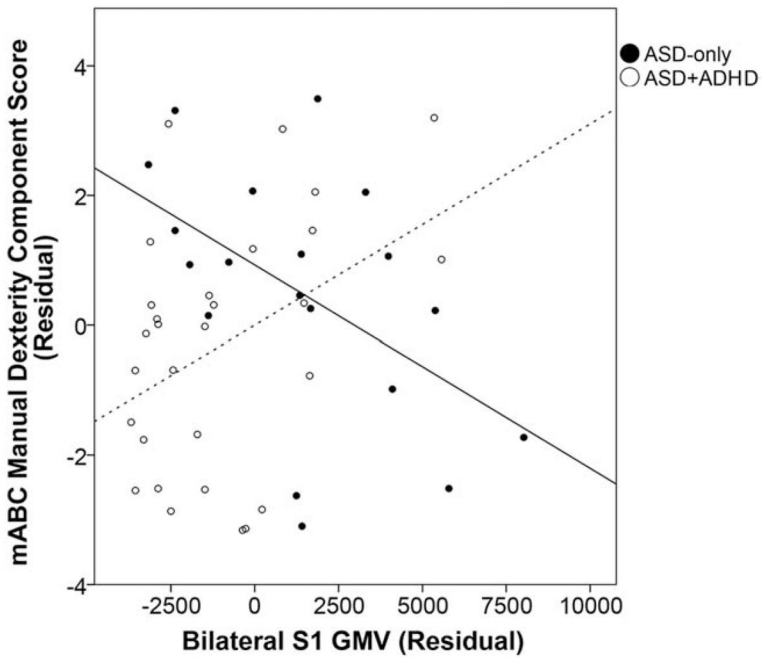

Figure 2.

Partial correlations (covarying for age) between bilateral postcentral cortex and MABC-2's manual dexterity component score. Higher scores signify better performance. Notably, ASD-only group (solid line and closed circles) shows a negative correlation (r=−0.52, P=0.032) suggesting that the increased GMV is associated with impaired manual dexterity. The ASD +ADHD group (dashed line and open circles) shows the opposite relationship (r=0.40, P=0.036). (MABC-2: Movement Assessment Battery for Children, Second Edition).

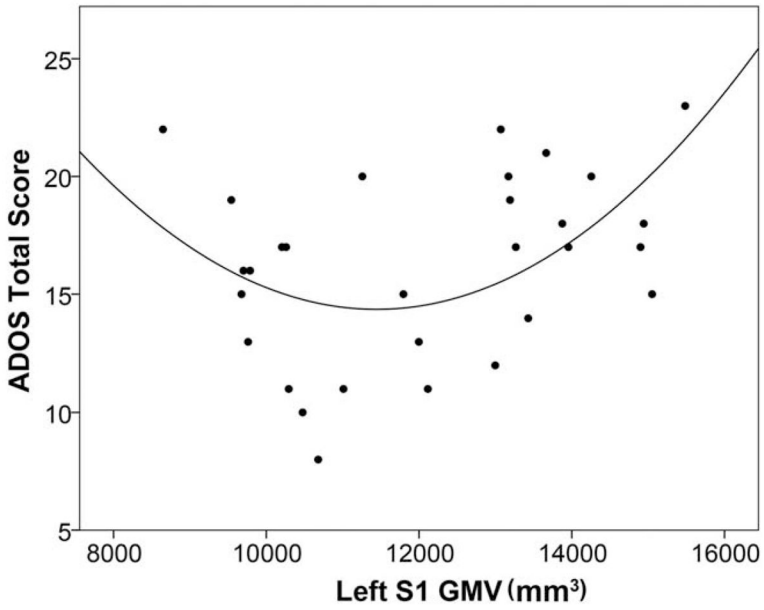

Figure 3.

Quadratic regression between ADOS total score (dependent variable) and left postcentral gyrus GMV. The GMV at the trough (10,833mm^3) corresponds to almost exactly the mean of GMV of the TD group for left postcentral gyrus (10,980mm^3; SD 1316). This suggests that a deviation from the TD mean is associated with increased autism severity (r=0.503, P=0.022).

Table 1

Demographic and Other Characteristics

	TD (*N*=63)	ASD Total (*N*=63)	ASD-only (*N*=30)	ASD+ADHD (*N*=23)
Age (SD) years	10.5 (1.3)	10.4 (1.5)	10.5 (1.7)	10.3 (1.4)
Gender (M/F)	54/9	54/9	25/5	29/4
TBV (SD)	10692667 (96713)	1098231 (103806)	1101079 (97588)	1095642 (110601)
SES (SD)	52 (10)	53 (10)	54 (11)	53(9)
FSIQ (SD)	112 (11)	102 (15)	102 (14)	103 (17)
VCI (SD)	115 (14)	108 (18)	107 (18)	110 (18)
PRI (SD)	110 (12)	107 (14)	110 (14)	105 (13)
Connor's Total *T*-Score	46 (4.5)	67(11)	64 (11)	70 (9.4)
ADOS-Total	–	16 (3.8)	16 (3.9)	15 (3.7)
Handedness (SD)	0.62 (0.57)	0.64 (0.54)	0.65 (0.55)	0.63 (0.55)
Racial Composition				
Caucasian	46	52	26	26
African American	10	5	2	3
Asian	2	3	0	3
Latino	0	1	1	0
Biracial	5	2	1	1
ADHD subtype				
Combined				23
Hyperactive/Impulsive				3
Inattentive				7

TBV, total brain volume; SES, Hollingshead four-factor index of socioeconomic status; PRI, perceptual reasoning index from the WISC-IV; Handedness, Edinburgh handedness inventory.

Table 2

Summary of the Post Hoc ROI Analysis

Cortical Metrics by ROI	ASD-only vs. TD	ASD+ADHD vs. TD	ASD-only vs. ASD+ADHD
	Precentral Gyrus		
GMV	R**	L+	R*
SA	R*	L**	
CT			
	Postcentral Gyrus		
GMV	L**,R+		L**,R+
SA	L*		L+
CT			
	Inferior Parietal Cortex		
GMV		L*	
SA	L*, R*	L**	
CT			

ROI, region of interest; GMV, gray matter volume; SA, surface area; L, left; R, right;

+ $P < 0.1$;

* $P < 0.05$;

** $P < 0.01$.

No effect of diagnosis was noted for CT in any region.