

# Lower synaptic density associated with gaming disorder: an $^{18}\text{F}$ -SynVesT-1 PET imaging study

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## ABSTRACT

**Background** Internet gaming disorder (IGD) is an ideal model to study the mechanisms underlying synaptic deficits in addiction as it eliminates the confounding effects of substance use. Synaptic loss and deficits are hypothesised to underlie the enduring maladaptive behaviours and impaired cognitive function that contribute to IGD.

**Aims** This study aimed to determine whether subjects with IGD have lower synaptic density than control subjects and the relationship between synaptic density and IGD severity.

**Methods** Eighteen unmedicated subjects diagnosed with current IGD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria and 16 demographically matched healthy controls (HCs) participated in the study and underwent  $^{18}\text{F}$ -labelled difluoro-analogue of UCB-J ( $^{18}\text{F}$ -SynVesT-1) positron emission tomography scans to assess the density of synaptic vesicle glycoprotein 2A (SV2A). The Internet Gaming Disorder Scale-Short Form (IGDS9-SF), Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Rating Scale (HAMA), Barratt Impulsiveness Scale Version 11 (BIS-11), Stroop Colour-Word Test (SCWT), stop-signal paradigms and N-back tasks were administered to all subjects.

**Results** Patients with IGD had significantly higher scores on the IGDS9-SF, HAM-D, HAMA and BIS-11 than HCs. HCs performed better on the two-back and SCWT tests as well as in terms of stop-signal reaction times (SSRTs) in the stop-signal paradigms than patients with IGD. Lower uptake was found in the bilateral putamen, right pregenual anterior cingulate cortex and Rolandic operculum of patients with IGD compared with HCs. Furthermore, in the IGD group, IGDS9-SF scores and daily gaming hours were negatively correlated with the standardised uptake value ratios of  $^{18}\text{F}$ -SynVesT-1 in the bilateral putamen. Longer SSRTs were significantly associated with lower SV2A density in the right pregenual anterior cingulate cortex and right Rolandic operculum.

**Conclusions** The *in vivo* results in this study suggest that lower synaptic density contributes to the severity and impairments in inhibitory control of IGD. These findings may provide further incentive to evaluate interventions that restore synaptic transmission and plasticity to treat IGD.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Synaptic loss and deficits have recently been found in various mental disorders.
- ⇒  $^{18}\text{F}$ -labelled difluoro-analogue of UCB-J ( $^{18}\text{F}$ -SynVesT-1) is a new synaptic vesicle glycoprotein 2A positron emission tomography (PET) radiotracer and a potentially sensitive biomarker indicating synaptic density *in vivo*.

## WHAT THIS STUDY ADDS

- ⇒ Using  $^{18}\text{F}$ -SynVesT-1 PET imaging, synaptic deficits in the bilateral putamen, right pregenual anterior cingulate cortex and right Rolandic operculum were closely linked to the severity of internet gaming disorder.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Our novel *in vivo* findings provide new insights into the neuropathological mechanisms of internet gaming disorder and may suggest possibilities for developing new treatments targeting synaptic function.

## INTRODUCTION

Internet gaming disorder (IGD) is an emerging and increasing problem worldwide that leads to clinically significant impairment or distress.<sup>1,2</sup> As a specific behavioural addictive disorder, IGD involves excessive or poorly controlled preoccupations, impulses or behaviours regarding persistent and recurrent online gameplay. The prevalence of IGD ranges from 1.2% to 8.5% in the USA and Europe<sup>3–5</sup> and from 6% to 12% in Asian countries,<sup>6</sup> with a particularly higher prevalence among men and young people. As a behavioural addiction unique to humans that has received recognition in the past decade, IGD has been observed in the clinic. However, understanding of the neurobiological mechanisms related to this disorder remains in its early stages. With the current lack of evidence-based treatments for IGD, neurobiological studies may be needed to inform the development of novel treatments.



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Synaptic deficits are evident in different behavioural addictions. For example, enduring impairments in transmission and synaptic plasticity were shown at glutamatergic synapses in the nucleus accumbens subcompartment in rats with diet-induced obesity and food addiction.<sup>7,8</sup> The effect of synaptic  $\gamma$ -aminobutyric acid release induced by dopamine rises was reduced or even reversed in problem gamblers.<sup>9</sup> Furthermore, dopamine transporter binding ratios in the bilateral caudate and putamen were inversely correlated with days spent gambling and reward-based decision-making in subjects with gambling disorders.<sup>10</sup> In terms of IGD, dysregulation of postsynaptic dopamine D2 receptors in the orbitofrontal cortex and striatum was found.<sup>11</sup> These findings provide evidence of aberrant synaptic connectivity and plasticity in individuals engaging in excessive and problematic non-substance use behaviours. However, abnormalities in synaptic density have not yet been elucidated in any behavioural addiction.

Synaptic vesicle glycoprotein 2A (SV2A) is an integral protein ubiquitously present in the presynaptic terminals of all synapses across the brain<sup>12</sup> and is a suitable marker of synaptic density. <sup>11</sup>C-UCB-J, a radioligand that has high specificity for SV2A,<sup>13</sup> has recently been shown to be sensitive to region-specific decreases in synaptic density in cocaine and cannabis use disorders,<sup>14,15</sup> depression, and post-traumatic stress disorder.<sup>16</sup> A new SV2A positron emission tomography (PET) radiotracer, the <sup>18</sup>F-labelled difluoro-analogue of UCB-J (<sup>18</sup>F-SynVesT-1), showed similar useful imaging properties, a longer radioactive half-life and a superior signal to noise ratio compared with <sup>11</sup>C-UCB-J in healthy humans.<sup>17</sup> Combined with PET data, these techniques allow the change in synaptic density in the brain to be evaluated in real time, dynamically and *in vivo*. We hypothesised that the region-specific abnormal synaptic density might also occur in IGD.

