NeuroImage 50 (2010) 589–599

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Predictive models of autism spectrum disorder based on brain regional cortical thickness

Yun Jiao [a,b,c,*], Rong Chen [c], Xiaoyan Ke [a,d], Kangkang Chu [d], Zuhong Lu [a,b], Edward H. Herskovits [c]

[a] Key Laboratory of Child Development and Learning Science (Southeast University), Ministry of Education, Nanjing, China
[b] School of Biological Science and Medical Engineering, Southeast University, Nanjing, China
[c] Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
[d] Child Mental Health Research Center of Nanjing Brain Hospital, Nanjing Medical University, Nanjing, China

ARTICLE INFO

Article history:
Received 9 October 2009
Revised 4 December 2009
Accepted 9 December 2009
Available online 21 December 2009

Keywords:
Autism spectrum disorder
Surface-based morphometry
Cortical thickness
Diagnostic model

ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a wide phenotypic range, often affecting personality and communication. Previous voxel-based morphometry (VBM) studies of ASD have identified both gray- and white-matter volume changes. However, the cerebral cortex is a 2-D sheet with a highly folded and curved geometry, which VBM cannot directly measure. Surface-based morphometry (SBM) has the advantage of being able to measure cortical surface features, such as thickness. The goals of this study were twofold: to construct diagnostic models for ASD, based on regional thickness measurements extracted from SBM, and to compare these models to diagnostic models based on volumetric morphometry. Our study included 22 subjects with ASD (mean age 9.2 ± 2.1 years) and 16 volunteer controls (mean age 10.0 ± 1.9 years). Using SBM, we obtained regional cortical thicknesses for 66 brain structures for each subject. In addition, we obtained volumes for the same 66 structures for these subjects. To generate diagnostic models, we employed four machine-learning techniques: support vector machines (SVMs), multilayer perceptrons (MLPs), functional trees (FTs), and logistic model trees (LMTs). We found that thickness-based diagnostic models were superior to those based on regional volumes. For thickness-based classification, LMT achieved the best classification performance, with accuracy = 87%, area under the receiver operating characteristic (ROC) curve (AUC) = 0.93, sensitivity = 95%, and specificity = 75%. For volume-based classification, LMT achieved the highest accuracy, with accuracy = 74%, AUC = 0.77, sensitivity = 77%, and specificity = 69%. The thickness-based diagnostic model generated by LMT included 7 structures. Relative to controls, children with ASD had decreased cortical thickness in the left and right pars triangularis, left medial orbitofrontal gyrus, left parahippocampal gyrus, and left frontal pole, and increased cortical thickness in the left caudal anterior cingulate and left precuneus. Overall, thickness-based classification outperformed volume-based classification across a variety of classification methods.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a prevalence of approximately in 1 in 150 children (Amaral et al., 2008). Children with ASD have abnormal social behavior, impaired communication and language skills, and repetitive/stereotyped behavior (Belmonte et al., 2004; Nordahl et al., 2007; Rapin, 1997). In studies of cognition, ASD has been defined as fundamental deficits in central coherence, executive function, and empathizing (Belmonte et al., 2004). MR examination has revealed that children with ASD have subtle structural changes in many brain structures, including the frontal lobe, parietal lobe, hippocampus, amygdala, cerebellum and brain stem (Courchesne et al., 2001; Geschwind, 2009; Hashimoto et al., 1995; Muller, 2007; Sparks et al., 2002).

Many morphological studies of ASD have used voxel-based morphometry (VBM), which measures voxel-wise gray- and white-matter volume changes across the entire brain. These VBM-based studies identified both gray- and white-matter volumetric changes (Aylward et al., 2002, 1999; Ke et al., 2008; Rojas et al., 2006). However, the intrinsic topology of the cerebral cortex is that of a 2-D sheet with a highly folded and curved geometry (Fischl et al., 1999), and VBM cannot directly measure this topology. Surface-based morphometry (SBM), which centers on the computation of cortical topographic measurements, has the potential to provide information

Abbreviations: ASD, autism spectrum disorder; SBM, surface-based morphometry; VBM, voxel-based morphometry; VC, volunteer controls; DSM-IV, the fourth edition of Diagnostic and Statistical Manual of Mental Disorders; ADI-R, Autism Diagnostic Inventory-Revised; CARS, Childhood Autism Rating Scale; MR, magnetic resonance; SVM, Support Vector Machines; MLP, Multilayer Perceptron; FT, Fictional Tree; LMT, Logistic Model Tree; ACC, accuracy; ROC, receiver operating characteristic; AUC, area under the ROC curve; TPR, true-positive rate; FPR, false-positive rare; ROI, region of interest.

* Corresponding author.
E-mail address: Jaio.Yun@uphs.upenn.edu (Y. Jiao).

1053-8119/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.12.047

complementary to that provided by VBM. SBM can derive features such as regional gray-matter thickness and regional surface area (Voets et al., 2008), as well as curvature and sulcal depth (Fischl et al., 1999; Kim et al., 2005).

There have been several SBM studies of ASD. For example, Hadjikhani et al. (2007) reported thickness differences in the mirror-neuron system and other areas involved in social cognition in individuals with ASD. Nordahl et al. (2007) demonstrated cortical-folding abnormalities in individuals with ASD, primarily in the left operculum, bilateral parietal operculum, and bilateral intraparietal sulcus.

