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Neuropsychological Investigation of Motor Impairments in Autism

Tyler Duffield¹, Haley Trontel⁵, Erin D. Bigler^{1,2,3,4}, Alyson Froehlich⁶, Molly B. Prigge^{6,7}, Brittany Travers¹⁰, Ryan R. Green¹, Annahir N. Cariello⁶, Jason Cooperrider^{6,7}, Jared Nielsen^{6,7}, Andrew Alexander^{9,10,11}, Jeffrey Anderson¹⁵, P. Thomas Fletcher^{4,12}, Nicholas Lange^{13,14}, Brandon Zielinski⁸, and Janet Lainhart^{9,11}

¹Department of Psychology, Brigham Young University, Provo, Utah

²Neuroscience Center, Brigham Young University, Provo, Utah

³Department of Psychiatry, University of Utah, Salt Lake City, Utah

⁴The Brain Institute of Utah, University of Utah, Salt Lake City, Utah

⁵Department of Psychology, University of Montana, Missoula, Montana

⁶Department of Psychiatry, School of Medicine, University of Utah, Salt Lake City, Utah

⁷Interdepartmental Neuroscience Program, University of Utah, Salt Lake City, Utah

⁸Department of Pediatrics and Neurology, School of Medicine, University of Utah, Salt Lake City, Utah

⁹Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin, Madison, WI, USA

¹⁰Department of Medical Physics, University of Wisconsin, Madison, Wisconsin

¹¹Department of Psychiatry, University of Wisconsin, Madison, Wisconsin

¹²School of Computing, University of Utah, Salt Lake City, Utah

¹³Departments of Psychiatry and Biostatistics, Harvard University, Boston, Massachusetts

¹⁴Neurostatistics Laboratory, McLean Hospital, Belmont, Massachusetts

¹⁵Department of Radiology, University of Utah, Salt Lake City, Utah

Abstract

It is unclear how standardized neuropsychological measures of motor function relate to brain volumes of motor regions in autism spectrum disorder (ASD). An all male sample composed of 59 ASD and 30 controls (ages 5–33 years) completed three measures of motor function: strength of grip (SOG), finger tapping test (FTT), and grooved peg-board test (GPT). Likewise, all participants underwent magnetic resonance imaging with region of interest (ROI) volumes obtained to include the following regions: motor cortex (pre-central gyrus), somatosensory cortex (post-central gyrus), thalamus, basal ganglia, cerebellum and caudal middle frontal gyrus. These traditional neuropsychological measures of motor function are assumed to differ in motor complexity with GPT requiring the most followed by FTT and SOG. Performance by ASD participants on the GPT and FTT differed significantly from controls, with the largest effect size differences observed on the more complex GPT task. Differences on the SOG task between the

two groups were non-significant. Since more complex motor tasks tap more complex networks, poorer GPT performance by those with ASD may reflect less efficient motor networks. There was no gross pathology observed in classic motor areas of the brain in ASD, as region of interest (ROI) volumes did not differ, but FTT was negatively related to motor cortex volume in ASD. The results suggest a hierarchical motor disruption in ASD, with difficulties evident only in more complex tasks as well as a potential anomalous size-function relation in motor cortex in ASD.

Keywords

autism; network disruption; motor impairment; brain volume differences; motor cortex volume

Although Kanner's (1943) classic paper outlined the core features of autism that eventually became the triad criteria for the diagnosis of autism—qualitative impairments in social interaction, communication, and repetitive and stereotyped behaviors—he also noted, "... several of the children were somewhat clumsy in gait and gross motor performance..." (p. 248). While most contemporary studies of autism spectrum disorder (ASD) have focused on the core diagnostic features of autism (Geschwind, 2009), clinically described delays in motor development and impairments in motor function are commonplace in ASD where meta-analytic findings have suggested a more central role (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010), described by some as a *motor coordination deficit* in ASD (Miyahara, 2013). While these reviews have shown motor differences between typically developing (TD) and ASD individuals, most individuals with ASD do not meet criteria for a developmental coordination disorder (Emck et al., 2009). While individuals with ASD may exhibit motor findings, as reviewed by Fournier et al. (2010), Miyahara (2013) and Emck (2009) there is considerable variability in how motor impairments have been assessed in these studies, many of which have been based on simple clinical rating scales and not traditional neuropsychological measures of motor functioning like strength of grip (SOG), the finger tapping test (FTT) or grooved-pegboard test (GPT; see Lezak, Howieson, Bigler & Tranel, 2012).

Studies that have used some of these traditional neuropsychological measures of motor function have found impairments in those with ASD when group compared to TD individuals (see Muller, Schafer, Kuhn, & Przuntek, 2000; Pedersen, Oberg, Larsson, & Lindval, 1997; Sachdev, Hume, Toohey, & Doutney, 1996); however, other studies have reported either mixed findings or an absence of any motor difference (Hardan, Kilpatrick, Keshavan, & Minshew, 2003; Jansiewicz, et al., 2006; Kern et al., 2011; Minshew, Goldstein, & Siegel, 1997; Rumsey & Hamburger, 1988; Szatmari, Tuff, Finlayson, & Bartolucci, 1990; Weimer, Schatz, Lincoln, Ballantyne, & Trauner, 2001; Williams, Goldstein, & Minshew, 2006).

