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Cortical Thickness and Voxel-Based Morphometry of Classic Motor Regions of Interest in Autism Spectrum Disorder

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ABSTRACT

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Prior research has suggested that any cortical volume (CV) abnormalities in Autism Spectrum Disorder (ASD) need to be further explored by examination of the two determinants of CV, that being cortical thickness (CT) and pial surface area (PSA; Murphy, Beecham, Craig, & Ecker, 2011). The current study suggests that the two determinants of CV should be explored even in the presence of null CV findings, if structure-function analyses are significant (i.e., bi-lateral precentral gyrus and neuropsychological motor test) as demonstrated in the current sample (see Duffield et al., 2013). The only significant anatomic finding was reduced CT in the left frontal motor regions (primarily left precentral gyrus), which also corresponded to the only significant relationship between a motor variable (i.e., grooved pegboard test) and motor region-of-interest (ROI) where ASD had a stronger relationship than typically developing controls (TDC; ASD > TDC). Left hemisphere biased CT group differences has been shown to have the highest classification accuracy (i.e., designation of ASD versus TDC) of morphological parameters (Ecker et al., 2010), yet PSA has been shown to have far greater modulation of CV abnormalities. This is particularly true for subthreshold PSA (Ecker et al., 2013). These prior findings are not only consistent with the current motor ROI findings, but also provide an explanatory framework for the functional neuroanatomy of a generally worse left handed performance (i.e., non-dominant hand) for ASD compared to controls in a generally right handed dominant sample (no significant group differences on handedness). The only significant motor ROI finding was in the left hemisphere (i.e., ipsilateral to worse left handed performance), but subthreshold PSA findings in the right precentral were found and likely provide explanatory power of motor performances in the aggregate, despite a lack of significant statistical differences in a specific motor ROI individually.

Keywords: cortical thickness, voxel-based morphometry, motor, autism spectrum disorder

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Cortical Thickness and Voxel-Based Morphometry of Classic Motor Regions of Interest in Autism Spectrum Disorder

General Overview of Autism

Kanner (1943) was the first author to outline the differentiating features of Autism from other disorders (e.g., schizophrenia), suggest key diagnostic features (focusing on an inability of persons with autism to relate themselves to others, an obsessive maintenance of sameness, and language abnormalities), and emphasize a constitutional origin of the disorder (Hollander, Kolevzon, & Coyle, 2011). Almost all of Kanner's observations are relevant today. At relatively the same time, Hans Asperger (1944) wrote about a population with many of the same features identified by Kanner, but apparently higher functioning than the group Kanner studied. Various authors in the 1960s observed high frequency patterns of symptoms similar to autism, but not meeting diagnostic criteria for the syndrome (Anthony, 1958; Lotter, 1966). Then in the late 1970s an epidemiological study, demonstrating children with autistic like features that did not fulfill usual diagnostic criteria laid the groundwork for the notion of the spectrum (Wing & Gould, 1979). The early epidemiologic studies of autism emphasized the need to incorporate varying levels of intelligence, ranging from severely impaired to normal, with the disorder. Twin studies then elaborated the diversity of the diagnosis by characterizing Autism Spectrum Disorder (ASD) as a multifactorial disorder with the interaction of multiple genes (Hollander et al., 2011).

Factors Involved in the Clinical Evaluation and Profile of ASD

With the current understanding of the multifaceted nature of the disorder, a contemporary comprehensive clinical evaluation for ASD should involve multiple aspects of a child's

development including: variability in levels of functioning within and across domains of development (i.e., speech, language, social functioning, motor functioning, cognition, adaptive behavior, and psychiatric symptoms); nature and course of a child's development over time; the role of genetic, family, medical, and educational histories and how these might impact the current presentation; and the child's ability to functionally apply his or her repertoire of skills to everyday life across settings and contexts (Hollander et al., 2011). An examination of language, communication, and social interaction skills, as well as behavioral presentation, including any restricted, repetitive, sensory or perseverative interests, or atypical patterns of behavior, and behavioral dysregulation must be conducted to evaluate suitability for meeting diagnostic criteria. Further, an ASD evaluation should also include the following: when developmental milestones were obtained (e.g., smiling, sitting, rolling, standing, walking, first words, phrases, sentences); feeding and sleeping patterns; behavioral disposition; socialization, communication, and play patterns; and sensory development (e.g., auditory, visual, and tactile responsiveness). Research shows diagnoses of ASDs in young children tend to be stable over time (Hollander et al., 2011), and thus the earlier diagnosis is made the earlier the interventions can be implemented. Early markers of ASDs in young children include atypical developmental behaviors (i.e., language delay, sensory sensitivities, visual tracking, and attention abnormalities) and the delay in or absence of normally developing milestones such as eye contact, social smiling, imitation, babbling, and responsiveness to name. Motor deficits are also common and can include impairment in fine and gross motor skills, coordination, spatial awareness, balance, posture, movement, muscle tone, motor planning, praxis, and sensory integration problems. Impairments in motor control that can affect social communication (e.g., oral praxis and gesture use) are also well documented (Hollander et al., 2011).

Despite these common symptoms, a consistent neuropsychological profile of ASD is challenging because of various methodological issues. Furthermore, an individual's neuropsychological performance can differ significantly over the course of development (Hollander et al., 2011). Variability in subject selection (i.e., age, functional level, diagnosis, comparison group, developmental maturation) creates difficulty comparing different research findings and can limit generalizability. This is largely driven by the inherent heterogeneity of the disorder (i.e., spectrum). Variability can exist within diagnostic categories, as well as within and between neuropsychological domains (e.g., executive functioning) leading to different neuropsychological theories of ASD (Sanders, Johnson, Garavan, Gill, & Gallagher, 2008).

However, neuropsychologists also examine motor functioning (including: muscle tone, gate, dominance and laterality, handedness, motor skills, praxis, and coordination and fine motor activities), which can be incrementally important for a diagnostic profile as a standardized neurological evaluation is necessary for defining neurodevelopmental abnormalities (Hollander et al., 2011). Two classes of neurological soft signs have been identified in ASD. First, *mild but classic neurological signs* refer to ataxia, hypotonia, asymmetry and muscle tone, and deficits in sensorimotor function. Second, *developmental soft signs* refer to sensorimotor functions that reflect a delay in maturation (Hollander et al., 2011). However, this is not necessarily a diagnostic improvement. Neurological soft signs are defined as abnormal or age related motor/sensory findings upon neurological examination, but performance does not indicate a fixed or transient neurological disorder. Thus to be considered a soft sign there should be no association between the observed behavior and a positive history of neurologic disease or trauma. Furthermore, related neurological soft signs should not be considered pathognomonic of neurologic disease. Thus by definition neurologic soft signs are indicative of central nervous

system dysfunction, but they are not indicative of specific central nervous system pathology or etiology. This is in contrast to hard neurological signs, which are medically documented symptoms of neurological disease (Shaffer, O'Connor, Shafer, & Prupis, 1983). Three types of soft neurological signs have been defined: those that may suggest immaturity or developmental delay; those that are mild expressions of hard neurological signs (which can be difficult to elicit and may be inconsistent); and behaviors that may be associated with non-neurologic causes. Soft signs are also not supplementary in that multiple soft signs do not equate a hard sign (Spreen, 1984). Additionally, subjectivity can affect the neurological examination findings (e.g., hypotonia). Therefore, neurological soft signs can simply be understood as abnormalities within a complex neural network of brain development in ASD (Hollander et al., 2011).

In contrast, standardized neuropsychological tests of motor functioning have the possibility to become a distinct neurological sign, or more reliable indicator of ASD, than clinical evaluations or other less reliable neuropsychological domains. For example, dyspraxia (impaired performance of skilled gestures/movement) is commonly reported in ASDs, although this is not ubiquitous. This can be elicited in several domains including buccofacial dyspraxia (difficulty performing purposeful learned skilled movements with the face, lips, tongue, cheeks, larynx, and pharynx), ideomotor dyspraxia (spatial and temporal errors in pantomiming the use of a tool or instrument), and ideational dyspraxia (inability to carry out or sequence a series of acts), among others. Imitation problems are also salient in autism and have been particularly observed in clinical tasks assessing dyspraxia with individuals who have ASD (Hollander et al., 2011). Imitation deficits, such as social reciprocity, have been theorized to account for several classic impairments in ASD (e.g., Hobson & Lee, 1999; Rogers & Pennington, 1991). In general though, standardized examinations of praxis have demonstrated difficulties in skilled motor

gestures that are evident not only in imitation, but also in different domains of purposeful movements (i.e., actions in response to commands, use of tools, choice of appropriate tools, etc.). Therefore a more generalized impairment affecting multiple praxic functions could be responsible for various difficulties in ASDs. It is unclear whether dyspraxia can be accounted for by basic motor skill abnormalities common in ASD is or whether additional factors should be considered. This is important because impaired performance of skill gestures could elucidate neural circuit abnormalities involved in the acquisition of sensory representations of movements and the motor sequences necessary for performing them. Thus, the neurological basis of dyspraxia is not well known and likely multifaceted, however at a functional level it is likely that dyspraxia cannot be entirely accounted for by impairment in basic motor skills (Hollander et al., 2011). Identified correlations of dyspraxia with social, communicative, and behavioral disturbances suggest that dyspraxia may be a major clinical component of ASDs (Dziuk et al., 2007). Therefore, a clinical profile of motor disturbances provided by standardized neuropsychological measures could be a more "hard", or reliable diagnostic indicator than current practices. 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.

Neuropsychological Motor Impairments in ASD

Although Kanner's (1943) classic paper outlined the core features of autism that eventually became the triad criteria for the diagnosis of autism, he also noted, "… several of the children were somewhat clumsy in gait and gross motor performance… (p. 248)." While most contemporary studies of ASD have focused on these core features of autism (Geschwind, 2009), studies that have examined motor deficits observe increased levels of clumsiness and various

forms of dyspraxia more frequently in autism than in individuals with typical development (TD; Downey & Rapport, 2012; Fournier, Hass, Naik, Lodha, & Cauraugh, 2010; Gowen & Hamilton, 2013).

Most studies of motor functioning in ASD have relied on clinical exam findings or rating scales, whereas, evidence for motor impairment on standardized neuropsychological assessment measures in ASD has been more inconsistent. For example, some studies have shown that compared to typically developing controls, those with ASD exhibit decreased strength-of-grip (SOG) or finger oscillation speed on the finger tapping test (FTT) (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; Williams, Goldstein, & Minshew, 2006). However, not all studies have reported such differences. More recently, Duffield et al. (2013) showed no significant differences between 56 male ASD individuals and 30 typically developing controls in SOG. In a study comparing 10 individuals with Asperger's to those with typical development, no significant differences were found on FTT (either dominant or nondominant hand), Grooved Pegboard Test (GPT; either dominant hand, nondominant hand, or total measures of time or number of drops), Trail Making (Part A, Part B, or difference between A and B), Finger-Thumb Apposition Test, or the Fregly-Graybiel tests of ataxia (Weimer, Schatz, Lincoln, Ballantyne, & Trauner, 2001). Three studies using the FTT task found no differences between the ASD and control groups in children and adolescents (Weimer et al., 2001; Williams et al., 2006), or in adults (Minshew et al., 1997), while only one study found significant differences (Hardan et al., 2003). More recently, Duffield et al. (2013) found that ASD individuals were significantly slower at tapping using both hands than typically developing controls. In the Hardan et al. (2003) study, the autism group performed significantly

worse on FTT for the nondominant, but not the dominant hand. Kern et al. (2011) found that ASD severity was correlated with SOG, with more severely affected children having weaker hand strength, suggesting level of motor deficit relates to severity of neuropsychiatric impairment (see Hadders-Algra, 2008), which was also the finding of Travers, Powell, Klinger, and Klinger (2013) in terms of postural stability.

Four studies using the GPT, a test of fine motor control, motor dexterity, and speed, reported no significant differences between ASD and control groups (Minshew et al., 1997; Rumsey & Hamburger, 1988; Weimer et al., 2001; Williams et al., 2006). Although Rumsey and Hamburger (1988) found no significant differences between the ASD group and the controls on GPT total time (dominant and nondominant hand), a trend for poorer performance in the ASD group was noted. In contrast, Hardan et al. (2003) found significant differences between ASD and controls on the GPT for the dominant and nondominant hand total time, but no differences existed on number of drops, findings consistent with those of Szatmari et al. (1990) who also found ASD subjects impaired. Recently, Duffield et al. (2013) found that ASD individuals were significantly slower than controls (per peg) on the GPT for both hands and had significantly more drops using the non-dominant hand.

The lack of consistent motor findings, including those with standardized neuropsychological measures, likely relates to design and methodological differences across studies as well as the level of motor complexity being assessed. Some studies only examined a single motor task while others used multiple measures, and not always standardized neuropsychological measures. Differences in age ranges represent another obvious factor potentially resulting in inconsistent motor performance, as some of the aforementioned studies were in children, others in adults and some spanned childhood to adulthood. Differences in

autism severity and associated cognitive factors also likely relate to motor findings (Carcani-Rathwell, Rabe- Hasketh, & Santosh, 2006) as Goldman et al. (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. Additionally, although positively related to neuropsychological measures of motor functioning, coarse clinical rating methods are not a substitute for direct measures like SOG, FTT and GPT (Lezak, Howieson, & Bigler; Müller, Schäfer, Kuhn, & Przuntek, 2000; Pedersen, Oberg, Larsson, & Lindval, 1997; Sachdev, Hume, Toohey, & Doutney, 1996).

