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ORIGINAL RESEARCH

Striatum morphometry is associated with cognitive control deficits and symptom severity in internet gaming disorder

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Abstract Internet gaming disorder (IGD), identified in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) Section III as a condition warranting more clinical research, may be associated with impaired cognitive control. Previous IGD-related studies had revealed structural abnormalities in the prefrontal cortex, an important part of prefrontal-striatal circuits, which play critical roles in cognitive control. However, little is known about the relationship between the striatal nuclei (caudate, putamen, and nucleus accumbens) volumes and cognitive control deficit in individuals with IGD. Twenty-seven adolescents with IGD and 30 age-, gender- and education-matched healthy controls participated in this study. The volume differences of the striatum were assessed by measuring subcortical volume in FreeSurfer. Meanwhile, the Stroop task was used to detect cognitive control deficits. Correlation analysis was used to investigate the relationship between striatal volumes and performance in the Stroop task as well as severity in IGD. Relative to controls, the IGD committed more incongruent condition response errors during the Stroop task and showed increased volumes of dorsal striatum (caudate) and ventral striatum (nucleus accumbens). In addition, caudate volume was correlated with Stroop task performance and nucleus accumbens (NAc) volume was associated with the internet addiction test (IAT) score in the IGD group. The increased volumes of the right caudate and NAc and their association with behavioral characteristics (i.e., cognitive control and severity) in IGD were detected in the present study. Our findings suggest that the striatum may be implicated in the underlying pathophysiology of IGD.

Keywords Cognitive control · Internet gaming disorder (IGD) · Striatum · Color-word Stroop task · Structural magnetic resonance imaging

Introduction

Although internet gaming disorder (IGD) has not been officially codified within a psychopathological framework, prevalence of this condition is growing and attracting the attention of psychiatrists, educators, and the public (Kühn et al. 2011; Bavelier et al. 2011). Notably, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders

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(DSM-V) identified IGD in Section III as a condition warranting more clinical research to provide mechanistic insight into its etiology and treatment (Hasin et al. 2013). Due to the immature brain development of adolescents, previous reports have revealed that the incidence rate of IGD is between 1.4 and 17.9 % among adolescents around the world, with the highest rates occurring in China and South Korea (Kucinski et al. 2013; Casey and Jones 2010; Kim et al. 2006). IGD may be associated with significant psychological distress and can interfere with daily life by causing depression (Ko et al. 2013a), loneliness, interpersonal problems (Meng et al. 2014; Li et al. 2014), sleeplessness, and even suicidal behavior (Kim et al. 2006). Previous studies have suggested that the IGD shows similar neural mechanisms to substance use and other behavioral addictions, such as pathological gambling (Yuan et al. 2011a). However, the current treatment of IGD is not satisactory (Byun et al. 2009; Block 2008; Winkler et al. 2013). Identification of the neural mechanisms for IGD is therefore of clinical significance for the prevention and early intervention of this disorder.

Regardless of whether IGD is conceptualized as a behavioral addiction or as an impulse-control disorder (Holden 2001), it is speculated to be associated with impaired cognitive control (Dong et al. 2011). Aspects of cognitive control include the ability to resolve conflict-inducing situations and to inhibit prepotent responses, both of which can be measured using Stroop tasks (Stroop 1935). These processes are especially relevant within the context of IGD, since inhibition of a prepotent response is critical for abstaining from internet usage when confronted with internet-related cues (Ko et al. 2009, 2013b). Impaired cognitive control was observed in IGD individuals in previous studies, e.g., more response errors during incongruent condition of Stroop task (Dong et al. 2011, 2013). Effective cognitive control is associated with the coordinated recruitment of different top-down prefrontal-striatal circuits (Nelson et al. 2005; Ko et al. 2014). Previous studies had revealed the association between the structural and functional abnormalities of the PFC (i.e., orbitofrontal cortex (OFC) in our previous findings) and impaired cognitive control in IGD (Weng et al. 2013; Yuan et al. 2013a; Ko et al. 2009, 2013b; Dong et al. 2013). For example, the reduced cortical thickness and increased amplitude of low frequency fluctuation value of the OFC were correlated with the color-word Stroop task performances in young subjects with IGD (Ko et al. 2009; Dong et al. 2013). Meanwhile, functional magnetic resonance imaging (fMRI) showed striatum dysfunction during response inhibition in the IGD subjects (Li et al. 2014). In addition, positron emission tomography (PET) imaging has demonstrated decreased dopamine D2 receptor availability in the bilateral caudate and right putamen in IGD subjects (Kim et al. 2011). However, there is a lack of studies focusing on the relationship between striatum volume abnormalities and cognitive control in IGD.