The lack of consistent motor findings in ASD across studies, including the aforementioned studies that did use standardized neuropsychological measures, likely relates to: design and methodological differences across studies; the level of motor complexity being assessed; the clinical heterogeneity of autism samples; utilization of a single motor task versus multiple measures; the use of non-standardized versus standardized measures; differences in sample sizes; differences in age ranges (i.e., childhood, adolescence, adulthood, lifespan); and differences in how autism severity is associated with cognitive factors (see Carcani-Rathwell, Rabe-Hasketh, & Santosh, 2006) since as Goldman and colleagues (2009) observed, lower cognitive ability was associated with greater motor impairment. Furthermore, given the heterogeneity of autism and its expression (Rapin, 1991), a universal motor impairment would not necessarily be expected.

Unfortunately, some of these limitations are inescapable given the nature and constraints of research with this clinical population. Yet, what is clear from the literature is that motor deficits in some fashion likely are associated with and related to ASD (Bhat, Landa, Galloway, 2011; Bonnet & Gao, 1996; Downey & Rapport, 2012; Dziuk et al., 2007; Emck, Bosscher, van Wieringen, Doreleijers, & Beek, 2012; Fournier, Hass, Naik, Lodha, & Cauraugh, 2010; Gowen & Hamilton, 2012; Jansiewicz et al., 2006; Landa et al., 2012; Miyahara, 2013; Nobile et al., 2011; Travers, Powell, Klinger, & Klinger, 2012). If so it is important to characterize motor performance in ASD using standardized neuropsychological measures like SOG, FTT and GPT.

While these standardized motor tasks represent the behavioral output related to motor function, they also reflect integrity of known motor regions of the brain such as primary motor cortex and other cortical and subcortical regions that support motor function (Lezak et al. 2012). What has not been systematically investigated in ASD, or even in TD individuals is how anatomical indices of known motor regions relate to motor control. Using contemporary neuroimaging methods to calculate region of interest (ROI) volume of key brain areas involved in motor function provides an anatomical metric about motor system integrity (see Draganski & Bhatia, 2010; Hervé et al., 2005). However, few studies have been systematic in the application of traditional neuropsychological measures of motor functioning in examining motor areas in ASD let alone neuroimaging findings (Mostofsky et al., 2009; Qiu, Adler, Crocetti, Miller, & Mostofsky, 2010). Furthermore because of the distributed anomalies that may be present in neuroimaging findings associated with ASD, it is important when ROI anatomical studies are performed that multiple regions be examined rather than one or just a few (Frith, 2003; Zielinski et al., 2012). Also, a variety of issues relate to morphological differences in the developing ASD brain where altered developmental trajectories may result in different volumes depending on age (Courchesne and Pierce, 2005; Courchesne, Carper, & Akshoomoff, 2003). Disruption of early brain development, even if that ROI eventually normalizes in volume with age, has the potential to significantly influence circuitry and resultant function (Polsek et al., 2011). Regardless of these developmental factors, assessing ROI volumes of key brain areas is an established quantitative method used as a marker of neural integrity (Tofts, 2008; Jara, 2013).

Given the need for characterization of ASD motor performance in comparison TD individuals on standardized neuropsychological tests and whether ROI differences in the volumes of classic motor areas are observed in ASD, the current investigation had three aims: (1) describe motor function based on traditional neuropsychological SOG, FTT and GPT measures in a large sample of individuals with ASD spanning child to adulthood, (2) compare neuroimaging-derived volumes of classic motor ROIs between ASD and typically developing participants, and (3) explore whether same or different relationships between neuroimaging identified motor ROIs were observed in ASD participants and TD controls. ROI volumes were derived from the automated FreeSurfer method, to include primary motor and sensory cortices, premotor regions of the frontal cortex, basal ganglia (caudate, globus pallidus, and putamen combined), thalamus, and cerebellum.

The GPT involves motor dexterity, visual processing, speed, attention, and continuous monitoring of accuracy, whereas FTT predominately measures simple motor coordination and dexterity and SOG essentially measures only upper extremity muscle strength (Lezak et al., 2012; Strauss, Sherman, & Spreen, 2006). Based in part on what and how these measures assess motor function, a hierarchy of motor control may be inferred. GPT performance reflects a more cognitively demanding task that would require a greater level of multiple and integrated motor regions than FTT and FTT requires greater motor complexity than SOG to carry out the task (Haaland & Delaney, 1981). Indeed, evidence for a motor hierarchical model is provided by factor analytic findings suggesting that FTT and pegboard

type tasks measure independent dimensions of manual proficiency (Baser & Ruff, 1987; Stanford & Barratt, 1996). Nonetheless, all of these motor tasks exhibit some degree of association (Schear & Sato, 1989; Strauss, Sherman, & Spreen, 2006), suggesting a common neural substrate likely involving the corticospinal system and associated motor pathways (Triggs et al., 2000).

From this hierarchical perspective of motor control, with increased motor system complexity necessary to perform the task, if ASD is associated with deficits in neural connectivity (Geschwind, 2009) then the greatest likelihood for motor differences between ASD and TD groups would be with the GPT and FTT tasks, with the least likelihood for differences in SOG. We hypothesized that participants with ASD would exhibit lower motor performance compared to TD participants, in particular with the FTT and GPT measures, and that correlates of motor functioning and neuroanatomical ROIs would differ between the two groups.

Method

Subjects and Assessment

Ascertainment—Participants diagnosed with autism and control subjects were a subset from the first wave of data collection of a longitudinal investigation of brain development. Participant selection from the larger sample was based on having complete motor data and time point 1 magnetic resonance imaging (MRI) performed in proximity to motor testing. Details of subject ascertainment are outlined in Alexander et al. (2007). All facets of this investigation were undertaken with the understanding and written consent of each subject or legal guardian, with the approval of the University of Utah and Brigham Young University Institutional Review Boards, where testing was performed, and in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association.

