ORIGINAL ARTICLE

PET imaging reveals brain functional changes in internet gaming disorder

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Abstract

Background Internet gaming disorder is an increasing problem worldwide, resulting in critical academic, social, and occupational impairment. However, the neurobiological mechanism of internet gaming disorder remains unknown. The aim of this study is to assess brain dopamine D_2 (D_2)/ Serotonin 2A (5-HT_{2A}) receptor function and glucose metabolism in the same subjects by positron emission tomography (PET) imaging approach, and investigate whether the correlation exists between D_2 receptor and glucose metabolism.

Methods Twelve drug-naive adult males who met criteria for internet gaming disorder and 14 matched controls were studied with PET and ^{11}C-N-methylspiperone (^{11}C-NMSP) to assess the availability of D_2/5-HT_{2A} receptors and with ^{18}F-fluoro-D-glucose (^{18}F-FDG) to assess regional brain glucose metabolism, a marker of brain function. ^{11}C-NMSP and ^{18}F-FDG PET imaging data were acquired in the same individuals under both resting and internet gaming task states.

Results In internet gaming disorder subjects, a significant decrease in glucose metabolism was observed in the prefrontal, temporal, and limbic systems. Dysregulation of D_2 receptors was observed in the striatum, and was correlated to years of overuse. A low level of D_2 receptors in the striatum was significantly associated with decreased glucose metabolism in the orbitofrontal cortex.

Conclusions For the first time, we report the evidence that D_2 receptor level is significantly associated with glucose metabolism in the same individuals with internet gaming disorder, which indicates that D_2/5-HT_{2A} receptor-mediated dysregulation of the orbitofrontal cortex could underlie a mechanism for loss of control and compulsive behavior in internet gaming disorder subjects.

Keywords Internet gaming disorder · Dopamine D_2 receptor · Glucose metabolism · Positron emission tomography (PET)

Introduction

Internet gaming disorder is reported as an increasing problem worldwide, shown to result in critical academic, social, and occupational impairment of individuals [1, 2]. More than one-eighth of adults in the United States show signs of being addicted to the internet [3] and a national weighted sample of 1,178 US youths found that 8.5% of gamers were classified as pathological gamers [4]. A similar or higher proportion has been reported in Europe and Asia [5], particularly, as many as 14.1% of adolescents (roughly 20 million people) in China [6]. Although cognitive and psychological dysfunctions associated with internet gaming disorder have been observed clinically, neurobiological alterations related to this disorder remain unclear [4, 7].

Recently, computer-assisted neuroimaging has helped us greatly to understand brain function and neuropsychiatric disorders [8–10]. Imaging evidence suggests that internet game overuse is a clinical disorder with brain microstructure and functional changes similar to those accompanying

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substance addiction [11]. For instance, structural magnetic resonance imaging (MRI) analysis has found regional gray matter density and volume abnormalities in internet game disorder subjects [12, 13]. Significantly lower fractional anisotropy has been identified throughout the brain in internet game disorder subjects but not in controls, which purport that internet game overuse may damage both gray matter and white matter fibers connecting emotional processing, attention, and decision making [11]. In the past decade, noninvasive functional examination by positron emission tomography (PET) has been used to monitor cerebral blood flow and glucose/oxygen metabolism, and provide further information on specific molecules (transporters and receptors) and cellular processes (neurotransmitter synthesis and release). The advantage of PET technology is that it can be used to trace the biologic changes in cognitive and behavioral brain function during real-time tasks without the interference of ambient noise generated by the MRI scanner [14]. A previous PET study using ^{11}C-raclopride, a reversible dopamine receptor ligand, found that striatal dopamine release was reduced in the internet addiction subjects under the resting state [15]. And another separate ^{18}F-fluoro-D-glucose (^{18}F-FDG) PET study observed altered glucose metabolism in the frontal lobe in internet addiction patients at resting state [5]. Those two studies, although groundbreaking, used only one PET tracer under resting state and did not compare resting and task conditions; therefore, could not provide an in-depth investigation of the connection between level of dopamine D_2 (D_2) receptor and glucose metabolism in internet disorder subjects under internet game playing condition.

In the present study, we assessed brain D_2 receptor function and glucose metabolism in the same subjects by PET imaging, and investigated whether the correlation exists between D_2 receptor function and glucose metabolism. To address these questions, PET imaging [with ^{11}C-N-methylspiperone (^{11}C-NMSP), as an irreversible D_2 receptor antagonist, and 2-deoxy-2-^{18}F-fluoro-D-glucose (^{18}F-FDG), a marker of brain function] was used to compare test and control subjects in both resting and internet gaming task states. To the best of our knowledge, this is the first PET study to examine the postsynaptic D_2 receptors and regional brain glucose metabolism in the same subjects with internet gaming disorder.