Duffield et al. (2013) viewed their comprehensive neuropsychological motor findings (i.e., SOG, FTT, GPT) from a hierarchical categorization of motor complexity and integration where the SOG measure is viewed as most basic (Lezak, et al., 2012). Coordinated movements necessary to perform the FTT are viewed as intermediate to the more complex and skilled motor movements necessary for GPT performance (Lezak, et al., 2012). With increased complexity of motor systems necessary to perform the task, if ASD were associated with deficits in neural connectivity (Geschwind, 2009) then the greatest likelihood for motor differences between ASD and typically developing groups would be with FTT and GPT tasks, and the least likelihood for differences in SOG. The authors state their findings (i.e. SOG, FTT, GPT) 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.

Basis for Investigation of Cortical Thickness (CT), Pial Surface Area (PSA), and Voxel-Based Morphometry (VBM) for Key Motor Areas in ASD

Using contemporary neuroimaging methods region of interest (ROI) morphology of key motor areas of the brain may readily be determined (see Draganski & Bhatia, 2010). Further,

examining morphological changes in the brain structure-by-structure (i.e., multiple ROIs) enhances understanding of cortical atrophy or enlargement and provides various metrics to explore neurobehavioral variables of clinical utility (Bigler et al., 2010). However, few studies have comprehensively examined motor areas in individuals with ASD, and those that have were not systematic in the application of traditional neuropsychological measures of motor function (Mostofsky et al., 2009; Qiu, Adler, Crocetti, Miller, & Mostofsky, 2010).

Duffield et al. (2013) examined region of interest (ROI) volumes in multiple motor areas of the brain in the same cohort as the current study, including establishing a neuropsychological motor hierarchy profile, which was examined in relation to cortical volume (CV). CV is determined by cortical thickness (CT) and surface area (SA; also known as pial surface area, or PSA; see Figure 1 in Appendix 2). Murphy, Beecham, Craig, and Ecker (2011) discuss the importance of examining how abnormalities in CV relate to both CT and SA because each of these anatomic measures have distinct genetic determinants, differing phylogeny, and developmental trajectories. Ecker et al. (2013) discuss the radial unit hypothesis (i.e., cells within a ontogenetic column share a common origin before migrating to their location within the cortex during development), where the number of cells within cortical columns mediates CT, and SA primarily reflects the number of columns within a cortical region. Thus, measurements of CV may therefore reflect structural properties that are unique to cortical SA or unique to CT, and establishing the relative contribution of each measure to disturbances in ASD across the age spectrum is important for understanding CV abnormalities (Ecker et al., 2013; Murphy et al., 2011). Further, Ecker et al. (2012) note that understanding the neuroanatomic profile of a disorder such as ASD requires a spatially unbiased analytical approach, such as VBM these authors suggest, thus VBM was added to our set of analyses.

The current research will incorporate the previous systematic application of neuropsychological motor measures and resulting motor profile with the systematic analysis of neuroanatomic structural differences, including CT, PSA, VBM analyses. This constitutes a follow-up morphological investigation from a previous ROI volumetrics analysis performed in this cohort (Duffield et al., 2013), to further understand the neuroanatomic relationship between group motor differences. It should be noted that any use of the term "volume" pertaining to results of the current analyses refer to VBM findings.

Background for Neuropsychological Tests of Motor Function Employed

Grip strength. SOG (Heaton, Grant, & Matthews, 1991) 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 hard 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 three trials was used.

Finger tapping. The FTT (Heaton, Grant, & Matthews, 1991) was used as a measure of motor speed and motor control. The FTT uses a manual device activated by the index finger that records the number of taps performed by a subject over a series of ten-second intervals. The finger tapping score is computed for each hand separately and is the mean of five consecutive 10-second trials.

Grooved pegboard. The GPT (Matthews & Klove, 1964) was used as a measure of fine motor control, motor speed, and dexterity. The test consists of a five-by-five-inch metal plate that contains a five-by-five matrix of keyhole-shaped holes in various orientations. The participant is required to insert pegs in a prescribed order as quickly as possible using the

dominant and nondominant hand separately. The score is the time required to place pegs into all 25 holes, and the timing is not interrupted in the event of a dropped peg. The number of pegs dropped is also recorded.

Background of Imaging Methods Employed

VBM. Traditionally, techniques used to analyze structural MRI included visual assessment and manual measurements of regions of interest (Whitwell, 2009). Today, automated techniques are used. VBM uses statistics to identify brain differences between groups of subjects, which are used to infer atrophy or enlargement. T1-weighted volumetric MRI scans are used and the technique performs statistical tests across all voxels in the volumes of both groups to identify intensity differences (Whitwell, 2009).

MRI scans need to be matched together spatially (i.e., registered) so that statistical analyses can be performed across multiple MRI scans from different individuals. This is so that a location in one subject's MRI scan corresponds to the same location in another subject's scan, which is a process known as spatial normalization (Whitwell, 2009). Registering all images from a study onto the same template image so they are on the same space generally completes this. Ashburner and Friston (2000) and (Davatzikos, Genc, Xu, & Resnick, 2001) have reported different algorithms can be used to perform this registration, but typically include a nonlinear transformation. The template image used for the spatial normalization can be a single MRI scan or can be created by averaging across a number of different MRI scans that of been put into the same space. Recent registration techniques involve the high dimensional DARTEL algorithm. For this registration method, rather using a template, intensity values are adjusted for individual brain size differences (Ashburner, 2007; Manjón, Coupé, Martí-Bonmatí, Collins, & Robles, 2010; Rajapakse, Giedd, & Rapoport, 1997; Tohka, Zijdenbos, & Evans, 2004). Before spatial

normalization, images are segmented into different tissue compartments (gray matter, white matter, CSF), and an analysis is performed separately on each tissue compartment. There are number of ways to perform the segmentation, including using prior probability maps as well as voxel intensity to guide segmentation. Image intensities are scaled by the amount of contraction that is occurred during spatial normalization, so that the total amount of gray matter remains the same as in the original image. Next, the images are smoothed (Ashburner & Friston, 2000; Good et al., 2002), by which the intensity of each voxel is replaced by the weighted average of the surrounding voxels, in essence blurring the segmented image. Following this, analysis of differences in intensities between groups is conducted. The number of voxels averaged at each point is determined by the size of the smoothing kernel, which can vary across studies (Fischl et al., 2002; Karas et al., 2003; Whitwell, 2009). Smoothing makes the data more normally distributed, increasing the validity of parametric tests, and reduces inter-subject variability, and increases the sensitivity to detect changes by reducing the variance across subjects (Ashburner & Friston, 2000; Salmond et al., 2002; Whitwell, 2009).

Although necessary to analyze data, these processing steps can also introduce errors and variability in the analysis, which will reduce sensitivity. Normalization accuracy will vary across regions and thus the ability to detect change will differ across regions. The accuracy of the segmentation will also depend on the quality of the normalization. Segmentation errors can also occur because of displacement of tissue and partial volume effects between gray matter and CSF (Whitwell, 2009).

For statistical analysis, the null hypothesis is that there is no difference in tissue between the groups. These analyses generate statistical maps showing all voxels of the brain that will either refute the null or show significance at a certain p-value. Parametric statistics using the

general linear model in the theory of Gaussian random fields are typically used. Both gray and white matter volumes can be assessed using VBM, the majority of VBM studies focus on gray matter as white matter changes can be more accurately assessed using techniques such as diffusion tensor imaging (DTI; Whitwell, 2009). Considering the statistical tests are performed across a large number of voxels, it is necessary to correct for multiple comparisons to prevent for the occurrence of false positives. Similar to traditional statistical tests, the power to detect differences between groups will typically be a function of sample size. Therefore, the larger the sample size, the greater the power to detect differences (Whitwell, 2009). Sample size should be considered a strength of the current study.

CT. Several automated techniques for examining CT are used in the scientific community (e.g., CIVET), but one of the most used extraction algorithms is the Freesurfer pipeline (Redolfi et al., 2015). Currently, CT analyses are performed using QDEC with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). QDEC is an acronym for Query, Design, Estimate, and Contrast. It is intended to aid researchers in performing inter-subject/group averaging and inference on the morphometry data (i.e., PSA, CT and CV) produced by the FreeSurfer processing stream (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecQDECGroupAnalysis). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl et al., 2002; Fischl, Salat, et al., 2004; Fischl, van der Kouwe, et al., 2004; Han et al., 2006; Jovicich et al., 2006; Reuter, Rosas, & Fischl, 2010; Reuter, Schmansky, Rosas, & Fischl, 2012; Ségonne et al., 2004). Briefly, this processing includes motion correction and averaging (Reuter et al., 2010) of multiple volumetric T1 weighted images (when more than one is available), removal of non-

brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002; Fischl et al., 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998) tessellation of the gray matter/ white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl, Sereno, & Dale, 1999), registration to a spherical atlas which utilizes individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999), parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006; Fischl, van der Kouwe, et al., 2004), and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of CT, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data, thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of CT have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg

et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012).

Review of CT, SA, and VBM in ASD

CT findings. Sowell, Thompson, and Toga (2004) hypothesized that cortical CT reflects dendritic arborization and pruning within gray matter or changes in myelination at the interface of gray and white matter. Examining CT in diagnostic groups can be challenging (Scheel et al., 2011) because many factors can influence CT results, including age (Salat et al., 2004), gender (Luders et al., 2006), intelligence (Shaw et al., 2006), handedness (Narr et al., 2007), total gray matter volume (Chung et al., 2005), total brain volume (Hardan, Muddasani, Vemulapalli, Keshavan, & Minshew, 2006), and cortical complexity and folding patterns (Thompson et al., 2005; White, Andreasen, Nopoulos, & Magnotta, 2003).

In the self-proclaimed first analysis of CT in individuals with high-functioning Autism (HFA), using a novel heat kernel smoothing method, Chung, Robbins, Dalton, Davidson, Alexander, and Evans (2005) found significant decreases in CT for 17 male, adolescents in the right inferior orbital prefrontal cortex, the left superior temporal sulcus, and the left occipitotemporal gyrus. These authors also found significant increases in CT in the left superior temporal gyrus, the left middle temporal gyrus and bilateral postcentral sulci. The authors controlled for age and total gray matter volume. They suggest that controlling for age reduces risk of false positive findings.

In examining CT and temporal changes in 28 (18 males and 10 females) adults with HFA, Scheel et al., 2011 found significantly thinner cortex clusters in right hemisphere precentral and postcentral gyri. The authors speculate that morphological alterations in these areas should

predominately be found in studies that focus on younger cohorts. This is due to discrepancies between DOSS (employed to examine whether a main effect of group exists independent of participant age) and DODS (used to explore whether CT is more related to age in one group than in the other) results in Freesurfer's QDEC design matrix. These two different design matrices provided by QDEC (i.e., DOSS and DODS) are useful in examining the time course of brain development in a linear model by considering offset and slope of the relationship (Scheel et al., 2011). In this study, DOSS assumed different CT measures for both groups in the youngest subjects (different offsets) and a similar impact of aging in both groups (same slope). DODS also assumed different offsets, but a different impact of aging between both groups (different slopes). Therefore, thinner clusters in DODS results reveal an age x diagnosis interaction with CT gradually decreasing over time in the controls, but not in HFA. Additional results suggest that the aberrant developmental cortex trajectory in ASD continues into adulthood, for at least some brain regions.

Few studies have examined CT (as well as CV and PSA) in ASD youth populations. Mak-Fan, Taylor, Roberts, and Lerch (2012) examined 25 male ASD individuals aged 6-15 years of age. These authors found thicker cortex in the left inferior frontal gyrus and left medial parieto-occipital fissure/precuneus for ASD individuals at younger ages only. The vertex-based analysis showed similar regions of age-related changes in CT for both groups except the inferior frontal gyrus and left precuneus, which showed steeper decreasing slopes with age in children with ASD across age compared to controls. Although an age by group interaction was not significant for CT, age effects were significant in the ASD group only (i.e., no significant temporal total CT changes for controls). The results suggest a pattern of increased CV, SA and CT at younger end of the age range of this sample (around 7.5 years), but decreased or similar

CV, SA, and CT at the older end of this age range (around 14.5 years). The authors suggest their findings support the growth dysregulation hypothesis (Akshoomoff, Pierce, & Courchesne, 2002) by providing additional evidence of atypical maturation of the cortex in children with ASD. No evidence was found for overall increase in CT on averages across lobes for the whole group. This is in contrast to Hardan et al.'s (2006) findings that showed thicker cortex in total cerebrum, particularly in the temporal lobe in 17 males with ASD aged 8 to 12 years using average measures of CT across lobes. These authors however did not use age as a covariate, and as Mak-Fan, Taylor, Roberts, and Lerch (2012) state, it is difficult to compare results from an averaging method to a vertex-based approach, which provides regionally specific detail.

Hardan, Libove, Keshavan, Melhem, and Minshew (2009) examined CT in 18 males with ASD and 16 aged matched controls between ages of 8 and 12 years at baseline and again at a 30-month interval. The authors found a greater decrease in total CT in ASD individuals relative to controls, in the temporal and occipital lobes, and a trend toward significance in the frontal lobes, but significant only in the occipital lobe after controlling for multiple comparisons. Within group analyses showed CT decreases in the frontal, temporal, parietal, occipital, and total brain in the ASD group, all which remained significant after correction for multiple comparisons except the temporal lobe. These results are consistent with Mak-Fan, Taylor, Roberts, and Lerch (2012), where significant decreases with age for total and lobar CT were observed in the ASD group only.

