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

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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.

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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 underlyng 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; Obikai 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; Wolf 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.
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, (e.g. 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 morphology 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 tal2mni 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.
using the tal2icbm transformation. The parameters, templates, smoothing kernels, and transformations applied to studies included in our analysis are described in Table 2.

2.2. ALE parameters

ALE analyses were performed using the Turkeltaub (2012) correction to the Eickhoff (2009) method, in order to minimize within-subject effects of subject groups with multiple experiments and the contribution of multiple-foci to modeled activation maps. Separate analyses were performed comparing clusters of voxel-based increases in CM (grey and white) and decreases in CM (grey and white) between individuals with ASD and TD controls. The analyses were performed comparing clusters of voxel-based increases in CM (grey and white) and decreases in CM (grey and white) between individuals with ASD and TD controls.

The developmental level of participants for all the studies included in our analyses ranged from children and adolescents (6–16 years of age), to younger and older adults (18–58 years of age). Consideration however, that cortical maturation of many areas peaks at pre-adolescence (11–13), with steady declines in late adolescence (Giedd et al., 1999; Gogtay et al., 2004; Redcay and Courchesne, 2005). As such, a dichotomous grouping based on univariate analyses may not present the complete picture of development in ASD. To address this concern, the age range of significance foci from our analysis will be reported in order to evaluate whether certain structures are more atypical in individuals with ASD across development or if they are confined to an isolated developmental window (i.e. less than 16 years of age or greater than 16 years of age).

3. Results

3.1. Significant clusters of the ALE analysis

The analysis of global decreases in CM found localized decreases in temporal and occipital brain regions in individuals with ASD, with left lateralized decreases in parietal, frontal limbic regions, and right lateralized decreases in limbic regions. Global increases in CM in ASD were primarily localized to the frontal lobe; however, increases in CM were also found in ASD in left anterior temporal and right cerebellar regions. When the analyses were narrowed by CM type, grey matter decreases in ASD were localized to smaller clusters of parietal, cerebellar, and hippocampal regions and all grey matter increases in ASD were predominantly in prefrontal and temporal grey matter. White matter decreases were lateralized to the left hemisphere within the parietal cortex, ACC, and thalamic white matter connections.

3.2. Significant decreases in cortical matter

Significant ALE clusters of less CM in ASD (FDR computed CFT; \( p < 0.002 \), ALE threshold \( < 0.008 \)) were found bilaterally within the inferior temporal gyrus (ITG) (LITG volume = 416 mm\(^3\); RITG volume = 296 mm\(^3\)), the left occipital pole (volume = 527 mm\(^3\)), and the left lateralized decreases in parietal, frontal limbic regions, and right lateralized decreases in limbic regions. Global increases in CM in ASD were primarily localized to the frontal lobe; however, increases in CM were also found in ASD in left anterior temporal and right cerebellar regions. When the analyses were narrowed by CM type, grey matter decreases in ASD were localized to smaller clusters of parietal, cerebellar, and hippocampal regions and all grey matter increases in ASD were predominantly in prefrontal and temporal grey matter. White matter decreases were lateralized to the left hemisphere within the parietal cortex, ACC, and thalamic white matter connections.
3.3. Significant increases in cortical matter

The analysis examining increased CM in individuals with ASD (FDR computed CFT; \( p < 0.002 \), ALE threshold \( > 0.0077 \)) revealed a number of significant clusters within the frontal lobe bilaterally. These included a large cluster within the left superior frontal gyrus (LSFG) (volume = 376 mm\(^3\)), the right precentral gyrus (volume = 520 mm\(^3\)), and three clusters within the frontal pole (FP) bilaterally (LFP volume = 376 mm\(^3\)) and volume = 224 mm\(^3\); RFP volume = 232 mm\(^3\)). A large cluster was also found in the left temporal pole (particularly the middle temporal gyrus, volume = 528 mm\(^3\)); and right area V/III of the cerebellum (volume = 352 mm\(^3\)).

The results of the global and focused CM increase analyses, significant at an FDR correction of \( p < 0.05 \), are displayed in Table 3 and Fig. 1.