Methods and materials

Subjects

Study participants were recruited via advertisements posted on the Bulletin Board System (BBS) and campus of the university or invitees from a local cyber bar in Hangzhou, China. All participants met the following criteria: age 18 years or above; Chinese-speaking; right-handed; college-level educated; capable of internet game playing; no history of substance use (including cigarettes and alcohol). They were required to complete a medical screening and thorough psychiatric interview to confirm the diagnosis of internet gaming disorder according the MINI-International Neuropsychiatric Interview [16] and the proposed diagnostic criteria for internet addiction [17, 18]. Exclusion criteria included significant medical condition including current or past chronic heart, renal, liver, endocrine, metabolic, neurological illness or injury; current or past mood disorder, anxiety disorder, psychotic disorder, or mental retardation based on DSM-IV criteria; current or past use of psychiatric medication; current use of over-the-counter medication or nutrition supplements; current or planned pregnancy; history of allergies and intolerability of PET scan; lack of capacity to provide informed consent. To exclude the possible influence on dopamine receptors and brain activity [19], subjects with current body mass index (BMI) below 18 or above 24 were excluded.

The internet disorder subjects were addicted to World of Warcraft, the most popular multiplayer, online strategy simulation game in China. The severity of internet game use was evaluated by the Young's Internet Addiction Test [20, 21]. This scale consists of a 20-item questionnaire regarding online internet use including psychological dependence, compulsive use, and withdrawal, as well as related problems with school, sleep, family, and time management. For each item, a graded response is selected from 1 ("rarely") to 5 ("always"). The possible total score ranged from 20 to 100 with the following cut-off points defining mild, moderate and severe stages of internet addiction: 20–49 points (mild), 50–79 points (moderate), and 80–100 points (severe). This approach has exhibited good psychometric properties, with the split-half reliability 0·859 and the Cronbach's alpha 0·902 [22, 23]. Participants were then divided into two groups: internet gaming disorder (scored>50) and the control (scored≤49). Finally, we recruited 12 male internet gaming disorder subjects addicted to specific internet games and 14 male controls, since the prevalence of internet game overuse is highest among 18–23-year-old men [6, 24, 25].

Table 1 lists the demographic information of each group. The mean age of the internet gaming disorder group and the

Table 1 Demographic information of participants in each group

	Game group (n=12)	Healthy group (n=14)	P value
Age (years)	23.50 ± 2.58	22.71 ± 1.27	0.351
Education level (years)	13.08 ± 0.67	13.29 ± 0.73	0.470
Age of onset of addiction (years)	20.08 ± 1.62	NA	NA
Duration of addiction (years)	3.42 ± 2.02	NA	NA
Young score	77.58 ± 6.82	28.71 ± 3.65	0.000

healthy control group was 23.5 ± 2.6 years and 22.7 ± 1.3 years, respectively. The mean educational background was 13.1 ± 0.7 educational years for the internet gaming disorder group, and 13.3 ± 0.7 years for the healthy control group. There was no significant difference in either age ($P=0.351$) or educational level ($P=0.470$) between these two groups. The total Young's Internet Addiction Test score of the internet gaming disorder group and control group were 77.6 ± 6.8 and 28.7 ± 3.7, respectively ($P<0.001$). The internet gaming disorder subjects were asked to provide a best estimate of the duration of years they spent on the internet game rather than academic or employment-related pursuits.

After the procedures and possible consequences of the study were explained to the participants, written informed consent according to the Declaration of Helsinki were obtained. This study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. This study is registered in the Chinese Clinical Trial Registry with number ChiCTR-OCC-09000358.

Procedures

The PET study was conducted at the PET Center of the Second Affiliated Hospital of Zhejiang University School of Medicine. Subjects were scanned on a PET scanner (SHR-22000; Hamamatsu Photonics) in two-dimensional imaging mode. Each of the participants received four PET scans using both radiotracers, two with ^{11}C-NMSP and two with ^{18}F-FDG PET, under resting and internet gaming task states, and on separate days. The time interval between PET scans performed under each of the two conditions did not exceed 2 weeks. A randomized crossover study using a computer-assisted random number generator was performed to compare the resting and task states. Before starting the PET scan, all subjects were familiarized with the process and acclimated to the PET facility. They were not allowed to play any internet games 24 h prior to each scan. An intravenous catheter was placed in one side of the antecubital vein and infused with normal saline to keep it open. Subjects were placed in the scanner with the head oriented approximately parallel to the canthomeatal line to include imaging from vertex to cerebellum. A head holder was used for comfort and to minimize subject motion.