Subject groups—All subjects were male, ages 5–33 years. All subjects had a nonverbal standard IQ score greater than 65 on formal psychometric assessment using either the Differential Ability Scales (Elliot, 1990), Wechsler Intelligence Scale for Children–III (Wechsler, 1991), Wechsler Adult Intelligence Scale–III (Wechsler, 1997) or the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999). Fifty-nine (59) participants formed the ASD group with 30 participants in the TD control group. Since this was a longitudinal project, for subjects with multiple test dates, neuropsychological data were taken on the date closest to the neuroimaging test date and first test administration. Subject demographics are presented in Table 1.

Autism Spectrum Disorder (ASD)—All cases of autism were idiopathic with all meeting ASD criteria as described. Autism was diagnosed based on the findings of the Autism Diagnostic Interview-Revised (ADI-R), a semi-structured, investigator-based interview with good reliability and validity (Lord et al., 2000) as well as directly assessed with the Autism Diagnostic Observation Schedule-Generic (ADOS-G), a semi-structured play and interview session designed to elicit social, communication, and stereotyped repetitive behaviors characteristic of autism (Lord et al., 2000). ADI-R and ADOS-G descriptive information is presented in Table 2. Where multiple administrations of these measures were available, since most of the participants were part of a longitudinal investigation, the administration on the date closest to the motor test administration was used. Diagnostic classification was based on available ADI-R and ADOS-G findings along with *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV; American Psychiatric Association, 1994) criteria, with the following breakdown: lifetime diagnosis

autistic disorder of 52 and pervasive developmental disorder, not otherwise specified of 7. History, physical exam, Fragile-X gene testing, and karyotype were performed on all subjects to exclude medical causes of autistic phenotypes.

Control sample—TDC participants had no developmental, neurological, or clinical history for major psychiatric disorders, and completed an ADOS-G assessment to ensure none met criteria for ASD.

Neuroimaging—Volumetric studies were based on magnetic resonance images acquired on a Siemens Trio 3.0 Tesla scanner at the University of Utah. A 12-channel, receive-only RF head coil was used to obtain 3D T1-weighted image volumes with 1mm isotropic resolution using an MP-RAGE sequence (TI = 900 msec, TR = 2300 msec, TE = 2.91 msec, flip angle = 9 degrees, sagittal, field of view = 25.6 cm, matrix = 256 × 256 × 160). Imaging from three ASD subjects could not be used and were not part of the quantitative MRI analyses.

Volumetric image analysis—All analyses were performed with FreeSurfer, version 5.1 (<http://surfer.nmr.mgh.harvard.edu/>) and followed the methods detailed by Bigler et al. (2010). The following gray matter ROIs were examined: precentral gyrus, postcentral gyrus, caudal middle frontal area (i.e., supplementary motor area), thalamus, cerebellum, and basal ganglia. Whole brain white and gray matter and intracranial volume were also estimated.

Justification for including these ROIs comes from Moritz, Haughton, Cordes, Quigley, and Meyerand (2000), who demonstrated involvement of the precentral and postcentral gyri, supplementary motor area, cerebellum, thalamus, and putamen during a FTT task using fMRI techniques. SOG has been shown to be associated with activation of the postcentral gyri and supplementary motor area as well as cerebellum (Cramer et al., 2002). All of the above motor regions are also the presumed motor control areas involved in the GPT, although GPT performance has not yet been examined from a neuroimaging perspective. Increased levels of motor skill and precision are required to manipulate the small pegs used with the GPT (Lezak, et al., 2012), suggesting coordination of primary motor, basal ganglia and cerebellar regions along with sensory-perceptual feedback to efficiently perform the GPT task.

IQ—Verbal skills are often diminished in autism (Rapin, 1999) along with considerable variability in verbal and performance IQ scores, often resulting in lower IQ in autism samples (Deutsch & Joseph, 2003). However, in disorders where intellectual compromise may be part of the clinical picture for the dependent variable in question, over controlling for IQ may, in fact, limit important findings (see Dennis, Francis, Cirino, Schachar, Barnes & Fletcher, 2009). Likewise, to be as inclusive of the ASD sample being assessed we utilized a liberal lower IQ limit [performance IQ (PIQ) ≥ 64] as the minimal level of intellectual functioning to participate in this investigation. Only three ASD participants had a PIQ score below 70 and only one with a PIQ of 64. To further examine issues related to IQ, because the ASD and control samples were sufficiently large, as part of a secondary comparison, participants with ASD were matched to controls to be within five IQ points, to control for differences that may be specific to IQ. Since the lowest PIQ score in the control sample was 88, in this secondary analysis matching on IQ, none of the lower functioning participants were included in those comparisons.

Head circumference and handedness—Standard occipitofrontal head circumference and handedness based on the Edinburgh Handedness Inventory (Oldfield, 1971) were obtained on all subjects. Demographic findings are reported in Table 1.

Motor tests—Standard FTT and SOG instruments from the Halstead-Retain Battery (Reitan Laboratories: www.reitanlabs.com; see also [Heaton, Grant, & Matthews, 1991]) were used along with the standard GPT (Matthews & Klove, 1964). All participants were administered the SOG, FTT, and GPT as outlined by Reitan and Wolfson (1986), Heaton et al. (1991), and Matthews and Klove (1964). The manual finger tapping board was used for the majority of subjects but for younger children the electronic FTT version was used. The number of taps performed over 10 second epochs was recorded for each trial, separately for each hand. To ensure consistency of responding, a minimum of five trials was administered with the total score required to be within ± 5 points. If this was not achieved, the total from all trials were averaged for each hand and both hands combined.

