

Impulsivity-related right superior frontal gyrus as a biomarker of internet gaming disorder

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ABSTRACT

Background Internet gaming disorder (IGD) is a mental health issue that affects individuals worldwide. However, the lack of knowledge about the biomarkers associated with the development of IGD has restricted the diagnosis and treatment of this disorder.

Aims We aimed to reveal the biomarkers associated with the development of IGD through resting-state brain network analysis and provide clues for the diagnosis and treatment of IGD.

Methods Twenty-six patients with IGD, 23 excessive internet game users (EIUs) who recurrently played internet games but were not diagnosed with IGD and 29 healthy controls (HCs) performed delay discounting task (DDT) and Iowa gambling task (IGT). Resting-state functional magnetic resonance imaging (fMRI) data were also collected.

Results Patients with IGD exhibited significantly lower hubness in the right medial orbital part of the superior frontal gyrus (ORBsupmed) than both the EIU and the HC groups. Additionally, the hubness of the right ORBsupmed was found to be positively correlated with the highest excessive internet gaming degree during the past year in the EIU group but not the IGD group; this might be the protective mechanism that prevents EIUs from becoming addicted to internet games. Moreover, the hubness of the right ORBsupmed was found to be related to the treatment outcome of patients with IGD, with higher hubness of this region indicating better recovery when undergoing forced abstinence. Further modelling analysis of the DDT and IGT showed that patients with IGD displayed higher impulsivity during the decision-making process, and impulsivity-related parameters were negatively correlated with the hubness of right ORBsupmed.

Conclusions Our findings revealed that the impulsivity-related right ORBsupmed hubness could serve as a potential biomarker of IGD and provide clues for the diagnosis and treatment of IGD.

INTRODUCTION

Internet use and gaming technology have developed quickly in the last two decades. Consequently, the number of subjects with internet gaming disorder (IGD) has also grown extensively.^{1 2} In 2013, the Diagnostic and Statistical Manual of Mental Disorders,

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The differences between patients with internet gaming disorder (IGD) and healthy controls (HCs) in the brain network mainly manifested in the hubness of nodes in previous studies.
- ⇒ But whether these findings are the biomarkers of addiction to internet games or just the results of recurrent engagement in internet games is unclear.

WHAT THIS STUDY ADDS

- ⇒ We included excessive internet game users (EIUs) as a control group for IGD to remove the effect of recurrent engagement in internet games and revealed that the hubness of the right ORBsupmed played a key role in whether individuals were addicted to internet games and can serve as a biomarker of IGD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The hubness of the right ORBsupmed highlighted in our data provides clues for the diagnosis and treatment of IGD.
- ⇒ Future studies on the treatment of IGD should consider developing a treatment plan that targets the right ORBsupmed.



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5th edition (DSM-5) included IGD in Section III and listed it as a disorder requiring further study.³ The World Health Organization (WHO) also listed gaming disorder (GD) in the 11th final revision of the International Classification of Diseases (ICD-11).⁴ Recently, the outbreak of the novel COVID-19 pandemic has also increased the risk of IGD because of higher stress during this period.⁵ However, the lack of knowledge about the biomarkers associated with IGD has restricted its diagnosis and treatment.

As a complex system, the behaviour of the brain—for example, in the addiction to internet games—is shaped by interactions among its constituent elements.^{6 7} Thus, the characteristics of the brain connection network can serve as the source of biomarkers

of IGD. With the development of modern brain imaging technologies such as functional magnetic resonance imaging (fMRI), we can construct the overall functional network of the brain with millimetre resolution. Then, with the help of network analysis methods in complex systems physics, we can reliably quantify the connectivity patterns of this brain functional network.⁸ For example, resting-state brain functional network analysis has been used for the investigation of biomarkers of mental disorders in previous studies.⁹ Brain network analysis has also been used to explore IGD-related changes in network functional connectivity patterns^{10–12}; the differences between those with IGD and healthy controls (HCs) mainly manifested in the hubness of nodes in the brain network.¹³ The concept of hubness has frequently been used in social network research¹⁴ and has recently been introduced into the analysis of brain networks. Various indices have been proposed to measure hubness, and they all assess a node's involvement in the walk structure of a network.¹⁴ Thus, hubness serves as a valuable tool in quantifying a node's significance in network organisation and identifying the key areas associated with brain disorders.¹⁵