For the PET scan under the internet game task state, each participant was instructed to play World of Warcraft attentively in a separate room. This game is a massive multiplayer online role-playing game. The players control a character avatar within a game world in third- or first-person view, exploring the landscape, fighting various monsters, completing quests, and interacting with non-player characters (NPCs) or other players. They began playing 30 min before radiotracer injection and continued until immediately before the initiation of PET acquisition. The participants received remuneration and reimbursement for travel expenses upon completion of the study.

For ^{18}F-FDG PET imaging, subjects were required to fast for more than 6 h. [18]F was synthesized on an automated synthesis system (F100; Sumitomo Heavy Industries) according to classical methods [26]. The 10-min transmission and 3-min emission scans were taken 60 min after a bolus intravenous (i.v.) injection of $4-6$ mCi [^{18}F]FDG.

For ^{11}C-NMSP PET imaging, the synthesis of ^{11}C-NMSP was performed by a simple modification based on the previous study [27] using an automated synthesis system (C-11-B II ^{11}C-methyl iodide; Sumitomo Heavy Industries). ^{11}C-NMSP PET studies were taken 40 min after a bolus i.v. injection of approximately 20 mCi ^{11}C-NMSP. To create the normal ^{11}C-NMSP SPM image template, additional dynamic scans were obtained at 0–60 min after injection of ^{11}C-NMSP under the resting state in healthy controls. Subjects were kept awake with eyes opened lying in the PET scanner throughout the PET study; the room was dimly light and noise was kept at a minimum. All PET scans were conducted between 9 a.m. and 12 p.m.

Data acquisition and analysis

All images from the PET scanner system were converted into statistical parametric mapping (SPM) format using MRIcro [28]. Subsequent image preprocessing and statistical analyses were performed using SPM8 package (Wellcome Department of Cognitive Neurology, London, UK) run on MATLAB 7.1 (MathWorks Inc., Natick, MA, USA). The PET images were normalized to Montreal Neurological Institute (MNI) space as described previously [29], by using the PET template in SPM for FDG and homemade template for NMSP. Other parameters for normalization were set with the default parameters of SPM8: no weighting; 25mm cutoff; 16 non-linear iterations; one non-linear regularization; bounding box [(-78:78) (-112:76) (-50:85)]; voxel size 3 * 3 * 2; tri-linear interpolation; no wrap. An 8-mm full-width-half-maximum Gaussian kernel was used to smooth the data for statistical analysis. As in the Wang, et al. study [30], templates of regions of interest (ROIs) including caudate, putamen, amygdala, occipital cortex, anterior cingulate, hippocampus, dorsolateral prefrontal cortex and cerebellum were defined by voxels in 5–7 mm best-fitted spheres centered at the corresponding MNI coordinates, and the difference in uptake intensity were calculated by REST 1.6 software [31].

Comparisons between internet gaming disorder and control groups were performed using a two-sample t test with SPM8 for imaging data and SPSS10.0 for demographics. Comparisons between resting and task states were performed using paired t tests with SPM8. The cerebellum was used as a reference region in NMSP binding analysis as the low density of $5\text{-}HT_{2A}$ and D_2 receptors in this brain region allow for minimal levels of specific binding [32]. The correlations

between the internet gaming disorder subjects' binding ratios for selected brain regions divided by cerebellar binding ratios, and severity or duration of addiction were calculated by Pearson linear correlation analysis. The significance of group differences was estimated by the theory of random Gaussian fields, significant levels for glucose metabolism were set at $P<0.01$ (uncorrected), and significant levels for NMSP binding were set at $P<0.001$ (uncorrected). Data analysts were blinded to subject identity and diagnostic grouping.

The striatum to cerebellum (S/C) ratio on ^{11}C-NMSP PET images and the regional cortex to cerebellum (R/C) ratio on FDG PET images under internet gaming task were calculated according to the previously established method [33]. The correlation between changes of D_2 receptor availability and glucose metabolism was calculated by comparing S/C and R/C ratios using Pearson's correlation analysis.

Results

Glucose metabolic changes: between-group differences (internet gaming disorder vs. normal volunteer)

Internet gaming disorder subjects had significantly decreased glucose metabolism in the bilateral superior temporal poles and right orbitofrontal gyrus, but significantly increased in the right supplementary motor area, right middle cingulum and left superior medial frontal cortex, compared to the normal controls (Fig. 1a and Table 2).

The immediate effect of the internet game task on glucose metabolic changes was compared between internet disorder subjects and controls. It is interesting that for the internet gaming task, significantly decreased regional glucose metabolism was found in the right rectus, the right orbital part of the inferior frontal cortex, and the left orbital part of the superior frontal cortex in the internet gaming disorder group (Fig. 1b and Table 2). However, no significant increased regional glucose metabolism was observed in comparison to normal controls.

