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Research report

Resting state functional magnetic resonance imaging and neural network classified autism and control

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ABSTRACT

Although the neurodevelopmental and genetic underpinnings of autism spectrum disorder (ASD) have been investigated, the etiology of the disorder has remained elusive, and clinical diagnosis continues to rely on symptom-based criteria. In this study, to classify both control subjects and a large sample of patients with ASD, we used resting state functional magnetic resonance imaging (rs-fMRI) and a neural network. Imaging data from 312 subjects with ASD and 328 subjects with typical development was downloaded from the multi-center research project. Only subjects under 20 years of age were included in this analysis. Correlation matrices computed from rs-fMRI time-series data were entered into a probabilistic neural network (PNN) for classification. The PNN classified the two groups with approximately 90% accuracy (sensitivity = 92%, specificity = 87%). The accuracy of classification did not differ among the institutes, or with respect to experimental and imaging conditions, sex, handedness, or intellectual level. Medication status and degree of head movement did not affect accuracy values. The present study indicates that an intrinsic connectivity matrix produced from rs-fMRI data could yield a possible biomarker of ASD. These results support the view that altered network connectivity within the brain contributes to the neurobiology of ASD.

1. Introduction

Autism spectrum disorder (ASD) is characterized by the impaired development of social interaction and communication skills and a restricted repertoire of activities and interests (A.P.A., 1994). Although extensive efforts have been made to create a neurodevelopmental model (Baron-Cohen, 2009; Frith, 2001) and to identify disease-specific genes (Levy, Mandell, & Schultz, 2009), ASD continues to be diagnosed using symptom-based clinical criteria. The identification of biomarkers with clear neural underpinnings in ASD would be helpful in ensuring an early and accurate diagnosis as well as an optimally effective treatment (Hill & Frith, 2003; Levy et al., 2009). Structural and functional magnetic resonance imaging has the potential to reveal brain abnormalities of ASD that could be used as biomarkers of the disease.

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A critical step in using neuroimaging abnormalities as biomarkers of ASD is applying a machine-learning algorithm such as the support vector machine (SVM) and/or an artificial neural network to the data (Orru, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). Structural properties of the brain, including cortical volume (Calderoni et al., 2012; Ecker, Rocha-Rego, et al., 2010; Uddin et al., 2011; Varol, Gaonkar, Erus, Schultz, & Davatzikos, 2012), thickness (Ecker, Marquand, et al., 2010; Jiao et al., 2011, 2010; Sato et al., 2013), and white matter integrity (Bloy et al., 2011; Ingalhalikar, Parker, Bloy, Roberts, & Verma, 2011), have been used as features to classify control subjects and patients with ASD; however, to date, these investigations have shown limited power of these measures as classifiers.

Investigating brain network activity during the resting state has emerged as a new method that eliminates the caveats of task-based fMRI studies (Menon, 2011). In this method, the fMRI signal is measured during the resting state and the data is analyzed based on a connectivity approach between subdivisions. To date, brain network activity during the resting state has been investigated in subjects with ASD and typical development in numerous studies (Assaf et al., 2010; Barttfeld et al., 2012; Cardinale, Shih, Fishman, Ford, & Muller, 2013; Di Martino et al., 2011; Di Martino, Zuo, et al., 2013; Ebisch et al., 2011; Lai et al., 2010; Lynch et al., 2013; Mueller et al., 2013; Murdaugh et al., 2012; Paakki et al., 2010; Tyszka, Kennedy, Paul, & Adolphs, 2014; Weng et al., 2010; Wiggins et al., 2011). Overall, intrinsic connectivity between subdivisions of the brain is altered in patients with ASD compared to controls (Muller et al., 2011; Uddin, Supekar, & Menon, 2010).