Raznahan et al. (2009) examined CT in 76 male ASD individuals ranging in age from 10 to 60 years old using two approaches: one which examined lobar and sublobar measures derived from automated parcellation of the cortical sheet and another which examined CT at several thousand points across the cortical sheet in a spatially nonbiased manner. Cortical parcellation,

or “regional” analysis, showed significant age by group interactions for CT in the temporal lobes and within these the fusiform and middle temporal gyri. Spatially nonbiased ‘‘vertex-based’’ analysis replicated these results and identified additional age by group interactions for CT within right (medial frontal, superior frontal, inferior frontal, precentral, inferior temporal, parahippocampal gyri, fusiform and inferior parietal lobule) and the left (medial frontal, middle frontal, and superior temporal gyri) cortical sheet. These authors found that in regions showing an age by group interaction, there was no relation between age and changes in CT in the ASD group, compared to a significant decrease in CT with age in the control group. They also found that at younger ages CT was decreased in ASD relative to typically developing controls, but increased relative to controls at older ages. These results contradict the findings by Mak-Fan, Taylor, Roberts, and Lerch (2012), however as these authors state, given the differences in age ranges between studies, is difficult to identify a source of the discrepant findings. Similar to Scheel et al., 2011, Raznahan et al. (2009) findings suggest cortical dysmaturation in ASD is not restricted to childhood or adolescence and continues into adulthood.

Ecker, Ginestet, Feng, Johnston, Lombardo, Lai, … and Murphy (2013) currently reiterate what few previous authors have stated, that very few studies have examined CV, SA, and CT in the same sample (see Hazlett et al., 2011; Mak-Fan et al., 2012; Raznahan et al., 2009; Scheel et al., 2011). The authors used a spatially unbiased vertex-based approach that provides measures of CV, SA, and CT at several thousand points across the cortical sheet to investigate regional differences in 84 individuals with ASD and 84 TDC who did not differ in age and FSIQ. Individuals with ASD had significantly decreased CV in the bilateral orbitofrontal cortex. Individuals with ASD had significantly increased CT in a large cluster located in the left lateral prefrontal cortex (ventrolateral and rostrolateral PFC), and had significantly decreased CT of the

right anterior temporal lobe (including the superior, middle, and inferior temporal gyrus) compared to matched controls. No between group differences for SA were found. To examine how variations in CT and SA relate to differences in CV and to investigate the spatial overlap between CT and SA, a more lenient statistical threshold of $P < .05$ (uncorrected) was used to reexamine the difference maps heuristically. Individuals with ASD had increased CT across the frontal lobe and temporal lobes, and also some areas of decreased CT in the temporal lobe. Individual with ASD also showed decreased ASD in various frontal regions and increased SA of the temporoparietal junction. Across both hemispheres, the number of vertices with a significant difference in CT only was approximately equal to those with a significant difference in SA only (51% vs. 45%, respectively). The patterns of significant differences in CT and SA were largely non-overlapping and shared only about 3% of all significantly different spatial locations on the cerebral surface. The authors stated the observed low percentage of overlap is consistent with the idea that differences in SA and CT are spatially independent and that SA and CT contribute in a unique way to the group differences in CV. Of all the underlying differences in CV ($P < .05$, uncorrected), a total of 67% overlapped with significant differences in CT only (8%), SA only (56%), or both CT and SA (5%). Thus, differences in SA explained a significantly larger proportion of differences in CV than did differences in CT (remaining 31% of all significant differences in CV could not be explained by significant differences in either SA or CT). Differences in CV observed in adults with ASD may therefore be underpinned by separable variations in its 2 components, CT and SA (exhibited statistically independent sources of variability), each which result from distinct developmental pathways that are likely modulated by different neurobiological mechanisms and thus potentially reflect different neuropathological processes.

Shi, Wang, Peng, Wee, and Shen (2013) state that the human brain network is generally comprised of several modules (e.g., community structures), which are more densely connected within modules than between the modules and the modularity property is ubiquitous in most complex systems in nature. It has been suggested that such modular organization provides a balance between brain functional segregation and integration, which are the two most fundamental aspects of brain organization. A module of a complex network is a subset of nodes that are densely connected within the modules but sparsely connected between the modules. Anatomically meaningful cortical regions were used as nodes and the correlations of inter-regional CT were taken as connections. Using 49 ASD children and 51 typically developing controls (age range of 6–15 years), brain networks were constructed for each population using inter-regional correlations of CT. Image processing and cortical reconstruction were performed with the Freesurfer image analysis suite and all images were resampled into isotropic voxel of 1x1x1 mm^3, intensity inhomogeneity corrected, and skull stripped. Local CT was measured as the distance between the inner and the outer cortical surfaces at each vertex. ROI based thickness differences between autism and control groups, and found significant lower thickness in autism subjects in ROIs of bilateral middle frontal gyrus, right superior frontal gyrus, and bilateral temporal pole. Autism subjects also demonstrated higher thickness in bilateral paracentral lobe. Regression revealed a negative linear correlation between thickness and age for both groups, agreeing with previous findings. The three main findings were: 1) when compared to healthy children, autistic children presented a significantly reduced gross network modularity, and a larger number of inter-module connections; 2) increased intra- and inter-module connectivity were both found among the module associated with brain functions of self-reference and episodic memory in autism (in brain regions including middle frontal gyrus, inferior parietal

gyrus, and cingulate); 3) inter-regional correlations revealed increased intra-connections in the frontal lobe (excessive local connections), and decreased connections between frontal lobe and other lobes such as temporal and parietal (and regions in temporal lobe have significantly reduced connection strength with regions in parietal lobe), which may contribute to the alteration of modular organization. In regards to the first finding, the autistic brain networks may have been re-organized in part to offset the CT alterations, inter-regional correlation abnormalities, and/or maintain cognitive functions and daily living activities. This re-organization could be a result of the autistic brain following a different developmental trajectory similar to the Raznahan et al. (2009) findings. In general, the results confirmed the author's hypothesis that autism has altered inter-regional correlations, which further contributes to the alteration of modular organization.

VBM findings. Ecker et al. (2012) discuss lack of replication as a current problem in understanding neuroanatomical relationships in ASD. This is often due to small, heterogeneous samples that differ within and across participants in various ways (diagnosis, intelligence, age, image analysis method). Also, understanding the neuroanatomic profile of a disorder such as ASD requires a spatially unbiased analytical approach, such as VBM these authors suggest. This approach relies on conservative statistical thresholds mandated by the large number of voxels compared between groups. Thus, large, relatively homogeneous samples are required to reliably detect subtle and spatially diffuse differences in brain anatomy. These authors note that regional or voxel-level analytic methods may not be optimal for detecting differences that are theoretically expected at a more distributed level the authors note.

To this end, Ecker, Suckling, Deoni, Lombardo, Bullmore, Baron-Cohen, and Catani et al. (2012) examined between group differences in regional neuroanatomy assessed by VBM in 89

high functioning adult males. They found significant differences between groups in four extensive clusters: (clusters 1 & 2) ASD individuals had significantly greater volume in bilateral anterior temporal regions (inferior, middle, superior temporal gyrus; fusiform gyrus; parahippocampal gyrus; insula; left putamen, caudate nucleus, and thalamus); and (clusters 3 & 4) ASD individuals had significantly greater volume in the right dorsolateral prefrontal cortex (i.e., middle frontal gyrus) and the dorsal precentral and postcentral gyrus. Additionally, ASD individuals had significantly less gray matter volume in the occipital lobe and medial parietal cortex (inferior, middle, and superior occipital gyrus); posterior cingulate/precuneus; cuneus; lingual gyrus and parts of the posterior fusiform gyrus. The authors did not find any significant relationships between age and gray matter volume in clusters of significant group differences, whether considering all participants or each group separately. Four clusters of significant white matter decreases in ASD individuals relative to controls were found: (1) the corticospinal and cerebellar tracts; (2) frontal connections, including the uncinate fasiculus and the fronto-occipital fasciculus; (3) the internal capsule comprising descending frontostriatal and ascending thalamocortical projections; and (4) the arcuate fasiculus connecting the Broca and Wernicke areas.

Greimel et al. (2013) examined gray matter structural differences using the Bayesian approach for VBM in 47 HFA individuals (including diagnoses of Asperger's and Autism) ranging in age from 10 to 50 years old. They found a significant decrease in the anterior cingulate cortex, bilateral posterior superior temporal sulcus, and the right middle temporal gyrus. No gray matter increases in the ASD group compared to control subjects were observed. The authors also used the cross-sectional design to examine group differences in age effects on regional gray matter volume in regards to linear, quadratic, or compound effects of age. Several

age-related changes in regional gray matter volumes were found: (1) gray matter volumes for the left amygdala, right temporoparietal junction, and left septal nucleus showed an inverted U-shaped trajectory in both groups, with this process occurring at a significantly younger age with HFA individuals; (2) gray matter volume increased in a negative quadratic fashion in the right amygdala until middle adulthood in both groups, again this occurred at significantly younger age in the HFA group (in contrast to the left amygdala gray matter volume curves in the right amygdala which converged with increasing age); (3) children and adolescents in the HFA group exhibited a curve parallel to controls in gray matter volume in the middle cingulate cortex, which began to differ approaching adulthood through adulthood, accounting for significant differences between groups; (4) gray matter volumes decreased linearly with age for the right precentral gyrus in the ASD group, while volumes in controls followed a U-shaped pattern accounting for significant differences between groups. The authors concluded that in most cortical regional differences, peak gray matter volume occurred earlier in HFA individuals compared to controls. No group differences in gray matter volume or volume changes with age could be attributed to potential differences between total brain volume, or intelligence between groups.

CT and VBM comparisons. Jiao et al. (2010) attempted to construct a diagnostic model of ASD based on regional thickness measures extracted from surface-based morphometry (SBM) and to compare this model to VBM measures using 22 individuals with ASD aged 6 to 15. The authors predicted superiority of this method because the intrinsic topology of the cerebral cortex is that of a 2-D sheet with highly folded and curved geometry (Fischl, et al., 1999), which VBM cannot directly measure (Jiao, Chen, Ke, Chu, Lu, & Herskovits, 2010). SBM centers on the computation of cortical topographic measurements (i.e., CT, SA, curvature, and sulcal depth) and can provide analyses complementary to that provided by VBM and thus likely to outperform

VBM based diagnostic models (Akshoomoff et al., 2002; Ecker et al., 2010) and voxelwise CT models (the authors state the limitation of this model is basing the feature dimension reduction step on all samples outside cross-validation). To avoid model-generation bias, the authors applied four machine-learning methods: support vector machines (SVMs), multilayer perceptrons (MLPs), functional trees (FTs), and logistic model trees (LMTs) to generate diagnostic models. In examining 33 structures (for each hemisphere) in 22 ASD individuals aged 6 to 15 years of age, the authors found that thickness-based classification was more accurate than volume-based classification, for each combination of classifier and performance metric. LMT was the best diagnostic model for CT (classification accuracy = 87%; Sensitivity = 95%; Specificity = 75%), which included seven structures. For these seven structures, relative to controls, CT in the ASD group was significantly thinner in the right pars triangularis, left medial orbitofrontal gyrus, left parahippocampal gyrus, left pars triangularis and left frontal pole, but thicker in the left caudal anterior cingulate gyrus and in left precuneus.

Hyde, Samson, Evans, and Mottron (2010) also examined structural differences between 15 ASD individuals (aged 14 to 33) and 13 controls using both CT and VBM analyses. The T1 anatomical MRIs for all subjects were submitted to ‘‘CIVET’’ (http://wiki.bic.mni.mcgill.ca/index.php/ CIVET) for CT and VBM analyses. These authors state that convergent findings of CT and VBM cortical gray matter differences allow researchers to make stronger conclusions regarding structural brain differences in autism. The CT and VBM cortical gray matter findings both found significant increases in middle and medial orbital frontal gyrus. Two analyses also converged in finding significant cortical decreases in the precentral and postcentral gyri. The authors state these findings indicate that the frontal, and pre-and postcentral regions are key areas in which brain structure differs in autism.

Hypothesis Formulations

1. **VBM of Motor ROIs (controlling for PIQ and age):**
    - precentral gyri ASD < precentral gyri TDC
2. **CT of Motor ROIs (controlling for age):**
    - precentral gyri CT/PSA ASD ≠ precentral gyri CT/PSA TDC
3. **CT and VBM Relationship (controlling for age):**
    - significant "r" for reduced CT and VBM for ASD precentral gyri
4. **Developmental Relations:**
    - CT and VBM across life span: childhood (ASD > TDC) → adolescence/adulthood (ASD ≤ TDC)

Method

Subjects

Ascertainment. Participants diagnosed with autism and control subjects were a subset of a longitudinal investigation of brain development selected from a larger sample based on having complete motor data and magnetic resonance imaging (MRI) performed in proximity to motor testing between 2003 and 2006. 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 (Elliott, Murray, & Pearson, 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 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. Subject demographics, from Duffield et al. (2013), are presented in Table 1.

Idiopathic autism sample. Autism was diagnosed using the Autism Diagnostic Interview-Revised (ADI-R), a semi-structured, investigator-based interview with good reliability and validity (Lord, Rutter, & Le Couteur, 1994). All autism subjects were also directly assessed using 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). All autistic subjects met ADI-R, ADOS-G, and the *Diagnostic and Statistical Manual of Mental Disorders*-IV (DSM-IV; American Psychiatric Association, 1994) criteria for autism. History, physical exam, Fragile-X gene testing, and karyotype were performed on all subjects to exclude medical causes of autistic phenotypes. For characterization of the ASD and TDC sample, from Duffield et al. (2013), see Table 2 (Appendix 1).

Control sample. To test for autism-related differences in motor and other neurocognitive performance variables, a comparison sample was composed of typically developing individuals. TDC participants had no developmental, neurological, or clinical history for major psychiatric disorders. Control subjects completed an assessment with the ADOS-G to ensure none met criteria for ASD.

Assessment

IQ. Verbal skills are often diminished in autism (Rapin, 1999) along with considerable variability in verbal and performance IQ scores in autism (Deutsch & Joseph, 2003). For these reasons, we chose a non-verbal or Performance IQ (PIQ) $\geq$ 65 as the minimal level of intellectual functioning to participate in this investigation. Three autism participants were assessed with just the short-form of the WASI but each had a full-scale IQ $\geq$ 65. Please see Appendix 2 (Figure 2-4) for IQ by age scatterplots.

