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Characteristic cortical thickness patterns in adolescents with autism spectrum disorders: Interactions with age and intellectual ability revealed by canonical correlation analysis

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ABSTRACT

To investigate patterns and correlates of cortical thickness in adolescent males with autism spectrum disorders (ASD) versus matched typically developing controls, we applied kernel canonical correlation analysis to whole brain cortical thickness with the explaining variables of diagnosis, age, full-scale IQ, and their interactions. The analysis found that canonical variates (patterns of cortical thickness) correlated with each of these variables. The diagnosis- and age-by-diagnosis-related canonical variates showed thinner cortex for participants with ASD, which is consistent with previous studies using a univariate analysis. In addition, the multivariate statistics found larger affected regions with higher sensitivity than those found using univariate analysis. An IQ-related effect was also found with the multivariate analysis. The effects of IQ and age-by-IQ interaction on cortical thickness differed between the diagnostic groups. For typically developing adolescents, IQ was positively correlated with cortical thickness in orbitofrontal, postcentral and superior temporal regions, and greater thinning with age was seen in dorsal frontal areas in the superior IQ (>120) group. These associations between IQ and cortical thickness were not seen in the ASD group. Differing relationships between IQ and cortical thickness implies independent associations between measures of intelligence and brain structure in ASD versus typically developing controls. We discuss these findings vis-à-vis prior results obtained utilizing univariate methods.

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Introduction

Autism spectrum disorders (ASD) are characterized by impairments in social interaction, communication, and repetitive behavior (American Psychiatric Association, 2000). Many studies have shown an atypical developmental trajectory of brain anatomy, particularly gray matter structures, in ASD compared to patterns observed in typical development (Hardan et al., 2009; Raznahan et al., 2010; Redcay and Courchesne, 2005; Scheel et al., 2011; Wallace et al., 2010, for review, see Amaral et al., 2008; Courchesne et al., 2007). These studies indicate that age is an important factor and key to understanding neuroanatomical differences in ASD.

In addition to age, intellectual ability (measured via IQ scores) is also related to gray matter structures in typical development (Narr et al., 2007; Shaw et al., 2006; Sowell et al., 2004; Wilke et al., 2003). However, discrepant associations between gray matter structure and IQ in ASD (versus typically developing individuals) have not been shown. Hardan et al. (2006) investigating the cortical thickness differences between typically developing and ASD children, report that no significant correlation between IQ score and cortical thickness was found in either group. Hadjikhani et al. (2006) also did not find any significant correlation between IQ and cortical thinning in ASD adults. These negative results even for typically developing participants could be due to limited sensitivity of their analyses with small sample sizes.

While most of the previous studies use univariate approaches in which the effect of ASD is evaluated at each local region independently, multivariate approaches may more effectively characterize neuroanatomical differences in ASD with higher sensitivity: the effect of ASD is not likely to be restricted to a specific brain region but instead distributed in broad areas; therefore, regional differences can be correlated with one another. In fact, it has been shown that multivariate classification analyses, in which multiple brain regions are used as a multivariate dataset, are more effective in discriminating an ASD group from controls than evaluating their difference at each individual region. Ecker et al. (2010), for example, show high accuracy of classification between ASD and control groups using a whole brain gray matter volume as input for a multivariate classification analysis (support vector machine), while no statistically significant difference between groups was observed with voxel-based analysis. Jiao et al. (2010) also demonstrated that multivariate classification analyses

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could discriminate ASD children from controls with high accuracy when they used cortical thickness of multiple regions as input for the analysis. They show that cortical thickness is a better classifier of groups than gray matter volume.

While the multivariate classification analysis handles multiple brain regions as a multivariate dataset, its output is still univariate (class label). This analysis, therefore, cannot account for age and IQ effects on multiple brain regions. In the previous studies these effects were excluded beforehand; any possible age confounds were removed at each voxel by a univariate regression in Ecker et al. (2010), or participants' ages were restricted to a small range in Jiao et al. (2010). In the current analysis, however, we do not exclude these factors beforehand because we were interested in evaluating how they and their interactions with group affected multivariate pattern of whole brain cortical thickness.

To investigate cortical thickness in ASD in a multivariate framework with age and IQ interactions taken into consideration, we utilized kernel canonical correlation analysis (KCCA) (Hardoon et al., 2004) in this study. Canonical correlation analysis (CCA) (Hotelling, 1936) evaluates correlations between two multidimensional datasets, so that it can find relationships between cortical thicknesses in multiple brain regions and multiple factors of ASD, age, and IQ. KCCA is an extension of CCA using a kernel method to handle a large dimensional dataset efficiently and robustly.

Even when we have two multidimensional datasets, multiple regression analysis or Pearson's correlation analysis can be utilized if we collapse the dataset into multiple univariate cases. This is called the 'mass-univariate' approach, in which data from each voxel/vertex is used as a univariate value, and univariate correlation analysis or multiple regression analysis is repeated for each voxel/vertex. However, CCA is disparate from the mass-univariate approach. While the mass-univariate approach evaluates correlation at each brain region independently, CCA can find a pattern correlation; a correlation between linear combinations of multiple variables, so that it can extract more information that can be seen in a pattern of multiple brain regions but cannot be seen at an individual brain region.