Therefore, the purposes of the present study were: 1) to examine the cognitive control deficits by using the Stroop task in IGD; 2) to assess the subcortical volume differences of the striatum between those with IGD and healthy controls; 3) to investigate the relationship between the striatum volume and cognitive control deficits, as well as with the severity of IGD. Based on previous findings in IGD and the enlarged volume of the striatum in substance use (Kühn et al. 2011; Janes et al. 2014; Berman et al. 2008; Wrase et al. 2008; Weinstein and Lejoyeux 2013), we hypothesized that the striatum volume would be different between IGD and healthy controls, and that the abnormal striatum volume might be associated with Stroop task performance in IGD.

Methods and materials

Ethics statement

The study was approved by the Xi'an Jiaotong University Subcommittee on Human Studies and conducted in accordance with the Declaration of Helsinki. The participants and their guardians provided written informed consent prior to participation in the study.

Participants

The patients in this study were recruited from the First Affiliated Hospital of Medical College, Xi'an Jiaotong University. The criteria of the IGD group included: (a) endorsement at least five (or more) of the nine DSM-V criteria for IGD over a 12-month period; (b) played League of Legends (LoL) (http://euw.leagueoflegends.com/), a Multiplayer Online Battle Arena (MOBA) style game by Riot Games, as their primary internet activity. In addition, the subjects were asked to fill in a basic information questionnaire to assess Internet gaming activities, with questions that include "How many internet games do you play?", "How many days on average do you spend on Internet gaming per week?", "How many hours on average do you spend on Internet gaming per day?", "For how long have you been using the Internet with this frequency?". Additionally, we asked the participants "Would you describe yourself as addicted to the Internet?" and "Do your parents know your Internet gaming activities?". The severity of IGD was measured by Young's online Internet Addiction Test (IAT), which consists of 20 self-rating questions with the Likert scale of one (rarely) to five (always) (Widyanto and McMurran 2004); we defined the subjects with scores over 50 as the IGD group as previously described (Pawlikowski and Brand 2011). We also confirmed the accuracy of the self-report from IGD individuals by talking with their parents, roommates, or classmates via telephone.

Twenty-seven right-handed adults with IGD (23 males, mean age=17.9±0.9, education 12.0±0.8 years) and thirty age-, gender-, and education-matched healthy persons (22 males, mean age=18.3±1.6, education 12.4±1.4 years) were recruited as the control group. The IGD group spent 6.9±2.2 hour per day and 4.1±1.6 days per week on Internet games. We chose healthy controls who spent 2.7±1.5 hour per day and 1.8±0.7 days per week on the Internet games. The healthy controls were also evaluated to ensure they did not suffer from IGD. Exclusion criteria for both groups were (a) existence of a neurological disorder as evaluated by the Structured Clinical Interview for DSM-V; (b) previous diagnosis of nicotine, alcohol, or substance dependence, (c) positive urine drug screening, pregnancy, or menstrual period in women, (d) any physical illness such as brain tumors, hepatitis, or epilepsy as assessed by clinical evaluations and medical records, (e) taking psychotropic medications, or (f) IQ score<90 (measured by Wechsler intelligence Scale). All recruited participants screened were native right-handed ethnic Chinese and were assessed by a personal self-report and an Edinburgh Handedness Questionnaire. The clinical characteristics of subjects with IGD are shown in Table 1.

Behavioral measures

Before undergoing an MRI, subjects were asked to perform a color-word Stroop task to test the cognitive control deficits of all subjects. Stimulus presentation, timing, and task performance measures were controlled using E-prime 2.0 software (http://www.pstnet.com/eprime.cfm) according to a previous study (Xu et al. 2006). This task employed a design with three conditions, i.e., congruent, incongruent, and rest. Here, we employed congruent and incongruent trials (for example: congruent, red written in red; incongruent, red written in green or blue). Congruent and incongruent items were presented in a random order. During resting blocks, a fixation cross was displayed at the center of the screen, and subjects were required to fix their eyes on this cross without responding. Three target words in Chinese, Red, Blue, and Green, were presented randomly in three colors (red, blue, and green) during the congruent and incongruent stimuli. Each run consisted of four congruent, four incongruent, and nine rest blocks. There were seven trials in each task block, and each stimulus was presented for 1 s, with an inter-stimulus interval of 2 s. Thus, each task block lasted 21 s. All rest blocks lasted 17 s, except for the first one, which lasted 19 s. Before each task block, the instruction, 'Identify the Color' was presented; and before each rest block, the instruction was 'Rest'. All instructions were presented for 2 s. Each participant was instructed to respond to the displayed color as quickly as possible by pressing a button on a Serial Response BoxTM with their right hand. Button presses by the index, middle, and ring fingers corresponded to red, blue, and green, respectively. Each subject was tested individually in a quiet room when he/she was in a calm state of mind. Before the task, there was an initial practice and the behavioral data was collected before MRI scanning.

MRI data acquisition

The MRI images were acquired on a 3-Telsa MRI system (EXCITE, General Electric, Milwaukee, Wisc.) at the First Affiliated Hospital of the Medical College, Xi'an Jiaotong University in China. The high-resolution 3D T1-weighted images were obtained for subcortical volumes measurements with the following parameters: repetition time (TR)=8.5 ms; echo time (TE)=3.4 ms; flip angle (FA)=12°; field of view (FOV)=240×240 mm2; data matrix=240×240; slices=140; voxel size=1×1×1 mm3. A head coil was used and head motion was minimized by filling the empty space around the head with sponge material. Images were screened by a

Table 1 Subject demographics for internet gaming disorder (IGD) individuals and healthy controls

Items	IGD (*N*=27)	Control (*N*=30)	t/χ^2	*p*-value
Age (years)	17.9±0.9	18.3±1.6	1.142	0.26
Sex, female (n%)[a]	23 (85.2 %)	22 (73.3 %)	1.949	0.16
Education (years)	12.0±0.8	12.4±1.4	1.192	0.25
IAT	61.6±10.5	24.6±4.5	−11.031	<0.001*
Hours of internet use (/hour)	6.9±2.2	2.7±1.5	−8.300	<0.001*
Days of internet use (/day)	4.1±1.6	1.8±0.7	−6.877	<0.001*
Duration time (/years) IAT	5.4±2.8	N/A	N/A	N/A

Values are mean±SD unless otherwise indicated. *IGD* internet gaming disorder, *IAT* internet addiction test.*$p<0.05$

[a] The *p* value for gender distribution in the two groups was obtained by chisquare test

neurologist for pathological findings and appropriateness for MR Image processing.

MR image processing

Subcortical volumetric segmentation of the whole brain was estimated using 3D brain structural images with the FreeSurfer v5.1.0 software (http://surfer.nmr.mgh.harvard.edu (Dale et al. 1999; Desikan et al. 2006). The processing stream included 1) removal of non-brain tissue; 2) automated Talairach transformation; 3) segmentation of the subcortical white matter and deep gray matter volumetric structures; 4) intensity normalization; 5) tessellation of the gray matter/white matter boundary; 6) automated topology correction; 7) surface deformation; and 8) registration of the subjects' brains to a common spherical atlas. The volumes of the striatum structures (i.e., bilateral caudate, putamen, NAc) and intracranial volume (ICV) were extracted and imported into SPSS 20.0 (SPSS Statistics, IBM, Armonk, NY). For each structure, a general linear model was fit with volume as the dependent variable, diagnosis (IGD and controls) as categorical predictors, and age and intracranial volume as continuous predictors, including age, education level, sex, and ICV as covariates. To correct for multiple comparisons, the Bonferroni procedure was applied in the current study. All tests were 2-tailed, and the level of significance was $P<.0083$ (.05/6). Pearson correlation was carried out between the absolute volumes of the striatum subsets and the cognitive control task performances in IGD.

Results

Demographic data

Table 1 showed the baseline demographic data in different subject groups. There were no significant group differences in age, sex, IQ, or years of education, between the two groups. However, the IGD group spent 6.9±2.2 hour per day and 4.1± 1.6 days/week on online gaming, which is significantly more than the healthy controls ($p<0.001$). In addition, IAT score was significantly higher in the IGD group (Table 1).

Color-word stroop task

Three controls were excluded due to practice failure; leading to a total sample of 54 participants. A two-way repeated measures ANOVA was carried out to investigate the main effect of the different groups (IGD, control) and different conditions (congruent vs. incongruent). The task results show that the IGD group committed more errors than the control group during the incongruent condition (errors: IGD: 6.3±0.5 vs CON: 4.4±0.5; $p<0.05$) (Fig. 1d), but that they reacted a bit faster than healthy controls during the congruent condition (time: IGD: 546.1±70.2 ms vs CON: 567.6±34.6 ms). Reaction time did not differ with statistical significance between the two groups during incongruent conditions (time: IGD: 629.6 ±94.0 ms vs CON: 663.6±151.8 ms) (Fig 1a and b). The response delay measured by reaction time during the incongruent condition minus congruent conditions was not significantly different between these two groups ($p>0.05$) (Fig. 1e).

Subcortical volume analysis

No significant difference of ICV was observed between IGD subjects and controls (Fig. 2, Table 2). Further analysis revealed a significant increase of the volume in the right caudate and right nucleus accumbens (NAc) in the IGD group as compared with the healthy controls group (Bonferroni corrected).

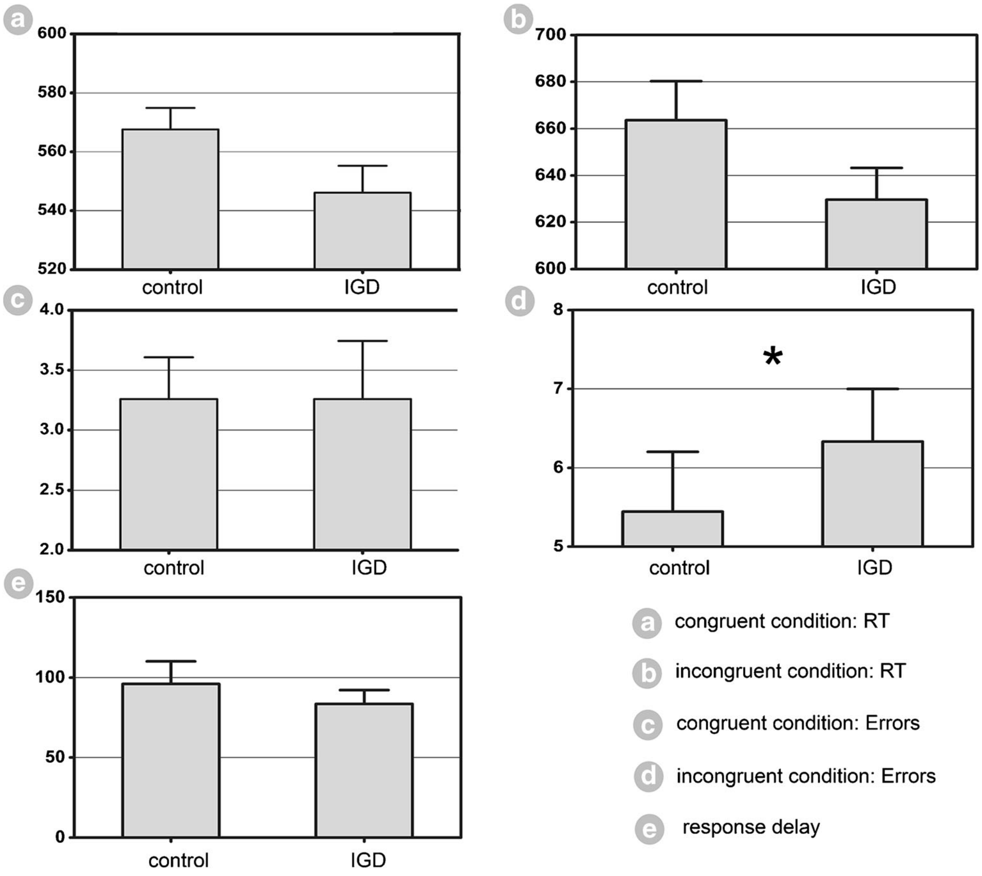
Correlation analyses

Correlation results indicated that the right NAc volume was positively correlated with the severity in IGD (Fig. 3, D; r= 0.483, $p=0.011$). In addition, right caudate volume was associated with response error numbers during the incongruent condition in IGD (Fig. 3c; r=0.455, $p=0.017$). No significant correlation was found between the striatum subsets volume and the relevant RTs in the color-word Stroop task in IGD (Fig. 3).

Discussion

IGD is characterized by the inability of an individual to control the amount of time he/she spends on internet games, which eventually causes psychological, social, and/or work related difficulties, and is becoming the major source of adulthood crime in China (Christakis 2010; Flisher 2010; Xing et al. 2014). Therefore, IGD has attracted considerable attention from psychiatrists, educators, and the public (Kühn et al. 2011). Previous IGD studies had detected impaired cognitive control ability in subjects with IGD (Brand et al. 2014; Yuan et al. 2013a, b). Effective cognitive control is associated with the coordinated recruitment of different top-down prefrontal-striatal circuits (Nelson et al. 2005; Ko et al. 2014). Numerous neuroimaging studies had revealed the association between the PFC structural and functional abnormalities and the impaired cognitive control in IGD (Weng et al. 2013; Yuan et al. 2013a; Ko et al. 2013b), however, less is known about striatum morphmetry. Therefore, the aim of this study was to explore the relationship between striatal nuclei (caudate, putamen, and NAc) volumes and cognitive control deficits and severity in IGD. In addition, performance on the color-word Stroop task was chosen as the behavioral assessment to investigate the functional implications of striatum volume

Fig. 1 Stroop task performances in both groups (IGD, control) are shown (**a**, **b**, **c**, **d**, **e**). The *grey star* indicates that the IGD group committed more errors than the control group during the incongruent condition ($p<0.05$) (**d**). *RT* response time; *IGD* Internet Gaming Addiction



differences. The demographic information showed that individuals with IGD spent more hours per day and more days per week on internet gaming than the normal controls. Consistent with previous findings, Stroop task results revealed that the IGD individuals committed more errors on average than the control group during the incongruent condition. Our results demonstrated that the IGD showed impaired cognitive control measured by the color-word Stroop task. The neuroimaging results demonstrated that the increased volume of dorsal striatum (right caudate) was associated with cognitive control impairments in the IGD group (Fig. 3). It is hoped that our findings can be used to develop novel imaging biomarkers that will enhance the understanding, diagnosis, and treatment of IGD.

In the current study, relative to healthy controls, the IGD group showed increased volume in the right caudate (Fig. 2). As a key target for dopamine, the caudate is most frequently mentioned in addiction by playing a major role in conditioned reinforcement and reward expectation (Volkow et al. 2011). Reduced dopamine receptor availability in the dorsal caudate was detected in individuals with IGD (Kim et al. 2011). Increased glucose metabolism in the caudate nucleus was also revealed in IGD (Park et al. 2010). These findings revealed the important roles of caudate nucleus in the pathology of IGD. In addition, the caudate has biological connections with the prefrontal cortex, particularly the dorsolateral PFC, as prefrontal-striatal circuits (Brand et al. 2014). Previous literature reported that both the DLPFC (Morein-Zamir and Robbins 2014) and the prefrontal-striatal circuits (Morein-Zamir and Robbins 2014) played a crucial role in cognitive control. Some fMRI studies found that the bilateral caudate dysfunction was found in impaired cognitive control task performances related to IGD, such as in the color-word Stroop task and the GO/NOGO task (Kühn and Gallinat 2014; Ko et al. 2014; Dong et al. 2013). Earlier animal, clinical, and neuroimaging research had discovered extensive evidence for a role of the caudate nucleus in cognitive control (Bari et al. 2014; Kucinski et al. 2013). Taken together, the findings in the current study may suggest the caudate nucleus played a key role in the cognitive control impairments in IGD. Consistently, our results revealed that the higher caudate volume was associated with more response errors during the incongruent condition in the color-word Stroop task in IGD (Fig. 3). The connection between striatum volume findings and the behavioral assessments could improve our understanding of the structural effects of IGD on the brain in young adults.

In the context of striatal nuclei, the increased volume of the right NAc in the IGD group was also detected (Fig. 2), which was in line with another VBM study (Kühn et al. 2011).

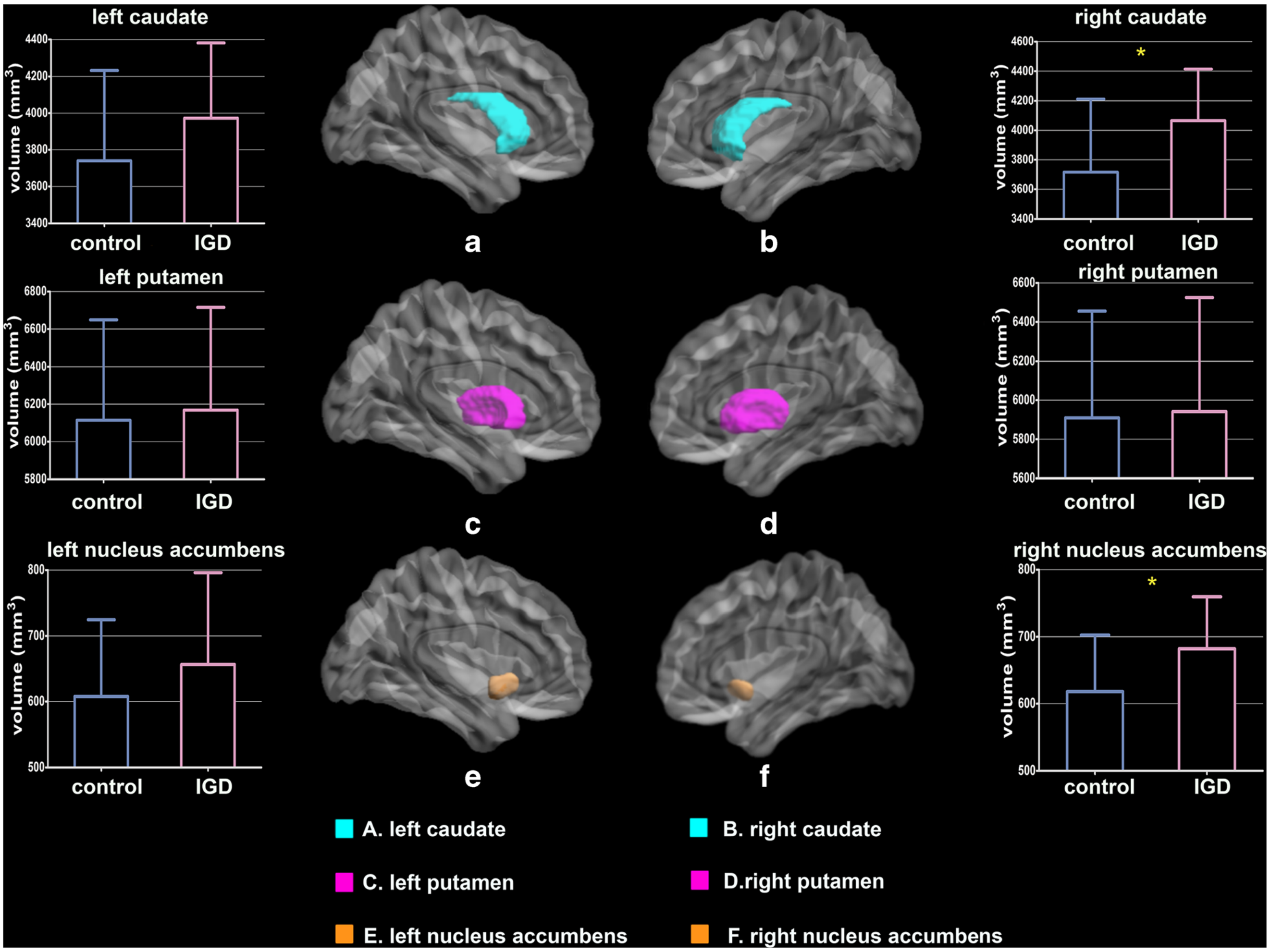


Fig. 2 Comparison between striatum (caudate, putamen, NAc) volume in the IGD individuals with the healthy controls. IGD individuals showed higher striatum volume in the right caudate and right NAc (Bonferroni corrections $p<0.005/6$). *NAc* nucleus accumbens, *IGD* Internet Gaming Addiction

Individuals with higher ventral striatum volume might experience gaming as more rewarding in the first place (Kühn et al. 2011). It may facilitate skill acquisition and lead to further reward resulting from playing (Kühn et al. 2011). A vast array of research had implicated the importance of the NAc in reward-related processing (Delgado 2007). In addition, the

Table 2 Subcortical volume of striatum comparison between internet gaming disorder (IGD) individuals and healthy controls

Region	Subcortical volume (MM^3,SD)		F value	Percent difference	p-value
	IGD (N=27)	Control (N=30)			
Left					
Caudate	3,972.6±400.9	3,780.4±472.2	3.518	5.1 %	0.066
Putamen	6,168.1±537.4	6119.6±534.2	0.131	0.8 %	0.719
NAc	656.6±136.8	614.9±115.5	1.926	6.8 %	0.171
Right					
Caudate	4,065.8±341.8	3,772.7±452.3	9.137	7.7 %	0.004*
Putamen	5,942.0±572.3	5,937.1±529.1	0.080	0.08 %	0.779
NAc	682.1±75.9	624±82.4	8.527	9.3 %	0.005*
ICV	1,342,049.1±168,054.7	1,316,482.4±230,054.9	0.194	1.9 %	0.661

Values are mean±SD unless otherwise indicated. *NAc* Nucleus Accumbens, *ICV* Intracranial Volume. *$p<0.05$

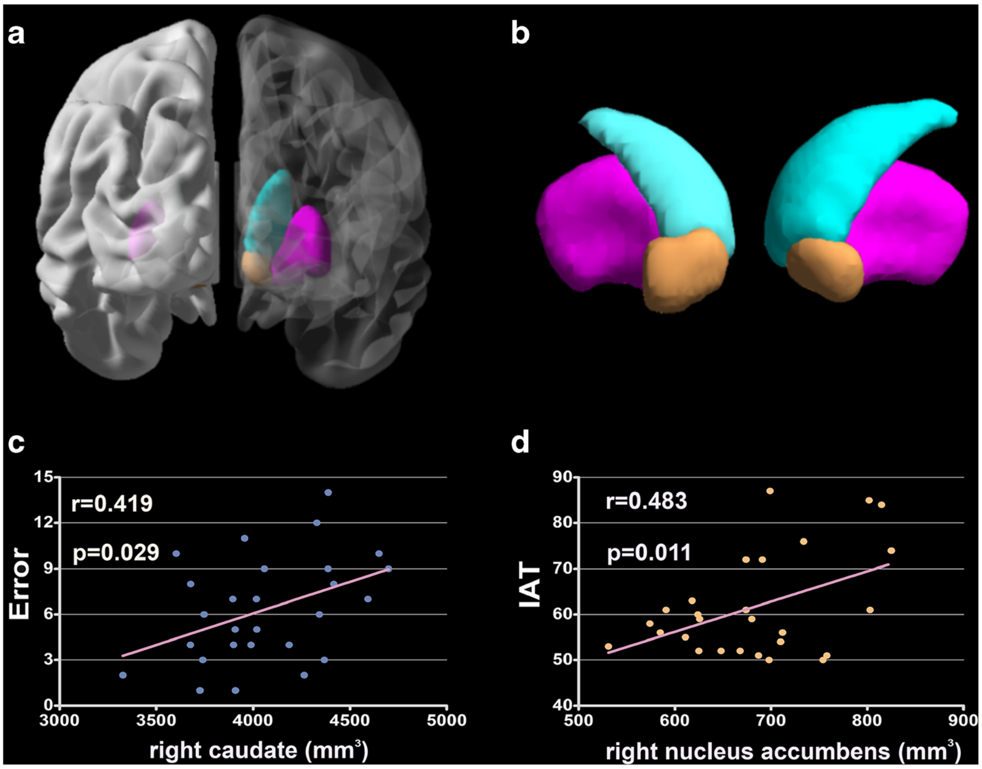


Fig. 3 Three-dimensional model of the human brain showing the position of the striatal nuclei (**a**, **b**). Caudate is indicated in *blue*, putamen in *pink* and NAc in *yellow*. Correlation analysis between striatum volume and color-word Stroop task performance, as well as IAT in IGD subjects. (**c**) The right caudate was significantly positively correlated with the errors performed during the incongruent condition in both groups. (**d**) The right NAc was significantly positively correlated with IAT results. *NAc* nucleus accumbens, *IGD* Internet Gaming Addiction, *IAT* internet addiction test

NAc is connected with the OFC and the ventromedial PFC via the limbic part of the prefrontal-striatal circuits, all of which are critically linked to reward anticipation, emotion processing, and decision making under ambiguity (Brand et al. 2014). Neurons in the nonhuman primate ventral striatum were shown to not only respond to the delivery (Apicella et al. 1991), but also to the anticipation of reward (Apicella et al. 1992). These findings showed the important roles of NAc in the pathology of IGD and that the alterations in volume may be associated with reward processing (Weinstein and Lejoyeux 2013). Rationally, we found that the right NAc was positively associated with the IAT score in IGD. Simone Kühn and colleagues had reported similar correlation using ALFF; they thought this correlation implicated that higher Internet addiction scores were associated with higher activity of the ventral striatum during resting state (Kühn and Gallinat 2014). Our findings, together with previous findings, may suggest that the NAc can be a biomarker of severity of IGD and play an important role in IGD in general.

Striatum volume abnormalities had previously been associated with Substance Use Disorder (SUD), such as nicotine (Janes et al. 2014), methamphetamine (Berman et al. 2008), and alcohol (Wrase et al. 2008; Howell et al. 2013). A recent study reported that higher caudate volume was significantly associated with cigarette craving (Janes et al. 2014). Neuroimaging studies demonstrate abnormalities in brain structure and chemistry convincingly in individuals who used methamphetamine, especially in the striatum (Berman et al. 2008). Furthermore, significantly larger volumes in the ventral striatum were detected in binge drinkers compared with controls (Howell et al. 2013). Our findings revealed striatum volume abnormalities, which provided more direct evidence for the similar pathology of IGD and SUD. Additionally, SUD studies have consistently demonstrated impaired dopamine function in the striatum (decreases in dopamine D2 receptors, reduced dopamine release) and its association with reduced baseline glucose metabolism in PFC. They suggested that the improper regulation by dopamine of reward regions in addicted subjects probably modulate prefrontal control system function, which could underlie the enhanced motivational value of drugs in their behavior and loss of control over drug intake (Volkow et al. 2011). Previous PET studies had proven that game playing can induce striatum DA release in reward circuitry. From these findings, we hypothesized that the increased caudate volume within reward circuitry probably modulated the PFC control system and influenced cognitive control. Recent studies revealed critical roles of the prefrontal-striatal circuits during cognitive control processes (Nelson et al. 2005; Ko et al. 2014). Thus, the increased striatum volume in IGD may influence the prefrontal-striatal circuits' function and impair cognitive control. However, the accurate role of increased caudate volume in the pathology of IGD should be investigated by more comprehensive experimental design in the future.

A developmental period from late adolescence to early adulthood entails substantial changes in risk-taking behavior and experimentation with behavior and substance addiction (Casey and Jones 2010). An imbalance model caused by different developmental trajectories of subcortical regions with reward and PFC regions with control give some clues for this. The reduced gray matter volume and cortical thickness of the PFC had been observed in IGD (Yuan et al. 2011a, b, 2013a, b), together with our increased striatum volume findings in the current study, we suggest that IGD may impede the brain development of youths.

The presented study has some limitations. Our study used a cross-sectional design, so it is difficult to answer the question that whether the volumetric differences in striatum between IGD subjects and controls lead to a vulnerability for preoccupation with gaming or a consequence of long-lasting activation during gaming cannot be determined; future longitudinal studies provide new insight into this issue. In addition, it is always a challenge to explain neuroimaging findings. On a cellular level, the observed higher striatum volume might be due to various processes, e.g., cell size or cell number increase, or increased extracellular volume (Koehler et al. 2013), which cannot be determined using the methods in the current study. However, previous PET studies had proven that game playing can induce striatum DA release (Koepp et al. 1998). The repeated game playing and striatum DA release possibly shaped striatum morphormetry in IGD individuals. More advanced technology and experimental design are necessary to investigate the mechanism of the striatum increased volumes in IGD.

Conclusions

This paper described a preliminary study of striatum volume in individuals with IGD. Relative to controls, the IGD group committed more incongruent condition response errors during the Stroop task, and showed increased volume of dorsal striatum and ventral striatum. In addition, caudate volume was correlated with Stroop task performance, which may be associated with cognitive control deficits in IGD. The NAc volume was associated with IAT scores in the IGD group. The connection between the structural connectivity findings and behavioral assessments could improve our understanding of the striatum as a critical role region in IGD. These findings may also provide implications for intervention methods or medical treatments for IGD.

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Competing Interests Chenxi Cai, Kai Yuan, Junsen Yin, Dan Feng, Yanzhi Bi, Yangding Li, Dahua Yu, Chenwang Jin, Wei Qin and Jie Tian declare that they have no conflict of interest.

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