Head circumference and handedness. Standard occipitofrontal head circumference along with handedness based on the Edinburgh Handedness Inventory (Oldfield, 1971) were obtained on all subjects. A score of +100 signifies complete right-handedness and -100 indicates complete left-handedness. Demographic findings are reported in Table 1 (please see Appendix 1).

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).

Image analysis for VBM. The twelfth version of Statistical Parametric Mapping was used (SPM12), which is a suite of MATLAB (http://www.mathworks.com/products/matlab/). The preprocessing pipeline included: 1) Files were converted from DICOM to NIfTI file format (The NifTI image format standard is the common standard used in scientific image processing, because the file is compact, simple, and versatile) using mri_convert (https://surfer.nmr.mgh.harvard.edu/pub/docs/html/mri_convert.help.xml.html); 2) The "acpcdetect" program, part of the automatic registration toolbox (ART) package

(http://www.nitrc.org/docman/view.php/90/917/acpcdetect.pdf), was used for registration; 3) The "N4BiasFieldCorrection" program, part of ANTS registration suite, was used for intensity nonuniformity normalization (http://manpages.ubuntu.com/manpages/precise/man1/N4BiasFieldCorrection.1.html).

Tissue segmentation and warping were completed through the batch editor interface using a standard probability map and the default Gaussian smoothing kernel of 8mm full width at half maximum (FWHM; http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf).

Image analysis for CT and PSA. CT and pial PSA analyses were performed using QDEC with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecQDECGroupAnalysis). As described above, the technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004; Fischl et al., 1999a; Fischl et al., 1999; Fischl et al., 2004; Han et al., 2006; Jovicich et al., 2006; Segonne et al., 2004, Reuter et al. 2010, Reuter et al. 2012). Prior to using the QDEC application, data was preprocessed by the standard FreeSurfer surface-based processing stream, via the recon-all script (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview). All analyses were performed with FreeSurfer, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) and followed the methods detailed by Bigler et al. (2010).

The preprocessing included the removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2002, 2004), intensity normalization tessellation of the gray matter/white matter boundary (Sled et al.,

1998), automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray matter/white matter and gray matter/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Resulting cortical models were registered to a spherical atlas utilizing individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999). The cerebral cortex was parcellated into regions based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004).

Results for each subject were visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Where necessary, manual editing was performed to optimize accuracy (i.e., 57 subjects required manual editing after completion of the initial pipeline, followed by a second round of edits for 30 subjects). Surface inaccuracies involving exclusion of brain parenchyma were edited either by (1) adding control points to aid FreeSurfer in the identification of white matter (since it uses the white matter/gray matter boundary as a starting place for reconstructing the pial surface), and (2) by adding back in the sections of brain that were inadvertently automatically removed. In all cases these modifications involved the cortical surface of the cerebrum (Bigler et al., 2010).

The following grey matter ROIs were examined without masking: precentral gyrus, postcentral gyrus, and the caudal middle frontal area (i.e., supplementary motor area). The thalamus, cerebellum, and basal ganglia were excluded from the group of motor ROIs examined in Duffield et al. (2013) as hypotheses based upon a literature review pertained generally to frontal cortical surface motor ROIs. Significant neuroanatomic findings are reported using Freesurfer surface labels.

Motor tests. Standard FTT and SOG instruments from the Halstead-Retain Battery (Reitan Laboratories: www.reitanlabs.com; see also Heaton et al., 1991) were used along with the standard GPT (Matthews & Klove, 1964). All participants were administered the SOG, FTT, and GPT as outlined by (Reitan & 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 three trials was used. The total SOG score was computed by combining the nondominant hand mean and the dominant hand mean. SOG was measured in kilograms.

Statistical analysis. Linear regressions were performed both for VBM analyses (performed within SPM12) and CT/PSA analyses (performed within QDEC) using linear modeling (describes the observed data as a linear combination of explanatory factors plus noise, and determines how well that description explains the data being analyzed) in a GUI front-end "statistics engine" that constructs the general linear model (GLM) in a matrix notation. This modeling includes: 1) a design matrix (can be user specified) containing the explanatory variables, 2) a parameter estimate matrix, which is a following estimation step where the model is fit to each to each vertex for CT, or at each voxel for VBM, 3) and the contrast vector (s), which is user-specified weighting to each column of the design matrix. This is completed in both the SPM and QDEC programs through effect coding, or slope coefficients representing differences from the overall mean (entire sample). Estimates of the parameter estimates can be converted into statistical parametric maps, which are visualized as a color-coded surface overlay on a model brain. The overlay assigns each vertex or voxel a value based on the likelihood that the null hypothesis is false at that vertex/voxel (i.e., different from zero). Parameter estimates can also be compared to see if one explanatory variable is more strongly related to the data than another (e.g., 1 -1 0 0). A linear combination of estimates of parameter estimates is used to encode the particular hypothesis of interest, which is accomplished through the contrast vector (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GlmReview). Default overlay thresholds were used: $-\log10(p) \leq -2.00$ indicates ASD group demonstrated a significantly thinner vertex

cluster than the TDC group, and -log10(p) ≥ 2.00 indicates the ASD group demonstrated a larger vertex cluster than the TDC group.

For the VBM analyses, grey matter (GM) analyses were performed on 89 subjects with complete motor and imaging data using the "classical" default model. A height threshold of $p \leq .001$ for significant uncorrected cluster level increases (ASD > TDC) or decreases (TDC > ASD) was used, including a family wise error (FWE; $p \leq .05$) correction for any significant uncorrected findings. VBM is likely to provide greater sensitivity for localizing small-scale regional differences in gray matter (Mechelli, Price, Friston, & Ashburner, 2005). Also, morphological trajectories in gray matter from childhood, to adolescence/teenage years, to young adulthood are known to differ in relation to functional and structural connectivity changes (see Giedd et al., 2012). Thus, to maximize the strength of this objective technique, GM analyses included separating the sample into phase of life age groups (i.e., children [5-10], adolescents [11-17], adults [18+]) to investigate if any group differences existed that were driven by factors related to maturational phases of life, but not age per se (e.g., fine motor control differences between children and adolescents). Age was used as a covariate to account for any within group differences (i.e., differences in 5 year-olds versus 10 year-olds) that may negate between group differences for the three maturational life phases, in an attempt to make each group as homogenous as possible to enhance VBM ability to detect group differences. Homogeneous samples are required to reliably detect subtle and spatially diffuse differences in brain anatomy using VBM (Ecker et al., 2012). PIQ was excluded from these models given the potential for this variable to absorb variance between the groups related to neuropsychological motor performance (Dennis et al., 2009). The analysis of children included 9 TDC and 19 ASD subjects (one ASD subject excluded due to missing PIQ data). The analysis of adolescents/teens included 11 TDC

subjects and 17 ASD subjects (two ASD subjects excluded due to missing PIQ data). The analysis of adults included 10 TDC and 20 ASD subjects. All trends towards significance were examined using the SPM viewing program, xjView (http://www.alivelearn.net/xjview/xjView%208%20Manual.pdf).

For the CT/PSA analyses, a default Gaussian smoothing kernel of 10mm full width at half maximum (FWHM) within the DODS (different offsets, different slopes) matrix of QDEC was used. Results were thresholded at a whole brain level using a false discovery rate of $p < .05$ and were corrected for multiple comparisons utilizing a cluster-wise Monte Carlo simulation implemented in QDEC at a threshold of $p < .05$.

An initial whole brain direct comparison without including motor variables was performed on 88 subjects, with complete motor and imaging data, just examining the relationship between CT/PSA and age between the groups, with group (ASD and TDC) as the discrete factor and age as a continuous covariate. The following analyses examined CT/PSA relationships with motor variables between groups, with group (ASD and TDC) as the discrete factor, motor variables as continuous covariates, and age as a nuisance factor (contrast matrix will have a value of '0' for these variables). PIQ was also excluded from these models given the potential for this variable to absorb variance between the groups related to neuropsychological motor performance (Dennis et al., 2009). The SOG analyses included 87 subjects with complete motor and imaging data. The FTT analyses included 88 subjects with complete motor and imaging data. The GPT-UCT (i.e., unit completion time) analyses included 88 subjects with complete motor and imaging data. ROI masking was not used to examine CT/PSA relationships with motor variables, such as secondary motor areas, that may functionally anatomic differences in the ASD brain to complete

the same processes compared to standard motor ROIs in typically developing individuals (e.g., Lombardo et al., 2015).

Results

VBM findings

The analysis of children (age 5-10) demonstrated a cluster-level uncorrected trend toward significance for volumetric increases (ASD > TDC), $p = .008$, in the left temporal lobe (stereotaxic coordinates = -30 -3 -40), that did not survive family wise error correction. The analysis of adolescents/teens demonstrated three significant uncorrected cluster-level volumetric decreases: the middle frontal gyrus to partially outside the brain parenchyma (stereotaxic coordinates = 52 19 49), t-value at peak vertex = 5.67, $p \leq .000$; the frontopolar prefrontal cortex (stereotaxic coordinates = 0 69 15), t-value at peak vertex = 5.12, $p \leq .001$; and the parietal cortex (stereotaxic coordinates = 51 -51 62), t-value at peak vertex = 4.94, $p \leq .000$. None of the uncorrected cluster-level volumetric decreases survived family wise error correction. The adult analysis (18-42 year olds) demonstrated no significant uncorrected cluster-level increases (ASD > TDC) or decreases (TDC > ASD) with a height threshold of $p \leq .001$, or trends towards significance. Given the lack of any general group differences, further analyses incorporating motor variables into the model were deemed unnecessary.

CT and PSA Findings

General CT/PSA differences without motor variables using age as a covariate. A DODS (i.e., different offsets, different slopes) based general linear model analysis with age as a covariate revealed two Monte Carlo corrected clusters that exceeded a cluster-wise probability of $p \leq 0.05$, where the strength of significant CT-age *correlations* was decreased in ASD compared to TDC (see Figure 5 in Appendix 2 and Table 3 in Appendix 1 for hemispheric peak vertices).

In terms of how the correlations for each diagnostic group differed: CT showed an almost linear decrease as age increased for ASD subjects (see Figure 5 in Appendix 2), while CT was generally stable across the age span for the TDC subjects. The DODS based general linear model analysis did not reveal any significant clusters for average CT/PSA between group differences with age as a covariate in the model. Additionally, no between group differences were found for CT-age correlations of greater strength in ASD compared to TDC, or general PSA-age correlations.

CT/PSA differences with SOG as a covariate. A DODS based general linear model analysis with SOG as a covariate (and age as a nuisance factor) revealed five Monte Carlo corrected clusters that exceeded a cluster-wise probability of $p \leq 0.05$, where the strength of significant CT-SOG *correlations* were decreased in ASD compared to TDC (1 for preferred hand and 4 for non-preferred hand). For the preferred hand, a right hemisphere cluster encompassing most of the frontal lobe from roughly the caudal middle frontal/pars opercularis regions anteriorly, wrapping around the frontal pole medially and extending back to approximately the RA Cingulate, with a peak vertex in the rostral middle frontal gyrus. For the non-preferred hand, two clusters in the left hemisphere were found, including the frontal pole area and the temporal-parietal-occipital junction area, with a peak vertex in the supramarginal gyrus; and two clusters in the right hemisphere were found, similar to the preferred hand right hemisphere findings, a cluster encompassing most of the frontal lobe roughly from the caudal middle frontal/pars opercularis regions anteriorly, wrapping around the frontal pole medially and extending back to approximately the RA Cingulate (also with a peak vertex in the rostral middle frontal gyrus), as well as a cluster in the parietal lobe encompassing dorsal regions of the post central,

supramarginal, and superior parietal. Please refer to Table 3 (Appendix 1) for information regarding peak vertices.

In terms of how the correlations for each diagnostic group differed: an almost linear decrease in CT as SOG increased for ASD subjects was demonstrated; however, TDC subjects were found to have similar thickness levels regardless of SOG performance for the right hemisphere (across both hands) and an increase in CT as SOG performance increased for the left hemisphere (for non-preferred hand).

The DODS based general linear model analysis did not reveal any significant clusters for average CT/PSA between group differences, with SOG as a covariate (and age as a nuisance factor). Additionally, no between group differences were found for CT-SOG correlations of greater strength in ASD compared to TDC, or general PSA-SOG correlations.

CT/PSA differences with FTT as a covariate. A DODS based general linear model analysis with FTT (non-preferred hand) as a covariate (and age as a nuisance factor) revealed two Monte Carlo corrected clusters that exceeded a cluster-wise probability of $p \leq 0.05$, where the strength of significant CT-FTT *correlations* were decreased in ASD compared to TDC. Both clusters were in the left hemisphere, one being distributed across the dorsal superior parietal, postcentral and precentral (with the peak vertex being in the postcentral) and a midsaggital cluster distributed across the rostral superior frontal, RA cingulate, and medial orbital frontal. A DODS based general linear model analysis with FTT (preferred hand) as a covariate (and age as a nuisance factor) revealed one Monte Carlo corrected cluster that exceeded a cluster-wise probability of $p \leq 0.05$, where the strength of a significant PSA-FTT *correlation* was decreased in ASD compared to TDC. This significant cluster encompassed the precentral and postcentral,

with the peak vertex being in the precentral. Please refer to Table 3 (Appendix 1) for information regarding peak vertices.

In terms of how the correlations for each diagnostic group differed: an almost linear decrease in thickness as FTT increased (i.e., slower times) for ASD was demonstrated, while for TDC, CT increased as FTT increased (i.e., slower times). PSA remained generally stable across FTT performance for the ASD group, while PSA increased as FTT performance increased (i.e., slower times) for the TDC subjects**.**

The DODS based general linear model analysis did not reveal any significant clusters for average CT/PSA between group differences, with FTT as a covariate (and age as a nuisance factor). Additionally, no between group differences were found for CT/PSA-FTT correlations of greater strength in ASD compared to TDC subjects.

