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PREDICTING CLINICAL SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER BASED ON TEMPORAL PATTERNS BETWEEN AND WITHIN INTRINSIC CONNECTIVITY NETWORKS

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Abstract—Attention deficit hyperactivity disorder (ADHD) is a common brain disorder with high prevalence in school-age children. Previously developed machine learning-based methods have discriminated patients with ADHD from normal controls by providing label information of the disease for individuals. Inattention and impulsivity are the two most significant clinical symptoms of ADHD. However, predicting clinical symptoms (i.e., inattention and impulsivity) is a challenging task based on neuroimaging data. The goal of this study is twofold: to build predictive models for clinical symptoms of ADHD based on resting-state fMRI and to mine brain networks for predictive patterns of inattention and impulsivity. To achieve this goal, a cohort of 74 boys with ADHD and a cohort of 69 age-matched normal controls were recruited from the ADHD-200 Consortium. Both structural and resting-state fMRI images were obtained for each participant. Temporal patterns between and within intrinsic connectivity networks (ICNs) were applied as raw features in the predictive models. Specifically, sample entropy was taken as an intra-ICN feature, and phase synchronization (PS) was used as an inter-ICN feature. The predictive models were based on the least absolute shrinkage and selectionator operator (LASSO) algorithm. The performance of the predictive model for inattention is $r = 0.79$ ($p < 10^{-8}$), and the performance of the predictive model for impulsivity is $r = 0.48$ ($p < 10^{-8}$). The ICN-related predictive patterns may provide valuable information for investigating the brain network mechanisms of ADHD. In summary, the predictive models for clinical symptoms could be beneficial for personalizing ADHD medications.

Key words: ADHD, clinical symptoms, intrinsic connectivity networks, temporal patterns, machine learning.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a highly prevalent brain disorder among school-age children. Approximately 5–10% of children and approximately 4% of adults suffer from ADHD worldwide (Biederman, 2005). Recent neuroimaging techniques identified altered structural and functional brain regions in ADHD patients. Smaller basal ganglia volumes were noted in children with ADHD than in normal controls based on structural magnetic resonance imaging (MRI) (Qiu et al., 2009). Decreased cortical thicknesses in attention- and executive-related cortical areas have also been reported in adults with ADHD based on structural MRI (Makris et al., 2007). Abnormal frontal- and cerebellar-related fractional anisotropy of white matter integrity was identified in ADHD-affected brains using diffusion tensor MRI (Ashtari et al., 2005). Altered anterior cingulate cortex-related resting-state functional connectivity patterns were observed in adolescents with ADHD (Tian et al., 2006). Moreover, neuroimaging data may be able to classify patients with ADHD from healthy controls based on machine learning techniques (Zhu et al., 2008;Wang et al., 2013a). The ADHD-200 competition has released a large dataset for research on disease classification and mechanisms (Milham et al., 2012). Several methods have been applied to automatically diagnosis patients with ADHD based on this dataset (Eloyan et al., 2012). Support vector machine-based feature selection methods have been applied to diagnose ADHD through structural and functional MRI (Colby et al., 2012). Non-negative matrix factorization of multimodal datasets has also revealed different changes in ADHD-related default mode networks (Anderson et al., 2014). The above machine learning-based methods could discriminate patients with ADHD from normal controls by providing label information of the disease for individuals. Inattention and impulsivity are the two most prominent clinical symptoms of ADHD. However, predicting individual clinical symptoms (i.e., inattention and impulsivity) based on neuroimaging data is a challenging task.

Investigating the relationships between neuroimaging data and clinical symptoms might be beneficial for

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Abbreviations: ADHD, attention deficit hyperactivity disorder; aDMN, anterior default mode network; AN, auditory network; DAN, dorsal attention network; FD, frame displacement; fDMN, fusiform-related default mode network; ICNs, intrinsic connectivity networks; LASSO, least absolute shrinkage and selectionator operator; LN, language network; LVN, lateral visual network; MRI, magnetic resonance imaging; MVN, medial visual network; OVN, occipital visual network; PS, phase synchronization; RFPN, right frontoparietal network; SCN, sub-cortical network; SMN, sensorimotor network; SN, salience network; SRN, self-referential network; TLN, temporal lobe network.