In studies that have used intrinsic connectivity during the resting state (Anderson et al., 2011; Barttfeld et al., 2012; Murdaugh et al., 2012) or during passive viewing of movies (Deshpande, Libero, Sreenivasan, Deshpande, & Kana, 2013) to classify ASD and control subjects, small sample sizes have limited the accuracy of the results. In a single study that used large samples from the same image database as the present study, the accuracy was as high as 60% (Nielsen et al., 2013). In the present study, using a large dataset ($n = 640$) obtained from the public database (Di Martino, Yan, et al., 2014) and a probabilistic neural network (PNN) algorithm, I report the successful classification of resting state fMRI data between subjects with ASD and subjects with typical development.

2. Materials and methods

2.1. Materials

The original imaging and demographic data were collected from the Autism Brain Imaging Data Exchange (ABIDE) database (http://fcon_1000.projects.nitrc.org/indi/abide/index.html), which allows unrestricted usage for non-commercial research purposes. Although the dataset included both adults and children, only subjects under 20 years of age were used in the present study. Brain images and related data from 312 subjects with ASD (male/female: 273/39) and 328 control subjects with typical development (CTL, male/female: 267/61) from 12 universities and research institutes were used. The names and abbreviations of these institutes and scanning parameters are listed in Table 1. The ethics committee of the Nagoya University School of Medicine approved the usage of this anonymous data for research purposes.

Autism was diagnosed according to both the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 1999) in almost all cases, the exception being cases from one institute where autism was diagnosed using only the DSM-IV-TR (A.P.A., 1994). The CTL subjects were screened in clinical interviews conducted by experts in child psychiatry; however, in some cases, other questionnaires were used. The details of the diagnostic procedures and questionnaires used are listed in Supplementary Table 1.

Demographic data for each group is shown in Table 2. Subjects were aged between 6 and 19 years. The full-scale IQ of all subjects assessed was 41–148; however, no IQ data was available for three subjects with ASD. Between-group comparisons were made using unpaired *t*-tests (two-tailed) for age and IQ, and chi-square tests for sex and handedness (statistical threshold was set at $p = .05$). Data on the medication

Table 1 – Scanning parameters and experimental settings in each site.

Institute	MRI vendor	TR (msec)	TE (msec)	FA (deg)	Voxel size (mm)	Volumes	Time (m)	Eyes
KKI	Phillips	2500	30	75	3 × 3 × 3	156	6.5	o
LEU	Phillips	1667	33	90	3.48 × 3.59 × 4	250	6.9	c
NYU	Siemens	2000	15	90	3.75 × 3.75 × 4	180	6.0	o/c
OHSU	Siemens	2500	30	90	3.75 × 3.75 × 3.8	82	3.4	o
OLIN	Siemens	1500	27	60	3.43 × 3.43 × 4	210	5.3	o
PITT	Siemens	1500	25	70	3.12 × 3.12 × 4	200	5.0	c
SDSU	GE	2000	30	90	3.44 × 3.44 × 3.4	180	6.0	o
STAN	GE	2000	30	80	3.12 × 3.12 × 4.5	180	6.0	c
TRIN	Phillips	2000	28	90	3 × 3 × 3.5	150	5.0	c
UCLA	Siemens	3000	28	90	3 × 3 × 4	120	6.0	o
USM	Siemens	2000	28	90	3.43 × 3.43 × 3	240	8.0	o
YALE	Siemens	2000	25	60	3.43 × 3.43 × 4	200	6.7	o

KKI, Kennedy Krieger Institute; LEU, University of Leuven; NYU, NYU Langone Medical Center; OHSU, Oregon Health and Science University; OLIN, Olin, Institute of Living at Hartford Hospital; PITT, University of Pittsburgh School of Medicine; SDSU, San Diego State University; STAN, Stanford University; TRIN, Trinity Centre for Health Sciences; UCLA, University of California, Los Angeles; USM, University of Utah School of Medicine; YALE, Yale Child Study Center; FA; Flip angle, Time: Scan time, Eyes; eyes were open (o) or closed (c) during the scan.