CT/PSA differences with GPT-UCT as a covariate. A DODS based general linear model analysis with GPT-unit completion time (GPT-UCT; preferred hand) as a covariate (and age as a nuisance factor) revealed two Monte Carlo corrected clusters that exceeded a cluster-wise probability of $p \leq 0.05$, with decreased *average* CT in ASD compared to TDC. Both clusters were in the left hemisphere, the first encompassing the precentral and caudal middle frontal. The second cluster extended from the dorsal precentral, postcentral, and superior parietal medially to the superior frontal and paracentral lobule (see Figure 6 (A) in Appendix 2). Please refer to Table 4 (Appendix 1) for information regarding the peak vertex.

Figure 6 (B.1) in Appendix 2 demonstrated an interaction between CT and group by time needed to place a single peg (i.e., GPT-UCT), in that the slower an ASD individual is at placing an individual peg, the greater their CT. However, for the TDC group, as CT decreased, the speed of placing individual pegs became slower. A qualitative examination of Figure 6 (B.1) in

Appendix 2 demonstrated that this interaction is driven by ten ASD outliers, each with >4 seconds required to place an individual peg.

Please refer to Table 5 (Appendix 1) for demographic features of these ASD outliers from Figure 6 (B.1). Generally, the relationship between CT and time needed to place an individual peg is similar between groups, and removal of the ASD outliers with performance >4 seconds would undoubtedly cancel the demonstrated interaction. The significant average CT group difference in the left precentral, with GPT-UCT (preferred hand) in the model, did not demonstrate a significant anatomic and group interaction by age.

Further, the GPT-UCT analysis demonstrated one Monte Carlo corrected cluster that exceeded a cluster-wise probability of $p \leq 0.05$, where the strength of the significant CT-GPT-UCT (preferred hand) correlation was increased in ASD compared to TDC (see Table 3 in Appendix 1). This cluster had almost complete overlap with the precentral and caudal middle frontal cluster of decreased average CT in the ASD group compared to TDC (see Figure 7 (B) in Appendix 2). Comparing Figure 7 (A) and Figure 7 (B) demonstrates the nature of these anatomically overlapping unique group differences.

The DODS based general linear model analysis did not reveal any clusters with average PSA between group differences, with GPT-UCT as a covariate (and age as a nuisance factor). Additionally, no between group differences were found for CT-GPT-UCT correlations of greater strength in TDC compared to ASD subjects, or general PSA-GPT-UCT correlations.

VBM and CT Comparison. Given the null VBM findings, correlations between VBM and CT analyses were not performed.

Discussion

Findings Concerning Hypothesis 1

It was hypothesized that VBM would demonstrate reduced precentral volume in the ASD subjects compared to TDC subjects while controlling for performance IQ and age. The analyses did not demonstrate any significant group differences, so in an attempt to further homogenize the groups, they were divided into maturational phases of life (i.e., children, adolescents/teens, and adults). This also produced no significant group differences, deeming further analyses incorporating motor variables into the model unnecessary. The current study's null VBM findings failed to replicate previous findings of reduced right precentral gyral volume in ASD samples (Greimel et al., 2013; Hyde, Samson, Evans, & Mottron, 2010), as well as findings of right precentral gyral enlargement in a larger sample (Ecker et al., 2012). *Therefore, hypothesis 1 was not supported.*

Despite earnest adherence to standard processing steps, including visualization of results following each processing step, it cannot be ruled out that error was introduced during the processing steps, and thus sensitivity was reduced (e.g., normalization accuracy varies across regions, resulting in differing ability to detect change across brain regions; Whitwell, 2009). Or, it may be that processing differences between the current study and the previous VBM studies cited resulted it different results (see below for further explanation; Whitwell, 2009). The current sample may also have been too heterogeneous both within and across participants in various ways (e.g., intelligence, age, etc.) to detect the subtle and spatially diffuse differences in brain anatomy that this method is designed for (Ecker et al., 2012). However, it may be that no group differences exist concerning this particular imaging method, which is plausible given the sample size. As such, the current null findings provide a valuable VBM replication study, which

Ecker et al. (2012) note is lacking in the ASD literature and results in a problem in the understanding of neuroanatomical relationships in this population.

Findings Concerning Hypothesis 2

It was hypothesized that precentral CT and/or PSA would differ for the ASD subjects compared to TDC subjects. Several significant group differences were found for the strength of *correlations* involving anatomic regions and motor variables. Generally, only CT by motor variable correlations were significantly different between the groups (i.e., only one PSA finding), and primarily demonstrated stronger anatomic by motor variable (i.e., GPT-UTC) relationships in the TDC group (i.e., only a single ASD > TDC correlational finding). Of these various significant correlational clusters between groups (i.e., anatomic region and motor variable), peak vertices primarily included the primary motor cortex (i.e., precentral), secondary motor areas, (i.e., rostral middle frontal), and primary sensory/sensory association areas (i.e., supramarginal in the parietal lobe). Only a single significant anatomic group difference was found, that being average CT in the left precentral with CT-GPT-UCT (preferred hand) as a covariate in the model. The precentral gyrus has consistently been found to differ between ASD and TDC groups across the age span (Chung et al., 2005; Ecker et al., 2012; Greimel et al., 2012; Hardan, Libove, Keshavan, Melhem, & Minshew, 2008; Hyde, Samson, Evans, & Mottron, 2010; Raznahan et al., 2010; Scheel et al., 2011). Interestingly, the only significant group difference in strength of anatomic-motor variable correlation where ASD > TDC had almost complete cluster overlap with the only significant anatomical group difference (i.e., left precentral). *Although no PSA differences were found, hypothesis 2 was supported by CT group differences in the precentral being confirmed.*

Findings Concerning Hypothesis 3

Given the null VBM findings, despite additional effort to homogenize the groups by dividing them into maturational phases of life (i.e., children, adolescents/teens, and adults), analyses examining the relationship between VBM and CT/PSA findings were not conducted. Thus, the current study was unable to replicate Hyde, Samson, Evans, and Mottron's (2010) findings of convergence of reduced CT and VBM findings on precentral gyrus measurements in an ASD group compared to a TDC group. Sample size (15 ASD individuals (aged 14 to 33) and 13 controls) was minimal for the Hyde, Samson, Evans, and Mottron (2010) study, and it may be that significant VBM reductions and this cortical feature's relationship with reduced CT are due to sampling bias given the current study's null findings in a significantly larger sample. *Hypothesis 3 was not supported.*

Findings Concerning Hypothesis 4

It was hypothesized that ASD would demonstrate greater thickness in childhood compared to TDC, which would begin to converge to equal levels, or show reduced thickness in adolescence/teens and adulthood for ASD individuals compared to TDC (Greimel et al., 2012; Hardan, Libove, Keshavan, Melhem, & Minshew, 2008; Mak-Fan, Taylor, Roberts, & Lerch, 2012). The only significant average CT group difference in the left precentral, with CT-GPT-UCT (preferred hand) as a covariate in the model, did not demonstrate a significant group by age interaction for CT. CT remained relatively stable (i.e., subtle decrease) across the age range of the ASD group. However, in the left precentral, TDC demonstrated a more negative slope in CT reductions as subjects advanced in age compared to ASD (i.e., increasing convergence), which potentially may have resulted in an interaction if there were more subjects in middle to late adulthood given this trend. This would be consistent with Raznahan et al. (2010) who found

significant age by group interactions for CT within mainly bilateral frontal regions in a sample of individuals that consisted of an age range from 10 to 60. These authors found that in regions showing an age by group interaction, there was no relation between age and changes in CT in the ASD group, compared to a significant decrease in CT with age in the control group. Please refer to Figure 3 (B.2) for this similar trend in the current study despite no significant interaction of age by group for CT. Raznahan et al. (2010) also found that at younger ages CT was decreased in ASD relative to typically developing controls, but increased relative to controls at older ages. This differed from the current study that found general stability for CT (i.e., subtle decrease) across the age range of the ASD group. Yet, the current findings generally replicate Raznahan et al. (2010) for age by group relationships for the precentral, which found generally inverse findings to a majority of literature regarding CT trajectories across age. These findings likely further represent the region-specific and dynamic nature of morphology in ASD, particularly in a cross-sectional design as was currently employed.

Zielinski et al. (2014) used a research design (i.e., a longitudinal linear mixed effects models using two time points) that is likely more sensitive to examine longitudinal changes in CT in largely the same ASD sample. These authors found similar findings as the current study regarding reduced CT in caudal middle frontal and precentral regions, although these findings were bilateral and only significant after controlling for full-scale IQ, which the current study did not control for. However, regarding cortical development in ASD, these authors suggest three distinct phases: accelerated growth in early childhood, accelerated thinning in later childhood and adolescence, and decelerated thinning in early adulthood. These authors further emphasize that CT abnormalities in ASD are region-specific, vary with age, and may remain dynamic well into adulthood.

Current CT/PSA Findings Relation to Previous CV Findings in the Same Cohort

Duffield et al. (2013) did not find any group differences for CV in the same cohort as the current study concerning motor ROIs. However, a hierarchical model of impaired motor functioning in ASD was found, where basic motor ability was preserved. However, as motor complexity increased, a greater likelihood of impaired motor function was observed in ASD using neuropsychological testing (i.e., SOG → FTT → GPT). Further, despite null neuroanamotic group differences, a negative relationship with motor function and precentral volume was found for the ASD group (i.e., as brain volume increased, motor performance decreased), which did not demonstrate an interaction between groups and this motor ROI.

The current findings are consistent with and an extension of these previous findings in Duffield et al. (2013) with relation to the primary motor cortex (i.e., the precentral). First, the only cortical group difference found was for CT in the left precentral (ASD < TDC) with the GPT in the statistical model, which is the most complex neuropsychological motor measure used in Duffield et al. (2013). No group differences were found for PSA. Secondly, two notable group differences for strength of correlation were: 1) the only group difference in terms of strength of CT-motor variable correlation where ASD > TDC was also the left precentral/caudal middle frontal regions, with an almost complete cluster overlap with the only average CT group difference finding (see Figure 4); 2) the only significant PSA finding was a lower strength of correlation with the FTT (i.e., ASD < TDC) compared to TDC in the right precentral.

It has been suggested that abnormal CV findings need to be further examined with CT and PSA analyses as these two different cortical features determine CV (Murphy, Beecham, Craig, & Ecker, 2011) and reflect different neurobiological processes associated with different genetic mechanisms (Panizzon et al., 2009). However, the current findings would suggest that

CT and PSA should be examined even for null CV findings if structure-function relationships are observed (i.e., Duffield et al., 2013), as this may indicate abnormalities in the two determinants of CV (i.e., CT and PSA) despite no group differences in CV. The current findings exploring the determinants of CV (i.e., CT and PSA), and their relation to the Duffield et al. (2013) CV findings in the same cohort, will further be examined in the context of Ecker and colleagues work. These authors have written extensively on structural morphology (i.e., CV, CT, PSA) in ASD.

Consistency of findings in the primary motor cortex with the current study and Duffield et al. 2013 has caveats worthy of discussion. First, to reduce family wise error, Duffield et al. (2013) combined dominant and non-dominant hand performances and left and right hemispheric volumes when examining ROI volume and function relationships. The single significant cortical group difference in the current study was hemisphere specific (i.e., left precentral) and handedness specific (i.e., dominant hand). It may be that the combined precentral CV-motor function relationship demonstrated in Duffield et al. (2013) was being driven *specifically by left sided CT group differences* found in the current study, as CT was the only significant finding of the two determinants of CV. Left hemisphere biased findings are consistent with Ecker, Marquand, Mourão-Miranda, Johnston, Daly, Brammer, ... and Murphy (2010) who demonstrated better classification accuracy for ASD in the left hemisphere (79% in left versus 65% in right) using a five morphological parameter classification approach (i.e., CT, mean curvature, sulcal depth, metric distortion [jacobian], and SA). These authors discuss how their findings may relate to evidence suggesting lower degrees of "leftward" (i.e., left > right) cortical asymmetry in ASD compared to controls (Herbert et al., 2005), and greater genetic control in the left hemisphere than the right (Thompson et al., 2001), which is particularly relevant considering

there are estimated to be between 600-1200 ASD risk genes (De Rubeis & Buxbaum, 2015). Also, Ecker et al. (2010) found CT provided the best classification accuracy and highest regional discrimination weights (i.e., "…spatial representation of the decision boundary, and thus represents a map of the most discriminating regions", p. 10615) for distinguishing ASD from TDC.

A lack of group differences for PSA is also generally consistent with Ecker and colleagues work. Ecker et al. (2010) demonstrated only a few, relatively small clusters, of surface-area group differences with generally low classification regional discrimination weights. Further examination of CV, CT, and PSA in an ASD sample of adult males by Ecker, Ginestet, Feng, Johnston, Lombardo, Lai, … and Murphy (2013) found no significant clusters of between-group differences in SA (i.e., only significant CT and CV group differences mainly in the frontal and temporal regions). Thus, the current study actually replicated these authors' findings, although, between group differences in SA clusters were found after an implementation of a more lenient statistical threshold (i.e., $p \leq .05$ for Ecker et al., 2013).

A second caveat to consider is in regard to handedness. Both ASD and TDC demonstrated right-handed dominance for a majority of subjects without a significant handedness group difference (see Table 1). Examination of the hierarchical motor profile in Duffield et al. (2013; see Table 3 in that manuscript) demonstrated consistently larger group differences (and larger effect sizes) in the non-dominant hand, generally the left hand in this sample, compared to the dominant hand across motor complexity (i.e., SOG → FTT → GPT). One would then expect to find right hemispheric functional neuroanatomy group differences to account for generally worse left handed motor performance. However, the only significant CT group difference was in the left hemisphere corresponding to dominant hand performance. In fact,

of the ten worse performing ASD subjects for the PGT (preferred hand; see Figure 3 (B.1) and Table 5), only one subject is ambidextrous, and the other nine show strong right-handedness. Thus their non-dominant hands are their left hands.