Currently, ASD is diagnosed based on behavioral criteria. Given the VBM and SBM findings described above, an MR-based diagnostic model holds the promise of enhancing, perhaps complementing, behavioral assessment. Toward this end, Akshoomoff et al. (2004) entered six pre-selected brain volume-based features into discriminant analysis and correctly classified 95% of very young people with ASD; however this accuracy rate was based on reclassification of the training set, rather than on cross-validation or classification of an independent test set. Ecker et al. (2009) investigated the predictive value of whole-brain structural volumetric changes in ASD, using SVM classifiers, and obtained 81% classification accuracy based on cross-validation. Singh et al. (2008) developed a diagnostic model generated by the LPboost based algorithm to distinguish autistic children from control subjects, based on voxel-wise cortical thickness, based on approximately 40,000 points for each subject; they reported 89% classification accuracy based on cross-validation. The principal limitation of their work was basing the feature dimension reduction step on all samples outside cross-validation.

In this study, we test the hypothesis that diagnostic models can distinguish children with ASD from controls based on regional cortical thickness, and that these models have greater accuracies than diagnostic models based on regional volumes. To test this hypothesis, we first computed average cortical thicknesses and volumes of 66 structures defined on a brain atlas, for each subject. We then applied four data-mining approaches to generate four diagnostic models based on either regional cortical thicknesses or regional volumes. Finally, we compared performance metrics of thickness-based diagnostic models with those of volume-based diagnostic models.

Methods

Participants

Participants in this study, aged 6–15 years, consisted of two groups: 22 children with ASD (mean age, 9.2 ± 2.1 years), and 16 volunteer control subjects (VC) (mean age, 10.0 ± 1.9). Children with ASD and control subjects were group-matched on age, sex, full-scale IQ, handedness, weight, height, and socioeconomic status. All participants with ASD were recruited by the Child Mental Health Research Center of Nanjing Brain Hospital. The diagnosis of ASD was based on the criteria of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Gmitrowicz and Kucharska, 1994), the Autism Diagnostic Inventory-Revised (ADI-R) (Lord et al., 1994), and the Childhood Autism Rating Scale (CARS) (Schopler et al., 1980). IQ scores were obtained using the Wechsler Intelligence Scale for Children-II (Chinese version). Volunteer control subjects were recruited from the local community in Nanjing. None of the VC subjects had a history of axis I or II psychiatric disorder. Exclusion criteria for all subjects included history of seizure, head trauma, genetic or neurological disorder, major medical problem, and full-scale IQ less than 70. Each participant's parents gave informed consent, and all research procedures were approved by Institutional Review Board of Nanjing Brain Hospital of Nanjing Medical University. The participants with ASD had similar IQ and ADI scores to those of participants in a voxel-based classification study for subjects with ASD (Ecker et al., 2009).

Magnetic resonance imaging protocol

We acquired MR images at Nanjing Brain Hospital, on a 1.5-Tesla Signa GE instrument (NVi, General Electric Medical System, Milwaukee, WI), using a standard quadrature head coil. For the purposes of this study, we acquired high-resolution images for surface-based analysis based on a T1-weighted three-dimensional spoiled gradient-echo sequence with the following parameters: TR = 9.9 ms, TE = 2.0 ms; flip angle = 15°; FOV = 24 cm; slice thickness = 2.0 mm; in-plane resolution = 0.94×0.94 mm; matrix = 256×256; number of slices = 132 contiguous; and number of excitations = 1.0. MR images were reviewed by an experienced radiologist for quality. We excluded subjects with poor MR image quality.

Image processing

Fig. 1 shows our image- and data-processing pipeline. We used FreeSurfer (Dale et al., 1999; Fischl et al., 1999) (http://surfer.nmr.mgh.harvard.edu/) to extract surface-based features from the high-resolution T1-weighted images. FreeSurfer can perform cortical reconstruction and volumetric segmentation, and has been demonstrated to have good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006).

Prior to surface-based morphometry, the high-resolution T1-weighted MR volume for each participant (Fig. 2A) was bias

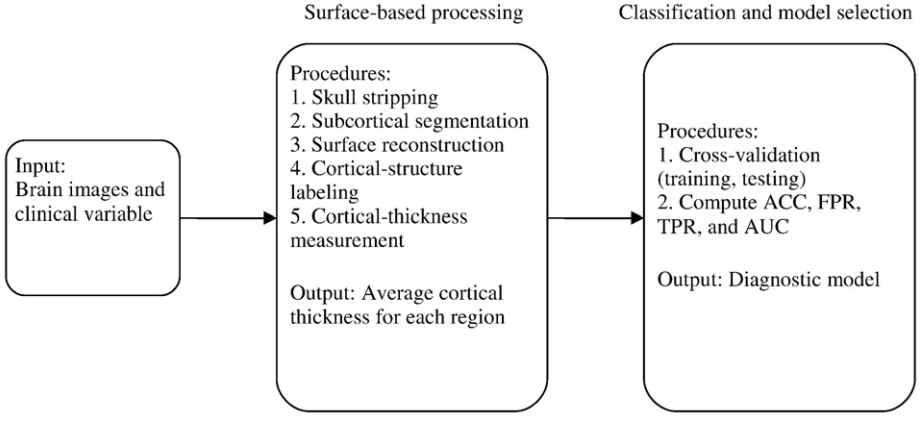

Fig. 1. Data-analysis pipeline.