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Functional connectivity classification of autism identifies highly predictive brain features but falls short of biomarker standards

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ABSTRACT

Objectives: Autism spectrum disorders (ASD) are diagnosed based on early-manifesting clinical symptoms, including markedly impaired social communication. We assessed the viability of resting-state functional MRI (rs-fMRI) connectivity measures as diagnostic biomarkers for ASD and investigated which connectivity features are predictive of a diagnosis.

Methods: Rs-fMRI scans from 59 high functioning males with ASD and 59 age- and IQ-matched typically developing (TD) males were used to build a series of machine learning classifiers. Classification features were obtained using 3 sets of brain regions. Another set of classifiers was built from participants' scores on behavioral metrics. An additional age and IQ-matched cohort of 178 individuals (89 ASD; 89 TD) from the Autism Brain Imaging Data Exchange (ABIDE) open-access dataset (http://fcon_1000.projects.nitrc.org/indi/abide/) were included for replication.

Results: High classification accuracy was achieved through several rs-fMRI methods (peak accuracy 76.67%). However, classification via behavioral measures consistently surpassed rs-fMRI classifiers (peak accuracy 95.19%). The class probability estimates, P(ASD|fMRI data), from brain-based classifiers significantly correlated with scores on a measure of social functioning, the Social Responsiveness Scale (SRS), as did the most informative features from 2 of the 3 sets of brain-based features. The most informative connections predominantly originated from regions strongly associated with social functioning.

Conclusions: While individuals can be classified as having ASD with statistically significant accuracy from their rs-fMRI scans alone, this method falls short of biomarker standards. Classification methods provided further evidence that ASD functional connectivity is characterized by dysfunction of large-scale functional networks, particularly those involved in social information processing.

1. Introduction

Autism spectrum disorders (ASD) are clinically characterized by marked social and communication impairments as well as restricted interests and repetitive behaviors. Diagnosis is typically made in early childhood based on clinical interviews and observation of behavior. There is significant need for biomarkers to improve diagnostic precision when behavioral symptoms are equivocal and to identify infants or young children who might be at risk for ASD before reliable behavioral symptoms manifest (Yerys and Pennington, 2011).

Recent studies applied multivariate classification techniques to neuroimaging data to characterize ASD using features that are predictive of a diagnosis on the level of individuals. These classifier studies achieved relatively high classification accuracy (~60–85%) using multiple imaging modalities including structural MRI (Sato et al., 2013; Ecker et al., 2010), diffusion tensor MRI (DTI) (Ingalhalikar et al. 2012; Lange et al., 2010), magnetoencephalography (Roberts et al., 2011) and resting-state functional MRI (rs-fMRI; which measures "functional connectivity", correlations between spontaneous BOLD signal fluctuations in different brain regions) (Uddin et al., 2013; Nielsen and Zielinski, 2013; Anderson et al., 2011). Rs-fMRI is a particularly interesting technique as it can investigate, in a task-independent manner, the hypothesis that ASD involves the disruption of large-scale brain networks (Castelli et al., 2002; Belmonte et al., 2004). These multivariate techniques have provided convergent evidence about brain differences that underlie ASD and unveiled additional informative brain features.

Given the recent success of these neuroimaging methods, it is tempting to cite these findings as grounds for establishing a neuroimaging-based diagnostic biomarker for ASD. However, several benchmarks must be met to fulfill the promise of neuroimaging-based biomarkers including: establishing standard analytic techniques, as such methodological factors influence connectivity measures (Jo et al., 2013; Gotts

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et al. 2013; Power et al., 2014); demonstrating biomarkers' robustness to variability across larger numbers of individuals and sites—to date, only one multisite classifier study exists (Nielsen, and Zielinski, 2013); and addressing the diagnostic potential of brain-based biomarkers by comparing their diagnostic or prognostic accuracy to that of simpler, more easily obtained ratings of behavior. The present study examines each of these issues.

In this study, we determined the best methods for performing classification of ASD vs. TD participants using rs-fMRI data by applying several popular classification techniques to three separate sets of brain-based features. We also addressed classifier generalizability by including a large in-house cohort of high-functioning ASD individuals and typically developing (TD) individuals (118 total participants) and a replication cohort obtained from the ABIDE dataset (178 individuals). Given similar accuracies achieved using different methods in previous rs-fMRI ASD classification studies (Uddin et al., 2013; Nielsen, and Zielinski, 2013; Anderson et al., 2011) we expected that there would be little effect of classifier method or brain region set.

Second, to determine the upper bounds of diagnostic performance using machine learning classification, we determined whether classification algorithms based on rs-fMRI data perform comparably to classifiers based on questionnaire data from the Social Responsiveness Scale (SRS) (Constantino, and Gruber, 2005). This questionnaire was expected to be highly predictive of ASD diagnoses as it is a measure of social functioning, the hallmark deficit in ASD. While SRS has been validated relative to "gold standard" interview and observation schedules, this measure is independent of the actual diagnosis criteria (Lord et al., 1994; Lord et al., 2000). The action of classifying participants as having a disorder characterized by social functioning deficits based on a measure of social functioning may be somewhat circular in its logic; however, the simplicity of the SRS and the ease of its administration make it an important benchmark of diagnostic utility for rs-fMRI based classification. In addition, such a behavioral classifier provides a more realistic ceiling of classifier performance that is tailored to the dataset in question. It is important to clarify that the SRS cannot be a biomarker as it is a clinical measure of social impairment designed to interrogate autistic symptoms. Performing classification on these measures simply gives an estimate of how well these individuals can be distinguished using a continuous measure of behavior that is independent of the diagnosis itself.

Finally, we investigated which connectivity features and brain networks are most predictive of ASD and further, which connections track individual symptom expression. We identified a disperse set of connections throughout the brain that were highly predictive of an ASD diagnosis. Classification accuracy increased by including regions beyond those seen in meta-analyses of task-based fMRI studies.

2. Methods and materials

2.1. Participants

2.1.1. NIMH

Fifty-nine typically developing (TD) male participants (mean age ± standard deviation (SD) = 18.3 ± 3.05) and 59 high-functioning participants with an autism spectrum disorder (ASD, mean age ± SD = 17.66 ± 2.72) took part in the study, including 29 ASD and 28 TD participants previously described (Gotts et al., 2012). Participants with ASD were recruited from the Washington, DC, metropolitan area and met Diagnostic and Statistical Manual-IV diagnostic criteria as assessed by an experienced clinician. Scores on the SRS (Constantino, and Gruber, 2005), an informant-based rating scale used to assess social and communication traits quantitatively, were obtained from parents for all ASD participants and 45 TD participants. Participant groups did not differ in terms of full-scale IQ or age (Table 1). Informed assent and consent were obtained from all participants and/or their parent/guardian when appropriate in accordance with the National Institutes of Health Institutional Review Board approved protocol. See Appendix A.1 and Table 1 for further details.

2.1.2. ABIDE

The ABIDE dataset is an open-access multi-site image repository comprising structural and rs-fMRI scans from ASD and TD individuals (Di Martino et al., 2014). Acquisition parameters and protocol information can be found at http://fcon_1000.projects.nitrc.org/indi/abide/. Data from three of the five sites with the most subjects that met the following criteria were included in our analyses: males with a full-scale IQ > 80 and age within one standard deviation of the range of our in-house sample. Other sites were excluded due to excessive difficulties with anatomical FreeSurfer parcellation. The included sites were New York University (NYU), University of Utah School of Medicine (USM), and University of California Los Angeles 1 (UCLA_1). Participants were included if their scans met quality assurance standards (see Appendix A.2). These inclusion criteria and an additional step for matching ASD and TD prevalence resulted in a cohort of 178 individuals (89 TD; 89 ASD). Participant demographic and clinical data are provided in Inline Supplementary Table S1.

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.nicl.2014.12.013.

2.2. fMRI acquisition

Functional MRI data were collected using a GE, Signa 3T whole-body MRI scanner at the NIH Clinical Center NMR Research Facility. For each participant, a high-resolution T1-weighted anatomical image (MPRAGE) was obtained (124 axial slices, 1.2 mm slice thickness, field of view = 24 cm, 224 × 224 acquisition matrix). Spontaneous brain activity was measured during functional MRI using a gradient-echo echo-planar series with whole-brain coverage while participants maintained fixation on a central cross and were instructed to lie still and rest quietly (repetition time = 3500 ms, echo time = 27 ms, flip angle = 90°, 42 axial interleaved slices per volume, 3.0 mm slice thickness, field of view = 22 cm, 128 × 128 acquisition matrix, single-voxel volume = 1.7 × 1.7 × 3.0 mm). Each resting scan lasted 8 min, 10 s for a total of 140 consecutive whole-brain volumes. A GE 8-channel send–receive head coil was used for all scans, with a SENSE factor of 2 used to reduce gradient coil heating during the session.

2.3. fMRI preprocessing

fMRI data were preprocessed using AFNI software package (Cox, 1996) in accordance with pipelines recommended by Jo et al. (2013) with one exception: we did not employ cardiac and respiratory denoising so that a common preprocessing pipeline could be used on ABIDE data that lacked physiological measures. See Appendix A.2 for further details.

2.4. Connectivity measures and feature matrices

Three sets of regions of interest (ROIs) were used to create three separate fMRI timecourse correlation matrices for subjects' processed EPI time series. These ROI sets included one set of 49 spherical regions (5 mm radius) derived from coordinates in Di Martino et al. (2009), one set of 264 spherical regions (5 mm radius) from Power et al. (2011) and one set of 162 cortical and subcortical ROIs from each subject's FreeSurfer Destrieux atlas anatomical segmentation. Timecourses were extracted and averaged within each region. Linear correlations were computed between the average timecourses of each region in a ROI set and Fisher transformed. For each ROI set, this process yielded a $N_s \times N_f$ feature matrix, F, for use in classification, where N_s = number of subjects and N_f = number of features (Fisher transformed correlation values). F has an associated label vector, L, containing the diagnoses of the participants (ASD or TD) coded as a binary variable.