It is thus counterintuitive why a sample generally worse on non-dominant, or left handed, motor performance tasks does not correspond to right primary motor cortex differences (i.e., the right precentral), while the only significant cortical group difference is in the left primary motor cortex (i.e., the left precentral) corresponding to the dominant hand, or right handed performance in this sample. Put another way, the only significant cortical finding to account for generally worse left handed/non-dominant performance in ASD compared to TDC is ipsilateral, which seemingly cannot account for the contralateral nature of the functional neuroanatomy of motor functioning.

May it be then that the unitary significant left sided CT group difference cannot fully account for the bilateral CV-motor function relationship found in Duffield et al. (2013), despite null PSA findings, which was posited earlier in the discussion? Particularly when one considers the generally worse left handed (i.e., ipsilateral) motor function profile for the ASD group compared to the TDC group? In addition to findings previously mentioned, Ecker et al. (2013) further found that: 1) patterns of significant differences in CT and SA were largely non-overlapping (only approximately 3%); 2) CT and SA were not correlated where overlap in regions did occur (i.e., uniquely contributed to measures of CV); 3) and of group differences found in CV, a total of 67% were modulated by (i.e., overlapped with) significant differences in CT only (8%), SA only (56%), or both CT and SA (5%). The remaining 31% of group difference in CV were purported to be due to subthreshold differences in CT and SA. The authors

concluded that differences in SA and CT are spatially independent and that SA and CT contribute in a unique way to the group differences in CV.

The Ecker et al. (2013) findings likely further illuminate the current findings and their relation to the Duffield et al. (2013) CV investigation in the same cohort. First, Ecker et al. (2013) and the current study both only found significant CT group differences and a lack of SA group differences (although significant SA findings were found after more lenient statistical threshold was applied for Ecker and colleagues). However, Ecker et al. (2013) found that subtle SA differences modulated a far greater percentage of CV group differences than CT. The only PSA related finding for the current study was a lowered strength of correlation between PSA and FTT in the right precentral. Thus, the relationship between poorer motor performance and right and left hemisphere combined precentral CV found in Duffield et al. (2013) could actually be modulated by spatially independent CT group differences in the left precentral gyrus, and subthreshold PSA differences in the right precentral gyrus. This may also help to explain the generally worse performance in the ASD group for the nondominant hand (generally the left hand for this sample) compared to the TDC group, despite no significant CT or PSA findings in the right precentral.

The Neurobiological Relation of the Current Findings

Ecker et al. (2013) discuss their findings within the context of the radial unit hypothesis (i.e., cells within a ontogenetic column share a common origin before migrating to their location within the cortex during development), and these authors state the number of cells within cortical columns mediates CT, whereas SA primarily reflects the number of columns within a cortical region (please refer to these authors for a full discussion). It may be that for neuropsychological tests of motor functioning within an ASD population, the precentral region is the most

structurally related to impaired performance; specifically, the number of cells within the cortical columns in this region in the left hemisphere and the number of columns within this region in the right hemisphere. Yet, Ecker and colleagues (2013) acknowledge that their findings of CT and SA clusters of significant between-group differences were caused by subtle and spatially distributed variations. Findings that are consistent with theories of the neuropathology of ASD not being expressed in the morphology of individual brain regions, but rather regional effects on wider neural systems, which may be difficult to detect using mass-univariate techniques.

Consistent with this notion, within the same ASD cohort, Travers et al. (2015) using a DTI protocol found that white matter microstructure of the brainstem's inferior corticospinal tract predicted both SOG performance and autism symptom severity within ASD, and the white matter microstructure of that region also mediated the relation between SOG performance and autism symptom severity (i.e., no causal relationship between SOG and autism symptom severity, rather both variables are effected by the corticospinal tract). These authors discussed that the corticospinal tract has a well-known role in motor function and that hand grip (i.e., SOG) depends on the integrity of the corticospinal tract fibers arising from the primary motor cortex (Schulz et al., 2012; i.e., the precentral region). Despite novel findings, the authors also discuss only finding marginally significant group differences, which may not be able to categorically define ASD from typical development. Thus, morphological findings in the primary motor cortex, such as the current CT and PSA findings, and structural connectivity findings with the primary motor cortex in the same cohort by Travers et al. (2015) each provide a piece of explanatory evidence in the impaired neuropsychological motor performance of ASD. Yet, remain insufficient individually as biomarkers of an ASD profile. For instance, Ecker, Bookheimer, and Murphy (2015) discuss that recent imaging reviews have demonstrated consistent differences in

neural activations where structural abnormalities are also found in ASD (Dichter, 2012; Hamilton, 2013; Mueller, Keeser, Reiser, Teipel, & Meindl, 2012).

Integration of imaging methods, taking advantage of each modality's temporal or spatial strengths, may further elucidate the neuropathology of ASD. Kana, Uddin, Kenet, Chugani, and Müller (2014) discuss how effective connectivity (i.e., the causal influence of one brain area on another), a multimodal neuroimaging approach, will likely be able to provide a more comprehensive understanding of brain network abnormalities in ASD. Classification analyses (i.e., designation of ASD or TDC) have found effective connectivity to have high accuracy levels (Deshpande, Libero, Sreenivasan, Deshpande, & Kana, 2013), particularly compared to other connectivity measures (e.g., functional). This novel approach will likely revolutionize biomarkers for ASD (Kana, Uddin, Kenet, Chugani, & Müller, 2014), and also be an important improvement in the understanding of cognitive function differences, such as motor functioning, between TDC and ASD individuals.

Methodological Differences Contribution to Null VBM and Significant CT findings

Beyond the acknowledgement that a multimodal neuroimaging approach will likely be a necessary research progression in the understanding of the neurobiology of ASD, it is important to consider that methodological differences may have accounted for null VBM findings and significant CT findings in the current cortical grey matter investigation. Each method is commonly used for investigating cortical grey matter in T1-weighted images, and can be considered complementary methods by being able to separate underlying grey matter changes (see Hutton, Draganski, Ashburner, & Weiskopf, 2009). Specifically, measurement of the quantity of tissue within each voxel for VBM is based upon cortical SA (and hence cortical folding), and CT (Hutton, Draganski, Ashburner, & Weiskopf, 2009). Also, although both

methods typically involve tissue segmentation (into grey matter, white matter and CSF) in the initial processing steps, subsequent steps may require substantially different processing (Hutton, Draganski, Ashburner, & Weiskopf, 2009).

Hutton, Draganski, Ashburner, and Weiskopf (2009) have used preprocessing and registration methods that are common across measures (i.e., use of a voxel-based CT measure), enhancing the sensitivity of finding unique neurobiological differences between the complementary methods, while minimizing any possibly confounding methodological differences. However, if researchers use methods such as the Freesurfer software utilized in the current study for CT (i.e., thickness calculated on the surface versus voxel-based CT measures where thickness is calculated for every volumetric point within the cortex; Hutton et al., 2008), robust comparisons between volume and surface-based anatomical methods requires a system that can integrate such representations (Hutton, Draganski, Ashburner, & Weiskopf, 2009), such as the system created by (Makris et al., 2006) using existing software packages, or the CIVET image-processing environment (http://mcin-cnim.ca/neuroimagingtechnologies/civet/).

Limitations

It is difficult to account for potential differences in the kinds of supportive therapies and interventions received by subjects, such as occupational therapy, that may impact motor functioning. There is also potential age, education, and family interaction variables that could influence motor function as measured by the SOG, FTT, and GPT that could not be controlled in this study. Also, ASD groups were not stratified in any manner for severity variables, which may have further illuminated ASD motor ROI and functioning differences. Thus, caution is recommended in the generalizability of these findings. Further, subjects who were not amenable to testing due to behavioral and/or cognitive factors (low-functioning participants) were not

included in the current study, which may also limit generalizability of the findings to the autism spectrum as a whole.

It should be further noted that automated image analysis methods used in this investigation have limitations, and it remains possible that more refined structural image analysis methods, may prove successful in defining brain structure function motor relations in ASD (Hanson et al., 2012). Volumetric differences will also mean differences in geometric features (e.g., cortical folding), which will also be important to investigate (e.g., gyrification index), as the brain exists in a finite space (Ecker, Bookheimer, & Murphy, 2015). Regional structural abnormalities in ASD also are linked to regional and functional connectivity differences using different activation paradigms (i.e., fMRI; Ecker, Bookheimer, & Murphy, 2015). In addition, resting-state fMRI (uses spontaneous low-frequency fluctuations in cerebral blood flow to measure correlations within and between brain regions) findings have generally supported the theory that individuals with ASD have reduced long-range connectivity and increased short-range connectivity (although these findings are controversial; Ecker, Bookheimer, & Murphy, 2015), which has implications for motor functioning in ASD. Further, methods elucidating the modular architecture of functional and structural networks (e.g., graph theory) and multivariate MRI-driven pattern classification techniques (e.g., machine learning), each often including CT analyses, are improving understanding of the complex differences in development and anatomy/systems of the ASD brain that univariate methods could not efficiently identify (Ecker, Bookheimer, & Murphy, 2015). Thus, although the current study used different image analysis methods to further explain previous volumetric findings, the current methods are simply not robust enough to fully explain functional motor differences that exist between individuals with ASD and typically developing individuals.

Lastly, the current study only examined cortical motor ROIs. A recent review by D'Mello and Stoodley (2015) suggest that cerebellar dysfunction may play a crucial role in the etiology of ASD, as the cerebellum is one of the most consistent sites of abnormality in ASD and it is diffusely interconnected with the cerebral cortex. The anterior cerebellum forms reciprocal loops with a number of motor ROIs examined in the current study, including the primary motor cortex supplementary motor area, and premotor cortices (Strick, Dum, & Fiez, 2009). Various imaging findings regarding cerebro-cerebellar loops have also been correlated with performance on the motor measures used in the current study (D'Mello & Stoodley, 2015). For example, functional activation differences in the anterior cerebellum for ASD during finger tapping tasks (e.g., Mostofsky et al., 2009). The FreeSurfer based methods explored in the current study did not examine the cerebellum.

Conclusions

Prior research has suggested that any CV abnormalities in ASD need to be further explored by examination of the two determinants of CV, that being CT and PSA (Murphy, Beecham, Craig, & Ecker, 2011). The current study suggests that the two determinants of CV should be explored even in the presence of null CV findings, if structure-function analyses are significant. The only significant anatomic finding was reduced CT in the left precentral/caudal middle frontal regions, which also corresponded to the only significant relationship between a motor variable (i.e., GPT) and motor ROI (precentral/caudal middle frontal regions) where ASD > than TDC. Left hemisphere biased CT group differences has been shown to have the highest classification accuracy (i.e., designation of ASD versus TDC) of morphological parameters (Ecker et al., 2010), yet PSA has been shown to have far greater modulation of CV abnormalities. This is particularly true for subthreshold PSA, as well as CT findings (Ecker et al., 2013). These

findings are not only consistent with the current motor ROI findings, but also provide an explanatory framework for the functional neuroanatomy of a generally worse left handed performance (i.e., non-dominant hand) for ASD in a generally right handed dominant sample. The only significant motor ROI finding was in the left hemisphere (i.e., ipsilateral to worse left handed performance), but subthreshold PSA findings in the right precentral were found and likely provide explanatory power of motor performances in the aggregate, despite a lack of significant statistical differences in a specific motor ROI individually.

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Appendix 1

Table 1

Demographic Information

	ASD (n = 59)			*Typically-developing (n = 30)*				
	Mean	SD	Range	Mean	SD	Range	*t*	*p*
Age in years	15.61	7.48	5.17-26.17	15.29	6.48	5.00-33.17	0.20	0.84
Head Circumference (cm)	55.54	2.36	49.20-59.30	55.40	2.30	50.60-60.20	0.27	0.79
Handedness Inventory	61.89	52.24	-80.00-100.00	69.90	42.98	-100.00-100.00	-0.72	0.47
Wechsler FIQ	100.30	17.71	95.00-153.00	120.23	16.72	58.00-137.00	-5.09**	0.00
Wechsler PIQ	101.38	17.01	88.00-155.00	118.03	19.02	64.00-129.00	-4.15**	0.00
Wechsler VIQ	98.54	21.34	94.00-151.00	117.57	14.82	51.00-138.00	-4.79**	0.00

*= $p < .05$; ** = $p < .01$. Edinburgh Handedness inventory on a scale from -100 (left-handed) to 100 (right-handed).

Table 2

Characterization of the Autism and Control Sample

	ASD			*Typically-developing*		
	n	Mean (*SD*)	Range	*n*	Mean (*SD*)	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

Significant Differences between Groups in Strength of Correlations

	Peak vertex region	Hemisphere	Surface coordinates			Significance Threshold (-log10(*p*))
			x	*y*	*z*	
ASD < TDC						
CT & age	Pars Opercularis	Left	-18	45	-14	-3.70
CT & age	Precentral	Right	-6	2	58	-4.00
CT & SOG (PH)	Rostral Middle Frontal	Right	11	84	7	-4.00
CT & SOG (NPH)	Supramarginal	Left	-29	-40	-33	-4.00
CT & SOG (NPH)	Rostral Middle Frontal	Right	11	84	7	-4.00
CT & FTT (NPH)	Postcentral	Left	2	-13	65	-2.55
PSA & FTT (PH)	Precentral	Right	-6	2	58	-2.04
ASD > TDC						
CT & GPT (PH)	Precentral	Left	-22	15	39	2.15

Note. Peak vertex region refers to cluster with greatest group difference. Surface coordinates are in Talairach space. p-values in Qdec are to the –log10. Default overlay thresholds were used: -log10(p) ≤ -2.00 indicates ASD group demonstrated a significantly thinner vertex cluster than the TDC group, and -log10(p) ≥ 2.00 indicates the ASD group demonstrated a larger vertex cluster than the TDC group.

