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Surface-based morphometry of the cortical architecture of autism spectrum disorders: volume, thickness, area, and gyrification

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ABSTRACT

Structural neuroimaging studies of autism spectrum disorder (ASD) have uncovered widespread neuroanatomical abnormalities, which may have a significant impact on brain function, connectivity, and on behavioral symptoms of autism. The findings of previous structural MRI studies have largely been distributed across several brain areas, with limited consistency. The current study examined neuroanatomical abnormalities by comparing surface-based measures of cortical morphology (CT: cortical thickness, CSA: cortical surface area, CV: cortical volume, and GI: gyrification index) in 55 high-functioning children and adults with ASD to 60 age-and-IQ-matched typically developing (TD) peers. A few brain areas, the fusiform gyrus (FG), middle temporal gyrus (MTG), and inferior frontal gyrus (IFG), emerged to be primarily different in their morphology between the two groups. Compared to TD participants, ASD participants had significantly smaller CV in left MTG, reduced CSA in bilateral MTG and FG, reduced GI in left supramarginal gyrus, and significantly increased CT in the pars opercularis of the IFG. As a function of age, ASD participants had significant reductions in: CT in the pars opercularis, CSA of the left rostral middle frontal gyrus, and GI for left supramarginal gyrus. Thus, alterations in cortical morphology in ASD were seen primarily in regions that are considered part of the social brain. Overall, these findings point to: neuroanatomical alterations in social brain areas, developmental differences in neuroanatomy, and the need to study neuroanatomy at multiple levels in order to better characterize the cortical architecture of ASD.

1. Introduction

Abnormal cortical anatomy has been identified as a central feature of the neuropathology of autism spectrum disorders (ASD) (Amaral, Schumann, & Nordahl, 2008; Nickl-Jockschat et al., 2012), with specific and consistent abnormalities found in brain volume (Courchesne, Campbell, & Solso, 2011; Hazlett et al., 2005, 2011; Stanfield et al., 2008), indicating early overgrowth, followed by abnormal decline and degeneration during adolescence and adulthood (Courchesne et al., 2011). Studies of head circumference indicate larger head size in ASD (Dawson et al., 2007; Elder, Dawson, Toth, Fein, & Munson, 2008; Hazlett et al., 2005), and studies of brain volume have indeed reported greater total volume in ASD as well (Hazlett et al., 2005; Piven et al., 1995). However, a closer look at regional volumetric differences reveals variable findings, with the relatively more consistent findings being increased gray matter volume in frontal, temporal, parietal, and limbic areas, decreased white matter volume in frontal, temporal, and limbic areas (Chen, Jiao, & Herskovits, 2011; Stanfield et al., 2008), and volumetric abnormalities in amygdala, hippocampus, corpus callosum, and cerebellum (Brambilla et al., 2003; Stanfield et al., 2008). Findings from previous studies examining neurodevelopment in ASD have further complicated the picture, reporting abnormal development of brain volume in infants and young children, but rather inconsistent results in older children and adults (Courchesne et al., 2001; McAlonan et al., 2002; Redcay & Courchesne, 2005).

Thus, studies examining brain anatomy in ASD have varied not only in their findings, but also in the nature of participants included; with age, IQ, and symptom severity differing widely from study to study, perhaps contributing to the inconsistencies in the findings. In addition, most studies comparing brain structure between typical controls and individuals with ASD have employed voxel-based morphometry (VBM), a technique that allows the quantification of the concentration of gray matter tissue. While this technique has been valuable in providing information about structural differences in the ASD brain, VBM has many limitations, including potential inaccuracies in normalization which lead to problems when attempting to statistically compare two different groups of participants directly (Bookstein, 2001; Davatzikos, 2004).

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This is troubling in terms of brain structure findings in ASD, with reports of anatomical shifting and alterations in the shape of sulci in the brains of children with ASD (Auzias et al., 2014; Levitt et al., 2003; Nordahl et al., 2007). Abnormal cortical sulcal and gyral patterns could dramatically alter the automated normalization procedure included in VBM software, thus invalidating any comparison with control groups. Surface-based morphometry (SBM) techniques using non-linear alignment to cortical folding patterns (the sulci and gyri), on the other hand, provide more accurate normalization of subjects' brains and are perhaps more useful, especially when attempting to examine the cortical morphology of participants with differing diagnostic status (Ghosh et al., 2010).

SBM as a technique not only marks a more accurate determinant of differences in brain volume, but also allows the comparison of the measurements that contribute to the volume of specific regions. For example, the use of surface-based morphometric methods allows subdivision of cortical volume (CV) into its two main constituents, cortical thickness (CT; the distance between the boundary of white matter/gray matter division and gray matter/pial surface) and cortical surface area (CSA; the total area of the surface encompassing a brain region), which in turn, can be further subdivided into the area of exposed cortical surface area (gyrus) and the non-exposed hidden surface area (sulci) (Raznahan et al., 2011). SBM also allows measurement of gyrification index (GI), the degree of cortical folding. This measure can be obtained as a ratio of the total to outer cortical contour (Hardan, Jou, Keshavan, Varma, & Minshew, 2004; Zilles, Armstrong, Schleicher, & Kretschmann, 1988). Gyrification is an important measure of brain organization, as the degree of gyrification is associated with overall brain size, and the amount of cortical folding is relevant to the development of neuronal connections in the brain (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995). CT represents dendritic arborization and pruning in gray matter in the brain (Huttenlocher, 1990) and alterations in myelination at the merging of gray and white matter tissue (Sowell et al., 2004). CSA is related to the maintenance and division of progenitor cells (Chenn & Walsh, 2002). Gray matter volume is a function of cortical surface area and cortical thickness, which are found to be globally and regionally independent (Panizzon et al., 2009; Winkler et al., 2010). Both CT and CSA are related to the migration of neurons and organization of minicolumns (Rakic, 1988). Investigation of the contributions of these more specific surface-based measures of CSA, CT, and gyrification can aid in understanding abnormalities in volume, adding information beyond the basic volumetric abnormalities uncovered in ASD. Such fine-grained investigation may be especially important in complex disorders like ASD, where neuroanatomical abnormalities are usually subtle. Since these measures stem from different genetic and cellular mechanisms in the brain (Armstrong et al., 1995; Panizzon et al., 2009; Raznahan et al., 2011), they have the potential to elucidate the underlying causes of alterations in brain structure and the cognitive processes impacted by these abnormalities. By measuring regional volumes, CT, gyrification, and CSA, neuroanatomical investigations using MRI may be able to uncover the underlying problems in the cortical architecture of ASD.