Glucose metabolic changes: within-group differences (internet gaming task vs. resting state)

In healthy control volunteers, glucose metabolism was increased significantly in the right cuneus and right calcarine, but decreased significantly in the left medial and temporal cortex, left medial frontal cortex after the internet gaming task (Fig. 1c and Table 2).

In the internet gaming disorder subjects, glucose metabolism was increased significantly in the right lingual gyrus, left cerebellum and calcarine, but decreased significantly in the left medial part of the superior frontal cortex, left rectus and left superior frontal cortex during the internet gaming task in comparison with the rest state (Fig. 1d and Table 2).

Monoamine receptor changes: between-group differences

Between-group comparison indicated that ^{11}C-NMSP binding levels were lower in the right inferior temporal gyrus in internet disorder subjects than in normal controls in the resting state (cluster level: $K_E=117$, $P_{FWE-corrected}=0.002$) (Fig. 2a).

The immediate effect of the internet game task on monoamine receptor activation was compared between internet disorder subjects and controls. After the internet gaming task, ^{11}C-NMSP binding in the putamen was significantly lower in internet gaming disorder subjects than in normal controls, especially on the right side (cluster level: $K_E=136$, $P_{FWE-corrected}=0.020$) (Fig. 2b).

Monoamine receptor changes: self-controlled comparison

When within-participant regional ^{11}C-NMSP binding was calculated in response to the internet gaming task in each group, no significant ^{11}C-NMSP binding changes were found in either the healthy or the internet gaming disorder group comparing internet gaming task and resting states.

Correlation between monoamine receptor changes and history of internet gaming disorder

^{11}C-NMSP binding in both right and left putamen negatively correlated with Young scores in internet gaming disorder subjects (Fig. 2c). We found that, under the internet gaming state, the ratio of regional ^{11}C-NMSP binding of left orbitofrontal cortex to the cerebellum correlated negatively to the years of internet overuse (Fig. 2d).

Correlation between monoamine receptor and glucose metabolism

Under the internet gaming task, the right and left striatum/cerebellum (S/C) ratios of D_2 receptors correlated positively to the regional orbitofrontal cortex to cerebellum (R/C) ratio of glucose metabolism (right: $P=0.036$; left: $P=0.016$, respectively) (Fig. 3).

Discussion

In this study, we investigated the D_2 receptor activation and glucose metabolism in internet gaming disorder subjects in comparison to normal controls. Our results demonstrated that internet gaming disorder altered brain activity. Decreased glucose metabolism in the prefrontal, temporal, limbic system and dysregulation of dopamine D_2 receptors in striatum were correlated to years of overuse. To the best of our knowledge, this is the first PET study in the level of D_2 receptors associated with glucose metabolism in internet gaming disorder subjects.
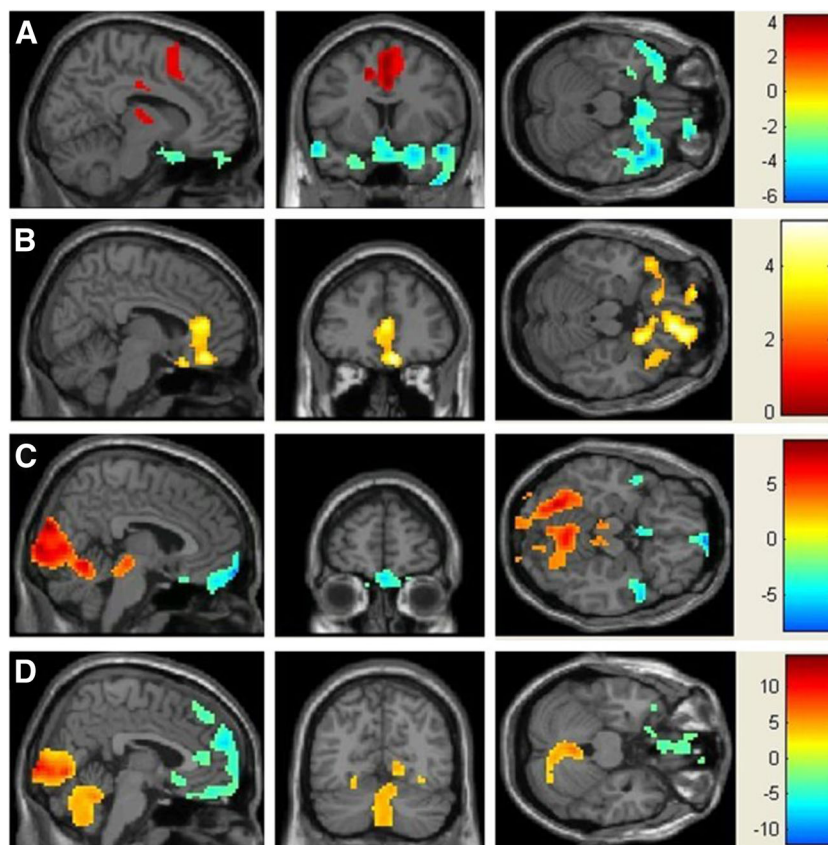
Fig. 1 a Whole brain SPM showing the results of ^{18}F-FDG PET study in internet gaming disorder subjects. In the resting state, there are areas of increased glucose metabolism in the right supplementary motor area, middle cingulum and thalamus (red color); decreased glucose metabolism in the right orbitofrontal gyrus and bilateral temporal poles, especially on the right (blue color) ($P<0.01$ uncorrected, $k=100$); and (b) in the gaming task state, areas of glucose metabolism decreased significantly in the insula, orbitofrontal gyrus, temporal pole bilaterally and the rectus gyrus, putamen, supramarginal gyrus, and anterior cingulum on the right side (yellow color) ($P<0.01$ uncorrected, $k=100$). c–d Whole brain SPM demonstrating the comparison results of ^{18}F-FDG PET study after game task compared with resting state. In the normal volunteers (c), glucose metabolism was significantly increased in the midbrain, right thalamus and bilateral occipital lobes especially in the right side (red color), while decreased in the right temporal pole, middle frontal gyrus, rectal gyrus and left side of medial temporal gyrus, superior temporal gyrus and medial frontal gyrus (blue color) ($P<0.01$ uncorrected, $k=100$). However, in the internet gaming disorder subjects (d), glucose metabolism was increased in the occipital lobe bilaterally (red color) but decreased in the left superior frontal gyrus and rectal gyrus (blue color) ($P<0.01$ uncorrected, $k=100$)

Interestingly, after the internet gaming task, both overuse and control groups showed increased glucose metabolism in the occipital region, but decreased glucose metabolism in the prefrontal and temporal regions. This finding suggests that these regions are predominantly involved in internet gaming task processing. Considering the role of the occipital region as the visual center, closely associated with vision stimulation, increased glucose metabolism after the gaming task indicated that internet games may modify visual selective attention [34] and cortical networks for complex visual motor transformations [35].

Prefrontal glucose metabolism in the internet gaming disorder subjects was lower than that of normal controls, supporting the hypothesis that internet disorder subjects have prefrontal dysfunction similar to drug addiction [36]. On the other hand, compared with the normal controls, internet gaming disorder subjects had fewer regions of increased glucose

metabolism. This suggested that internet gaming disorder subjects concentrated more attentively during the internet gaming task than the normal controls.

By the further between-group comparison of ^{11}C-NMSP binding in the resting and internet gaming task states, we found that after the internet gaming task, ^{11}C-NMSP binding in the putamen, especially on the right side, was significantly lower in internet gaming disorder subjects than in normal controls. ^{11}C-NMSP bindings in both the right and left putamen negatively correlated with Young scores in internet gaming disorder subjects in this study. The putamen is located in the rostral division as part of the striatum, which is known to regulate movement and influence various types of learning. The striatum dopamine pathway attracts the most attention for addiction studies as it has been strongly implicated in addiction and reward processing [37]. A previous PET study using ^{11}C-raclopride finds that striatal dopamine release is reduced

Table 2 Comparison of FDG uptakes in internet gaming disorder and control groups

Region	Cluster level				Peak level					Coordinates		
	K_E	P (FWE-corrected)	P (FDR-corrected)	P (uncorrected)	P (FWE-corrected)	P (FDR-corrected)	P (uncorrected)	T	Z	x	y	z
Internet gaming disorder vs. control under rest state												
Decreased												
Bilateral superior temporal pole	1549	0.000	0.000	0.000	0.045	0.096	0.000	6.200	4.667	48	5	−20
					0.077	0.096		5.905	4.523	39	17	−26
					0.189	0.167		5.390	4.258	−51	17	−17
Right orbital part of the superior frontal cortex	114	0.859	0.898	0.080	0.708	0.295		4.433	3.707	24	50	−23
					0.999	0.664		3.455	3.055	18	59	−14
					1.000	0.905		3.035	2.744	12	53	−32
Increased												
Right supplementary motor area/Right middle cingulum/Left superior medial frontal cortex	611	0.011	0.016	0.000	0.737	0.632	0.000	4.388	3.679	3	11	55
					0.794	0.632		4.295	3.621	3	11	40
					0.903	0.632		4.075	3.480	0	38	46
Pulvinar/Right sub-lobar/Right thalamus	145	0.717	0.898	0.051	0.992	0.632	0.001	3.645	3.189	21	−31	4
					0.993	0.632		3.642	3.187	27	−22	16
					1.000	0.788		3.113	2.803	21	−19	−2
Internet gaming disorder vs. control under internet gaming task												
Decreased												
Right rectus/Right orbital part of the medial frontal cortex/Right anterior cingulum	403	0.042	0.074	0.002	0.287	0.783	0.000	5.207	4.159	9	38	−20
					0.476	0.783		4.859	3.962	15	50	−20
					0.904	0.783		4.149	3.528	3	38	10
Right orbital part of the inferior frontal cortex/Right rectus/	174	0.501	0.298	0.025	0.748	0.783	0.000	4.446	3.715	15	14	−23
					0.957	0.795		3.983	3.419	3	20	−23
Left orbital part of the superior frontal cortex/Left medial part of the superior frontal cortex	222	0.304	0.207	0.013	0.789	0.783	0.000	4.378	3.673	−21	56	−14
					0.895	0.783		4.171	3.542	−6	65	13
Right putamen/Right insula	123	0.775	0.395	0.053	0.980	0.891	0.000	3.859	3.336	36	−16	−5
					0.999	0.978		3.534	3.111	33	−10	4
					1.000	0.979		3.331	2.965	36	11	1
Left insula/Left superior temporal pole	268	0.183	0.173	0.007	0.987	0.894	0.001	3.791	3.290	−36	11	−8
					0.989	0.894		3.767	3.273	−36	−4	10
					0.999	0.978		3.551	3.123	−45	17	−23
	121	0.785	0.395	0.055	0.995	0.921	0.001	3.678	3.212	54	−31	13

Table 2 (continued)

Region	Cluster level				Peak level					Coordinates		
	K_E	P (FWE-corrected)	P (FDR-corrected)	P (uncorrected)	P (FWE-corrected)	P (FDR-corrected)	T	Z	P (uncorrected)	x	y	z
Right superior temporal cortex/Right supramarginal gyrus					0.999	0.978	3.527	3.106	0.001	48	−40	25
Right superior temporal pole/Right orbital part of the inferior frontal cortex/Right inferior temporal cortex	118	0.801	0.395	0.058	1.000	0.979	3.359	2.986	0.001	42	14	−26
					1.000	0.979	3.047	2.753	0.003	33	26	−20
					1.000	0.979	3.032	2.741	0.003	48	8	−50
Task vs. rest state in control group												
Decreased												
Right cerebrum/Right orbital part of medial frontal cortex/Right rectus	308	0.138	0.062	0.006	0.145	0.257	8.142	4.544	0.000	6	65	−17
					0.461	0.257	6.569	4.106	0.000	9	68	−8
					0.705	0.406	5.852	3.866	0.000	3	53	−23
Right medial temporal pole	183	0.493	0.188	0.026	0.431	0.257	6.669	4.137	0.000	54	8	−20
					1.000	0.958	3.550	2.837	0.002	42	20	−35
Left medial and temporal cortex/Left medial frontal cortex	392	0.058	0.050	0.002	0.982	0.826	4.663	3.393	0.000	−48	5	−26
					0.993	0.826	4.474	3.308	0.000	−48	2	−14
					0.995	0.826	4.413	3.279	0.001	−3	8	−17
Increased												
Right cuneus/Right calcarine	2491	0.000	0.000	0.000	0.073	0.101	8.969	4.737	0.000	12	−103	7
					0.084	0.101	8.838	4.708	0.000	6	−91	22
					0.098	0.101	8.665	4.668	0.000	12	−76	7
Right midbrain/Right thalamus/Left midbrain	182	0.498	0.507	0.026	0.976	0.495	4.734	3.425	0.000	9	−25	−11
					1.000	0.689	3.914	3.034	0.001	24	−28	1
					1.000	0.709	3.757	2.951	0.002	−9	−28	−17
Task vs. rest state in internet in internet gaming group												
Decreased												
Left medial part of the superior frontal cortex/Left rectus/left superior frontal cortex	2841	0.000	0.000	0.000	0.030	0.252	11.780	4.912	0.000	0	59	19
					0.271	0.371	9.066	4.464	0.000	−3	26	−23
					0.437	0.371	8.550	4.361	0.000	−24	65	4
Increased												
Right Lingual gyrus/Left cerebelum crus1/Left calcarine	3514	0.000	0.000	0.000	0.006	0.049	14.365	5.236	0.000	12	−88	−8
					0.059	0.091	10.901	4.782	0.000	−9	−88	−17
					0.080	0.091	10.503	4.719	0.000	3	−100	1