For the GPT, the participant was required to insert pegs in a prescribed order as quickly as possible using the dominant and nondominant hand separately. The number of pegs dropped was also recorded. The score was the time required to place pegs into all 25 holes, and the timing was not interrupted in the event of a dropped peg. For participants over eight years of age, 25 pegs were administered and for aged 5–8 participants, only 10 pegs were administered. To compare all subjects' motor performance for this test, the standard metric variables of drop rate (number of pegs dropped/total number of peg holes), and unit completion time (number of pegs placed/total completion time) were calculated. The total GPT score was computed by combining the nondominant hand completion time and the dominant hand completion time. SOG was measured by use of a hand dynamometer. The test requires the person to hold the upper part of the dynamometer in the palm of the hand and squeeze the stirrup with the fingers as tightly as possible. The average strength in kilograms of the two trials was recorded for each hand if they were within a 5-point range. If the two trials were not within ± 5 points, a third trial was completed and the average of those 3 trials was used. The total SOG score was computed by combining the nondominant hand mean and the dominant hand mean.

Statistical analysis—Group means were calculated and compared for autism and control subjects, using analysis of covariance (ANCOVA) with age, head circumference, and PIQ as covariates. FTT mean scores for both hands, GPT unit completion time (single peg) and peg drop rate for both hands, and the SOG means for both hands were compared between ASD and control groups. Motor findings were then examined in relation to key neuroimaging identified motor areas based on the volumetric data using partial correlations. FTT, GPT, and SOG totals were used for the partial correlations to reduce family wise error rates, including linear regressions that explored possible group by region interactions. A testwise false-positive error rate was set at 0.05, thus controlling for potential experimentwise errors. Analyses were run using version 20 of the IBM SPSS Statistics package. Clinical impairment on standardized neuropsychological measures is often conservatively defined as falling two standard deviations (z -score = -2.0) below the mean of a normative sample (Lezak et al., 2012; Strauss, Sherman, and Spreen, 2006). For each measure a simple frequency count was determined for who performed at this level of impairment based on normative data derived from the Lafayette Instrument Company (2002), Strauss et al., 2006, Mathiowetz, Wiemer, and Federman (1986), and Nussbaum and Bigler, (1997).

Results

Sample Characteristics

As previously shown in Table 1, no significant differences were found for group-matching variables (age, head circumference, handedness index) except IQ, as expected.

Motor Test Performance in Autism and Controls

SOG, FTT and GPT results, along with effect size differences between the ASD and TDC groups, are summarized in Table 3. Motor tasks were all positively inter-correlated as shown in Table 4. The distributions for SOG and GPT were not normally distributed; however, after applying log transformations homogeneity of variance assumptions were met. Results of SOG, FTT and GPT performance by group are detailed in Table 4. As shown in Table 1 because of the IQ differences between TD controls (TDC) and those with ASD, an IQ matched sample (matching on PIQ) was created from the original sample (within ± 5 PIQ points) consisting of 24 participants in each group, resulting in no significant difference on PIQ between groups [$t(46) = -.63, p = .54$]. Even after matching on IQ, there was no difference in the pattern of motor task findings between the IQ matched group and the original sample using PIQ as a covariate; therefore, the findings reported below were based on all subjects with PIQ as a covariate.

SOG

Participants with ASD had lower SOG scores, which only approached significance for the nondominant hand (see Table 3). For the ASD group, 7 participants (11.8%) were clinically impaired (i.e., z-score -2.0) for either hand with 3 (10.0%) participants found in the impaired range for the TDC group.

FTT

ASD individuals were significantly slower (i.e., less taps per 10 second epoch) for both hands on the FTT (see Table 3), although effect size differences were nominal to small (Cohen, 1988). For the ASD group, 5 (8.5%) participants were clinically impaired (i.e., z-score -2.0) for both hands, 6 (10.1%) for the dominant hand only and 8 (13.6%) for the nondominant hand only. No individuals in the TDC group performed at a level meeting clinically impaired cutoffs.

GPT

On the GPT task ASD individuals were also subtly but significantly slower than controls in the time that was required to retrieve a single peg and correctly place it on the board (i.e., UCT) with either hand and had significantly more drops using the nondominant hand, differences that remained significant even after log transformation of the non-normally distributed GPT (see Table 3). As shown in Table 3 for these significant GPT findings, effect size differences were small but substantially larger than what was observed with FTT. For the ASD group concerning total completion time, 2 (3.3%) participants were clinically impaired (i.e., z-score -2.0) for both hands, 4 (6.7%) for the dominant hand only and 2 (3.3%) for the nondominant hand only. No individuals in the TDC group below the clinical cutoff.

Age Effects and Motor Performance

Because of the age range examined in this investigation, group comparisons by age and motor performance were undertaken and plotted as shown in Figure 1, which revealed cross-sectional similarities and differences for ASD and TDC participants. Motor performance is clearly age-dependent regardless of group. The ASD and TDC slopes for cross-sectional age-related changes were similar for FTT and GPT performance (although longitudinal investigations will be more apt at detecting true age-related changes in these motor measures). As shown in Figure 1, overall FTT performance is slower by just a few taps per 10 second epoch. However, for GPT performance, while the regression lines have similar slopes at all age levels ASD subjects are slower. Using an arbitrary cut point based on visual

inspection of approximately 145 seconds to completion, 29/59 (49.2%) of the ASD subjects had slower times but only 6/30 (20%) of controls.

