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Mapping cortical anatomy in preschool aged children with autism using surface-based morphometry

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ABSTRACT

The challenges of gathering in-vivo measures of brain anatomy from young children have limited the number of independent studies examining neuroanatomical differences between children with autism and typically developing controls (TDCs) during early life, and almost all studies in this critical developmental window focus on global or lobar measures of brain volume. Using a novel cohort of young males with Autistic Disorder and TDCs aged 2 to 5 years, we (i) tested for group differences in traditional measures of global anatomy (total brain, total white, total gray and total cortical volume), and (ii) employed surface-based methods for cortical morphometry to directly measure the two biologically distinct sub-components of cortical volume (CV) at high spatial resolution—cortical thickness (CT) and surface area (SA). While measures of global brain anatomy did not show statistically significant group differences, children with autism showed focal, and CT-specific anatomical disruptions compared to TDCs, consisting of relative cortical thickening in regions with central roles in behavioral regulation, and the processing of language, biological movement and social information. Our findings demonstrate the focal nature of brain involvement in early autism, and provide more spatially and morphometrically specific anatomical phenotypes for subsequent translational study.

1. Introduction

Autism is a relatively common (Baird et al., 2006; CDC, 2009), early-onset (Zwaigenbaum et al., 2005) syndrome characterized by impairments in communication, social interaction and behavioral flexibility (Volkmar et al., 2004). Children who meet full criteria for Autistic Disorder (American Psychiatric Association, 2000) show clearly abnormal socio-communicative development within the first 3 years of life, and over 50% will also fulfill diagnostic criteria for mental retardation [referred to as intellectual disability (ID) below] (Charman et al., 2011). This severe, paradigmatic autism phenotype, first formally described over 65 years ago (Kanner, 1943), is now considered to be part of a range of autistic presentations (including Asperger Disorder and Pervasive Developmental Disorder Not Otherwise Specified) that vary in severity and are collectively referred to as Autism Spectrum Disorder (ASD).

Although it is clear that genetic risks (Abrahams and Geschwind, 2008) and early disruptions of brain development (Amaral et al., 2008) play central roles in ASD pathogeneses, it has been hard to establish firm links between specific risk factors and markers of aberrant neurodevelopment in ASD. One way forward may be to better leverage recent insights regarding the biological architecture of typical brain development, when seeking to delineate aspects of disrupted brain development for closer study in ASD. For example, to date, structural neuroimaging studies of the cortical sheet in young children with autism have largely used volume-based approaches, and focused on measurement of global or lobar cortical anatomy (Calderoni et al., 2012; Courchesne et al., 2001; Hazlett et al., 2005, 2011; Schumann et al., 2010). However, it is now clear from studies of typically developing populations that cortical volume (CV) can be fractionated into biologically distinct morphometric sub-components (Raznahan et al., 2011b), that are differentially impacted by genetic (Panizzon et al., 2009) and environmental (Raznahan et al., 2012) factors in a regionally specific manner. The capacity to tease apart such biologically informative, non-volumetric aspects of cortical anatomy at high spatial-resolution has largely arisen through the advent of tools for Surface Based Cortical Morphometry (SBM) (Fischl and Dale, 2000; MacDonald et al., 2000) from structural Magnetic Resonance Imaging (sMRI) data. Our current study represents the first application of SBM to characterize disruptions of cortical anatomy in preschool aged children with an ASD.

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The early developmental period spanned by our study is particularly important for models of autism biology because it captures the time when typically developing individuals are undergoing profound neuro-behavioral change (Courchesne et al., 2000; Knickmeyer et al., 2008), and when the symptoms of autism are clearly manifested in most affected individuals (Shumway et al., 2011). Neurostructural alterations already apparent in young children with ASD may also better index primary disease processes than disruptions of brain anatomy charted in older populations; the latter being more prone to inclusion of secondary neuroanatomical alterations reflecting consequences of having an ASD on brain structure (Murphy et al., 2011). The challenges of gathering high-quality neuroimaging data from preschool aged children have however proven to be a significant obstacle, particularly for groups with ASD. To date, reports are available for three independent single-site cohorts (Calderoni et al., 2012; Hazlett et al., 2011; Schumann et al., 2010), and two composite cohorts (Estes et al., 2011; Hoeft et al., 2011). These pioneering studies have shed light on altered brain anatomy in ASD during early childhood, but fail to reach consensus on several fundamental issues including: the developmental stability of brain volume differences between individuals with ASD and typically developing controls (TDCs) [stable differences (Hazlett et al., 2011), vs age-dependent differences (Schumann et al., 2010)]; the presence of significant differences in total brain volume (TBV) between individuals with ASD and TDCs once age-effects have been taken into account [presence (Courchesne et al., 2001) vs. absence (Calderoni et al., 2012; Hazlett et al., 2005, 2011) of differences]; and which sub-divisions within the brain exhibit volume alterations in ASD [fronto-temporal only (Schumann et al., 2010) vs all lobes (Hazlett et al., 2011)]. These inconsistent findings regarding global and lobar measures of brain anatomy are accompanied by the absence of any spatially fine-grained surface-based analyses of brain anatomy in young children with ASD.