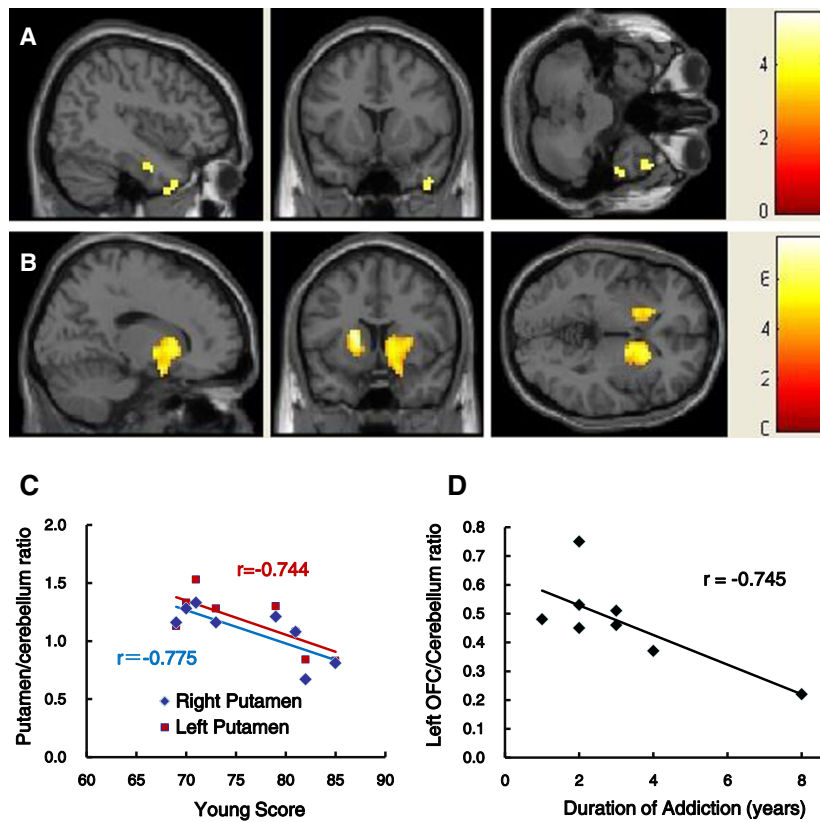*KE* cluster size; *FWE* Family-Wise Error; *FDR* False discovery rate corrected

Fig. 2 **a** Whole brain SPM results of ^{11}C-NMSP PET study in the resting state. A lower level of ^{11}C-NMSP binding was found in the right inferior temporal gyrus in the resting state in the internet gaming disorder subjects than that in normal controls (yellow color) ($P<0.001$ uncorrected, $k=100$), while in the game task state (**b**), ^{11}C-NMSP binding in the putamen was significantly lower in the internet overuse group than the normal control group, especially in the right side (yellow color) ($P<0.001$ uncorrected, $k=$

100). **c** Correlation of the putamen to the cerebellum ratio of ^{11}C-NMSP binding and Young score. Both right ($P=0.024$, $r=-0.775$) and left P/T ratio ($P=0.034$, $r=-0.744$) correlated negatively with the Young score in the internet disorder subjects. **d** Correlation of the left orbitofrontal cortex (OFC) to the cerebellum ratio of ^{11}C-NMSP binding and the years of internet overuse history. The L/C ratio of ^{11}C-NMSP correlated negatively with the duration of internet overuse ($P=0.034$, $r=-0.745$)

in the internet addiction subjects [15]. However, ^{11}C-raclopride competes with the endogenous dopamine for binding to the receptor; higher or lower synaptic concentration of dopamine results in less or more radioligand binding, respectively [29]. Thus, ^{11}C-raclopride binding is often used to

Fig. 3 Correlation between D$_2$ receptors in striatum and glucose metabolism in regional orbitofrontal cortex under internet gaming task. Significant positive correlation was found between either right or left striatum/cerebellum (S/C) ratio and orbitofrontal cortex/cerebellum (R/C) ratio. (Right S/C ratio vs. R/C ratio: $R=0.664$, $P=0.036$; Left S/C ratio vs. R/C ratio: $R=0.731$, $P=0.016$, respectively)

reflect the presynaptic dopamine release level, which is prone to be affected by human behavior [38, 39]. In contrast, the radiotracer ^{11}C-NMSP, which we used in this study, binds the D$_2$ receptors substantially irreversibly in the time frame of a PET scan and represents the D$_2$ receptors more accurately [29, 40]. Therefore, our results imply that internet gaming disorder subjects could acquire dopaminergic pathway dysfunction in the striatal region as a result of their chronic gaming behavior.
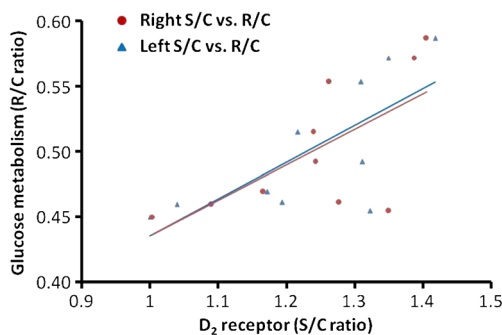
We also found that the regional ^{11}C-NMSP binding ratio of the left orbitofrontal cortex correlated negatively to the years of internet gaming disorder, which indicates that dopaminergic dysfunction is more significant in chronic internet gaming disorder. Although we found that there is no relevant with exclusion of that 8 years addiction subject, we consider that this is very important for us to understand the long-term internet gaming effect. Furthermore, D$_2$ receptor availability in the striatum during the internet gaming task correlated positively to glucose metabolism in the orbitofrontal cortex. The orbitofrontal cortex is involved in decision-making, especially in signaling expected rewards or punishments associated with an action given the particular details of a situation