The current study aimed to investigate the behavioural performance of individuals with IGD and the neural correlates of cognitive function that underlie this disorder.

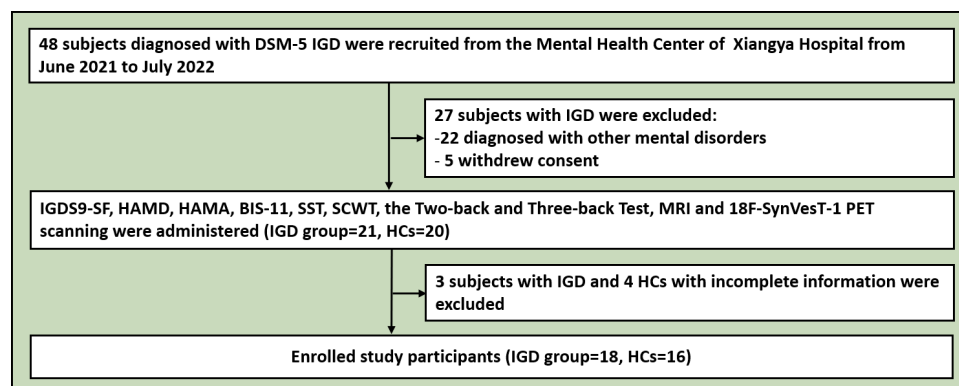
We assessed the differences in synaptic density by using <sup>18</sup>F-SynVesT-1 and PET imaging approaches in subjects with IGD and healthy controls (HCs). The Stroop Colour-Word Test (SCWT),<sup>18</sup> stop-signal paradigms<sup>19</sup> and N-back tasks<sup>20</sup> are widely used to examine cognitive function in IGD and other addictions, and we also examined potential correlations between synaptic density and severity of IGD and specific cognitive impairment. We hypothesised that patients with IGD would exhibit lower synaptic density in executive function or reward-seeking brain regions compared with HCs and that there is a relationship between synaptic density and the severity of gaming addiction.

## METHODS

### Participants

The study included unmedicated clinical subjects diagnosed with current IGD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)<sup>21</sup> and 16 age-matched and sex-matched HC subjects who participated in the study. Participants were recruited by word of mouth, posters and flyers. All study participants provided written informed consent before inclusion in the study. They were screened with the Structured Clinical Interview for DSM-5, Clinician Version, within 3 days of the PET scan to determine the presence of major psychiatric disorders. All subjects were medication-naïve during the assessment. The flow chart of this study is shown in figure 1.

The inclusion criteria for participants with IGD were as follows: (1) primary use of the internet to play games and regular internet game use over the past 12 months (daily internet game use >7hours/day or >30hours/week), (2) an Internet Gaming Disorder Scale-Short Form (IGDS9-SF) score  $\geq 32$ <sup>22</sup> and (3) an IGD diagnosis based on the DSM-5 criteria. The inclusion criteria for HCs were as follows: (1) regular use of a smartphone, laptop or other electronic device but not diagnosed with



**Figure 1** Flowchart of study enrolment. <sup>18</sup>F-SynVesT-1, <sup>18</sup>F-labelled difluoro-analogue of UCB-J; BIS-11, Barratt Impulsiveness Scale Version 11; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression; HC, healthy control; IGD, internet gaming disorder; IGDS9-SF, Internet Gaming Disorder Scale-Short Form; MRI, magnetic resonance imaging; PET, positron emission tomography; SCWT, Stroop Colour-Word Test; SST, stop-signal task.

IGD based on the DSM-5 criteria and (2) IGDS9-SF score <21. The exclusion criteria for IGD and HCs included (1) a lifetime or current diagnosis of a major psychiatric disorder (eg, met the DSM-5 criteria for gambling disorders, nicotine or alcohol use disorders, neurodevelopmental disorders, schizophrenia spectrum disorders, bipolar disorders, or related disorders), (2) clinically significant medical conditions or laboratory abnormalities, (3) other illicit substance use or nicotine use in the past 12 months, (4) pregnancy or lactation before any scan, and (5) contraindications to magnetic resonance imaging (MRI).

The custom-designed questionnaire included age, sex, education level and game usage and was used to collect sociodemographic data. The participants were evaluated to determine internet use patterns and were screened for IGD using the Chinese version of the IGDS9-SF.<sup>22 23</sup> The IGDS9-SF has been validated for use among Chinese participants and has high internal consistency (Cronbach's  $\alpha$  was 0.91).<sup>24</sup> We used the Chinese version of the Hamilton Rating Scale for Depression (HAM-D) (reliability coefficient of 0.714 and validity coefficient of 0.92),<sup>25 26</sup> the Chinese version of the Hamilton Anxiety Rating Scale (HAM-A) (reliability coefficient of 0.88)<sup>27 28</sup> and the Barratt Impulsiveness Scale Version 11 (BIS-11)<sup>29</sup> to test impulsivity. The BIS-11 has been translated into Chinese with good internal consistency and test-retest reliability.<sup>30</sup> The BIS-11 consists of three subscales: cognitive impulsivity, motor impulsivity and non-planning impulsivity.

