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Striatal subregional functional connectivity and its association with sustained attention in adults with attention deficit hyperactivity disorder

Muhammad Abdullah[1], Li-Chung Huang[2,3], Shih-Hsien Lin[4,5], Yen Kuang Yang[4,5,6]*

[1] Taiwan International Graduate Program in Interdisciplinary Neuroscience, National Cheng Kung University and Academia Sinica, Taipei, Taiwan,
[2] Institute of Clinical Medicine, National Cheng Kung University, Tainan, Taiwan,
[3] Department of Psychiatry, Chia-Yi Branch, Taichung Veterans General Hospital, Chia-Yi, Taiwan,
[4] Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan,
[5] Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan,
[6] Department of Psychiatry, Tainan Hospital, Ministry of Health and Welfare, Tainan, Taiwan,
** Email: ykyang@mail.ncku.edu.tw*

The functional connectivity (FC) of striatal subregions is correlated with cognitive functions in child attention deficit hyperactivity disorder (ADHD). However, increasing age changes the pattern of cognitive functions and clinical presentation. The changes in the pattern of cognitive functions may be associated with underlying age-dependent striatal subregional FC alterations. We attempted to explore aberrancies in FC in striatal subregions and their associations with a predominant cognitive symptom (inattention) in adult ADHD. The FCs of ten bilateral subregions (seeds) of the striatum along with the whole brain were investigated, and FC maps of adults with ADHD (N=15) and healthy controls (N=15) were compared. Finally, we evaluated the associations of striatal subregional FCs with cognitive functions. Case-control differences in striatal subregional FC were not significant; however, attention scores were marginally significantly positively correlated with FC between the right dorsal-caudal putamen and right-superior temporal gyrus in the ADHD group. Our results suggested that cognitive deficits (inattention) may be associated with FC aberrancy in a substriatal connection (between the right dorsal-caudal putamen and right-superior temporal gyrus) in adult ADHD.

Key words: adult ADHD, attention, cortico-striatal networks, resting state fMRI, functional parcellation

INTRODUCTION

The dopaminergic system densely inhabits basal ganglia, particularly the striatum. Dopaminergic system dysfunction as a core pathological mechanism of attention deficit hyperactivity disorder (ADHD) (Tripp and Wickens, 2009; Volkow et al., 2009; Lin et al., 2021) has been previously found to be associated with aberrant cortico-striatal functional connectivity (CSFC) (Qian et al., 2018; Shang et al., 2021). Due to its role in a number of functions (including motor and cognitive functions), researchers have attempted to segregate the striatum into multiple functional subregions (Di Martino et al., 2008; Helmich et al., 2010) and identify associations between ADHD and CSFC based on these striatal subregions (Hong et al., 2015; Oldehinkel et al., 2016; Rhein et al., 2016; Shang et al., 2021). However, the results have been diverse, some studies having reported no change in striatal

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subregional to cerebral cortex connectivity (Oldehinkel et al., 2016; Rhein et al., 2016), and others indicating aberrancies (Hong et al., 2015; Shang et al., 2021). The heterogeneity in results may be due to multiple reasons, including treatment status (drug-treated *vs.* drug-naive) and age (children only or a broad age range combining children and adolescents). Striatal subregional connectivity has not been previously investigated in drug-naive adults with ADHD.

Adult ADHD may be segregated from child ADHD based on an altered pattern of cognitive functions. Among the core cognitive deficits, which include impulsivity/hyperactivity and inattention, the latter is more prevalent in adult ADHD (Zalsman and Shilton, 2016). Researchers believe that the pattern of cognitive deficits shifts with increasing age (Faraone et al., 2006). Declining hyperactivity/impulsivity symptoms below the diagnostic threshold and inclining attention-associated symptoms may occur across the lifespan (Biederman et al., 2000; Willcutt, 2012). It has been reported that along with a shift in the pattern of cognitive functions, the pattern of neuronal connectivity also changes with increasing age. For example, in a recent article, Guo et al. (2020) reported that some functional connectivity (FC) aberrancies are common in child and adult ADHD, but an aberrant inter-network FC between the somatomotor network and dorsal attention network is unique to child ADHD, while an aberrant inter-network FC between the limbic network and default mode network is more specific to adult ADHD. As an important part of the limbic system and a major site of the dopaminergic system, the FCs of striatal subregions and their associations with ADHD- associated symptoms have been studied in child ADHD by parcellating the striatum into functional subregions. However, it is as yet unknown how cognitive dysfunctions in adult ADHD are associated with the whole-brain FCs of striatal subregions.

We speculate that ADHD may be associated with disrupted FCs of striatal subregions in adults. Herein, we explored how striatal subregional connectivity is affected in adult ADHD. Further, as a most prevalent dysfunction specific to adult ADHD, we aimed to explore the association between inattention and striatal subregional connectivity in drug-naive adult subjects.

