Altered Functional Connectivity of Emotional Network in Children with Attention-Deficit/Hyperactivity Disorder

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Purpose: Emotion dysregulation has long been recognized as a common and predominant deficit in individuals with attention deficit/hyperactivity disorder (ADHD), particularly in childhood patients. It is suggested that the combination of ADHD and emotional problems represents a major source of impairment and presages a poor clinical outcome in patients[1]. Previous functional imaging studies using different stimulus paradigms have indicated a *striato-amygdalo-medial prefrontal cortical* network that underlies the emotional problems, and structural imaging studies also revealed deficits in striatum and amygdala in ADHD patients[2]. However, little is known about the network activity at resting-state.

Methods: We recruited 51 drug-naïve boys without comorbid ADHD and 50 age matched healthy controls. The diagnosis of ADHD is established based on criteria of DSM-IV and the Conners' Parent Rating Scale (CPRS) was conducted to evaluate the individual's behavioral problems. 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 Siemens 3T MRI system. The fMRI data processing was conducted by DPARSF software to calculate the parametric maps of functional connectivity (FC) with bilateral amygdala, caudate nucleus, pallidum and putamen as ROI seeds. 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 smoothed (8-mm full width half-maximum). Voxel-based analyses of FC between two groups were performed using two-sample t-test in SPM8 with age as covariate, threshold at $P< 0.005$ at cluster-level (corrected for AlphaSim $P<0.05$). The correlations between altered FC and the scores of CPRS in ADHD group were performed by using the partial correlation analysis in SPSS with age as covariate.

Table 1

CPRS	ADHD	HC	P value
No of subjects	51	50	/
Mean age (years)	10.0±2.3	10.8±2.4	0.10
Conduct problem	11.3±7.9	4.5±4.5	<0.000
Study problem	6.9±3.3	2.8±2.7	<0.000
Psychosomatic	1.1±1.5	0.38±0.9	0.006
Hyperactivity /Impulsivity	5.4±3.2	1.8±1.8	<0.000
Anxiety	1.2±1.5	1.4±1.6	0.438
Hyperactivity index	12.7±6.7	4.5±4.4	<0.000

Result: Compared to controls, ADHD patients got higher scores in all indices of CPRS except Anxiety (**Table 1**). As for FC differences (**Figure 1**), ADHD patients showed increased FC between basal ganglia and a number of cortical and subcortical structures, iucluding middle temporal gyrus (MTG), mid-cingulate cortex (MCC), precentral gyrus (PreCG), postcentral gyrus (PostCG), fusiform gyrus (FG) and precuneus (Pcun). Similarly, increased FC was also revealed between amygdala and PreCG, PostCG and FG in ADHD. More intreastingly, both amygdala and basal ganglia showd decreased FC with cerebellar including the vermis and bilateral lobules. In ADHD group, the increased FC between left amygdala and right PreCG (r=0.335,p=0.027), left PreCG (r=0.322,p=0.029) and left PostCG (r=0.299, p=0.043) showed positive correlations with the scores of Hypractivity/Impulsivity of CPRS.

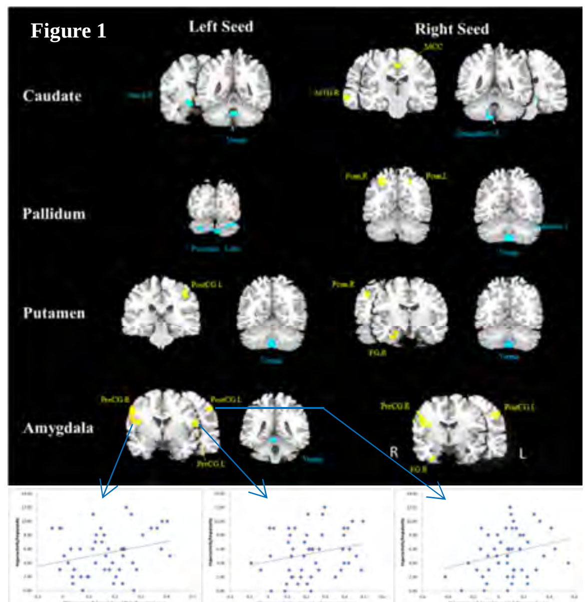

Figure 1. Two sample t-test of FC between ADHD and healthy controls. The yellow clusters indicated increased FC in ADHD relative to controls, the blue clusters indicate decreased FC. In ADHD groups, the FC between left amygdala and right precentral gyrus, left precentral gyrus and left postcentral gyrus all showed positive correlations with the scores of Hyperactivity/Impulsivity.

Discussion: To our best of knowledge, this is the first study to evaluate the resting-state FC using amygdala and basal ganglia, the two key nodes of emotional network, as ROI seeds in children with ADHD. Consistent with task fMRI studies, our results demonstrated altered FC within the emotional network, and more importantly the connectivity of left amygdala to various regions are related with scores of CPRS, suggesting its important role in disease pathology. Increased FC at parietal areas and cingulate cortex might indicate an abnormal interaction with executive network. Our study also revealed significant decreased FC between emotional related seeds and cerebellum. Cerebellum has long been recognized as a key node in the *fronto-striato-cerebellar* network of ADHD, involving in cognition and emotion as well as motor control[3]. Thus our finding gave direct evidence for the role of cerebellum in the pathophysiology of ADHD by demonstrating its close relationship with emotional network.

Conclusion: In current study, we demonstrated that the emotion network of ADHD children is abnormal even at resting-state, without the confounding from the effects of gender, medication and comorbidity. Besides, our findings also suggested the deficits of top-down regulation from executive network in response to emotional stimulus, and that the cerebellum plays an important role in the pathophysiology of ADHD.

Reference: 1. Riley AW, et al. Eur Child Adolesc Psychiatry 2006; 2. Shaw P, et al. Am J Psychiatry 2014; 3. Stoodley CJ, et al. Front Syst Neurosci 2014.