### Cognitive function measures

#### Stop-signal task

Before entering the PET scanner, participants performed a manual version of the stop-signal task (SST)<sup>31</sup> (online supplemental figure S1). During the SST, subjects were instructed to press the 'F' button in response to a circle and the 'J' button in response to a fork with the index finger of their left or right hand as rapidly and accurately as possible. In a minority of trials, a 'Stop' signal (in which the green box turned red unpredictably) was presented at varying delays after the 'Go' stimulus signals, indicating that the subject should withhold that motor response. A fixation cross was presented for a period of 1–5 s and the 'Go' reaction time (Go RT) was shorter than 1 s. For each run, the 'Stop' signal delay (SSD) time was initially set at 250 ms and then either increased or decreased by 50 ms after a successful or failed 'Stop' response, respectively. The staircase algorithm adjusted the temporal delay between 'Go' and 'Stop' stimuli in 50 ms increments to achieve a 50% target 'Stop' inhibition rate in stop trials. The stop-signal reaction time (SSRT) was calculated by subtracting the critical SSD from the mean RT in all correct-response go trials. The Go RT and SSRT were the primary performance measures, representing response initiation and inhibitory control, respectively. A shorter SSRT reflects a faster 'stop' process and represents better inhibitory control ability. Subjects with impaired motor

inhibition are less able to inhibit their motor response and thus have longer SSRTs.<sup>32</sup>

#### Stroop Colour-Word Test

We administered the SCWT,<sup>33</sup> consisting of three parts: word reading (WR), colour naming (CN) and colour word (CW). In each part, subjects were requested to read WR and name the colour of the ink of each item (a series of Xs in CN and the name of a colour different from that of the ink in CW) in a list of 100 elements. In each part, we recorded the number of elements correctly completed in 45 s and the interference score (IS). The IS, considered a measure of inhibitory control, was calculated from the other three scores [IS=CW-(WR×CN/WR+CN)].

#### Two-back and three-back tests

Subjects had to indicate whether the graphic presented in the centre of a computer screen was the same as the graphic presented two or three positions before (two-back or three-back).<sup>34</sup> Participants responded by pressing the 'F' button of a keyboard with their left index finger when the graphic was the same (target) or the 'J' button with their right index finger when the graphic was different (non-target). In each test, a total of 63 trials were performed, but the first three non-target trials were not included in the analyses. The number of target trials was 20 (ie, ~32% of the total set). The stimulus duration was 500 ms, with a 2500 ms interstimulus interval. Accuracies on the whole test were recorded.

#### Magnetic resonance imaging

High-resolution MRIs were collected on a General Electric (GE) Healthcare 3.0 T MRI scanner. To register with PET images and check for structural abnormalities, a sagittal three-dimensional (3D) T1 bravo sequence was employed (echo time (TE)=3.2 ms, repetition time (TR)=8.5 ms, matrix=256×256 mm<sup>2</sup>, phase field of view (FOV)=1, voxel size 1.0×1.0×1.0 mm<sup>3</sup>, slice thickness=1.0 mm). All MRI data were quality-checked by a skilled neuroradiologist.

#### Positron emission tomography

<sup>18</sup>F-SynVesT-1 was synthesised using a previously described method with radiochemical purity >99%.<sup>17 35</sup> None of the participants took drugs targeted at SV2A for at least 1 day before the PET scans. The PET/computed tomography (CT) was carried out with a GE PET/CT scanner (Discovery 690 Elite; GE Healthcare, Waukesha, Wisconsin). <sup>18</sup>F-SynVesT-1 PET/CT imaging was performed 60 min after the radiotracer was intravenously injected at a dose of 3.7–4.44 MBq (0.1–0.12 mCi) per kilogram of body weight. Static PET images were acquired in three dimensions for 30 min. First, a low-dose CT scan (120 kV; automatic mAs; pitch, 1:1; slice thickness, 3.75 mm; matrix, 512×512) was performed for attenuation correction. Next, all PET images were reconstructed as a 256×256 transaxial matrix (35 cm field of view) using the 3D VUE Point (GE Healthcare) ordered-subset expectation-maximisation algorithm with six iterations and six subsets, which produced 47 transaxial images at 3.25 mm intervals. Participants were also monitored on-site for other

signs of adverse effects for 90 min after injection of  $^{18}\text{F}$ -SynVesT-1 and were asked to report any ensuing adverse effects.

### MRI and PET analysis

The structural MRIs were standardised with automatic anatomical marker templates in the Montréal Neurological Institute space using statistical parametric mapping software (SPM V.12; Wellcome Department of Imaging Neuroscience, London, UK). Then the transformation parameters determined by MRI spatial normalisation were applied to the coregistered  $^{18}\text{F}$ -SynVesT-1 PET image for PET spatial normalisation. The standardised uptake values (SUVs) were calculated for all regions of interest. The SUV ratio (SUVr) with the centrum semiovale (CS) as a reference region was calculated for interpatient comparisons using SPM, as the CS has been reported to be free of SV2A and thus can be used as a reference region.<sup>36</sup> The height threshold for synaptic

density changes was set at  $p < 0.001$  with a cluster size of at least 50. After data preprocessing with SPM, the xjView MATLAB toolbox was used to visualise and anatomically label significant clusters.