METHODS

Participants and procedure

In this case-control study, fifteen drug-naive adult ADHD participants (nine males and six females, mean age=26.40±4.37 years) were enrolled based on the DSM-IV criteria for ADHD after assessment by a senior psychiatrist from 2012 to 2017. Subjects had stable vital signs, and no co-morbid physical, mental, or neurological illnesses were diagnosed. Their IQ was ≥70. Fifteen age- and sex-matched healthy controls (nine males and six females, mean age=26.47±4.27 years) were also enrolled. The healthy subjects were screened using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), and found to be free of any mental condition. All participants were reimbursed with a minimum wage per hour at the level dictated by current Taiwanese law.

The Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital approved the research protocol, and this protocol conformed to the provisions of the Declaration of Helsinki. All participants signed written informed consent forms after the procedures had been fully explained.

Continuous Performance Test (CPT)

The CPT is a psychological test that is mainly used to measure attention (Chen et al., 1998; Hsieh et al., 2005). The CPT was performed in two sessions, the mask d' and unmask d' task. During the CPT, a set of numbers was presented randomly from 0 to 9, for 50 ms each, at a rate of one per second. During the random presentation of numbers, the subjects responded to target stimulus numbers (X task: subjects were asked to respond to number "9") or to a particular sequence of two stimuli out of the whole set (AX task: subjects were asked to respond whenever the number "9" was preceded by the number "1"). Only the AX task was employed in the present study. A total of 341 trials were presented over a 5-min session, 31 of which were target stimuli. During the task, the subject's responses were automatically recorded on hard disk using the CPT apparatus (Sunrise Systems V2.20, Pembroke, MA, USA) (Smid et al., 2006). A 2-min practice session was also conducted before each test (repeated if the participants desired it) to make sure that the button-pressing response of each participant was correct. The purpose of the mask d' session was to blur the target. In the mask d' task, a snow pattern was used to cover the background, rendering the image less distinct. The d' (sensitivity) represents the subject's ability to discriminate a signal (target stimuli) from the background noise (non-target). A high value of d' indicates a better processing capability (Hsieh et al., 2005). An experienced

research psychologist conducted and supervised the CPT sessions of every subject.

Image and psychological data acquisition

Resting-state functional magnetic resonance imaging (fMRI) images were acquired (eyes closed, head still but relaxed, without thinking) using a 3.0 Tesla MRI scanner (MR750, GE Medical Systems, Milwaukee, WI, USA) with an 8-channel head coil. High-resolution T1-weighted 3-dimensional structural images ([TR] / [TE] = 7.7 ms / 2.9 ms, flip angle=12°, field-of-view=224 mm^2, in-plane matrix size=256×256, slice thickness=1 mm, slices=166) and T2*-weighted echoplanar imaging sequences ([TR] / [TE] = 2000 ms / 33 ms, flip angle=90°, field-of- view=240 mm^2, in-plane matrix size=64×64, slice thickness=3 mm, slices=40, obtained in 5 min and 10 s) were collected to attain high-resolution anatomical T1 images and fMRI images. The initial 10 s of the scan containing 5 TRs of each resting-state fMRI series were removed owing to a possible signal saturation effect and magnetic field fluctuations. Preprocessing of resting-sate functional images was completed utilizing the DPARSF toolbox V5.1. Steps followed in preprocessing included slice timing correction, realignment for head-motion correction (≤2 mm or 2°), and co-registration against each subject's anatomical image, as well as segmentation and normalization against the International Consortium for Brain Mapping (ICBM) space template for East Asian brains. Whole-brain resting-state connectivity (time series=0.01–0.1 Hz) was studied using ten bilateral spherical seeds of 3-mm radius centered on the ventral and dorsal striatal regions of interest (ROIs), including the dorsal-caudal putamen (dcP) [MNI coordinates: ±28, 1, 3], dorsal-rostral putamen [±25, 8, 6], ventral-rostral putamen [±20, 12, -3], dorsal caudate [±13, 15, 9], and superior ventral striatum [±10, 15, 0] based on previous studies (Di Martino et al., 2008; Shang et al., 2021). Voxel-wise whole-brain FC correlations were computed as a linear function of CPT score.

Image analysis

We used SPM12 and xjView 8.0 (Human Neuroimaging Lab, Baylor College of Medicine, Houston, TX, USA) operating under MATLAB R2016a to analyze the FC maps. Statistical maps were computed to find linear models between CPT scores and striatal-seeded FC values in the whole brain. Group and CPT scores were inserted as regressors of interest, and contrasts for group by CPT scores interaction (Group*CPT score > 0 and Group*CPT score < 0) were generated. Significance was set at a threshold with a peak-level uncorrected $P<0.001$, with a family-wise error rate (FWE)-corrected cluster level of $P<0.05$. Along with group differences, to confirm the existence of a significant association with CPT score in at least one of the groups, two one-sample T-tests under the SPM framework were employed to ensure that regions had positive or negative associations with CPT score in the ADHD group or the healthy control group that overlapped with regions identified in previous analyses.

Statistical analyses

SPSS Statistics 20.0 (SPSS Inc., Chicago, IL) was used for the remainder of the analyses. The results were considered significant at $P<0.05$ (two-tailed). Due to the small sample size, the Mann-Whitney U test was conducted to identify between-group differences.

RESULTS

Demographic data and cognitive functions

We analyzed the groups to identify differences in demographic data and cognitive function scores. Table 1 shows the demographic data and test scores for cognitive functions. Differences were not significant for age, sex, or educational level between the two groups ($P>0.273$). However, regarding the cognitive tests, the patients with ADHD had poorer CPT scores than the matched controls (unmask d': 4.33±0.62 *vs.* 4.77±0.16, $P=0.036$; mask d': 4.13±0.63 *vs.* 4.52±0.30, $P=0.089$).

Whole-brain functional connectivity of ten striatal subregions and association with cognitive functions

We did not observe case-control variations in FC in any of the ten striatal subregions. The CPT was used to measure attention, which is one of the predominant cognitive deficits associated with adult ADHD. The CPT mask d' was marginally significantly ($P=0.051$) positively correlated with FC between the right dorsal-caudal putamen [MNI coordinates: 28, 1, 3] and right-superior temporal gyrus [MNI coordinates: 48, -28, 4, cluster size 175] in the ADHD group (Fig. 1); however, no significance was found if age and sex were added as regressors of non-interest.

Table 1. Demographic and cognitive function data of the ADHD group and healthy controls.

	HCs (N=15)	ADHD Drug-Naive (N=15)	Statistic	
	Mean±SD	Mean±SD	Mann-Whitney U	*P*
Sex (M/F)	9/6	9/6		
Age (years)	26.47±4.27	26.40±4.37	-0.06	0.950
Educational years	17.07±1.75	16.30±1.94	-1.10	0.273
CPT unmask d'	4.77±0.16	4.33±0.62	-2.10	0.036*
CPT mask d'	4.52±0.30	4.13±0.63	-1.70	0.089

ADHD, attention deficit hyperactivity disorder; HCs, healthy controls; SD, standard deviation; CPT, continuous performance test. *P<0.05.

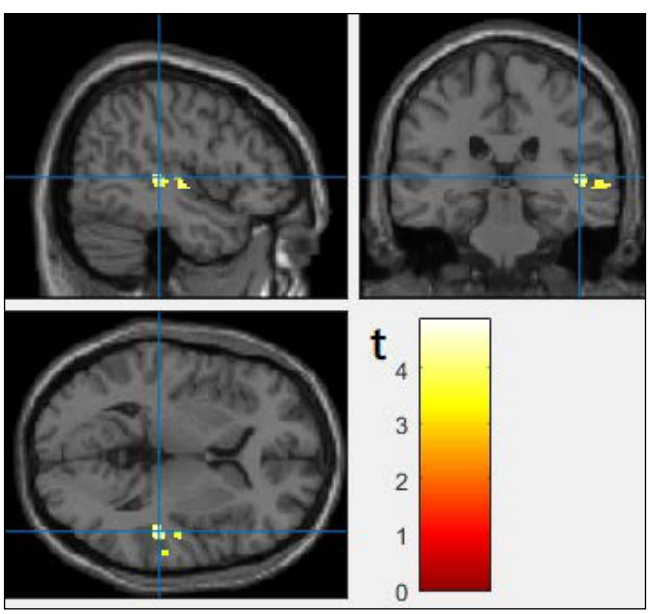

Fig. 1. Right-superior temporal gyrus. The CPT mask d' was marginally significantly (P=0.051) positively correlated with functional connectivity between this region and the seed at the right dorsal-caudal putamen in the ADHD group. CPT, continuous performance test; ADHD, attention deficit hyperactivity disorder.