3.4. Age-related contributions to reported maxima

An important aspect of characterizing the neurobiology of a pervasive developmental disorder like ASD is to understand its neurodevelopmental trajectory. Due to the variability in participant selection criteria across different studies, isolating specific developmental windows is challenging. Nevertheless, our analysis revealed some interesting results. In the global analysis (analysis of all matter), decreases in the ACC and cerebellar vermis \\((V/III)\\) emerged from studies on children and adolescents with ASD (6–18 years of age). These results were also seen in the decreased grey matter (along with a decrease in the parietal operculum) and white matter analyses. However, we found increases in volume in the superior frontal and precentral areas in the global increase analysis specific to studies of older individuals with ASD (18–52 years of age), which also persisted within the grey matter analysis.
The rest of the significant clusters are formed across one of three categories based on the age range of foci forming the MA map: child to young adult (6–20 years), adolescent to adult (12–59 years), and throughout development (6–59 years). Clusters for studies of child to young adult participants included thinning of the postcentral gyrus in the global CM decrease and grey-matter specific increases in RITG and area VIIIb of the cerebellum vermis. A large majority of the significant foci stemmed from the adolescent to adult age group. This included global decrease of the occipital pole, anterior temporal, frontal pole, and lateral occipital gyri, grey matter decrease in the temporal and frontal poles, and white matter decrease in the internal capsule and superior parietal clusters. Clusters that formed from foci with large age ranges (6–59 years) included the internal capsule and hippocampus in the global CM decrease analysis, with the hippocampus persisting into the grey matter decrease analysis, area VIIIb of the cerebellum vermis in the global increase analysis, and the fusiform gyrus in the grey matter increase analysis. A comprehensive list of which studies contributed to each focus and colour-labelled maps of each group outlined above are displayed in Table S1 and Figs. S1 and S2 of the supplementary material.

4. Discussion

The results of this coordinate-based meta-analysis suggest alterations in grey and white matter volume (increase and decrease) in individuals with ASD, relative to TD control participants. Clusters reflecting increases in grey matter were found in frontal, temporal, and cerebellar areas, and clusters indicating decreases in grey matter were found in parietal–temporal, right hippocampal/amygdala, and cerebellar regions. This is consistent with previous structural MRI findings of increased CM (Carper and Courchesne, 2000; Carper et al., 2002; Duerden et al., 2012; Hazlett et al., 2005; Hazlett et al., 2006; Schumann et al., 2010; Via et al., 2011) and decreased CM (see Chen et al., 2011 for review) in individuals with ASD. Some of these findings are also consistent with previous meta-analyses of brain volumetric differences in the ASD population which survived leave-one-out tests of validity (Cauda et al., 2011; Duerden et al., 2012; Nickl-Jockschat et al., 2012; Via et al., 2011).

White matter decrease in ASD was seen primarily within the ACC and internal capsule of the basal ganglia, and lateral–occipital cortex. This may reflect underlying microstructural organization, as alterations in fractional anisotropy (FA) in these areas have been reported in diffusion tensor imaging (DTI) studies of ASD (Alexander et al., 2007; Brito et al., 2009; Ingbalilakar et al., 2011; Keary et al., 2009; Keller et al., 2007; Shukla et al., 2010; Shukla et al., 2011; Travers et al., 2012).

4.1. Increased prefrontal cortex volume in autism

One of the key areas of volumetric alterations found in this study is the prefrontal cortex which, in general, has been considered as the epicenter of neurobiological abnormalities in ASD. Significant clusters of grey matter increase were located within the left superior, middle, and inferior frontal gyri, and right medial prefrontal cortex (SFG, MFG, and MFPC respectively). MRI and lesion studies have suggested that these structures contribute to a number of cognitive processes, including inhibition (MPFC, IFG; Talati and Hirsch, 2005; Aron et al., 2014), working memory (MFG, SFG; Leung et al., 2002; du Boisgueneheuc et al., 2006), motor sequencing and imitation (IFG, SFG; Toni et al., 1999; Rushworth et al., 2004), and language (IFG; Hischorn and Thompson-Schill, 2006), all of which have been reported to be atypical in ASD (Bennetto et al., 1996; Dziuk et al., 2007; Kana et al., 2006; Kleinhaus et al., 2005; Minshew and Goldstein, 2001; Ozonoff et al., 1991; Sinzig et al., 2008). Clusters of increased frontal grey matter are especially interesting considering recent post-mortem findings of significantly increased number of neurons in the frontal cortex, especially in MPFC and dorsolateral prefrontal cortex in ASD (Courchesne et al., 2011). Increased levels of microglia and astroglia in active states in the frontal cortex have also been reported in ASD (Vargas et al., 2005). Cell-structure studies in the frontal and temporal lobes of individuals with ASD have found that cortical minicolumns (basic functional unit of the cerebral cortex) are both smaller and more numerous (Casanova et al., 2002). Numerous neurons packed in smaller columns can lead to altered patterns of connectivity favoring local overconnectivity and long-distance underconnectivity (Cherkassky et al., 2006; Courchesne and Pierce, 2005; Kana et al., 2009). Thus, it is possible that the complex neurobiology of ASD may entail such widespread (anatomical, functional, microstructural, and cellular) abnormalities. The increase in prefrontal cortex grey matter in ASD found in our meta-analysis could reflect a noticeable structural alteration in individuals with ASD, which could contribute to or be the result of cytoarchitectural differences in the brain.

4.2. Frontal-posterior differences

The findings of the present study also suggest distinct morphometric differences between frontal and posterior brain regions in ASD, with increases in grey matter primarily localized to frontal regions, and decreases in grey and white matter localized to parietal–occipital–temporal, limbic, and circulate areas. Such differences have been reported by previous structural neuroimaging studies (Hazlett et al., 2006). A similar pattern was also seen in terms of altered asymmetry of the IFG and posterior superior temporal cortex in autism (Herbert et al., 2005). Additionally, functional neuroimaging studies of visual and visuospatial processing have reported increased parietal and occipital activation and intact or enhanced connectivity among relatively posterior areas of the brain (Kana et al., 2013). A recent review of the relationship between development and functional connectivity suggested that children with ASD may display increased connectivity, and adolescents and adults display decreased to normal functional and structural connections between frontal–parietal and default mode regions of the brain (Uddin et al., 2013). It should be noted that the increases in temporal and frontal regions, and decreases in parietal regions found in our study are specific to adolescents and adults with ASD, and may support a developmentally shifted pattern of cortical development reflecting less communication between frontal and parietal–temporal regions. Alternatively this could arise from posterior autonomy, which entails a more parietal and occipital reliant method of information processing. However, it is difficult to find direct support for either account, as VBM studies rely on the assumption that MR signal

Table 3

| Region                      | Hem | x   | y   | z   | Volume | ALE value |
|-----------------------------|-----|-----|-----|-----|--------|-----------|
| **TD > ASD**                |     |     |     |     |        |           |
| Inferior temporal           | L   | −46 | −60 | −8  | 416    | 0.014264904** |
| Occipital pole              | L   | −32 | −94 | −10 | 400    | 0.01464336**  |
| Anterior cingulate          | R   | 2   | 34  | 10  | 376    | 0.01319522**   |
| Internal capsule            | L   | 14  | −6  | 0   | 352    | 0.0167158**    |
| Cerebellum IX/VIII vermis   | L   | −2  | −60 | −40 | 320    | 0.01216301**   |
| Inferior temporal           | R   | 52  | −60 | 16  | 296    | 0.01550702**   |
| Hippocampus                 | R   | 32  | −10 | −20 | 256    | 0.010775952**  |
| Postcentral gyrus           | L   | −32 | −38 | 60  | 256    | 0.011418079**  |
| Angular gyrus               | L   | −44 | −56 | 26  | 240    | 0.010977356**  |
| Lateral occipital cortex    | R   | 46  | −64 | 28  | 200    | 0.010175092**  |
| **TD > ASD grey matter**   |     |     |     |     |        |           |
| Cerebellum IX vermis        | L   | −2  | −60 | 40  | 344    | 0.012163029**  |
| Hippocampus                 | R   | 32  | −10 | −20 | 280    | 0.010775952**  |
| Parietal operculum          | L   | −54 | 30  | 22  | 208    | 0.009826495*    |
| **TD > ASD white matter**  |     |     |     |     |        |           |
| Internal capsule            | R   | 14  | −6  | 0   | 376    | 0.010779265*    |
| Anterior cingulate          | R   | 4   | 34  | 10  | 352    | 0.010652142*    |
| Lateral occipital cortex    | R   | 46  | −64 | 28  | 336    | 0.010174075**   |

Hem: hemisphere; L: left; R: right.
* Significant at p < .001.
** Significant at p < .002.
intensity correlates with white matter fiber integrity. This does not always seem to be the case in normal or clinical populations (Buchel et al., 2004; Filippi et al., 2001). Despite this limitation, some support for the frontal-posterior differences has come from DTI literature, which report reduced FA and increased mean and radial diffusivity values within temporal, and frontal regions in ASD (Barnea-Goraly et al., 2004; Shukla et al., 2011; Travers et al., 2012). One of the most consistently reported region of white matter alteration (including our meta-analysis) is in the ACC, which serves as an integration hub for many different types of executive and social processes, and has been associated with cytoarchitectural abnormalities in children with ASD (Simms et al., 2009). What these structural differences contribute to the ASD phenotype and how they develop is an important topic of debate and should be addressed by future studies.

4.3. Cerebellar volumetric differences

Consistent with some previous meta-analyses of VBM in ASD (Cauda et al., 2011; Duerden et al., 2012), we found statistically significant clusters of grey matter alterations (less GM in area VIIIb/IX on the left, more GM on area VIIIb on the right) within the vermis of the cerebellum. Grey matter abnormalities within the cerebellum are widely reported in ASD literature (Carper and Courchesne, 2000; Courchesne et al., 1994; Courchesne et al., 2001; Courchesne et al., 2007; Courchesne, 1997; Courchesne et al., 1988; Fatemi et al., 2002; Fatemi et al., 2001; Hashimoto et al., 1995; Levitt et al., 1999; Piven et al., 1992; Vargas et al., 2005). A consistently reported neuroanatomical abnormality in cerebellum in ASD is a significant reduction in the number of Purkinje cells (see Baumann and Kemper, 2005 for review), which can have a significant impact on connectivity (Kern, 2003). The cerebellum has reciprocal connections with the basal ganglia and prefrontal cortex (Doyon et al., 2003; Middleton and Strick, 2000; Terry and Rosenberg, 1995), the latter of which was found to be enlarged in the right hemisphere in individuals with ASD in the present study. Reduced connectivity between cerebellum and motor cortex was reported in fMRI studies of sequential finger-tapping (Mostofsky et al., 2009). This is interesting not only due to the relationship between the cerebellum and motor cortex, but also because our results suggest increases in grey-matter along the precentral gyrus. This could reflect possible communication deficits between these two regions. Additionally, studies on children with cranial

Fig. 1. Significant clusters of decreased CM in individuals with ASD. A) Clusters of global decreases in CM (blue), B) clusters of decreased grey matter in ASD (teal), C) clusters of decreased white matter in ASD (green), D) overlap between comparisons (magenta; global/GM overlap, yellow; global/WM overlap).
fossa tumours (who have regions of the cerebellum near the vermis removed), frequently report communication and social deficits such as mutism, which overlap with some communication and social deficits present in autism (Poggi et al., 2005; Pollack et al., 1995).

4.4. Implications for social cognition

Our findings of increased grey matter in the angular gyrus, frontal and temporal pole, and middle temporal gyrus have strong implications for social cognition, especially Theory-of-Mind (ToM) in individuals with ASD as these three regions are routinely activated during ToM tasks (Castelli et al., 2000; Frith and Frith, 2003; Gallagher et al., 2000; Gallagher and Frith, 2003; Ohnishi et al., 2004). In addition, the FP shares functional and white matter connections with the angular gyrus, temporal pole, and ACC (Barnea-Goraly et al., 2004; Kelly et al., 2009; Koski and Paus, 2000; Liu et al., 2013). Atypical connections between these regions have been found in ASD during mentalizing tasks (Castelli et al., 2002; Frith, 2001; Kana et al., 2009; Zilbovicius et al., 2006).

Fusiform activation has consistently been reported as decreased in ASD when viewing faces (and some have argued increased compensatory ITG activation) (Schultz et al., 2000). A recent study by Nickl-Jockschat et al. (2014) used a combination of meta-analytic connectivity modeling (MACM) of co-activating ROIs, and resting state-connectivity analysis using the fusiform (which was an area of significant grey

| Region                  | Hem | X     | Y     | Z     | Volume | ALE value |
|-------------------------|-----|-------|-------|-------|--------|-----------|
| ASD > TD grey matter    |     |       |       |       |        |           |
| Superior frontal        | L   | −18   | 32    | 44    | 592    | 0.013148831* |
| Superior frontal        | L   | −22   | 22    | 48    | 0.010468714* |
| Temporal Pole           | L   | −42   | 6     | −28   | 528    | 0.013823562** |
| Precentral              | R   | 48    | 0     | 40    | 520    | 0.013296759** |
| Frontal Pole            | L   | −32   | 50    | −6    | 376    | 0.013463693** |
| Frontal Pole            | R   | 4     | 64    | −12   | 232    | 0.01040588**  |
| Frontal Pole            | L   | −32   | 42    | 12    | 224    | 0.01076785**  |

| Region                  | Hem | X     | Y     | Z     | Volume | ALE value |
|-------------------------|-----|-------|-------|-------|--------|-----------|
| ASD > TD                |     |       |       |       |        |           |
| Cerebellum area VIIIb   | R   | 14    | −62   | −42   | 616    | 0.0137533387** |
| Superior frontal        | L   | −18   | 32    | 44    | 592    | 0.013148831** |
| Superior frontal        | L   | −22   | 22    | 48    | 0.010468714** |
| Temporal Pole           | L   | −42   | 6     | −28   | 528    | 0.013823562** |
| Precentral              | R   | 48    | 0     | 40    | 520    | 0.013296759** |
| Frontal Pole            | L   | −32   | 50    | −6    | 376    | 0.013463693** |
| Frontal Pole            | R   | 4     | 64    | −12   | 232    | 0.01040588**  |
| Frontal Pole            | L   | −32   | 42    | 12    | 224    | 0.01076785**  |

Fig. 2. Significant clusters of increased CM in individuals with ASD. A) Clusters of global increases in matter (red), B) clusters of increased grey matter in ASD (yellow), C) overlap between comparisons (magenta; global/GM overlap).
manner increase in our analysis) as a seed. They found bilateral decreases in connectivity with the IFG, temporal–occipital cortex, middle temporal gyrus, SMA, SPL, thalamus, and left medial temporal lobe in both face processing and resting state data, in addition to decreased connections with the cerebellum in ASD. Bilateral alterations in ITG (including the fusiform gyrus), left middle temporal gyrus and angular gyrus volume are also important considering the role of these regions in face, object, and word processing (Koyama et al., 2011; Pierce et al., 2001; Samson et al., 2012). Meta-analyses of activation for faces, objects, and words have suggested that middle and superior frontal, middle and superior temporal, and fusiform regions show altered, predominantly left lateralized activation in ASD (Samson et al., 2012), which overlaps with some of the anatomical regions in the results of our meta-analysis. The connectivity results from this meta-analysis overlap relatively well with our study, as well as previous meta-analyses of VBM, in addition to surface based morphometric approaches (Libero et al., 2014) in ASD. These findings highlight disruptions in discrete, task-dependent networks that may contribute to the ASD phenotype (Caspers et al., 2014; Mishkin and Ungerleider, 1982; Niclš-Jockschat et al., 2014; Ungerleider and Haxby, 1994).

4.5. Sensory and motor circuitry

Consistent with other meta-analyses and DTI, we report a decrease in white matter integrity in ASD in the posterior limb of the internal capsule of the right hemisphere (Duerden et al., 2012; Radua et al., 2011). This particular region consists of many cortical and spinal white matter tracts, including the thalamic radiation, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior frontal–occipital fasciculus (IFOF), and spinal-thalamic tracts (Lebel et al., 2008; Mori et al., 2008). Due to the widespread targets of these tracts, many have argued that white matter compromises in this area may contribute to problems with sensory and motor integration within individuals with ASD, and it is posited as a culprit for decreased longitudinal connectivity within the brains of ASD individuals (Keller et al., 2007; Shukla et al., 2010; Shukla et al., 2011).

5. Strengths and limitations

Any meta-analytic approach in neuroimaging may be inherently constrained by variables, such as differences in scanner strength, method of data analyses, data quality control measures used, coregistration techniques used, and differences in statistical threshold at which results are reported by individual studies. The studies used in this meta-analysis represent almost 15 years of VBM data on ASD, with significant advances in technologies over the years. As such, a coordinate-based approach was preferred due to the availability of reported results and established methods of anatomical likelihood (Salimi-Khorshidi et al., 2009). Studies by Salimi-Khorshidi et al. (2009) reported that ALE results were closest in concordance with image-based meta-analysis when compared to other coordinate based approaches. While scanner resolution, inter-program registration techniques, and threshold criteria are difficult to control for in a coordinate-based meta-analytic approach, strict precautions were taken in our study to control for experimenter bias and coordinate transformation errors. For the former, we used the Turkeltaub et al. (2012) correction, which reduces potential inflations from multiple foci in close proximity within a single experiment by calculating modelled activation (MA) maps across groups of subjects, rather than by experiment and uses the union/overlap of these maps to report significant results. This is done by using single foci from each experiment or subject group with the shortest Euclidian distance from the voxel of interest as the maximum probability of activation for that voxel (Turkeltaub et al., 2012). As an additional precaution against artefacts, the coordinate space from each study was evaluated and individual transformation into MNI space was applied instead of automated transformations into MNI space.

There are some universal caveats to anatomy-based imaging of individuals on the ASD spectrum. Avino and Hutslar (2010) suggested that individuals with ASD display less defined grey/white matter boundaries than TD individuals. As such, intensity-based imaging techniques such as VBM could artificially inflate or deflate measures of cortical morphometry in this population. Surface-based studies registering to sulcal landmarks have found abnormalities in frontal and temporal cortices (Levitt et al., 2003), along the angular/supramarginal gyrus (Hardan et al., 2004; Libero et al., 2014). Since VBM does not register based on sulcal and gyral landmarks, morphometric alterations in these regions could be a result of these shifts that have not been detected by the technique (Bookstein, 2001; Davatzikos, 2004).

Theories relating meta-analytic assessments of morphometric changes in ASD relative to activation, neurodevelopment, or connectivity has some conjectural limitations. Regarding neurodevelopment, many of the VBM studies included in this study, with the exception of one (Grémel et al., 2013), analysed age-dependent changes in VBM results in favour of univariate approaches controlling for age and IQ. While this is an adequate approach for establishing main effects of group at discrete developmental windows, it does not address the fact that cortical measures differ as a function of age and development, which many studies of the ASD brain have been shown to be longitudinally different from TD individuals especially at younger ages (Courchesne et al., 2007; Redcay and Courchesne, 2005; Schumann et al., 2010). As such, researchers are limited to discrete developmental windows, which may not fully explain the course of ASD. Regarding connectivity, as stated previously in the discussion, a limitation of using VBM to infer white matter integrity is that MR signal does not necessarily correlate with white matter fiber integrity, making it a less optimal approach than diffusion tensor or weighted fiber tractography. Meta-analytic approaches to co-activation of brain regions such as MACM can provide some information with regard to inter-cortical communication across large database samples (Eickhoff et al., 2011). Such approaches to white-matter tractography would benefit ASD research by potentially validating activation or morphometric differences associated with brain connections.

6. Conclusions

To our knowledge, this ALE meta-analysis is the first to conduct a focused analysis within a high functioning subgroup of individuals with ASD. Many of the cluster results suggesting atypical cortical volumes are specific to regions associated with social cognition, which is frequently found to be atypical in individuals with ASD. Additionally, these differences seem to favor CM increases within the frontal cortex of older individuals with ASD, and white matter abnormalities in fiber integrity (such as the cingulate and internal capsule) relatively early in development. These results point to the difference in structural integrity of frontal and posterior brain areas in individuals with ASD which may have an impact on the functions and connections of these regions. Additionally, improvements in meta-analytic approaches for fiber-tractography would greatly aid in substantiating the argument that disrupted connectivity contributes to or is influenced by morphometric alterations in ASD. Furthermore, the localization of frontal grey matter increases in older adults illustrates a need for studying brain development in ASD as a longitudinal process, rather than across developmental windows.

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2014.11.004.

Conflicts of interest

Both authors had full access to all of publications used in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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