### Demographic and clinical data analysis

Differences between the IGD and HC groups in demographic, clinical and radiotracer characteristics were assessed using independent-sample t-tests for continuous measures and  $\chi^2$  tests for categorical variables. The Mann-Whitney U test was applied to compare non-normally distributed variables. The Kolmogorov-Smirnov one-sample test was used to determine whether variables were normally distributed. The Bonferroni correction was adopted to adjust for multiple comparisons. Furthermore, group differences in the SUVr of  $^{18}\text{F}$ -SynVesT-1 between patients with IGD and the HCs were analysed

**Table 1** Demographic and clinical characteristics

Variable	IGD Mean (SD)	HC Mean (SD)	t	P value
Age (years)	20.53 (3.69)	22.44 (5.44)	-1.305	0.201
Male:female	14:4	10:6		0.456
Education (years)	13.12 (1.87)	13.38 (1.94)	-0.382	0.705
Daily gaming (hours)	11.47 (2.83)	N/A	N/A	N/A
Duration of IGD (years)	3.61 (1.64)	N/A	N/A	N/A
Frequency of IG usage after midnight per week	4.29 (2.31)	N/A	N/A	N/A
Frequency of IG usage overnight per week	2.81 (2.60)	N/A	N/A	N/A
IGDS9-SF	35.33 (2.00)	13.00 (5.56)	15.753	<0.001
HAMA	11.00 (6.67)	3.1 (3.16)	3.999	<0.001
HAMD	18.89 (10.08)	3.46 (3.52)	5.268	<0.001
BIS-11 cognitive	44.06 (15.10)	33.27 (11.96)	-2.634	0.035
BIS-11 motor	48.89 (15.56)	27.50 (14.03)	-3.472	<0.001
BIS-11 non-planning	55.58 (20.58)	32.11 (15.37)	-2.580	0.002
BIS-11 total	49.54 (12.66)	30.22 (10.81)	-1.008	<0.001
Two-back test accuracy	0.73 (0.19)	0.87 (0.09)	-2.419	0.022
Three-back test accuracy	0.62 (0.20)	0.74 (0.13)	-1.842	0.076
SCWT				
WR	89.06 (11.97)	98.08 (3.33)	-3.039	0.006
CN	67.39 (17.45)	86.46 (10.91)	-3.735	0.001
CW	39.50 (12.20)	49.69 (8.60)	-2.728	0.011
IS	1.43 (6.48)	3.94 (7.31)	-0.988	0.333
SST				
Go RT, ms	682.06 (106.57)	619.79 (120.25)	1.739	0.091
SSD, ms	382.28 (84.53)	337.95 (100.13)	1.235	0.226
SSRT, ms	300.36 (35.94)	274.34 (26.90)	2.434	0.021

BIS-11, Barratt Impulsiveness Scale Version 11; CN, colour naming; CW, colour word; Go RT, reaction time in correct go trials; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression; HC, healthy control; IG, internet gaming; IGD, internet gaming disorder; IGDS9-SF, Internet Gaming Disorder Scale-Short Form; IS, interference score; N/A, not applicable; SCWT, Stroop Colour-Word Test; SD, standard deviation; SSD, stop-signal delay; SSRT, stop-signal reaction time; SST, stop-signal task; WR, word reading.



in various brain regions using a two-sample t-test as a confounding covariate. However, given the exploratory nature of these analyses and the limited sample size, no adjustments for multiple comparisons were made. The relationship between the SUVR of <sup>18</sup>F-SynVesT-1 and clinical/cognitive parameters was explored with a scatter plot in subjects with IGD. Pearson correlation analyses were used to examine the relationship between the SUVR of <sup>18</sup>F-SynVesT-1 and clinical/cognitive parameters. SPSS V.23.0 was used to perform the analysis, and GraphPad Prism V.7.0 (GraphPad Software, Boston, Massachusetts, USA) was used to generate figures. The two-tailed p values had a significance level of  $\alpha=0.05$ .

**RESULTS**

In total, 18 patients were enrolled in the IGD group and 16 in the HC group. The demographics were well matched between the two groups. All participants enrolled in the study were right-handed. The mean (SD) age was 20.53 (3.69) for the IGD group and 22.44 (5.44) for the HC group. There were four women enrolled in the IGD group and six in the HC group. None of the participants reported previous or current neurological or psychiatric disorders, illegal drug use, or nicotine or alcohol use disorders. The <sup>18</sup>F-SynVesT-1 injection was well tolerated, with no subjective or objective adverse effects detected. In addition, all the participants were free of depressive and anxiety disorders. However, a minority of subjects with IGD had mild to moderate anxiety or depression symptoms, as assessed by the HAMA and HAMD, respectively (table 1).

The IGD group scored higher on the IGDS9-SF than the HC group ( $p<0.001$ ). The mean (SD) daily internet gaming (IG) usage reached 11.47 (2.83) hours, and IG usage after midnight/overnight each week reached 4.29 (2.31)/2.81 (2.60) times in the IGD group. The

details of the demographic and clinical characteristics of the subgroups are summarised in table 1. The results also indicated the presence of significant group differences on the BIS-11 cognitive ( $t=-2.634$ ,  $p=0.035$ ), motor ( $t=-3.472$ ,  $p<0.001$ ) and non-planning subscales ( $t=-2.580$ ,  $p=0.002$ ), in addition to the BIS-11 total scores ( $t=-1.008$ ,  $p<0.001$ ).