DISCUSSION

We investigated whole-brain FC while taking ten subregions of the striatum bilaterally, as seeds, in drug-naive adult ADHD patients and healthy controls. Researchers believe that cognitive, affective, and motor functions are differentially attributed to the subregions of the striatum (Alexander et al., 1986; Di Martino et al., 2008). These striatal subregions have been studied in terms of the impact of ADHD on whole-brain FC in children and other broad-range age groups. The notion that the pattern of cognitive symptoms changes with increasing age (i.e., decline in hyperactivity/impulsivity symptoms and incline in inattention) (Faraone et al., 2006; Zalsman and Shilton, 2016), which may be associated with distinct aberrations in whole-brain FC (Guo et al., 2020), led us to explore the interaction of ADHD and FCs of striatal subregions in adults. Consistent with previous work on child ADHD (Oldehinkel et al., 2016; Rhein et al., 2016), we did not find any alterations in major cortico-striatal networks in drug-naive adult ADHD patients in comparison with healthy subjects. However, contrasting results have been reported in some child and adolescent ADHD studies, in which these cortico-striatal connections were aberrant in FC as compared with healthy controls (Hong et al., 2015; Shang et al., 2021). There may be multiple factors responsible for the heterogeneity of results, including genetics, ADHD subtype, and phenotypic as well as cognitive characteristics. Confirming the role of genetics, a recent study by Shang et al. (2021) showed that polymorphism in the dopamine transporter gene may affect the FCs of striatal subregions differentially in child ADHD. Similar future studies of dopaminergic gene-associated subclassifications may produce promising results in adult ADHD.

Further, we investigated the associations between attention and the FCs of striatal subregions. The CPT mask d' was marginally significantly (P=0.051) positively correlated with the FC between the right dorsal-caudal putamen and right-superior temporal gyrus in the ADHD group. We did not replicate other results of associations between attention and cortico-striatal FC in specific striatal subregions in adult ADHD as have been reported in previous studies of child, adolescent, and broad age range ADHD groups. Recent studies have reported that in the aforementioned groups, the FCs of different sets of striatal subregions to the cerebral cortex are associated with attention (Hong et al., 2015; Oldehinkel et al., 2016).

The superior temporal gyrus has been previously discovered to be associated with visuotemporal attention, sustained attention and related phenomena (Shapiro et al., 2002; Ellison, 2004; Gharabaghi et al., 2006). Studies have shown that deactivation of the superior temporal gyrus may affect tasks related to sustained attention and spatial perception (Gharabaghi et al., 2006). All the aforementioned tasks have been found to be compromised in ADHD. Considering the role of the superior temporal gyrus in attention, our results support the notion that superior temporal gyrus dysfunction could be one of the pathologies associated with decreased attention in adult ADHD. Furthermore, the results suggested that the higher the connectivity between the right dorsal-caudal putamen and right-superior temporal gyrus, the higher attention. As an elaboration, we may elucidate that the striatum may modulate activity of the superior temporal gyrus. This relationship predicts one of the important outcomes of drugs used in adult ADHD to improve attention. As a core pathological feature of ADHD, decreased striatal activity due to a compromised dopaminergic system is of prime importance (Tripp and Wickens, 2009; Volkow et al., 2009; Lin et al., 2021). A class of drugs (i.e., CNS stimulants such as methylphenidate and amphetamine) is used in ADHD primarily to increase the activity of the striatum by increasing the dopamine level/dopaminergic system activity (Buoli et al., 2016). Drugs that induce increased striatal activity may be predicted to increase the activity of the superior temporal gyrus, which could be one of the pharmacological mechanisms of ADHD drugs to improve attention. Future studies are required to investigate the effects of drugs and electroceuticals on this connectivity, the activity of the superior temporal gyrus, and the suitability of the superior temporal gyrus as a therapeutic target.

Several limitations should be noted. First, due to the small sample size, the results were not corrected for multiple comparisons, and an influence due to age and sex could not be completely ruled out, resulting in a lack of statistical power. Second, subjects were not classified into subtypes of ADHD, as previous studies have reported that subtypes of ADHD may affect brain network organization distinctly (Saad et al., 2017). Third, genetic tendencies were not defined, as previous studies have shown that genetic variations may affect the resting state functional connectivity in ADHD (Shang et al., 2021). Fourth, sleep can affect the resting-state fMRI data (Tagliazucchi and Laufs, 2014; Wang et al., 2017), while the radiologist communicated with subjects via an intercom prior to the resting scan to confirm that they were awake, no measures were taken to ensure that the subjects remained awake during the scan.

CONCLUSION

In this study, we investigated the FC of the striatum by dividing it into 10 bilateral functional subregions and examining their associations with attention in drug-naive adult ADHD. According to the results, case-control differences were not significant between the drug-naive adult ADHD patients and control group. However, the FC between the dorsal caudal putamen and superior temporal gyrus was directly correlated with attention. Our results supported the findings of previous studies regarding the role of the superior temporal gyrus in attention and associated phenomena.

Furthermore, based on evidence from previous child and adolescent ADHD studies examining the FCs of similar subregions in the striatum, we observed that the FC of a different set of the neuronal network was associated with ADHD-associated symptoms in the drug-naive adults. We may speculate that correlation of the same cognitive function (attention) with FC may be attributed to different striatal subregions in child and adult ADHD. Future FC studies to compare the connectivities of striatal subregions between adults and children may be helpful in the future to validate our speculations.

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