ROI Volumes in Autism and Controls

ANCOVA comparing the following motor areas including the precentral gyrus, postcentral gyrus, caudal middle frontal area (i.e. supplementary motor area), thalamus, cerebellum, and basal ganglia volumes revealed no significant volume differences between the two groups (Table 5), after controlling for age, head circumference, and PIQ. There were no differences between the groups in total gray matter volume, total white matter volume, and intracranial volume using the same covariates (data not shown).

Relationship between ROI Volume and Motor Performance

The relationship between motor ROI volumes and motor performance was examined using partial correlations controlling for age and head circumference; Table 6. To reduce the number of statistical comparisons, right and left motor performance scores were combined into a total score for SOG, FTT and GPT yielding a single motor index for each measure. Bilateral ROI volumes were also combined to create a total volume for each motor ROI. In ASD, the FTT score was negatively correlated with the volume of the precentral gyrus ($r = -.30, p = .025$), indicating that as brain volume increased, motor performance decreased (Table 5). The FTT-precentral gyrus volume relationship was not significantly different in ASD and TDC participants; there was no significant group by precentral gyrus interaction ($t = -.54, p = .59$). No ROI volumes were significantly correlated with motor performance for TDC participants. Partial correlations between total white matter volume and motor performance were all insignificant regardless of group (Table 7). Similarly, individual ROI volumes for gray matter and white matter did not show significant correlations with overall motor performance.

Discussion

Two major aims of this investigation were to characterize motor function in a large sample of individuals with ASD spanning child to adulthood using traditional neuropsychological SOG, FTT and GPT measures and determine if any gross differences in ROI volumes derived from classic motor areas of the brain were present. As a group, ASD participants exhibited reduced motor performance on standard FTT and GPT neuropsychological tasks compared to age- and sex-matched (all males) TD counterparts, even after controlling for differences in IQ. Although significant, the magnitude of difference was generally subtle, as effect size differences were only small for the comparisons that yielded significant differences. Likewise, only a small number of individuals in the ASD group exhibited what could be described as clinical impairment on all three motor tasks, in contrast to the TDC group. Anatomically, there were no gross volumetric differences in key motor areas between the ASD and control participants. Thus, the observed diminished finger oscillation speed and dexterous motor control on the FTT and GPT tasks in the ASD group cannot be attributed to gross anatomical difference within key motor regions. Motor cortex volume was negatively correlated with FTT performance in ASD but not in controls. Although SOG was lower in the ASD group it did not differ significantly from controls. The findings of reduced FTT and GPT performance in ASD, tasks that require more dexterous motor control than grip strength, fits with the supposition that where motor dysfunction may occur in ASD is at higher levels of motor integration. Furthermore, it was only with the GPT task that the differences were present at all age levels (see Figure 1).

Furthermore, the lack of significance with SOG but with FTT and GPT would be expected if ASD is, in part, related to abnormal networks and connectivity, since both FTT and GPT

would require larger integrated networks for motor performance than basic strength. Motor deficits in ASD could also be related to a disturbance in functional organization of the motor cortices (Muller et al., 2001). The one observation of a negative correlation between motor cortex and FTT would be consistent with an overgrowth theory of autism, where overgrowth may be associated with less efficient networks (Amaral, Dawson, & Geschwind, 2011; Courchesne, Webb, & Schumann, 2011), and therefore, larger size associated with poorer function. Mostofsky and colleagues (2007), relying on clinical motor exam findings only, observed that increased white matter volume of motor cortex in autism was associated with abnormal clinical motor findings. In the current study, volume differences of motor cortex were not observed, but nonetheless, a larger motor cortex was associated with reduced FTT speed in ASD participants. It is possible that subtle overgrowth and/or lack of pruning within neural systems that control motor function leads to inefficiency (Miyoshi & Okada, 2004) and to the general negative relationships of motor cortex volume and FTT in ASD. The normal developmental process of synaptic pruning has been postulated to be compromised in autism (Frith, 2003; Schultz, Klin, & Lombroso, 2002), disrupting how activity and experience support the organization of functional networks in typical brain development (Just, Keller, Malave, Kana, & Varma, 2012; Kandel et al., 2000). Just, Keller, Malave, Kana, and Varma (2012) have postulated that the developing autistic brain may not support an appropriate balance between maturation and experience. Errors in pruning may interfere with the emergence of the specialized functions of one or more of a set of neuroanatomical structures (see Pelphrey, Shultz, Hudac, and Vander Wyk (2011)). In TD individuals normal pruning could help eliminate faulty connections and optimize coordinated neural functioning, which compromised pruning might fail to accomplish. Compromised pruning processes possibly result in some degree of aberration in typical anatomical size-function relations that adversely influences communication among cortical regions (Just et al., 2012). However, there is much to be discovered about development, pruning, white matter connectivity and cortical maturation in ASD (Cassanova et al., 2006). While the findings of larger motor cortex being associated with poorer motor function in this ASD sample fits with aberrant development and potential faulty pruning and/or overgrowth, the precise meaning of these findings is unknown.