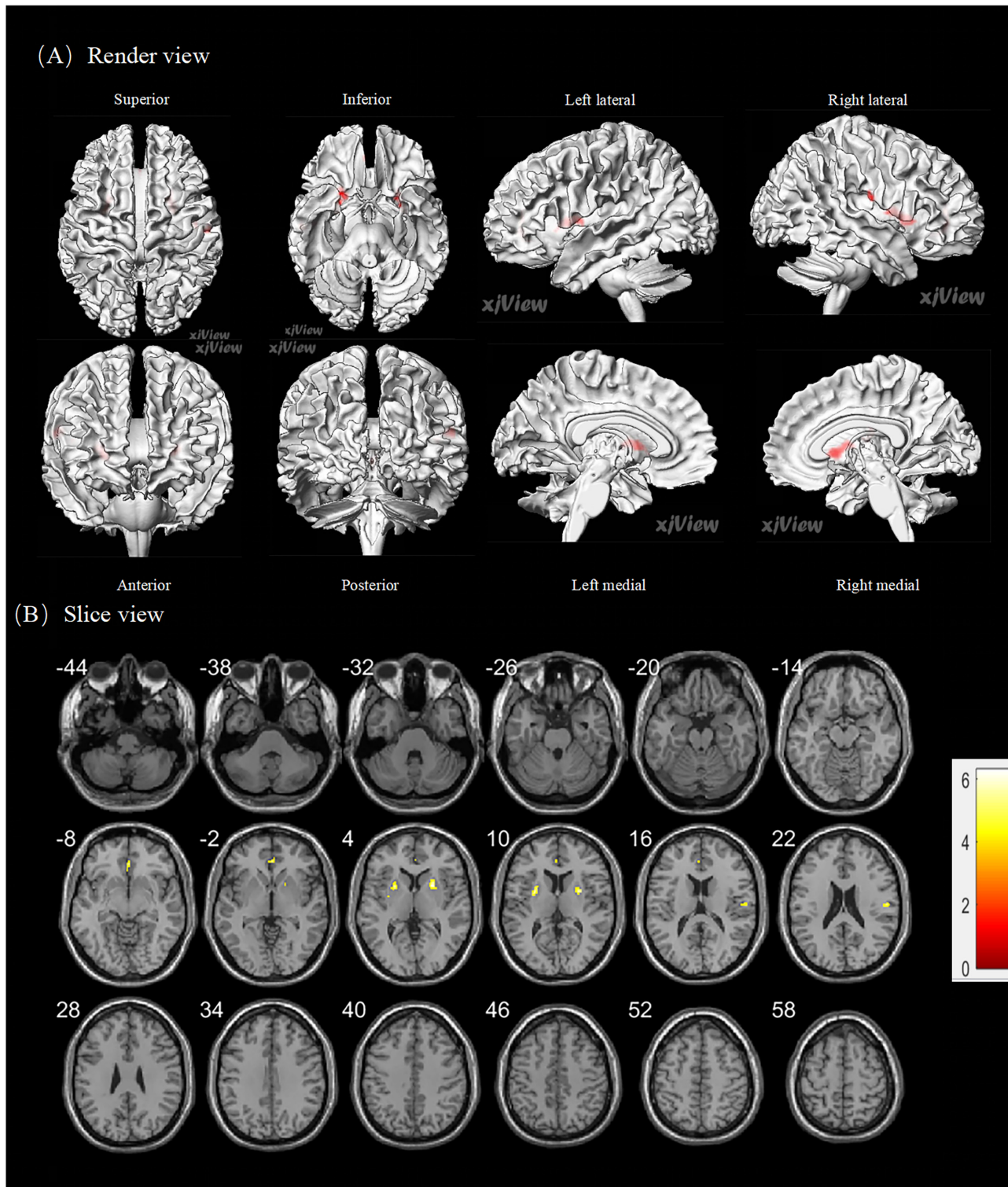
HCs performed better on the two-back test ( $t=-2.419$ ,  $p=0.022$ ), but not on the three-back test ( $t=-1.842$ ,  $p=0.076$ ), than patients with IGD. On the Stroop test, the accuracies for WR ( $t=-3.039$ ,  $p=0.006$ ), CN ( $t=-3.735$ ,  $p=0.001$ ) and CW ( $t=-2.728$ ,  $p=0.011$ ) were significantly higher in HCs than in patients with IGD, but no difference in IS scores on the SCWT was found between the groups ( $t=-0.988$ ,  $p=0.333$ ). The staircase algorithm in the SST guaranteed that the participants had an approximately 50% success rate in stop trials. Both the IGD and HC groups had accuracy rates higher than 50% in the stop trials despite a group difference, indicating that the present task was conducted successfully. Relative to HCs, patients with IGD had significantly longer SSRTs ( $t=2.434$ ,  $p=0.021$ ). Regarding the other indices of the SST (Go RT and SSD), no significant group difference between the IGD and HC groups was found.

