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Original Article

Structural Gray Matter Differences During Childhood Development in Autism Spectrum Disorder: A Multimetric Approach

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ABSTRACT

BACKGROUND: Autism spectrum disorder is a complex neurodevelopmental disorder characterized by impaired social interaction and communication, repetitive behaviors, and restricted interests. Gray matter differences linked to autism spectrum disorder have been studied using a variety of structural imaging methods, but yielded little consensus; the extent to which disparate results reflect differences in methodology or heterogeneity within autism spectrum disorder is not yet clear. Moreover, very few studies have examined gray matter changes as a function of age in autism spectrum disorder. **METHOD:** A detailed investigation of gray matter structural development was performed via voxel-based morphometry, cortical thickness, and cortical surface area analyses in 38 autism spectrum disorder versus 46 typically developing children. **RESULTS:** Relative to typically developing children, the autism spectrum disorder group showed gray matter increases most prominently in the frontal and temporal lobes (including regions such as medial frontal gyrus, Broca's area and posterior temporal cortex), as well as certain parietal and occipital subcortical regions. Gray matter decreases were found only near the temporoparietal junction. Subcortical gray matter increases were found in the putamen and caudate nucleus, while decreases were found in cerebellum. There were age-dependent GM differences in distributed regions including prefrontal cortex, primary sensorimotor cortex, and temporoparietal junction. **CONCLUSION:** The results underline the distributed nature of gray matter structural differences in autism spectrum disorder and provide a more comprehensive characterization of autism spectrum disorder–related cortical and subcortical gray matter structural differences during childhood and adolescent development.

Keywords: autism, cortical thickness, surface-based morphometry, voxel-based morphometry, magnetic resonance imaging, developmental disabilities

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Introduction

Autism spectrum disorder (ASD) is principally a behaviorally defined syndrome, with limited reliable biological markers. In efforts to discover useful markers in ASD, neuroimaging studies have examined brain differences in ASD. However, mirroring the wide behavioral variation across the autism spectrum, neuroimaging findings are also

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[1] http://www.neurodevnet.ca/research/asd

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heterogeneous, and gray matter (GM) structural differences in ASD are particularly variable across studies.

Several factors might contribute to the variability of structural GM differences found in ASD. Studies have used a variety of brain structural metrics that measure different parts and properties of the brain.[1] For example, volumetric techniques can provide information on both cortical and subcortical parts of the brain, but surface-based techniques are necessary to examine detailed cortical surface properties. Moreover, most structural brain imaging studies of ASD have omitted or only provided limited examination of how age affects structural brain development in ASD.[2] This is problematic because age has a strong modulatory effect on brain structure in ASD from infancy to adolescence, and possibly into adulthood. Global brain size (estimated by head circumference) is normal or smaller in ASD at birth, but then undergoes an increased rate of growth,[3,4] leading to enlargement of brain volume as well as component gray and white matter volumes by 2 years of age compared to typically developing children.[3,5-8] Longitudinal studies confirm an early period of brain volume overgrowth in ASD,[9,10] with convergence with typical volumes around 10 years of age followed by accelerated decline into adulthood.[10] However, regional contributions to this differential age trajectory in ASD, when they have been examined, are not consistent across studies.[11-13]

Structural brain imaging studies of ASD have most commonly used voxel-based morphometry (VBM), a volumetric technique that provides a probabilistic measure of local GM volume or concentration.[14] An activation likelihood estimate meta-analysis of VBM studies by Nickl-Jockschat et al.[2] noted a wide variability in methodology and results across studies, but found converging findings of altered cortical GM in ASD versus typically developing (TD) individuals primarily in frontal and temporal cortex. Compared with cortical surface-based analyses that only examine the cortex, VBM has the advantage of measuring both cortical and subcortical structures. VBM studies have reported GM differences in ASD in subcortical areas including the caudate nucleus,[15] claustrum,[16] thalamus,[17] basal ganglia,[18] and brainstem.[19]

