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Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders

Thomas P. DeRamus, Rajesh K. Kana*

Department of Psychology, University of Alabama, Birmingham, USA

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ABSTRACT

Autism spectrum disorders (ASD) are characterized by impairments in social communication and restrictive, repetitive behaviors. While behavioral symptoms are well-documented, investigations into the neurobiological underpinnings of ASD have not resulted in firm biomarkers. Variability in findings across structural neuroimaging studies has contributed to difficulty in reliably characterizing the brain morphology of individuals with ASD. These inconsistencies may also arise from the heterogeneity of ASD, and wider age-range of participants included in MRI studies and in previous meta-analyses. To address this, the current study used coordinate-based anatomical likelihood estimation (ALE) analysis of 21 voxel-based morphometry (VBM) studies examining high-functioning individuals with ASD, resulting in a meta-analysis of 1055 participants (506 ASD, and 549 typically developing individuals). Results consisted of grey, white, and global differences in cortical matter between the groups. Modeled anatomical maps consisting of concentration, thickness, and volume metrics of grey and white matter revealed clusters suggesting age-related decreases in grey and white matter in parietal and inferior temporal regions of the brain in ASD, and age-related increases in grey matter in frontal and anterior-temporal regions. White matter alterations included fiber tracts thought to play key roles in information processing and sensory integration. Many current theories of pathobiology ASD suggest that the brains of individuals with ASD may have less-functional long-range (anterior-to-posterior) connections. Our findings of decreased cortical matter in parietal–temporal and occipital regions, and thickening in frontal cortices in older adults with ASD may entail altered cortical anatomy, and neurodevelopmental adaptations.

1. Introduction

Autism spectrum disorders (ASD) are characterized by impairments in social communication as well as the presence of restricted interests/repetitive behaviors (American Psychiatric Association, 2013). While the etiology of ASD is still unclear, many current theories suggest alterations in genetic and neurobiological mechanisms as key underlying factors of this disorder (Amaral et al., 2008; Geschwind and Levitt, 2007). Neuroimaging studies have revealed abnormalities in brain functioning and brain connectivity as critical in defining the phenotype of ASD, and such differences may underlie neuroanatomical alterations in this population. For example, voxel based morphometry (VBM), a technique that measures regional grey and white matter volume using probabilistic mapping (Ashburner and Friston, 2000, 2001), has been used extensively to study the neuroanatomy of ASD in: children and adolescents (Bonilha et al., 2008; Brieber et al., 2007; McAlonan et al., 2005; McAlonan et al., 2008; McAlonan et al., 2009), and adults (Beacher et al., 2012; Ecker et al., 2012; Kosaka et al., 2010, 2010; Schmitz et al., 2006; Schmitz et al., 2008; Toal et al., 2010). These studies have regularly reported differential anatomical measures (i.e. concentration, density, volume) of grey and white matter in brain regions associated with processing cognitive and social functions in individuals with ASD. These include the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), prefrontal cortex, amygdala, caudate nucleus, putamen, and somatosensory cortex (Hollander et al., 2005; Just et al., 2007; Kennedy and Adolphs, 2012; Langen et al., 2007; Oblak et al., 2011; Schumann et al., 2004; Schumann et al., 2010). Many of these anatomical differences also strongly correlate with ASD symptom severity (Hollander et al., 2005; Rojas et al., 2006; Wolff et al., 2013) suggesting a brain–behavior relationship. Some neuroanatomical studies have applied their findings to pattern classification analyses in order to identify potential diagnostic markers of ASD (Ecker et al., 2010, 2010; Uddin et al., 2011).

Despite the promising directions in morphometric investigations of ASD neuroanatomy, the findings have been relatively inconsistent across studies. This inconsistency likely emerges from the differences in approaches to morphometry, specifically VBM, across studies.

* Corresponding author at: Department of Psychology, University of Alabama, CIRC 235G, 1719 6th Ave South, Birmingham, AL 35294 0021, USA. Tel.: +1 205 934 3171; fax: +1 205 975 6330.
E-mail address: rkana@uab.edu (R.K. Kana).

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Methodological differences, type of participants included (high-functioning versus low-functioning, classic ASD versus ASD with comorbid conditions), and age and developmental level of the participants can significantly affect the findings of these studies. Methodological variations are related to the use of different software and toolboxes available for image processing, (i.e. Brain Activation and Morphological Mapping [BAMM], CIVET, "Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra [DARTEL, Ashburner, 2007]), each of which may use different algorithms (Klein et al., 2009; Senjem et al., 2005). While difference in participant selection across studies is another source of variability in findings, perhaps the biggest contributor to this heterogeneity is the developmental stage of participants targeted. Many studies have reported that individuals with ASD show aberrant growth and developmental trajectories from early childhood into adulthood, but relatively few studies are longitudinal, limiting the analyses to cross-sectional designs with smaller numbers of participants and relatively narrow age ranges. This is potentially confounding given the findings of strong age-related effects on cortical development in both typically developing (TD) (Giedd et al., 1999; Gogtay et al., 2004) and ASD (Courchesne et al., 2007; Courchesne et al., 2011; Raznahan et al., 2010; Schumann et al., 2010) individuals. Thus, region-specific morphometric findings in ASD have largely been inconsistent, making it difficult to identify emerging consensus on neuroanatomical differences in this population.