Compared with HCs, patients with IGD showed lower uptake of <sup>18</sup>F-SynVesT-1 in the right pregenual anterior cingulate cortex (ACC), bilateral putamen and right Rolandic operculum (height threshold at  $p<0.001$ , with a level above 50 contiguous voxels; table 2, figures 2 and 3, online supplemental table S1). The associations between synaptic density (SUVRs of <sup>18</sup>F-SynVesT-1) and clinical characteristics are summarised in online supplemental table S2. Significant linear relationships between higher IGDS9-SF scores or longer daily gaming hours and lower synaptic density (SUVR of <sup>18</sup>F-SynVesT-1) of the left putamen ( $r=-0.476$ ,  $p=0.046$ ;  $r=-0.573$ ,  $p=0.015$ ) and the

**Table 2** Location and peaks of significant synaptic density reduction in patients with IGD compared with HC

Location	Cluster level		Peak level			Coordinates		
	Cluster $K_E$	P value (uncorrected)	t	Z-score	P value (uncorrected)	x (mm)	y (mm)	z (mm)
Left lenticular nucleus, putamen	77	0.002	5.371	4.501	<0.001	-28	2	8
			3.527	3.217	<0.001	-32	-4	4
			3.442	3.151	<0.001	-24	16	0
Right lenticular nucleus, putamen	130	<0.001	5.308	4.462	<0.001	24	10	4
			4.716	4.079	<0.001	28	4	8
Right Rolandic operculum	53	0.008	5.048	4.297	<0.001	56	-16	18
			3.612	3.283	<0.001	44	-10	14
Right anterior cingulate cortex, pregenual	59	0.005	4.477	3.916	<0.001	2	38	-6
Left anterior cingulate cortex, pregenual	77	0.002	3.788	3.417	<0.001	-2	40	10

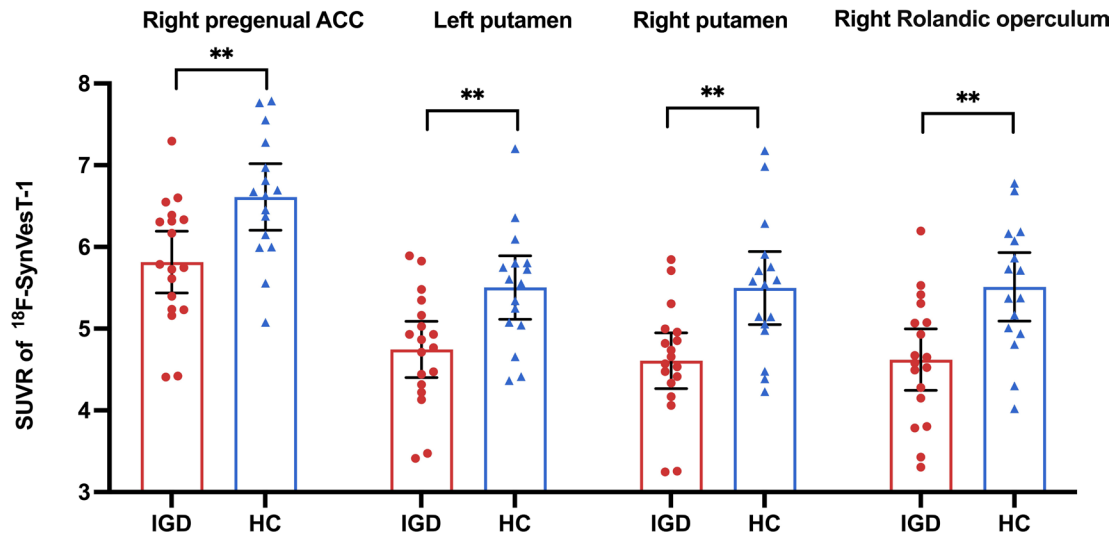
HC, healthy control; IGD, internet gaming disorder;  $K_E$ , cluster size.



**Figure 2** Comparison of the clusters of synaptic changes by  $^{18}\text{F}$ -SynVesT-1 PET with patients with IGD versus HCs was performed in (A) render view and (B) slice view ( $p < 0.001$  with cluster thresholding,  $k = 50$  voxels). Voxels with significantly low uptake are shown in red.  $^{18}\text{F}$ -SynVesT-1,  $^{18}\text{F}$ -labelled difluoro-analogue of UCB-J; HCs, healthy controls; IGD, internet gaming disorder; PET, positron emission tomography.

right putamen ( $r = -0.479$ ,  $p = 0.044$ ;  $r = -0.479$ ,  $p = 0.010$ ) were observed in patients with IGD (figure 4). SSRTs were negatively correlated with the SUVR of  $^{18}\text{F}$ -SynVesT-1 in

the right pregenual ACC ( $r = -0.573$ ,  $p = 0.013$ ) and the right Rolandic operculum ( $r = -0.527$ ,  $p = 0.025$ ). There were no associations between SV2A availability and



**Figure 3** Voxel-wise analysis results of group comparison with  $^{18}\text{F}$ -SynVesT-1 SUVR in IGD and HCs using a two-sample t-test (\*\* $p < 0.001$ ).  $^{18}\text{F}$ -SynVesT-1,  $^{18}\text{F}$ -labelled difluoro-analogue of UCB-J; ACC, anterior cingulate cortex; HC, healthy control; IGD, internet gaming disorder; SUVR, standardised uptake value ratio.

frequency of IG usage, BIS-11 subscales and total scores, accuracies for WR, CN and CW, and IS scores for SCWT.