[41]. Significantly reduced glucose metabolism in the orbitofrontal cortex is found in individuals with borderline personality disorder who have high levels of impulsivity [42]. A significant connection was found between dopamine D_2 receptors in the putamen and glucose metabolism in the orbitofrontal cortex, a brain region involved with compulsive behaviors, suggested that dysregulation of the orbitofrontal cortex may be one of the mechanisms by which disruption of dopamine activity in methamphetamine abusers could lead to compulsive drug-taking behavior [43, 44]. In our study, the correlation between ^{11}C-NMSP binding and ^{18}F-FDG activity suggested that dysregulation of striatal D_2 receptors maybe via striatal prefrontal pathways. This is consistent with the previous study using ^{11}C-raclopride to assess D_2 receptors and ^{18}F-FDG to assess regional brain glucose metabolism in obese subjects [45]. Some other studies using fMRI also found that the prefrontal cortex strongly correlated with the striatum in self-control and the regulation of different kinds of appetitive desires [46, 47].

Additionally, we found that low levels of dopamine D_2 receptors in the striatum significantly correlated with decreased serotonin 5-HT_{2A} receptors in both the right and left temporal cortices in internet gaming disorder subjects ($R=0.904$, $P=0.002$ and $R=0.950$, $P=0.001$, respectively). These data suggest the likelihood of an interaction between bindings at dopamine D_2 and serotonin 5-HT_{2A} receptors. Thus, internet gaming disorder, resulting from a complex interaction of multiple receptor and neurotransmitter systems, does not lend itself ideally to an analysis of isolated receptor systems.

This study presented several important findings, deepening our understanding of the pathological mechanism of internet overuse. However, there were several limitations. Firstly, the monoamine binding potential was estimated using region-to-cerebellum ratios. Since test and control subjects declined arterial blood withdrawal, we could not obtain data for arterial input function. Therefore, we could not exclude the possibility that reduced monoamine binding potential was a result of change in K_D (radioligand equilibrium dissociation constant) and not a result of change in Bmax (receptor density). BP_{ND} (the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue) for the simplified reference tissue model (SRTM) is the only possible binding outcome measure, as total and free arterial plasma concentrations are necessary for calculation of BP_P (the ratio at equilibrium of the concentration of specifically bound radioligand in tissue to the concentration of free radioligand in tissue) and BP_F (the ratio at equilibrium of specifically bound radioligand to that of total parent radioligand in plasma) [45]. Secondly, there was no control group for those with a history of prolonged internet use for purposes other than gaming, such as work or study. It is unclear whether prolonged internet use can impair brain function. Thirdly, potential effects of the motor task should also be considered between the internet disorder and control groups. For instance, after long-term internet game playing, internet disorder subjects' arm, hand or body motor movements may have potential effect on their ^{18}F-FDG-brain scan. In addition, although the measures of pleasure or reward have been done at the subjects' screening stage, in future studies, these measures should be acquired immediately after internet gaming tasks to compare the level of pleasure or reward. Fourthly, some clusters appear to be outside the orbitofrontal cortex, since the mask was defined manually based on the standard SPM template. Theoretically, only cortical regions should be included in the mask. While for the SPM result of PET images, clusters outside the cortex were inevitable sometimes [48]. Lastly, since diagnostic criteria for internet game disorder and exclusion criteria for the participants are still under investigation, the criteria used in this study may have some limitations. In addition, the sample size was relatively small due to the difficulties of enrolling research subjects for sequential PET scans. Therefore, the cross-sectional comparison cannot determine if changes in brain function were due to chronic game play or if those brain dysfunctions caused internet overuse. Further longitudinal study should be performed to confirm whether the findings of our study represent either the cause or the effect of internet overuse.

In summary, for the first time, we found a significant association between D_2 receptor level and glucose metabolism in the same subjects with internet gaming disorder, which indicates that D_2 receptor-mediated dysregulation of the orbitofrontal cortex could underlie a mechanism for loss of control and compulsive behavior in internet gaming disorder subjects.

Conflict of interest The authors declare that they have no conflict of interest.

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