Table 4

The only Significant CT Group Difference

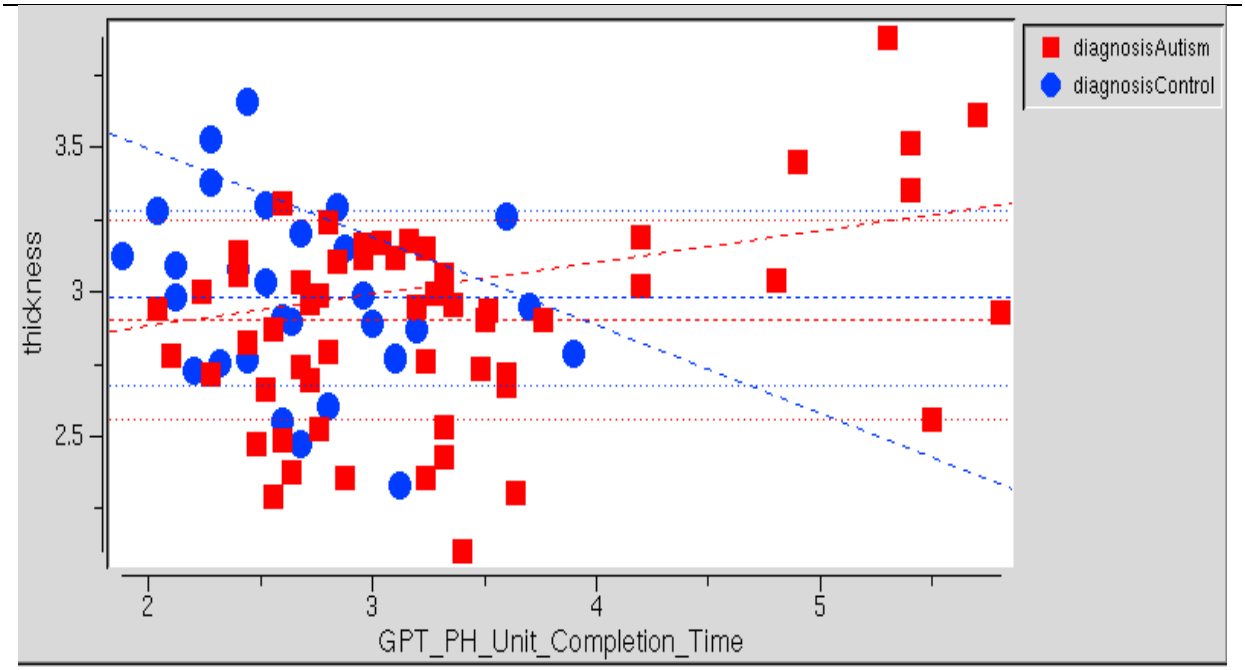
	Peak vertex region	Hemisphere	Surface coordinates			Significance Threshold (-log10(*p*))
			x	*y*	*z*	
GPT (PH) in model	Precentral gyrus	Left	-19	19	42	-2.29

Note. GPT (PH) = grooved pegboard test, preferred hand; also not total time but time per peg placement. Peak vertex region refers to cluster with greatest group difference. Surface coordinates are in Talairach space. p-values in Qdec are to the –log10. Default overlay thresholds were used: -log10(p) ≤ -2.00 indicates ASD group demonstrated a significantly thinner vertex cluster than the TDC group, and -log10(p) ≥ 2.00 indicates the ASD group demonstrated a larger vertex cluster than the TDC group.

Table 5

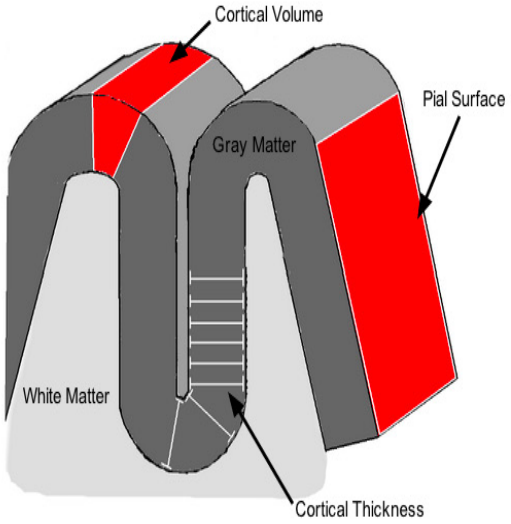
Qualitative Features of ASD Subjects >4 Seconds for GPT in Figure 3 (B.1)

Handedness Inventory	Age (years)	PIQ	ADOS Module	ADOS Total	GPT-PH-UCT (seconds)
60.00	8	83	3	20	5.3
66.67	6	121	3	12	5.7
93.33	6	117	3	10	5.4
80.00	6	109	2	17	4.8
80.00	8	68	3	14	5.8
0.00	6	118	3	14	5.4
93.33	5	70	2	15	4.9
93.33	8	126	3	4	4.2
93.33	6	104	1	17	4.2
100.00	5	92	2	12	5.5



Note. Edinburgh Handedness inventory on a scale from -100 (left-handed) to 100 (right-handed). ASD subjects are red in the scatterplot and TDC subjects are blue.

Appendix 2



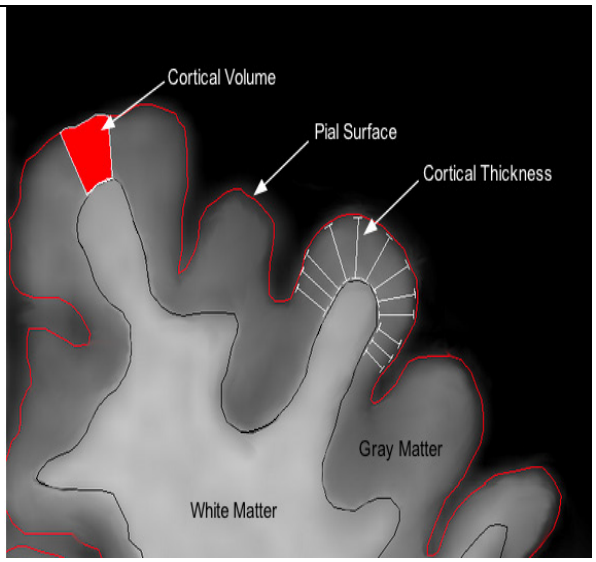


Figure 1. Neuroanatomic Relationship of CV, CT, PSA. Figure created by Trevor Huff

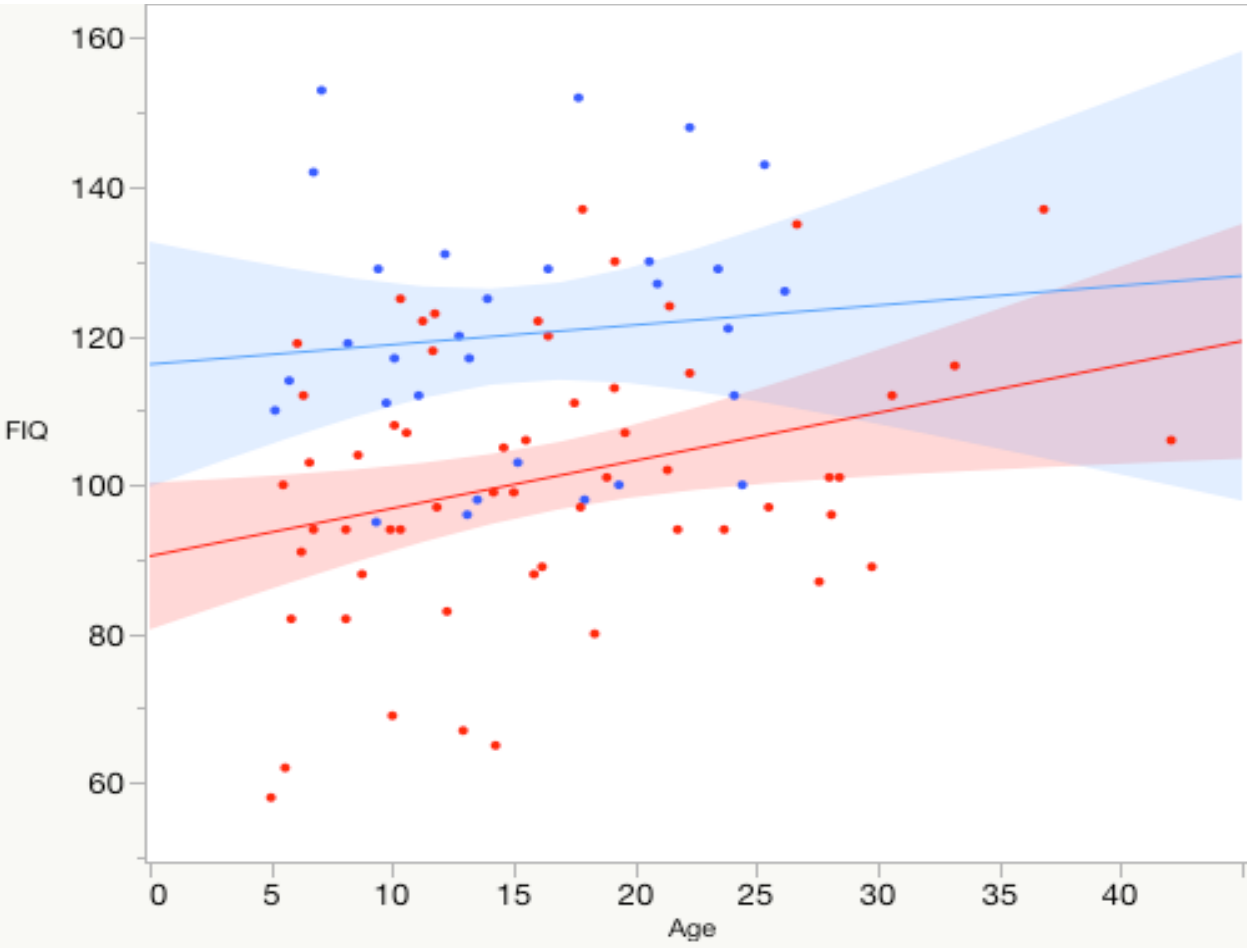


Figure 2. Full Scale IQ by Age Scatterplot. ASD subjects are red in the scatterplot and TDC subjects are blue. Scatterplots include line of best fit.

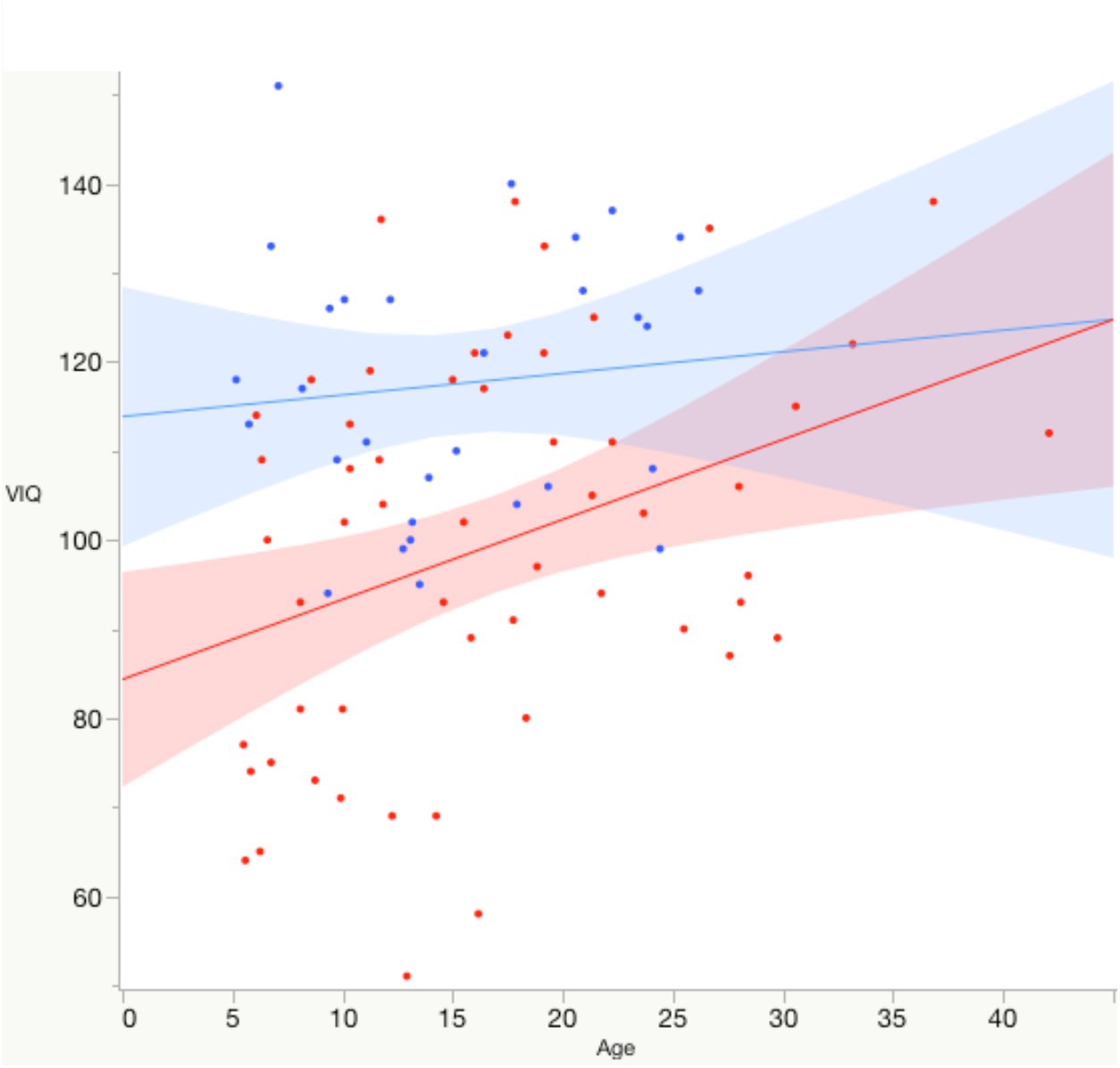


Figure 3. Verbal IQ by Age Scatterplot. ASD subjects are red in the scatterplot and TDC subjects are blue. Scatterplots include line of best fit.

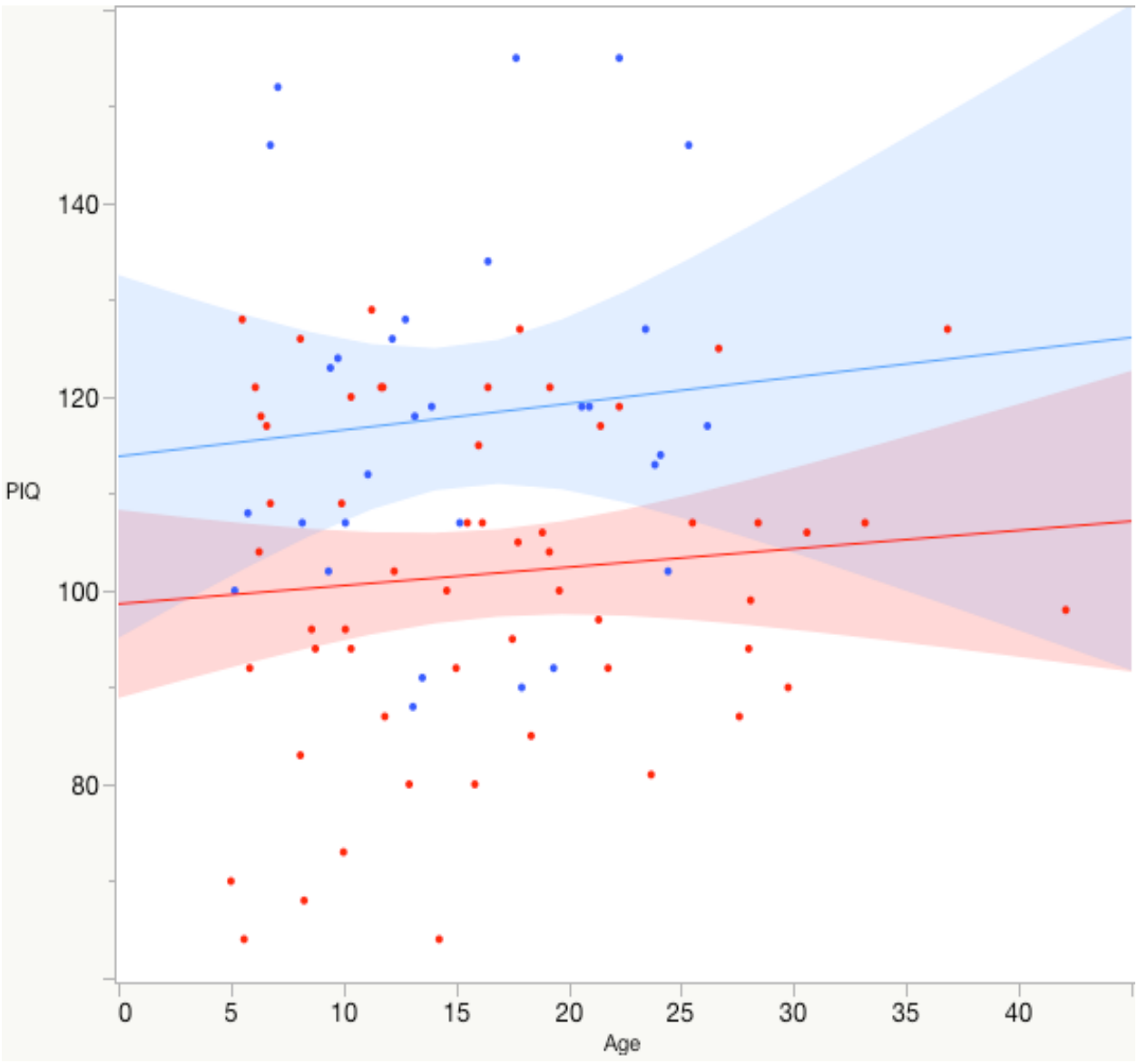


Figure 4. Performance IQ and Age Scatterplot. ASD subjects are red in the scatterplot and TDC subjects are blue. Scatterplots include line of best fit.

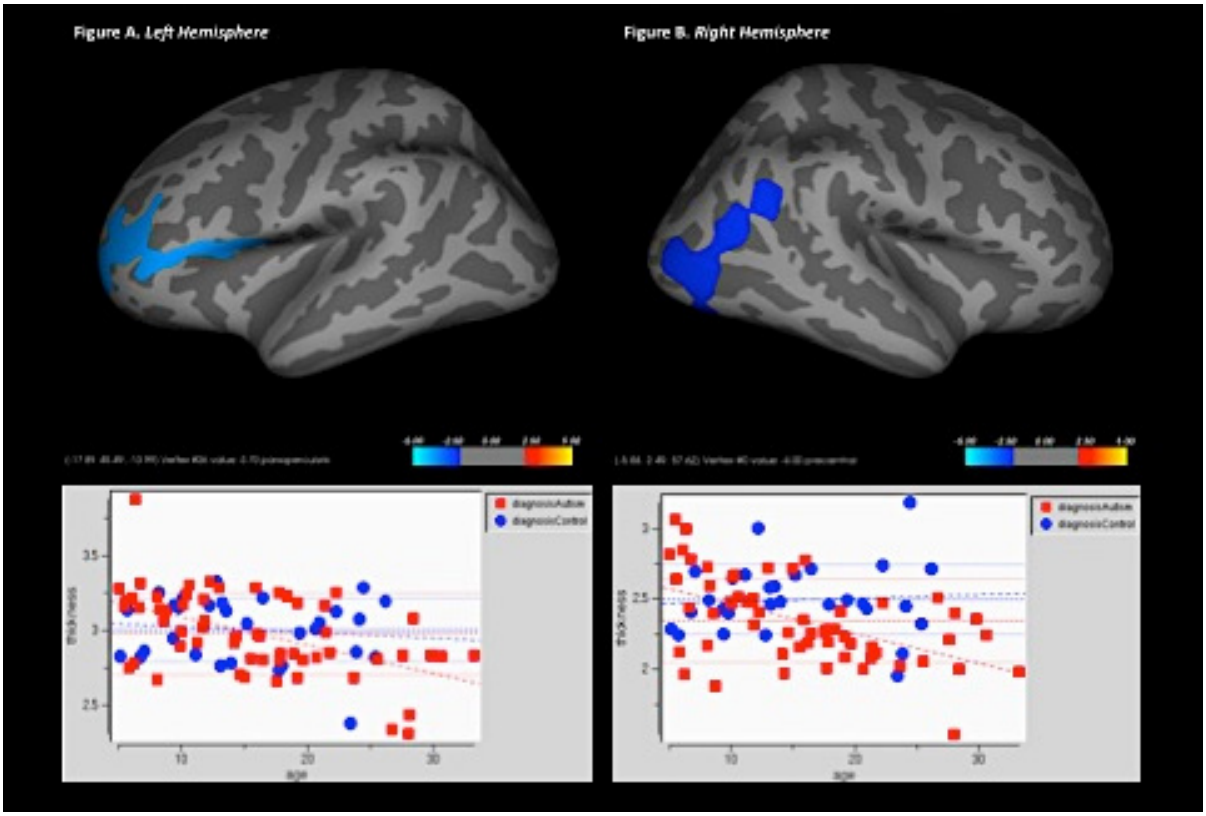


Figure 5. Significant Group Difference for CT-Age Strength of Correlation, ASD < TDC. Blue indicates thinner vertex clusters for the ASD group for color overlays. ASD subjects are red in the scatterplot and TDC subjects are blue. Age is on the x-axis and thickness is on the y-axis for the scatterplot.

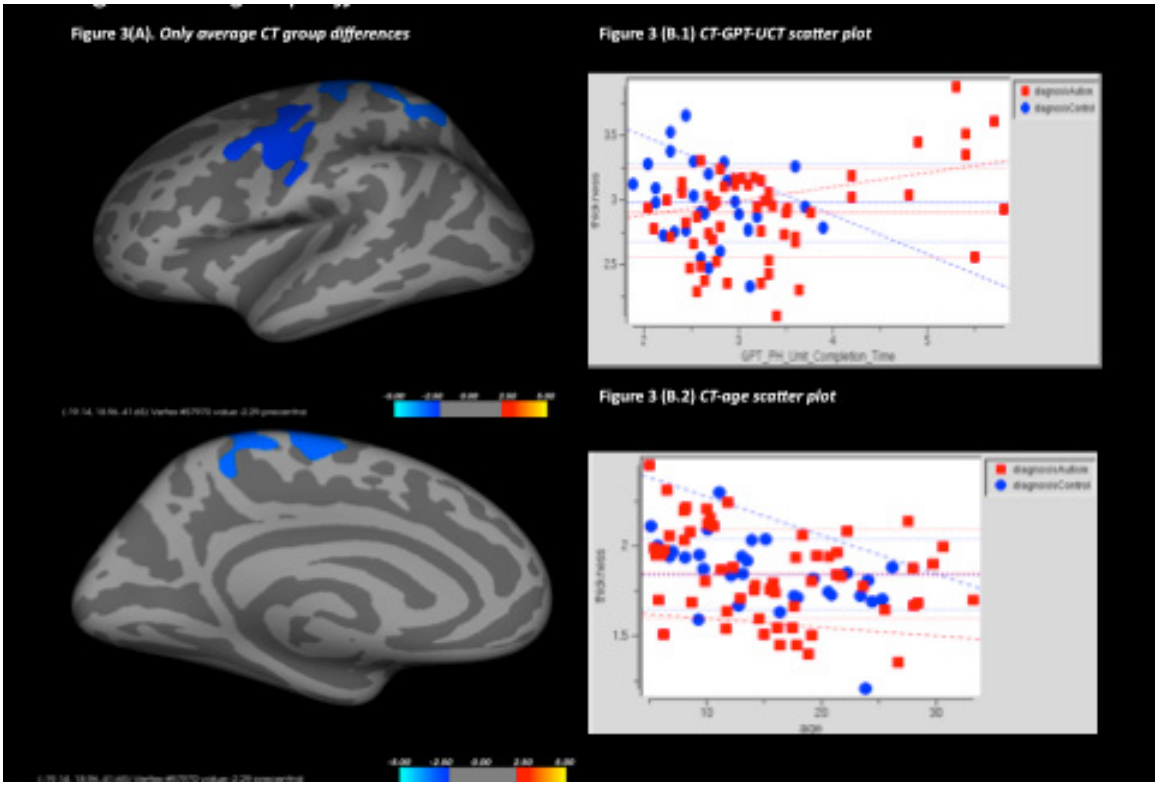


Figure 6. CT Group Differences with GPT-UCT as a Covariate. Blue indicates thinner vertex clusters for the ASD group for color overlays in A. ASD subjects are red in the scatterplot and TDC subjects are blue. Grooved pegboard unit completion time is on the x-axis for B.1 and age is on the x-axis for B.2. Thickness is on the y-axis for both scatterplots.

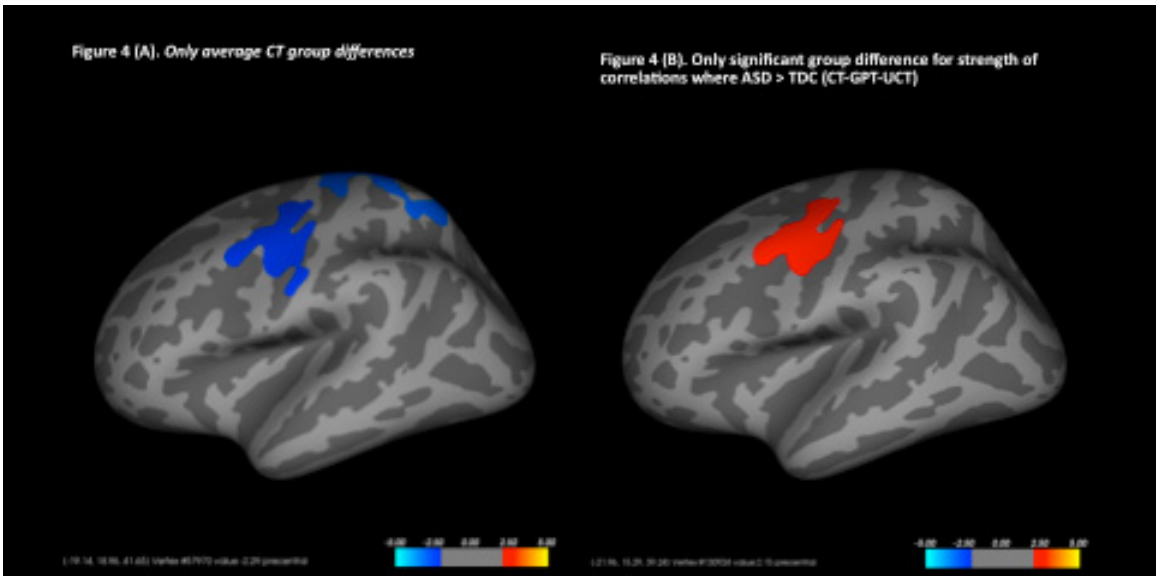


Figure 7. Unique Findings Overlap (with GPT-UCT as a Covariate). For color overlays, blue indicates thinner vertex clusters in the ASD (A) and red indicates a significantly stronger CT-motor variable relationship for ASD at those vertex clusters (B). GPT-UCT = grooved pegboard test, unit completion time