## DISCUSSION

### Main findings

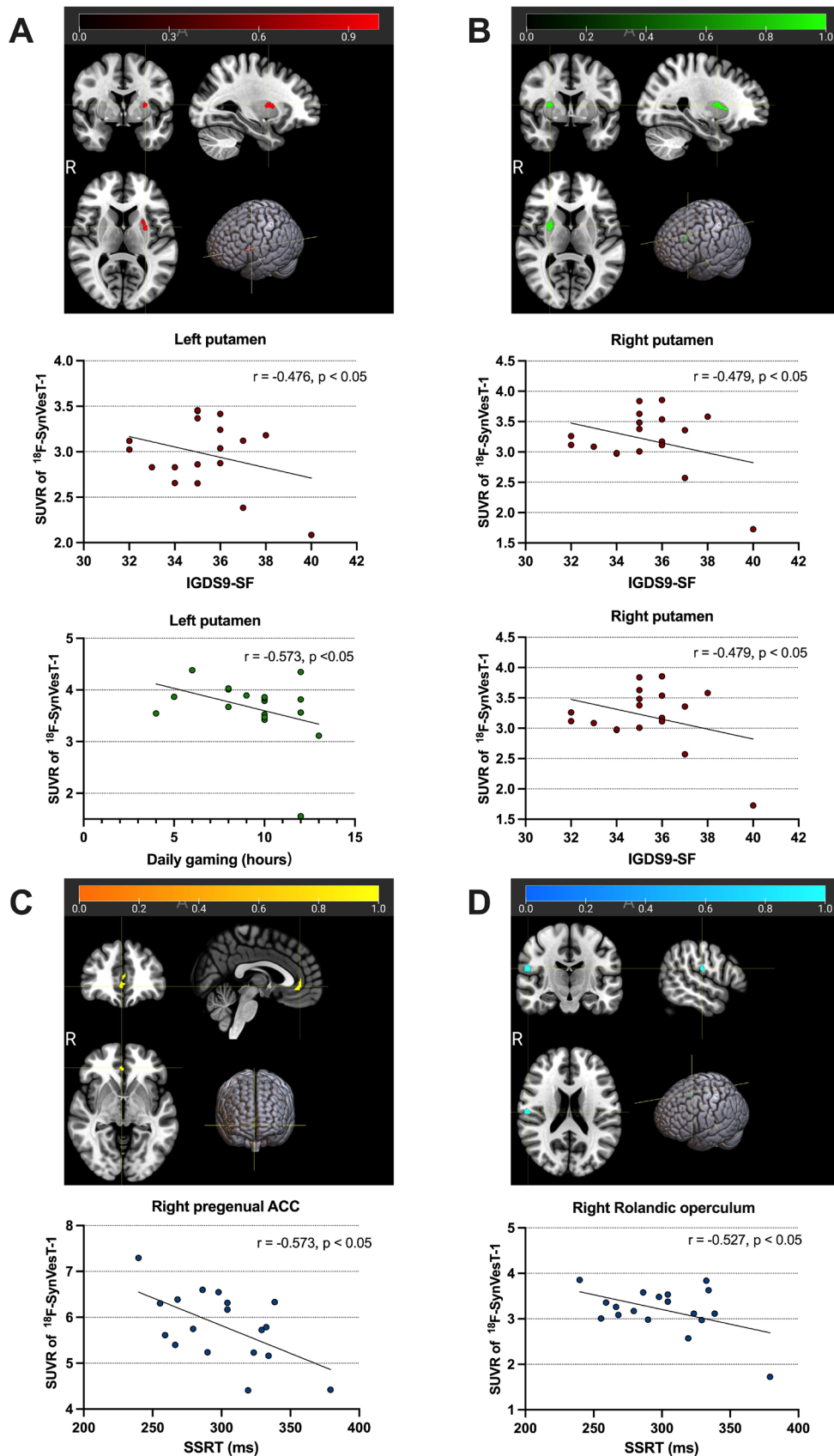
To the best of our knowledge, this is the first study to measure SV2A synaptic density using SV2A in IGD *in vivo*. Using the new radiotracer ( $^{18}\text{F}$ -SynVesT-1), patients with IGD had significant reductions in synaptic density compared with HCs in three prespecified brain areas: right ACC, bilateral putamen and right Rolandic operculum. Lower synaptic density in the bilateral putamen, which is part of the reward system, is correlated with the severity of IGD. Moreover, a correlation between worse inhibitory control and lower synaptic density in the right ACC and Rolandic operculum was found in the IGD group. Therefore, the pattern of associations between altered synaptic integrity and behavioural measures of IGD suggests that such alterations may be disorder-specific and a potentially novel candidate for a brain-based functional biomarker of this disorder.

The findings of this study add to the evidence indicating that synaptic density changes occur in addictive disorders. To date, a relationship between synaptic density and addictive behaviour has been demonstrated only in substance use disorder (SUD). Two recent studies using  $^{11}\text{C}$ -UCB-J PET found lower levels of the synaptic terminal protein SV2A in the frontal and temporal cortices of patients with cocaine and cannabis use disorders.<sup>14,15</sup> Based on the above research, we believe that IGD and SUDs likely share at least a subset of similar underlying neurobiological mechanisms. Furthermore, results from recent studies suggest that reduced metabolism, volume and synaptic deficits in brain regions involved in executive function, reward-related processing, decision-making and impulse inhibition occur in these disorders, according to *in vivo* PET<sup>11,37</sup> and functional MRI studies,<sup>38–40</sup> which is in line with our findings.