Many neuroimaging findings in ASD pertain to abnormalities within brain areas related to social information processing. Particularly, abnormalities have been found in the function and synchronization of *social brain* regions (see Just, Keller, Malave, Kana, and Varma (2012), Kana, Libero, and Moore (2011) and Minshew and Williams (2007) for reviews) in those with ASD. The regions implicated in the social brain include the amygdala, fusiform gyrus, cingulate cortex, middle temporal gyrus (MTG), superior temporal sulcus (STS), and temporoparietal junction (TPJ), parts of frontal cortex and premotor cortices (Adolphs, 2001; Pelphrey & Carter, 2008a, b). fMRI studies in ASD have uncovered functional differences in many of the regions in this network in ASD (see Philip et al. (2012) for a review). These findings include alterations in STS/TPJ (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007; Kaiser et al., 2010; Kana, Keller, Cherkassky, Minshew, & Just, 2009; Kana, Libero, Hu, Deshpande, & Colburn, 2014; Pelphrey, Morris, & McCarthy, 2005; Wang, Lee, Sigman, & Dapretto, 2007), amygdala (Hadjikhani et al., 2007), fusiform (Koshino et al., 2008), prefrontal cortex (Luna et al., 2002; Ring et al., 1999; Schulte-Rüther et al., 2011; Wang et al., 2007), cingulate (Kana et al., 2009; Kana, Keller, Minshew, & Just, 2007; Luna et al., 2002), middle temporal (Cherkassky, Kana, Keller, & Just, 2006; Koshino et al., 2008), and premotor cortex/inferior frontal gyrus (Dapretto et al., 2005; Kana et al., 2014; Manjaly et al., 2007); in addition to disrupted functional connectivity among these regions (see Just et al. (2012), Kana et al. (2011) and Schipul, Keller, and Just (2011) for reviews). Alterations in overall volume (based on VBM) in social brain regions, particularly cingulate, fusiform, amygdala, temporal, and frontal cortices (see Cauda et al. (2011) and Nickl-Jockschat et al. (2012) for reviews) have been reported in studies of ASD. However, information on surface-based measures (CT, CSA, GI, and CV) underlying volume, function and connectivity problems in ASD are still relatively uncharted. Few, if any, studies to date have examined all of these measures together in participants with ASD. Information regarding CT, CSA, and GI could provide a comprehensive picture of the neuroanatomical differences, and potentially help explain the mechanisms driving differences in ASD. Considering impaired social interaction and communication are key symptoms of ASD, understanding the neural basis of the social behavioral dysfunction will be critical in characterizing the neuropathology of autism as well as in targeting treatments to improve alterations in the brain.

Meta-analyses of previous volume-based results in ASD suggest volumetric decreases in the inferior parietal lobule (composed of the angular and supramarginal gyri), medial temporal, precentral, and fusiform gyri, and volumetric increases in anterior cingulate, and medial frontal regions (Cauda et al., 2011; Duerden, Mak-Fan, Taylor, & Roberts, 2012; Jiao et al., 2010; Nickl-Jockschat et al., 2012; Via, Radua, Cardoner, Happe, & Mataix-Cols, 2011). However, there is evidence that volumes within these regions may alter as a function of age due to altered growth trajectories in ASD, which will be evaluated in this analysis (Duerden et al., 2012; Ecker et al., 2014; Schumann et al., 2010). To gain a better understanding of the anatomical differences in the brain in ASD, the current study examines surface-based measures of CT, CSA, GI, and CV in children and adults with ASD. Based on previous findings of widespread abnormalities in brain structure in ASD (see Chen et al. (2011) for a review), we expect to find significant alterations in cortical thickness and surface area in participants with ASD, particularly in fronto-temporal brain regions. As previous studies have uncovered abnormal development of brain structures in ASD, we also predict abnormalities in the surface based measures as a function of age. With relatively large number of participants and multiple measures of brain structure, the findings of this study provide valuable information about the developmental trajectory of the neuroanatomy of ASD in general and the structural integrity of the social brain in particular.

2. Method

2.1. Participants

MRI data was collected from 60 high-functioning children and adults with ASD and 61 typically developing (TD) peers. After a thorough visual inspection of the data for quality by three researchers independently, data from one TD participant and four ASD participants were excluded due to head motion distortion or scanner artifacts. One additional ASD subject was excluded due to an incidental finding in his brain. The resulting 55 participants with ASD (49 males/6 females; mean age: