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Diagnostic classification of intrinsic functional connectivity highlights somatosensory, default mode, and visual regions in autism

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ABSTRACT

Despite consensus on the neurological nature of autism spectrum disorders (ASD), brain biomarkers remain unknown and diagnosis continues to be based on behavioral criteria. Growing evidence suggests that brain abnormalities in ASD occur at the level of interconnected networks; however, previous attempts using functional connectivity data for diagnostic classification have reached only moderate accuracy. We selected 252 low-motion resting-state functional MRI (rs-fMRI) scans from the Autism Brain Imaging Data Exchange (ABIDE) including typically developing (TD) and ASD participants (n = 126 each), matched for age, non-verbal IQ, and head motion. A matrix of functional connectivities between 220 functionally defined regions of interest was used for diagnostic classification, implementing several machine learning tools. While support vector machines in combination with particle swarm optimization and recursive feature elimination performed modestly (with accuracies for validation datasets <70%), diagnostic classification reached a high accuracy of 91% with random forest (RF), a nonparametric ensemble learning method. Among the 100 most informative features (connectivities), for which this peak accuracy was achieved, participation of somatosensory, default mode, visual, and subcortical regions stood out. Whereas some of these findings were expected, given previous findings of default mode abnormalities and atypical visual functioning in ASD, the prominent role of somatosensory regions was remarkable. The finding of peak accuracy for 100 interregional functional connectivities further suggests that brain biomarkers of ASD may be regionally complex and distributed, rather than localized.

1. Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous disorder, diagnosed on the basis of behavioral criteria. From the neurobiological perspective, 'ASD' can be considered an umbrella term that may encompass multiple distinct neurodevelopmental etiologies (Geschwind and Levitt, 2007). Since any given cohort is thus likely composed of ill-understood subtypes (whose brain features may vary subtly or even dramatically), it is not surprising that brain markers with perfect sensitivity and specificity remain unavailable. Nonetheless, given the specificity of diagnostic criteria (American Psychiatric Association, 2013), the hope that some (potentially complex) patterns of brain features may be unique to the disorder is not unreasonable and worthy of pursuit.

Issues of heterogeneity and cohort effects can be partially addressed through the use of large samples, as provided by the recent Autism Brain Imaging Data Exchange (ABIDE) (Di Martino et al., 2014), which incorporates over 1100 resting state functional MRI (rs-fMRI) datasets from 17 sites. The use of these data for examining functional connectivity matrices for large numbers of ROIs across the entire brain is further promising, as there is growing consensus about ASD being characterized by aberrant connectivity in numerous functional brain networks (Schipul et al., 2011; Vissers et al., 2012; Wass, 2011). However, the functional

Abbreviations: DMN, default mode network; SMH, somatosensory and motor [hand]; VIS, visual; SAL, salience; SUB, subcortical; SMM, somatosensory and motor [mouth]; FPTC, frontal parietal task control; AUD, audio; UN, unknown; VA, ventral attention; COTC, cingulo-opercular task control; DA, dorsal attention; MR, memory retrieval; CEB, cerebellum.

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connectivity literature in ASD is complex and often inconsistent (Müller et al., 2011; Nair et al., 2014), and data-driven machine learning (ML) techniques provide valuable exploratory tools for uncovering potentially unexpected patterns of aberrant connectivity that may characterize the disorder.

A few previous ASD studies have used intrinsic functional connectivity MRI (fcMRI) (Van Dijk et al., 2010) for diagnostic classification, i.e., for determining whether a dataset is from an ASD or typically developing participant solely based on functional connectivity. Anderson and colleagues (2011), using a large fcMRI connectivity matrix, reached an overall diagnostic classification accuracy of 79%, which was however lower in a separate small replication sample. Uddin et al. (2013a) used a logistic regression classifier for 10 rs-fMRI based features identified by ICA, which corresponded to previously described functional networks. The classifier achieved accuracies about 60–70% for all but one component identified as salience network, for which accuracy reached 77%. Imperfect accuracy in these studies may be attributed to moderate sample sizes ($N \leq 80$). However, in a recent classification study using the much larger ABIDE dataset, Nielsen et al. (2013) reported an overall accuracy of only 60%, suggesting that the approach selected, a leave-one-out classifier using a general linear model, may not be sufficiently powerful.