Consistent with our hypothesis, lower SV2A availability in reward circuit-related brain regions was found in patients with IGD. The putamen, along with the globus pallidus, forms the lentiform nucleus; it and the caudate nucleus compose the striatum, a subcortical limbic structure. The putamen is involved in reward-related processing and the development of addiction.<sup>41,42</sup> In addition, the ACC, particularly the pregenual component, and the adjacent medial prefrontal cortex have been implicated in the craving processes related to cocaine and gambling.<sup>43</sup> The cingulate gyrus is part of the limbic system, which activates in response to addiction-related cues, resulting in immediate, strong emotional reactions. Studies assessing reward processing in individuals with IGD have shown reduced putamen functional connectivity of the putamen with the posterior insula-parietal operculum<sup>44</sup> and decreased bidirectional interactions between the putamen and ACC.<sup>45</sup> A PET study using  $^{11}\text{C}$ -raclopride found that striatal dopamine release is reduced in subjects with internet addiction.<sup>46</sup> Another  $^{18}\text{F}$ -fluoro-2-deoxyglucose PET study reported that the regional cerebral metabolic rate of glucose in the right ACC was associated with the severity of IGD.<sup>47</sup> Notably, a longitudinal study of recovered subjects with IGD showed increased ACC lentiform connectivity at 1 year relative to onset.<sup>45</sup> Together with our observations, these results suggest that patients with IGD exhibit hypometabolism, synaptic loss and lower connectivity in the ACC and putamen.

In addition, we also found significant reductions in synaptic density in the right Rolandic operculum (ie, postcentral operculum) in patients with IGD compared with the HCs. The Rolandic operculum is implicated in the semantic processing of language, emotional processing of facial expressions, sensorimotor integration and bodily self-consciousness. Our result is consistent with those of previous voxel-based morphometry studies showing decreased grey matter volume in the bilateral





**Figure 4** Significant relationships between synaptic density with severity of IGD and inhibitory control in subjects with IGD. The SUVR of  $^{18}\text{F}$ -SynVesT-1 PET was negatively correlated with IGDS9-SF and daily gaming hours in the bilateral putamen (A and B) and also negatively correlated with SSRT in the right pregenual ACC and right Rolandic operculum (C and D).  $^{18}\text{F}$ -SynVesT-1,  $^{18}\text{F}$ -labelled difluoro-analogue of UCB-J; ACC, anterior cingulate cortex; IGD, internet gaming disorder; IGDS9-SF, Internet Gaming Disorder Scale-Short Form; SSRT, stop-signal reaction time; SUVR, standardised uptake value ratio.



Rolandic operculum in individuals with addiction-related disorders compared with HCs ( $p < 0.005$ ).<sup>48</sup> Resting-state functional MRI data from subjects with IGD revealed lower static functional connectivity between the dorso-lateral prefrontal cortex and the Rolandic operculum.<sup>49</sup> However, the exact mechanism of Rolandic operculum abnormalities in IGD remains unclear, and more research is needed to explain this in the future.

Similar to those with SUD, patients with IGD might display faulty inhibitory control mechanisms. Consistent with findings in this field,<sup>50–52</sup> we observed greater impulsivity and worse performance on the gaming working memory task, attentional inhibition and prepotent motor inhibitory control in patients with IGD than in HCs. Regarding the effect of synaptic density on SST performance, decreased synaptic density of the right pregenual ACC and right Rolandic operculum was associated with a more negative SSRT change. Previous work has established that lower activation in the ACC<sup>19,53</sup> and Rolandic operculum<sup>54</sup> is associated with worse behavioural inhibition and execution (longer Go RTs and SSRTs). Additionally, we also demonstrated that the severity of IGD was associated with synaptic density changes in the putamen, providing a possible molecular explanation for synaptic density alterations that may underlie behavioural and cognitive impairments in IGD. This hypothesis needs to be evaluated with further studies exploring the longitudinal trajectories of these measures and investigating the synaptogenic effects of interventions, such as transcranial direct current stimulation,<sup>55</sup> cognitive-behavioural therapy, family therapy or electronic-based intervention,<sup>56</sup> to reduce cravings and promote recovery in patients with IGD.

### Limitations

Several limitations of this study should be noted. First, although the sample size of this study was appropriate for the standards of previous similar PET/CT studies,<sup>14–16, 57</sup> it was relatively small. Therefore, the presence of false-negative results in the frontal and temporal lobes cannot be ruled out. We readily acknowledge that this is a preliminary analysis, and replication in a larger sample is needed to support our interpretations. Second, this is a cross-sectional study. Therefore, we cannot determine whether the lower synaptic density in patients with IGD represents a cause or a consequence of IGD. Further longitudinal investigations measuring synaptic density after a period of gaming abstinence could help to determine whether the lower synaptic density increases after withdrawal, enabling us to better understand the relationship between synaptic density changes and the course of IGD.

### Implications

To the best of our knowledge, this study is the first to provide *in vivo* evidence of synaptic alterations in patients with IGD using <sup>18</sup>F-SynVesT-1-PET imaging. This investigation provided intriguing preliminary translational support for relatively low uptake distribution in the right ACC, bilateral putamen and right Rolandic operculum in patients with IGD compared with HCs. These findings

also imply that the synaptic deficits in these regions are closely linked to the severity of addiction and impairment of inhibitory control in IGD, although further work is needed to clarify the nature of this association. Such work can advance our understanding of the role of synaptic function in IGD and identify more effective and novel treatment approaches based on synapse-related mechanisms.

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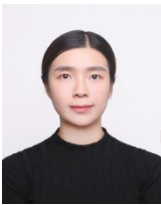
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