In contrast to VBM, surface-based structural metrics permit precise quantification of cortical thickness (CT) and surface area (SA) as separate, essentially orthogonal components of local cortical volume (CV).[1] Surface-based analyses also avoid ambiguities that can arise in VBM from variation in shape and position of the cortical mantle, because extraction of the cortex follows the GM surface despite local variations in its position.[20] Studies of regional CT differences in ASD adults have reported mainly increased CT in frontal, temporal, and parietal brain cortex.[19,21,22] In ASD children, increased CT has been found in inferior frontal gyrus and precuneus[11] and decreased CT in middle temporal and fusiform gyrus.[12] In terms of mean CT, TD individuals exhibit a progressive overall thinning of cortex from around age 10 to adulthood.[23] In contrast, some studies found that children with ASD have thicker cortex relative to TD before adolescence,[24] but then show a greater rate of cortical thinning during adolescence.[11,13] Cortical SA has received less study in ASD than CT. Mak-Fan et al.[11] examined both CT and SA development in ASD; they found that total SA stayed constant in TD (8-15 years old), but that regional SA in the occipital lobe decreased with age in the ASD group. However, a study by Raznahan et al.[12] found no group differences in total SA, lobular SA, or a group interaction with age. Another study in children and adults with ASD found increased SA in the right cingulate cortex.[25] Differences in these results between adult and child ASD studies speak to the need to carefully examine the effect of age on brain structure.

Taken together, the spatial extensiveness of GM structural differences in ASD fits well with findings of functional brain differences in areas involved in core features of ASD such as social cognition,[26] repetitive behaviors,[27] and atypical sensory perception,[28] particularly in frontal and temporal brain areas. The distributed nature of GM structural differences in ASD also fits well with functional differences in brain networks involved in the mirror neuron system, which is involved in imitation and action understanding and includes brain areas such as inferior frontal lobe and the temporoparietal junction[29] as well as the default mode network, which is engaged at rest and during internally focused tasks and involves brain areas such as medial frontal lobe and the temporoparietal junction.[30]

However, the variable structural neuroimaging findings in ASD signal the need for further, more detailed study to better characterize regional structural GM changes in ASD as well as to consider wider ranges of ages and explicitly account for age during structural analysis. To these aims, in the present study, a multiple-metric approach was used that combines VBM and surface-based measures (CT, SA, and CV) within the same patients to thoroughly examine structural GM development in ASD. This combined approach benefits from the convergence and complementarity of the techniques to detect differences in GM properties at both a cortical and subcortical level over the course of development. Based on the previous structural brain imaging studies, we expected to find both cortical and subcortical regional GM structural differences in ASD across distributed brain regions, and particularly in frontal and temporal cortex. Further, we expected to find decreased GM with age in TD individuals, with an altered trajectory of GM development in ASD.

Materials and Methods

Participants

Two groups of children participated in the present study: 38 boys with ASD and 46 TD boys. Participants were recruited as part of the NeuroDevNet Autism Demonstration Project, a multisite initiative to study brain structural and behavioral development in ASD.[31] Participants were assessed at two collaborating sites: (1) Montreal, Canada at the Montreal Children's Hospital and Montreal Neurological Institute, and (2) Toronto, Canada, at the Holland Bloorview Kids Rehabilitation Hospital and Toronto Sick Kids Hospital.

ASD diagnoses were based on expert clinical best estimate using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision[32] supported by the Autism Diagnostic Interview-Revised[33] and Autism Diagnostic Observation Schedule (ADOS and ADOS-2; wpspublish.com).[34] No TD participants had a history of neurological or psychiatric illness. Exclusion criteria included IQ below 70, gestational age of 35 weeks or less, any primary psychiatric diagnoses (excepting ASD for the clinical group), a medical history of neurological disease, family history of ASD (for the TD group), and hearing impairment.