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Altered temporal features of intrinsic connectivity networks in boys with combined type of attention deficit hyperactivity disorder

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A B S T R A C T

Purpose: Investigating the altered temporal features within and between intrinsic connectivity networks (ICNs) for boys with attention-deficit/hyperactivity disorder (ADHD); and analyzing the relationships between altered temporal features within ICNs and behavior scores.

Materials and methods: A cohort of boys with combined type of ADHD and a cohort of age-matched healthy boys were recruited from ADHD-200 Consortium. All resting-state fMRI datasets were preprocessed and normalized into standard brain space. Using general linear regression, 20 ICNs were taken as spatial templates to analyze the time-courses of ICNs for each subject. Amplitude of low frequency fluctuations (ALFFs) were computed as univariate temporal features within ICNs. Pearson correlation coefficients and node strengths were computed as bivariate temporal features between ICNs. Additional correlation analysis was performed between temporal features of ICNs and behavior scores.

Results: ADHD exhibited more activated network-wise ALFF than normal controls in attention and default mode-related network. Enhanced functional connectivities between ICNs were found in ADHD. The network-wise ALFF within ICNs might influence the functional connectivity between ICNs. The temporal pattern within posterior default mode network (pDMN) was positively correlated to inattentive scores. The subcortical network, fusiform-related DMN and attention-related networks were negatively correlated to Intelligence Quotient (IQ) scores.

Conclusion: The temporal low frequency oscillations of ICNs in boys with ADHD were more activated than normal controls during resting state; the temporal features within ICNs could provide additional information to investigate the altered network patterns of ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized as age-inappropriate levels of hyperactivity, impulsivity and inattention [1], is a highly prevalent brain disorder which starts at childhood and persists into adulthood [2]. Nearly 5–10% of children and 4% of adults in the USA were affected by ADHD [2,3]. Structural MRI studies found thinning cortical thickness and decreased brain volume in children and adults with ADHD [4,5]. Diffusion tensor imaging studies found reduced fractional anisotropy (FA) in patients with ADHD [6,7].

Resting-state fMRI has drawn increasing interests in neuroimaging studies of ADHD. Altered amplitude of low frequency fluctuations (ALFFs) and regional homogeneity (ReHo) were found in certain brain regions (i.e., frontal cortex, anterior cingulated cortex, sensorimotor cortex, thalamus, cerebellum, etc.) in ADHD [8,9]. Reduced network homogeneities were found in default mode network (DMN)-related brain regions [10]. Increased local efficiencies and altered network topologies were found in ADHD [11]. Although various altered brain patterns were found in ADHD by different indices of resting-state fMRI, the network patterns of ADHD remains unclear. Therefore, the brain of ADHD could be further investigated by emerging network measures.

The network organizations of human brain could be investigated via two methods: (1) complex network based on graph theoretical analysis [11,12]; (2) intrinsic connectivity networks (ICNs) based on independent component analysis (ICA) or dual regression [13,14]. Previous complex network-related studies of ADHD focused on the static graph indices, while ICA-related methods focused on the spatial maps of ICNs [11,15]. Recently, several studies started to analyze the temporal patterns within ICNs, which could reflect the dynamical properties of brain networks [16,17].

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Table 1
Subjects' demographic variables.

	ADHD	Normal	*p*-Value
Number of subjects	36	36	–
Gender (male:female)	36:0	36:0	1
Age (year)	11.04 ± 2.74	11.83 ± 2.88	0.242
ADHD index	70.14 ± 7.03	45.66 ± 8.05	$<10^{-18}$
Inattentive	68.69 ± 8.31	45.34 ± 7.78	$<10^{-18}$
Hyperactive/impulsive	70.83 ± 10.41	45.66 ± 4.9	$<10^{-18}$
Verbal IQ	108.86 ± 14.2	113.69 ± 13.56	0.148
Performance IQ	104.72 ± 14.04	109.91 ± 14.13	0.125
Full IQ	107.83 ± 14.45	113.26 ± 13.64	0.109

The temporal patterns of ICNs could be investigated by two categories of features: (1) univariate temporal patterns (e.g., Hurst exponent, ALFF/fALFF, and complexity measures) based on individual time-course of ICN [16,17]; (2) bivariate temporal patterns based on functional connectivity between each pairs of ICNs [12,18]. However, the relationships between univariate and bivariate temporal features of ICNs in ADHD remain unexplored.

Based on current studies, we hypothesized that patients with ADHD would possess characteristic brain networks, which could be reflected by temporal patterns within and between ICNs. To test this hypothesis, univariate and bivariate temporal features of ICNs were analyzed between ADHD patients and normal controls. First, the resting-state fMRI datasets of all participants were preprocessed and normalized into standard brain space; second, univariate and bivariate temporal features were computed based on individual time-courses of ICNs; third, temporal features within and between ICNs of ADHD were compared with that of normal controls; fourth, correlation analysis was performed between univariate and bivariate temporal features of ICNs for both ADHD group and normal control group; fifth, correlation analysis was performed between univariate temporal features of ICN and behavior scores for ADHD group; finally, the altered temporal features within and between ICNs were discussed to exploring the dysfunction of brain network in ADHD.