Although CCA has been used in analyses of brain imaging data (Correa et al., 2010; Hardoon et al., 2009), it has not, to our knowledge, been applied to evaluations of cortical thickness in ASD. This analysis enables us to find multivariate patterns of cortical thickness correlating with multiple explaining variables. We applied KCCA to the cortical thickness data from groups of ASD and age and IQ matched typically developing control males.

Materials and methods

The cortical thickness data used in this study was the same as in Wallace et al. (2010). Only the summary of demographics is described here. More details regarding diagnostic procedure, medication history, and criteria for exclusion of participants can be found in Wallace et al. (2010).

Participants

Participants were 40 typically developing (TD) males (12–23 years of age, mean = 17.04, sd = 2.73) and 41 males with an autism spectrum disorder (12–24 years of age, mean = 16.75, sd = 2.84) recruited from the Washington, DC metropolitan area. Informed assent and consent were obtained from all participants and/or their parent/guardian when appropriate in accordance with a National Institutes of Health Institutional Review Board-approved protocol.

Participants with autism spectrum disorders (ASD) included 26 with Asperger's syndrome, 11 with high-functioning autism, three with pervasive developmental disorder not otherwise specified, and one with either Asperger's syndrome or high-functioning autism, which could not be distinguished because of missing early language developmental milestones data. An ASD diagnosis was based on both Diagnostic and Statistical Manual-IV (DSM-IV) criteria as assessed by an experienced clinician and scores from the Autism Diagnostic Interview (ADI or ADI-R; Le Couteur et al., 1989; Lord et al., 1994) and/or the Autism Diagnostic Observation Schedule (Lord et al., 2000), administered by a trained, research-reliable clinician.

Full-scale IQ (FSIQ) was measured for all participants using the Wechsler Abbreviated Scale of Intelligence (34 ASD, 40 TD), the Wechsler Adult Intelligence Scale-III (three ASD), the Wechsler Intelligence Scale for Children-III (two ASD), or the Wechsler Intelligence Scale for Children-IV (two ASD). FSIQ did not differ between groups with scores ranging from 85 to 143 (mean = 113.27, sd = 15.09) for the ASD group and 97 to 136 (mean = 114.03, sd = 10.74) for the TD group. Participant groups also did not differ in terms of handedness (ASD: right/left = 37/4, TD: 36/4).

Imaging parameters and cortical thickness calculation

A T1-weighted structural image was obtained from each subject with a magnetization prepared rapid gradient echo sequence on a 3 T General Electric Signa scanner (Milwaukee, Wisconsin) using an 8-channel head coil. Imaging parameters were 124 axial slices, 224×224 acquisition matrix, flip angle = 6°, field of view = 24 cm, and voxel size = $1.07 \times 1.07 \times 1.2$ mm.

The FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) was used to extract cortical thickness. Cortical surface models were delineated on the gray/white boundary and on the pial surface (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999). Spatial intensity gradients across tissue classes were used to create surface maps that are capable of detecting sub-millimeter differences between areas. The resulting surface models were reviewed for accuracy and manually edited when needed. Cortical thickness was quantified at each surface location (vertex) as the distance from the gray/white boundary to the pial surface (Fischl and Dale, 2000). This method of cortical thickness measurement has been validated in Rosas et al. (2002), Kuperberg et al. (2003), and Salat et al. (2004), and has shown good reliability across sites and platforms (Han et al., 2006).

Vertex-wise cortical thickness values were mapped onto a normalized cortical surface and smoothed with a 15 mm full width at half maximum kernel. After excluding unreliable areas in the hippocampus and amygdala (cortex label in the FreeSurfer was used as an inclusive mask), 299,881 cortical thickness values on the normalized surface of both hemispheres were obtained for each participant. These values were used in the kernel canonical correlation analysis.

Kernel canonical correlation analysis

The canonical correlation analysis (CCA) finds linear combinations of two multidimensional datasets that have maximum correlation with each other (Hotelling, 1936). Given the two multidimensional datasets, X (each column corresponds to the explaining variables including age, IQ, diagnosis and their interactions, and each row corresponds to one participant) and Y (each column corresponds to cortical thickness at one vertex, and each row corresponds to one participant), canonical correlation ρ is defined as:

$$\rho = \max_{w_x, w_y} \frac{w_x' S_{XY} w_y}{\sqrt{w'_x S_{XX} w_x w'_y S_{XY} w_y}} \quad (1)$$

$$\text{subjected to } w_X' S_{XX} w_X = 1 \text{ and } w_Y' S_{YY} w_Y = 1,$$

where $S_{XX} = X'X$, $S_{YY} = Y'Y$, and $S_{XY} = X'Y$. w_x and w_Y are column vectors. w_x is given by solving the following eigenproblem:

$$B w_X = \rho^2 w_X, \quad (2)$$