In the present study, we implemented several multivariate learning methods, including random forest (RF), which is an ensemble learning method that operates by constructing many individual decision trees, known in the literature as classification and regression trees (CART). Each decision tree in the forest makes a classification based on a bootstrap sample of the data and a random subset of the input features. The forest as a whole makes a prediction based on the majority vote of the trees. One desirable feature of the random forest algorithm is the bootstrapping of the sample to have a built-in training and validation mechanism, generating an unbiased out-of-bag error that measures the predictive power of the forest. Features were intrinsic functional connectivities (Van Dijk et al., 2010) between a standard set of regions of interest using only highest quality (low motion) datasets from ABIDE.

2. Methods and materials

Data were selected from the Autism Brain Imaging Data Exchange (ABIDE, http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino et al., 2013), a collection of over 1100 resting-state scans from 17 different sites. In view of the sensitivity of intrinsic fcMRI analyses to motion artifacts and noise (as described below), we prioritized data quality over sample size. We excluded any datasets exhibiting artifacts, signal dropout, suboptimal registration or standardization, or excessive motion (see details below). Sites acquiring fewer than 150 time points were further excluded. Based on these criteria, we selected a subsample of 252 participants with low head motion (see details below). Groups were matched on age and motion to yield a final sample of 126 TD and 126 ASD participants, ranging in age from 6 to 36 years (see Table 1 for summary and see Inline Supplementary Table S1 for fully detailed participant and site information).

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.nicl.2015.04.002.

2.1. Data preprocessing

Data were processed using the Analysis of Functional NeuroImages software (Cox, 1996) (http://afni.nimh.nih.gov) and FSL 5.0 (Smith et al., 2004) (http://www.fmrib.ox.ac.uk/fsl). Functional images were slice-time corrected, motion corrected to align to the middle time point, field-map corrected and aligned to the anatomical images using FLIRT with six degrees of freedom. FSL's nonlinear registration tool (FNIRT) was used to standardize images to the MNI152 standard image (3 mm isotropic) using sinc interpolation. The outputs were blurred to a global full-width-at-half-maximum of 6 mm. Given recent concerns that traditional filtering approaches can cause rippling of motion confounds to neighboring time points (Carp, 2013), we used a second-order band-pass Butterworth filter (Power et al., 2013; Satterthwaite et al., 2013) to isolate low-frequency BOLD fluctuations ($.008 < f < .08$ Hz) (Cordes et al., 2001).

Regression of 17 nuisance variables was performed to improve data quality (Satterthwaite et al., 2013). Nuisance regressors included six rigid-body motion parameters derived from motion correction and their derivatives. White matter and ventricular masks were created at the participant level using FSL's image segmentation (Zhang et al., 2001) and trimmed to avoid partial-volume effects. An average time series was extracted from each mask and was removed using regression, along with its corresponding derivative. Whole-brain global signal was also included as a regressor to mitigate cross-site variability (Power et al., 2014). All nuisance regressors were band-pass filtered using the second-order Butterworth filter ($.008 < f < .08$ Hz) (Power et al., 2013; Satterthwaite et al., 2013).

2.2. Motion

Motion was quantified as the Euclidean distance between consecutive time points (based on detected six rigid-body motion parameters). For any instance greater than 0.25 mm, considered excessive motion, the time point as well as the preceding and following time points were censored, or "scrubbed" (Power et al., 2012a). If two censored time points occurred within ten time points of each other, all time points between them were also censored. Datasets with fewer than 90% of time points or less than 150 total time points remaining after censoring were excluded from the analysis. Runs were then truncated at the point where 150 usable time points were reached. Motion over the truncated run was summarized for each participant as the average Euclidean distance moved between time points (including areas that were censored) and was well matched between groups ($p = 0.92$).

2.3. ROIs and connectivity matrix

We used 220 ROIs (10 mm spheres) adopted from a meta-analysis of functional imaging studies by Power et al. (2011), excluding 44 of their 264 ROIs because of missing signal in >2 participants. Mean time courses were extracted from each ROI and a 220×220 connectivity matrix of Fisher-transformed Pearson correlation coefficients was created for each subject. We then concatenated each subject's functional connectivities to construct a group level data matrix. For each ROI pair, we regressed out age (as numerical) and site (as categorical) covariates

Table 1
Participant information.

Full sample	ASD, M ± SD [range, #391]	TD, M ± SD [range, #391]	*p*-Value (2-sample *t*-test)
N (female)	126 (18)	126 (31)	
Age (years)	17.311 ± 6.00 [8.2–35.7]	17.116 ± 5.700 [6.5–34]	0.800
Motion (mm)	.057 ± .020 [.018–.108]	.058 ± .020 [.020–.125]	0.923
Non-verbal IQ	106.86 ± 17.0 [37–149]	106.28 ± 12.8 [67–155]	0.800