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personalized medication of ADHD patients. Several significant relationships have been identified between default mode network-related functional connectivity and ADHD-related behavior scores (Chabernaud et al., 2012). Significant correlations were observed between regional homogeneity and clinical symptoms (Wang et al., 2013a). Moreover, inter-network functional connectivity could predict clinical symptoms based on multisite ADHD datasets (Cai et al., 2015). Whole-brain functional connectivity may also serve as a potential biomarker for inattention according to a study of resting-state fMRI across a large number of patients with ADHD (Rosenberg et al., 2016). However, prediction of clinical symptoms based on neuroimaging data remains a challenging task for ADHD. Conventional voxel-wise or inter-regional measures based on MRI or fMRI typically possess tens of thousands of attributes, which are unfit for machine learning tasks. Thus, novel resting-state measures with an appropriate number of attributes are required to build a behavioral predictive model for ADHD.

Intrinsic connectivity networks (ICNs) are spatiotemporally coherent patterns of resting-state functional connectivity and are consistent across healthy subjects (Damoiseaux et al., 2006). The spatial patterns of ICNs exhibited moderate-to-high test–retest reliability based on independent component analysis and dual regression (Zuo et al., 2010). The temporal patterns of ICNs exhibited good test–retest reliability based on intra-ICN complexity (Wang et al., 2013b). There are two types of ICN-related temporal patterns: the temporal measure within ICNs and the temporal measure between ICNs. Moreover, the amplitude of low-frequency fluctuations within the posterior default mode network was significantly related to inattentive scores (Wang and Li, 2015). The phase synchronization (PS) between ICNs could reflect different attention-related eyes-open/closed resting-states (Wang et al., 2015). Therefore, the temporal patterns within and between ICNs might be beneficial for building predictive models of clinical behaviors for ADHD based on neuroimaging data.

In this paper, we hypothesized that the clinical symptoms of patients with ADHD could be predicted by the temporal patterns within and between ICNs, and the predictive powers of the temporal features within and between ICNs could be discovered by machine learning techniques. To test this hypothesis, a cohort of school-age children with and without ADHD were recruited from a publicly available database. In the methods employed here, sample entropy was used as a temporal pattern within ICNs, whereas PS was used as a temporal pattern between ICNs. The combined features of sample entropy and PS were taken as inputs for the predictive model. The performance of the predictive model was evaluated using cross-validation in the results section. Moreover, the predictive weights of the combined features are reported in various illustrations. In the discussion section, we describe the performance of the predictive model and the relationships between temporal patterns of ICNs and behavior scores (i.e., inattention and impulsivity). In addition, we discuss the advantages and limitations of this study.

EXPERIMENTAL PROCEDURES

Participants and MRI protocols

A cohort of school-age boys with ADHD [74 subjects, mean age (11.98 ± 1.88)] and a cohort of age-matched male healthy controls [69 subjects, mean age (11.72 ± 1.8)] were recruited from the Institute of Mental Health, Peking University. All participants were initially diagnosed using the Computerized Diagnostic Interview Schedule IV (C-DIS-IV). In addition, one parent of each participant was asked to complete the test of the Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version (KSADS-PL). The clinical symptoms of ADHD and normal controls were evaluated based on the ADHD Rating Scale (ADHD-RS) IV. Additional intelligence quotient (IQ) scores were obtained using the Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R). All participants included in this study had an IQ greater than 80. Each subject agreed to participate in this study and provided informed consent. The Research Ethics Review Board of Institute of Mental Health, Peking University, approved this study. The data usage agreement was provided by the functional 1000 connectome project. All data can be publicly obtained from the ADHD-200 Consortium (http://fcon_1000.projects.nitrc.org/indi/adhd200/) (Milham et al., 2012). The demographic variables are listed in Table 1.

For each participant, structural and resting-state functional brain images were collected from a SIEMENS 3T MRI scanner at Peking University. High-resolution structural brain images were collected using T1-weighted sequences (magnetization prepared rapid acquisition gradient echo, MPRAGE). Resting-state brain images were based on standard functional sequences (echo-planar imaging, EPI). The detailed scan parameters were provided by the ADHD-200 Consortium website. All participants were requested to remain still and relaxed during the resting-state fMRI scan sessions. Each participant watched a black screen with a white cross during the scan.

Data preprocessing

The structural MRI images were preprocessed using the following steps: (1) deobliqued and reoriented to the fsl-friendly space; (2) skull stripped; (3) segmented into different brain tissues (i.e., white matter, gray matter,

Table 1. Subjects' demographic variables

	ADHD	Normal	*p*-value
Number of subjects	74	69	-
Gender (male: female)	74:0	69:0	1
Handless (R:L)	74:0	69:0	1
Age (year)	11.98 ± 1.88	11.72 ± 1.8	0.398
Full IQ	107.35 ± 12.31	118.81 ± 14.26	$< 10^{-6}$
Inattentive scores	28.12 ± 3.66	16.04 ± 4.04	$< 10^{-38}$
Impulsive scores	22.54 ± 6.04	13.61 ± 3.55	$< 10^{-18}$

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