2. Material and methods

2.1. Participants

Participants were recruited from ADHD-200 Consortium [19]. To remove the effects of population, gender and subtypes, 37 boys with combined type of ADHD and 35 normal developed boys were selected from the NYU site. The ADHD scores were evaluated by Conners' Parent Rating Scale-Revised, Long Version (CPRS-LV). The Intelligence Quotient (IQ) scores were measured by Wechsler Abbreviated Scale of Intelligence (WASI). The diagnostic information could be found in the ADHD-200 website (http://fcon_1000.projects.nitrc.org/indi/adhd200/). The demographic variables for quality-controlled subjects used in this study were listed in Table 1.

2.2. Imaging methods

Both structural and functional datasets were scanned for each subject on a Siemens Allegra 3.0 Tesla scanner: (1) A high-resolution T1-weighted volume was obtained via magnetization prepared gradient echo sequence (TR = 2530 ms; TE = 3.25 ms; T1 = 1100 ms; flip angle = 8; 128 slices with thickness of 1.3 mm; FOV = 256 mm); (2) Resting-state fMRI images scan was consisted of 176 continuous echo-planar imaging (EPI) functional volumes (TR = 2000 ms; TE = 15 ms; flip angle = 90; 33 slices; matrix = 64×64; FOV = 192 mm; acquisition voxel size = $3\text{ mm} \times 3\text{ mm} \times 4\text{ mm}$). A black screen was presented to each subject during all scan-sessions. Participants were instructed to remain relaxed with their eyes closed, think of nothing systematically and not fall asleep [19].

2.3. Data preprocessing

The resting-state datasets were preprocessed with AFNI (afni.nimh.nih.gov/afni) and FSL (www.fmrib.ox.ac.uk), according to the scripts released by 1000 Functional Connectomes Project [20]. Structural MRI datasets were skull-striped, segmented, and linearly normalized to Montreal Neurological Institute (MNI) standard brain space. For resting-state fMRI datasets, the preprocessing pipeline contained the following steps: (1) the first five volumes were discarded; (2) slice timing correction; (3) motion correction; (4) spatial smoothing with a 6 mm full width at half maximum (FWHM) Gaussian kernel; (5) intensity normalization based on grand-mean scaling; (6) regress out nuisances of cerebrospinal fluid, white matter, global signal, and Friston 24-Parameters of head motion [21,22], as well as linear and quadratic trends; (7) temporally band-pass filtering (0.01–0.1 Hz); (8) linearly register functional volumes to MNI standard brain space ($3\text{ mm} \times 3\text{ mm} \times 3\text{ mm}$). The head motion for all subjects was less than 3 mm in translation and 3° in rotation. Given recent concerns on head motion, frame-wise displacement (FD) and root-mean-square variance of the temporal derivative (DVARS) [23] were applied to evaluate the qualities of resting state datasets. One subject from the cohort of patients was discarded due to marked motions (percentage of outliers >20%), leaving 36 patients and 35 health controls for further analysis (Table 1). The details of quality evaluations for head motion were presented in Supporting Information.

After preprocessing, the templates of 20 ICNs obtained from the 1000 Functional Connectomes Project were taken as spatial regression templates. The names of the 20 ICNs were listed in Table 2. For spatial demonstrations of the 20 ICNs, please see [20] and Supporting Information.

2.4. Individual time-courses for ICNs

To investigate the temporal dynamics of ICNs, spatial general linear regression was applied on each fMRI volume using the 20 ICNs as spatial templates: (1) for each ICN and each subject, spatial multiple regressions were performed on every spatial normalized resting functional volume, resulting in a beta value at each time point; (2) the individual time-course of each ICN was produced by combining the beta values at every time points, representing the temporal dynamics of each ICN [14]; (3) for each subject, steps 1–2 were repeated 20 times to loop through the 20 ICNs. The pipeline of obtaining individual time-courses for ICNs was illustrated in Fig. 1.

2.5. Temporal patterns within and between ICNs

To investigate the univariate temporal pattern within brain network, amplitude of low frequency fluctuation (ALFF) was computed for each ICN. ALFF was defined as the total power within a specific frequency range (i.e., 0.01–0.1 Hz) [24]. The computation of ALFF contained the following steps [8]: first, the time-course of each ICN was transformed to frequency domain by fast Fourier transform (FFT); second, the square root values were computed at each frequency of the power spectrum; finally, the averaged square root at 0.01–0.1 Hz was obtained at each time-course as network-wise ALFF for each ICN.

To investigate the bivariate temporal pattern between brain networks, node strengths were computed from the correlation matrices of the 20 ICNs. First, a 20×20 matrix of Pearson correlation coefficients was derived from the 20 time-courses of ICNs