Hadders-Algra (2008) postulated that the relationship between preterm birth injury, white matter damage and motor deficits in children diagnosed with ASD was a problem of connectivity. Ligam et al. (2009) have shown a greater incidence of thalamic pathology in periventricular leukomalacia (PVL) associated with prematurity, and speculate about the relation between thalamic damage, white matter pathology and autism (see also Limperopoulos et al., 2008). Since PVL has the potential to disrupt neuronal migration, the potential thalamic damage and disrupted white matter connectivity being related to ASD is intriguing. Furthermore, Nair, Traiber, Shukla, Shih and Muller (2013) recently reported impaired thalamocortical connectivity in ASD. In the current study, prematurity was excluded as a risk factor for the ASD cohort examined. Thalamic volume in the ASD cohort did not differ from the TDC group and therefore no gross thalamic pathology was found. Thalamic volume did not significantly relate to any motor measurement nor did white matter volume. As such, the current findings are unlikely related to any gross neural insult or abnormality, but these methods do not specifically address issues of connectivity and development. Unfortunately, ROI volumes likely represent poor proxies as indices of brain connectivity and studies that employ more direct measures of functional connectivity should be conducted in relation to motor performance in ASD (see Miyahara, 2013).

While SOG is primarily a basic measure of the integrity of the corticospinal tract (Schulz et al., 2012), functional MRI (fMRI) studies also indicate that SOG performance results in some basal ganglia and cerebellar activation (Cramer, et al., 2002; Keisker, Hepp-Reymond, Blickenstorfer, & Kollias, 2010; van Nuenen, Kuutz-Buschbeck, Schulz, Bloem, & Siebner,

2012). Nonetheless, this SOG network is far more simple than the activation patterns observed during FTT performance as assessed by functional neuroimaging (De Guio, Jacobson, Molteno, Jacobson, & Meintjes, 2012; Lopez-Larson et al., 2012; Witt, Laird, & Meyerand, 2008), where coordinated finger movement has been shown to depend on widespread motor connections (Jin, Lin, & Hallett, 2012; Roessner et al., 2012).

Because of the motion restrictions imposed by fMRI studies of motor function, the SOG and FTT methods have been readily adapted to the scanner environment, but not the GPT task. Neuroimaging lesion studies as well as low frequency transcranial magnetic stimulation associated with GPT performance have found correlations between GPT proficiency and connectivity between motor, premotor and supplemental motor cortices, corpus callosum and cerebellum (Franc et al., 2011; Kodl et al., 2008; Miall & Christensen, 2004; Otten et al., 2012) where reduced parietal white matter integrity on DTI was associated with worse GPT performance. These latter findings may be best explained by GPT performance not only requires motor skill but guided attention as well (Lezak, et al., 2012). The preceding considerations suggest that the GPT task requires far greater neural complexity than SOG. The significant differences observed with FTT and GPT in autism, and that these tasks depend on both short- and long-range connectivity, is consistent with the postulated functional connectivity problems associated with ASD (Dowell, Mahone, & Mostofsky, 2009; Mostofsky & Ewen, 2011).

ROI Volumes and Motor Function

Previous voxel-based morphometry studies found enlargements in the right postcentral gyrus, right medial frontal gyrus, and the right posterior lobe of cerebellum (Ke et al., 2008) and decreases in the left precentral gyrus (Cauda et al., 2011) and left supplementary motor area (Mengotti et al., 2011) in autism when compared with controls. The Mengotti et al. (2011) and Ke et al. (2008) studies differ from the current study in that they have much smaller sample sizes and a smaller age range. Cauda et al. (2011) was a meta-analysis of 16 studies with a total of 350 ASD subjects (which included high-functioning autism, Asperger's Syndrome, and unspecified diagnoses), and male and female subjects. None of the above studies examined motor function with the SOG, FTT or GPT tasks systematically as have been done in this investigation.

Size-function relationships may emerge in brain development potentially reflecting optimal size (e.g., volume) of a given structure that may best relate to cognitive function as measured by neuropsychological variables (Koscik & Tranel, 2012). However, ROI volume relationships with neuropsychological functioning are complex, particularly in individuals with neuropsychiatric disorders (Crespo-Facorro, Barbadillo, Pelayo-Teran, & Rodriguez-Sanchez, 2007). Because of the complexities of brain development and individual differences in cognitive and neurobehavioral functioning, brain volumetry may not correlate with neuropsychological variables in a consistent and systematic pattern. Given the general lack of ROI volume relationships, it is likely that such an approach as used in the current investigation may simply be insensitive in detecting motor network abnormalities. Therefore, given prior reports of white matter pathway abnormalities in autism (Lainhart & Lange, 2011; Mak-Fan et al., 2012; Weinstein et al., 2011), it may be that measures more directly assessing white matter connectivity, such as diffusion tensor imaging (DTI) and functional connectivity MRI, may provide improved understanding of motor abnormalities in autism. In fact, those investigations are underway with this cohort.

Limitations and Conclusions

The autism sample was all male and comprised of high functioning individuals who do not represent those with lower functioning abilities, or females with autism. As already stated

this investigation did not directly assess connectivity where direct measures of motor performance using functional MRI techniques may yield much more specific findings related to motor differences in ASD compared to controls. Also, this study did not assess presence of clinical motor signs and their relationship to objective neuropsychological measures of motor functioning.

