Altered spontaneous neural activity in large-scale brain systems associated with executive dysfunction in attention deficit hyperactivity disorder

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Introduction:

Attention deficit hyperactivity disorder (ADHD) is a disorder of inattention, impulsivity and hyperactivity that affects 8-12% of children worldwide (1), which also has a primary deficit in executive functions (EF). Recent advances in resting-state functional magnetic resonance imaging (rfMRI) have facilitated the models of ADHD pathophysiology that encompass a number of different large-scale resting-state networks (2). And the amplitude of low-frequency fluctuations (ALFF) and functional connectivity (FC) of blood oxygen level-dependent (BOLD) signal of rfMRI can reflect the intrinsic neural activity and temporal correlation (3). However, there's no research to explore the relationship between the altered spontaneous brain activity and executive dysfunction of ADHD patients. In this study, changes in ALFF and FC were examined to characterize the multi-systemic underlying pathophysiology in ADHD and try to find the association between the executive dysfunction.

Subjects and Methods:

The study was approved by the local ethical committee and written informed consent was obtained from guardians of all subjects. The Structural Clinical Interview for DSM-IV (SCID) patient edition was used to establish diagnosis for ADHD. A total of 33 drug-naive right-handed male ADHD patients (mean ages 10.1±2.6 years) and 32 right-handed male healthy controls (mean age 10.9±2.6 years) were recruited. All participants had a full scale IQ above 90 according to Weschler test, and there's no difference in IQ scores between two groups. The Wisconsin Card Sorting Test (WCST) was adopted to assess EF, and the differences between two groups were analyzed by SPSS 16.0 using General Linear Model with age as a covariant. The resting-state fMRI sensitized to changes in BOLD signal levels were obtained via a GE-EPI sequence (TR/TE=2000/30msec, flip angle=90°, slice thickness=5mm without gap, 30 axial slices, 205 volumes in each run) via a Seimens 3T MRI system. During scanning, subjects were instructed to relax with eyes closed without falling asleep. The fMRI data processing was conducted by DPARSF software to calculate the parametric maps of ALFF (head translation movement <2 mm, rotation < 2°). Then, the FC was examined using a seed correlation approach based on regions with altered ALFF. A reference time series for each seed was extracted by averaging the rfMRI time series of voxels within each seed. Correlation analysis was carried out between each seed and the filtered time series in the rest of the brain. The correlation coefficients in each voxel were transformed to z values, and then spatial smoothing (8-mm full width half-maximum). Voxel-based analyses of the ALFF and FC between two groups were performed using two-sample t-test in SPM8, and *P* value of less than 0.05 after family-wise error (FWE) correction was deemed to be significant with age as a covariant. The correlations analyses between altered ALFF and FC and scores of EF in ADHD group were carried out by SPSS 16.0 using partial correlation with age as a covariate.

Results:

Related to controls, ADHD patients got less total correct number and archived categories and more total and perseverative and non-perseverative errors in WCST (Table 1). Compared to controls, ADHD group showed significantly increased ALFF in bilateral globus pallidus (GP) and right dorsal superior frontal gyrus (dSFG) (BA9) and decreased ALFF in left orbitofrontal cortex (OFC) (BA11) and ventral superior frontal gyrus (vSFG) (BA10) (Figure 1). The FC analyses based on the regions with altered ALFF showed increased FC within fronto-striatal networks including GP, OFC and SFG, and decreased FC within fronto-striato-parieto-temporal and fronto-cerebellar circuits in ADHD group than controls (Figure 1). In ADHD group only, the altered FC was associated with executive dysfunction, e.g. increased FC between bilateral GP and left OFC negatively correlated with correct number and archived categories and positively correlated with total error in WCST; increased FC between left OFC and right angular gyrus positively correlated with perseverative error in WCST (Table 2).

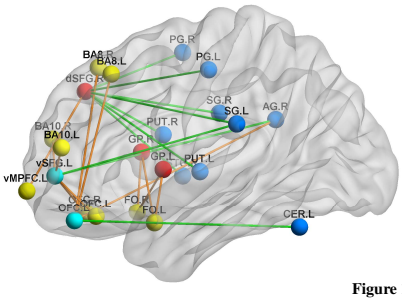

Figure 1

(**Table 1**) EF Measures (WCST)	ADHD	Controls	*F* value	*P* value*
Correct response	28.5 (11.1)	35.7 (7.4)	8.606	0.005
total error	16.9 (13.5)	9.3 (8.3)	6.157	0.016
perseverative error	6.0 (7.7)	2.2 (2.8)	6.151	0.016
non- perseverative error	10.9 (8.1)	7.2 (6.1)	3.024	0.039
categories achieved	4.2 (2.1)	5.4 (1.8)	4.587	0.036

(**Table 2**)	Increased Functional Connectivity			
EF Measures (WCST)	R_GP L_FO	L_GP L_FO	L_GP R_FO	L_OFC R_AG
total correct	-	-	-	
total error	+	+		
perseverative error				+
categories achieved	-	-		

Figure 1. Red/light blue nodes indicate the regions with increased/decreased ALFF; Yellow nodes/orange lines represent regions with increased FC, while deep blue nodes/green lines represent regions with decreased FC in ADHD compared to controls.
Table 1. Performances on executive function (WCST) between ADHD patients and controls ($P < 0.05$, General Linear Model with age as a covariant).
Table 2. Altered functional connectivity (FC) associated with executive dysfunction in ADHD patients group ($P < 0.05$, two-tailed, partial correlation with age as a covariant) (FO, frontal operculum; AG, angular gyrus; L, left; R, right; -/+, negative/ positive correlation).

Conclusion:

To our knowledge, this is the first study evaluating the relationship between altered spontaneous brain activity and functional connectivity and executive dysfunction in ADHD. In accord with the revised model of ADHD pathophysiology, the present findings indicate intrinsic brain activity altered not only in fronto-striatal circuit dominantly with regional deficit and excess, but also accompany with increased fronto-striatal FC and decreased fronto-parieto-temporal and fronto-cerebellar FC within different large-scale resting-state networks in ADHD (4). Furthermore, the altered FC associated with performance in WCST show the linkage between executive dysfunction and ADHD tentatively established by not only fronto-striatal hypothesis (5) also dysfunction in fronto-parietal networks.

Reference:

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