These inconsistencies have made meta-analytic approaches such as anatomical likelihood estimation (ALE) an attractive approach to identifying trends and convergence across a large number of studies. ALE is a coordinate-based meta-analysis technique that uses statistically significant foci reported from different studies to create probability distribution maps for voxels of interest across experiments or foci, which are then used to generate structural or functional maps across groups of datasets or experiments (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2002). This method and other similar techniques (such as Signed Differential Mapping: SDM) have been used to conduct meta-analyses of VBM studies of ASD, and have been useful in identifying areas of consistent differences in cortical matter (CM, which refers to either grey or white matter depending on specific analyses) across studies (Cauda et al., 2011; Duerden et al., 2012; Nickl-Jockschat et al., 2012; Radua et al., 2011; Via et al., 2011). However, many of these meta-analyses have included studies comparing ASD participants with IQ scores below the cutoff for intellectual delay (IQ > 70), to TD controls with average IQ scores (Cauda et al., 2011; Duerden et al., 2012; Nickl-Jockschat et al., 2012). Additionally, some meta-analyses also included region of interest (ROI)-based analyses in their study pool (Via et al., 2011), which may alter statistical outcomes due to the differential statistical models and differences in anatomical boundaries of ROIs across studies (Glahn et al., 2008; Laird et al., 2005).

Limiting these potential sources of variability, the current study included 21 structural neuroimaging studies using conservative inclusion criteria for an ALE analysis of VBM results reported in ASD literature. The participants in these 21 studies largely include individuals with high functioning autism (HFA) and Asperger's syndrome (AS). There are 3 main points that guided our decision to group the participants from each study in this manner. The first is the difficulty in identifying morphometric differences between HFA and AS participants using a meta-analytic approach (as illustrated by Yu et al., 2011) since HFA and AS are rarely separated in morphometry studies. The second is that as per the DSM-V classification, AS is no longer considered a separate diagnosis, with the new criteria focusing on a spectrum diagnosis using 1 of 3 functional levels (dependent on the amount of support needed for the individual) (American Psychiatric Association, 2013). Our decision to group what was previously AS with what was previously HFA is meant to reflect this change. The third is that by combining the two high-functioning diagnostic groups, we are hoping to limit the contribution of intellectual impairment or developmental delay on cortical morphometry without sacrificing power to detect any potential effect. A thorough quality control process was followed to verify the quality of all spatial transformations for regional accuracy, matter type, and limit within-study and within-group contributions that may arise from the inclusion of multiple studies from the same authors (Turkeltaub et al., 2012). Rather than conducting individual ALE maps for age ranges, effectively "blocking" participants by age groups and limiting power due to the strict selection criteria followed, we report the studies contributing to each significant cluster and the age range under which each study falls. By doing so, we hope to identify clusters of anatomical regions that are atypical at younger stages of development, older stages of development, and regions that are consistently atypical in the brains of individuals with HFA/AS. Thus, the focus of this study is to identify the emerging themes from the structural neuroimaging literature in ASD with an emphasis on the neurodevelopmental trajectory of this disorder. The findings of this study will provide important insights into the characterization of the morphology of the brain in ASD, and further illuminate its developmental significance.

2. Methods and materials

2.1. Publication selection (inclusion/exclusion criteria)

The selection criteria for this meta-analysis consisted of studies involving HFA and AS participants with reported IQ measures greater than 70, and methodologies limited to whole-brain VBM. A comprehensive literature search was conducted using *Pubmed, Google Scholar, and the Brainmap.org*, and the VBM database within the *Sleuth 2.2* software (Fox et al., 2005; Fox and Lancaster, 2002; Laird et al., 2005) in order to identify peer reviewed articles investigating neuroanatomical differences in ASD. Keywords used in the search parameters for the databases included: ASD, VBM, morphometry, grey matter volume, white matter volume, autism spectrum disorders, autism, and Asperger's syndrome. Additional papers were located by reviewing the references of studies selected for the meta-analysis, in addition to studies used or reported in previous meta-analyses (Cauda et al., 2011; Duerden et al., 2012; Nickl-Jockschat et al., 2012; Radua et al., 2011; Via et al., 2011). Our search criteria yielded a total of 36 peer-reviewed published articles. Of the 36, two articles were excluded as they used non-VBM modalities (i.e. DTI, Freesurfer), another two were excluded due to region of interest (ROI) analysis as opposed to whole brain analyses, and another eleven were excluded as those studies had subjects with comorbid conditions in the comparison group (i.e. Intellectual disability, ADHD, Fragile X), or in which participants had IQs < 70. The exception to these was Brieber et al. (2007), which included comparisons between individuals with ADHD and autism, and participants from Salmond et al. (2007), and Toal et al. (2010) that had IQs less than 70. In the former, only the significant results comparing individuals with ASD to TD controls were used, in the latter, only results from comparisons of HFA (IQ > 70) to TD controls were used. This conservative selection process yielded a total of 21 articles containing a total of 1055 participants reporting 478 separate neuroanatomical foci. The selected publications had a total of 506 ASD participants (mean age = 19.56 ± 9.15) and 549 (mean age 19.14 ± 9.26) TD controls. The age range was 6–59 years for the ASD group, and 6–58 years for TD controls (see Table 1 for demographic information by study).

MNI coordinates of significantly different grey and white matter measures were extracted from each study meeting the selection criteria. Studies that reported their results in Talairach coordinates were converted to MNI space using the *tal2icbm* script in Matlab (R2012b) (Laird et al., 2010; Lancaster et al., 2007), and articles that reported Talairach coordinates converted from MNI space using the Brett Transform were converted back to MNI using the *tal2mni* script (Brett et al., 2001). Articles reporting MNI coordinates converted from Talairach coordinates using the Brett Transform were converted back to Talairach space using the *mni2tal* function, and then transformed to MNI space