The current study had three main objectives. First, we sought to re-visit the question of whether young children with ASD (specifically diagnosed with Autistic Disorder) show global and lobar abnormalities of total brain volume, within a fourth (Calderoni et al., 2012; Hazlett et al., 2011; Schumann et al., 2010) independently recruited single-site clinical cohort. Second, with the aim of distinguishing separate morphometric components of cortical development that could be differentially impacted by ASD, we sought to decompose CV into cortical thickness (CT) and surface area (SA). This fractionation of CV builds on a recent report that CV dysmaturation in adolescents and older adults with ASD is driven by CT rather than SA (Raznahan et al., 2010b). To date, the only study to have tested for dissociable abnormalities of CT and SA in young children with ASD inferred SA from measures of CV and CT (Hazlett et al., 2011). In the current study, we use SBM to directly measure CV, CT and SA.

The third, and perhaps most critical objective of our study was to provide the first spatially fine-grained SBM analysis of cortical anatomy in young children with autism. All but one (Hoeft et al., 2011) of the existing studies in this age range only assayed regional cortical anatomy using classical lobar boundaries (Carper et al., 2002; Hazlett et al., 2005, 2011; Schumann et al., 2010). Therefore, using a well-validated (Kabani et al., 2001; MacDonald et al., 2000; Shaw et al., 2008) SBM method to fine-map CT and SA across the cortical sheet, we tested the hypothesis that regions of the cortex previously reported as structurally abnormal in older groups with ASD (Chung et al., 2005; Ecker et al., 2010; Hadjikhani et al., 2006; Raznahan et al., 2010b) (see Fig. 1), and known to be crucial for social cognition (Adolphs, 2003), language (Price, 2010), and behavioral control (Langen et al., 2011a; Langen et al., 2011b), would already show focal disruption at the early ages evaluated in our study. These regions include (but are not limited to) inferior frontal gyrus, medial prefrontal cortex, superior temporal sulcus, middle temporal gyrus, fusiform gyrus, and inferior parietal lobule. We were particularly interested in whether focal disruptions of cortical anatomy in autism during early childhood would be better captured by CT or SA.

Since several existing reports suggest that anatomical differences between groups with ASD and controls may vary with age (Carper et al., 2002; Mak-Fan et al., 2012; Raznahan et al., 2010b; Wallace et al., 2010), we directly examined whether anatomical differences between children with autism and TDCs were modulated by age.

2. Materials and methods

2.1. Participants

All 95 participants were male and aged between 2 and 5 years of age. Sixty-six participants fulfilled DSM-IV diagnostic criteria for Autistic Disorder (AUT), and 29 were typically developing controls (TDCs). Initially, children diagnosed with autism or referred with concerns of a possible autism diagnosis were screened for participation, after responding to recruitment materials placed in the community (e.g. pediatricians' offices and early intervention providers). The presence of Autistic Disorder was then established by doctoral level clinicians after research-reliable administrations of the Autism Diagnosis Interview-Revised (Lord et al., 1994) (or a Toddler version), the Autism Diagnostic Observation Schedule [ADOS (Lord et al., 2000)], and clinical judgment. None of the participants had defined genetic disorders associated with an increased risk for ASD (e.g. Tuberous Sclerosis, Fragile X, Smith–Magenis syndrome), as determined by clinical assessment, karyotyping Fragile X testing, and CGH microarray testing. Other exclusionary criteria were a diagnosis of cerebral palsy or other neurological conditions that would prevent study procedure completion. Recruitment of TDCs was through advertisement in the local community and inclusion required cognitive scores higher than 1.5 standard deviations below standardized test means. Exclusionary criteria for TDCs included a first-degree relative with ASD, a history of extremely low birth-weight, or a history of receiving special education services/early intervention prior to study enrollment. Screening for TDCs included cognitive testing, as well as administration of the ADOS (Lord et al., 2000), Social Communication Questionnaire (Berument et al., 1999) and Child Behavior Checklist (Achenbach et al., 1991).

Developmental quotients [full (DQ), verbal (VDQ) and nonverbal (NVDQ)] were measured for all participants using either the Mullen Scales of Early Learning (Mullen, 1995) or the Differential Ability Scales (2nd edition) (Elliott, 2007). Due to floor effects on tests, Developmental Quotient (DQ's), based on age equivalent divided by chronological age multiplied by 100, were used to fully characterize individual variation. Since two TDC participants had DQs greater than 130, we tested for and confirmed robustness of our findings by removal of these two individuals.

In all cases, written informed consent was obtained from the participant's parent(s). The study was approved by an NIH Institutional Review Board.

2.2. Neuroimaging

The neuroimaging methods used in this study have been previously described (Lenroot et al., 2007; Raznahan et al., 2011b; Shaw et al., 2008) and are fully detailed in Supplementary Texts 1 and 2. Briefly, all scans were T-1 weighted images with contiguous 1.5 mm axial slices, obtained on the same 1.5-T General Electric (Milwaukee, WI) Signa scanner using a 3D spoiled gradient recalled echo sequence. Given the difficulty of obtaining high-quality neuroimaging data in young children with autism, we scanned children with autism under sedation using propofol. Sedation was performed at the NIH by board-certified