Despite these limitations the current findings do fit with a hierarchical model of impaired functioning in autism where basic motor ability is preserved, but as motor complexity increases, a greater likelihood of impaired motor function is observed in ASD. As Miyahara (2013) posited, it is more meaningful and clinically practical to use *standard* assessments thereby insuring common metrics used by researchers and clinicians in the study of ASD. Using all three standardized neuropsychological measures (i.e., SOG, FTT, GPT), as in the current study provides a motor profile that hopefully will be useful to clinicians assessing motor function in ASD. As shown in Figure 1, regardless of age there were consistently more individuals with ASD that exhibited slowed performance times on the GPT than observed in control participants. The hierarchical model of motor control used in the current investigation as well as the findings reported herein, provide information and heuristics to further explore motor findings associated with ASD.

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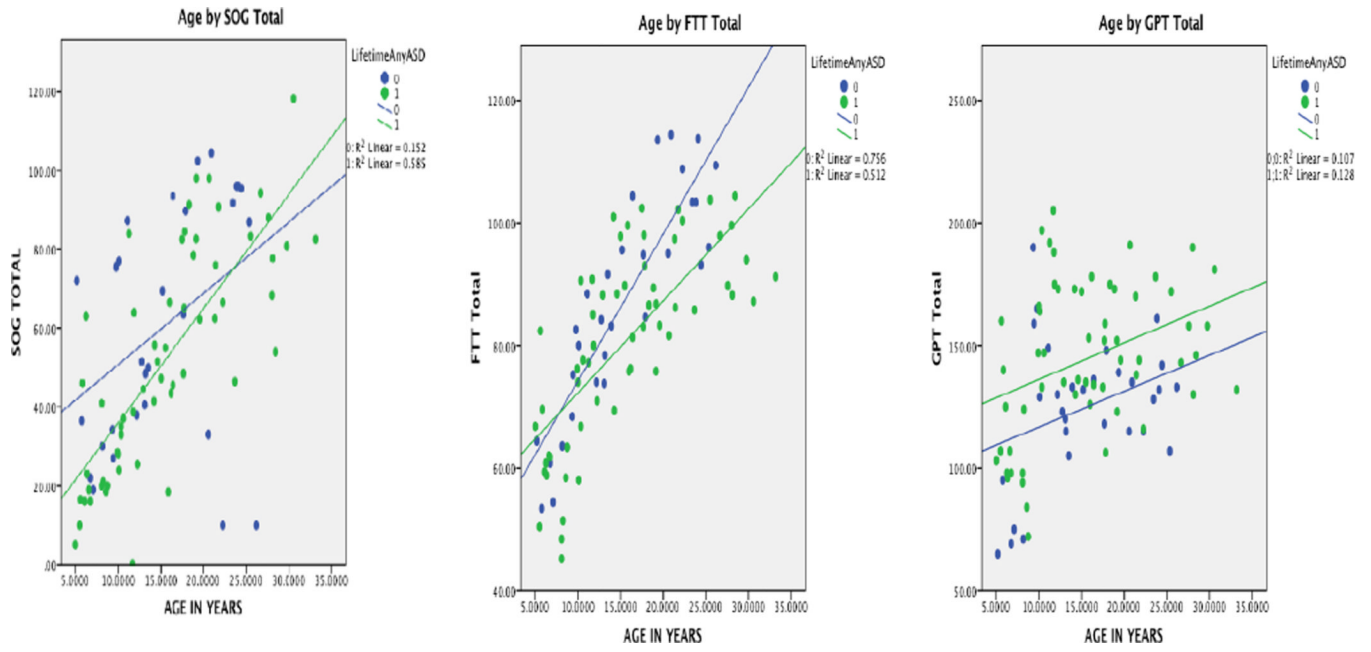


Figure 1.
Age by motor task performance plots. Green = ASD; Blue = TDC

Table 1

Demographic Information

	ASD (n = 59)			Typically-developing (n = 30)			t	p
	Mean	SD	Range	Mean	SD	Range		
Age in years	15.61	7.48	5.00-33.17	15.29	6.48	5.17-26.17	0.20	0.84
Head Circumference (cm)	55.54	2.36	50.60-60.20	55.40	2.30	49.20-59.30	0.27	0.79
Handedness Inventory	61.89	52.24	-100.00 to 100.00	69.90	42.98	-80.00-100.00	-0.72	0.47
Wechsler FIQ	100.30	17.71	58.00-137.00	120.23	16.72	95.00-153.00	-5.09**	0.00
Wechsler PIQ	101.38	17.01	64.00-129.00	118.03	19.02	88.00-155.00	-4.15**	0.00
Wechsler VIQ	98.54	21.34	51.00-138.00	117.57	14.83	94.00-151.00	-4.79**	0.00

* Note. = $p < .05$

** $p < .01$. Edinburgh Handedness inventory on a scale from -100 (left-handed) to 100 (right-handed).

FIQ = Full Scale IQ, PIQ = Performance IQ, VIQ = Verbal IQ

Table 2

Characterization of the Autism and Control sample

	ASD				Typically-developing			
	<i>n</i>	Mean (<i>SD</i>)	Range	<i>n</i>	Mean (<i>SD</i>)	Range		
ADOS S+C: Module 1	1	17.00 (0)	0	0				
ADOS S+C: Module 2	5	17.20 (4.15)	12–23	1	0 (0)	0		
ADOS S+C: Module 3	22	14.77 (3.62)	7–21	11	1.55 (1.44)	0–4		
ADOS S+C: Module 4	31	12.32 (3.90)	1–20	16	.75 (1.00)	0–3		
ADI-R Soc	51	20.11 (5.71)	6–30	0				
ADI-R Com	51	15.65 (4.64)	7–25	0				
ADI-R RSB	51	7.02 (2.36)	2–12	0				

Note. ADOS S+C = Autism Diagnostic Observation Schedule: Social and Communication Total. The ADOS consists of 4 modules and the individual being evaluated is given just one module, depending on expressive language level and chronological age. Each module has different cut-off scores and as such should not be considered equivalent. Two control participants had incomplete ADOS data, which is not reported above. ADI-R Soc = Autism Diagnostic Interview, Revised: Reciprocal Social Interactions; ADI-R Com = Autism Diagnostic Interview, Revised: Language/Communication; ADI-R RSB = Autism Diagnostic Interview, Revised: Restricted, Repetitive, and Stereotyped Behaviors and Interests. Four participants in the autism sample were missing ADI-R data and no ADI-R data were available for the control group.

Table 3

Motor Performance ANCOVAs controlling for Age, Head Circumference, and PIQ

Hand	Mean ASD (SD) N=56	Mean TD (SD) N=30	F	p	η^2
<u>SOG</u>					
DH	27.23(14.94)	31.34(15.92)	1.57	.21	.019
NDH	25.56(14.16)	29.06 (14.87)	3.47	.07	.040
<u>FTT</u>					
DH	41.40(8.46)	44.94(8.87)	5.90*	.02	.070
NDH	38.95(8.27)	41.95(9.55)	9.51**	.003	.110
<u>GPT-Drop Rate</u>					
DH	0.03(0.06)	0.02(0.04)	0.99	.32	.012
NDH	0.04(0.06)	0.01(0.02)	9.32**	.005	.231
<u>GPT-UCT</u>					
DH	3.34(0.96)	2.70 (0.49)	18.70**	<.001	.182
NDH	3.86 (1.27)	3.03 (.73)	19.93**	<.001	.192

Note. TD = typically-developing; ASD = Autism Spectrum Disorder; FTT = Finger Tapping Test; SOG = Strength of Grip; GPT = Grooved Pegboard Test; DH = dominant hand; NDH = nondominant hand; UCT = Unit Completion Time; η^2 = partial eta squared. Partial eta squared is the default effect size measure reported in SPSS. If you have only one predictor variable, then partial eta squared is equivalent to eta squared. SOG was measured in kilograms.

* $p < .05$

** $p < .01$. SOG-DH, Unit Completion Time-DH and NDH, and Drop Rate-NDH did not pass the homogeneity of variance assumption. Log transformations were performed for these variables and homogeneity assumptions were met. Means for the SOG and GPT-Drop Rate and GPT-UCT are untransformed.

Table 4

Correlation Matrix of Motor Performance in ASD and TD

	ASD			TD		
	SOG	FTT	GPT	SOG	FTT	GPT
SOG	---	.56**	.28*	---	.51**	.35
FTT	---	---	.49**	---	---	.42*

* $p < .05$

** $p < .01$

Table 5

ROI ANCOVAs controlling for Age, Head Circumference, and PIQ

Structure	Mean ASD (SD) N=59	Mean TD (SD) N=30	F	p	η^2
Thalamus	16.92 (1.46)	17.05 (2.17)	0.09	.76	.001
Precentral	30.84 (4.51)	31.48 (3.78)	0.35	.55	.004
Postcentral	21.28 (3.83)	21.91 (2.93)	1.06	.31	.013
Caudal Middle Frontal	17.26 (3.44)	17.98 (3.30)	0.18	.67	.002
Basal Ganglia	25.46 (2.44)	25.02 (3.07)	2.38	.13	.030
Cerebellum	124.97 (13.34)	127.55 (14.38)	0.01	.92	<.001

Note. ROI volumes combine left and right hemisphere volumes for each ROI structure. ROI units are measured in centimeters cubed. Basal Ganglia comprised the caudate, putamen, and pallidum volumes. η^2 = partial eta squared. Partial eta squared is the default effect size measure reported in SPSS. If you have only one predictor variable, then partial eta squared is equivalent to eta squared. TD = typically-developing; ASD = Autism Spectrum Disorder.

* $p < .05$ ** $p < .01$.

Table 6

Partial Correlations between motor ROI volumes and motor performance for ASD – controlling for Age and Head Circumference

Structure	Finger Tapping		Grooved Pegboard (Completion Time)		Strength of Grip (kgs)	
	ASD	TD	ASD	TD	ASD	TD
Precentral gyrus	-.30*	.08	-.25	-.07	-.07	-.20
Postcentral gyrus	-.19	.28	-.08	-.09	-.15	.07
Caudal Middle Frontal	-.18	.10	-.19	.03	-.06	-.10
Thalamus	-.06	-.20	-.10	-.19	-.12	-.16
Cerebellum	-.18	-.09	-.13	-.08	.04	-.12
Basal Ganglia	-.15	-.14	.26	-.11	.08	-.30

Note. ROI volumes combine left and right hemisphere volumes for each ROI structure. ASD = Autism Spectrum Disorder; TD = typically-developing; ASD = Autism Spectrum Disorder.

* $p < .05$.

Table 7

Partial Correlations between total white matter volume and motor performance for ASD – controlling for Age and Head Circumference

Structure	Finger Tapping		Grooved Pegboard (Completion Time)		Strength of Grip (kgs)	
	ASD	TD	ASD	TD	ASD	TD
TD						
Total White Matter Volume	-.02	.03	.03	-.14	-.14	-.29

Note. ASD = Autism Spectrum Disorder; TD = typically-developing; ASD = Autism Spectrum Disorder.

* $p < .05$