However, another existing problem in dissecting biomarkers associated with the development of addiction is the interpretation of the findings: are such changes factors leading to addiction or just the consequences of addictive behaviour? This general question can be posed for virtually all addiction studies without prospective data on their pre-abuse state. However, it is indeed challenging to address.¹⁶ Similarly, the altered hubness of nodes found in patients with IGD compared with HCs might result from recurrent engagement in internet games rather than the core biomarkers associated with the development of IGD. To address this issue, we included excessive internet game users (EIUs) as a control group for IGD in this study. EIU is a group of subjects who also recurrently play internet games like those with IGD, but their engagement in internet games does not lead to clinically significant impairment or distress. Thus, including the EIUs as the control for the IGD group enables us to eliminate the effect of recurrent engagement in internet games and explore the core biomarkers of IGD in a cross-sectional study.

Additionally, there is a lack of explanation and evidence for the cognitive significance of the changed hubness of specific nodes. The decision-making paradigm is an effective tool for investigating cognitive significance and has been widely used to explore cognitive differences in addiction-related disorders in previous studies.^{17–23} For example, a delay discounting task (DDT) was used in earlier studies to measure impulsivity in decision-making. IGD and many other behavioural addictions were found to be associated with impulsivity measured by DDT.²⁴ The Iowa gambling task (IGT), a classic risk decision-making task, has also been widely applied to investigate deficits in decision-making in the field of addiction. Evidence from IGT computational models suggests that subjects addicted

to stimulants, opioids, etc, have deficits in decision-making.^{23–25} Few studies have used IGT to explore the decision-making process of IGD, and these studies have not been able to draw consistent conclusions.^{26–28}

In the present study, we investigated the biomarkers of IGD through resting-state brain network analysis. Based on the review of the above literature, we hypothesised that nodal hubness—a measure quantifying the importance of a node to network organisation—would identify the core nodes associated with the development of IGD. To remove the effect of high engagement in internet games, we also included EIU as a control group. Some decision-making paradigms, DDT and IGT, were used to investigate the cognitive significance of nodal hubness further.

METHODS

Participants

In this study, we recruited a total of 78 subjects, including 26 patients with IGD, 23 EIU and 29 HCs. A priori power analysis for a two-sided independent t-test was performed to estimate the sample size needed before the formal study.²⁹ Type I error rate was set to 5%, and target power was set to 80%. Effect size (Cohen's *d*) was assumed to be 0.9, based on a recent IGD-related meta-analysis.²⁴ The estimated sample size for one group is 21. The sample size of each group meets this requirement in the present study.

Subjects with IGD were recruited from the General Hospital of the Beijing Military Region's Addiction Medicine Center from October 2012 to December 2015. Their age ranged from 16 to 22 years. The inclusion criteria for the IGD included the following: (1) diagnosed with IGD based on DSM-5 criteria (meeting at least five of the nine inclusion criteria in a 12-month period) by two experienced psychiatrists. (The diagnostic conclusions of two psychiatrists were consistent for each patient with IGD included in the present study); (2) did not have any pharmacological treatment before the experiment; (3) did not have comorbid disorders, including smoking, stimulant, alcohol, cocaine, 3,4-methylenedioxy-methamphetamine (MDMA) consumption, attention deficit hyperactivity disorder, conduct disorder or neurosis (as determined by two experienced psychiatrists during DSM-IV-based structured clinical interviews before the study). These patients with IGD did not receive any specific treatment and were only in a state of forced abstinence for the week before the experiment. The other subjects were recruited from the community using local advertisements and grouped into EIU and HC. Their age ranged from 17 to 31 years. None of those in the EIU and HC groups met the IGD criteria proposed in DSM-5. We further grouped these subjects based on Young's Diagnostic Questionnaire.³⁰ Young's Diagnostic Questionnaire was developed by Kimberly Young to diagnose internet use dependence. However, previous studies also pointed out that even if the diagnosed person meets the Young's Diagnostic Questionnaire cut-off score, his or her internet use behaviour may not impair normal life.³¹ A

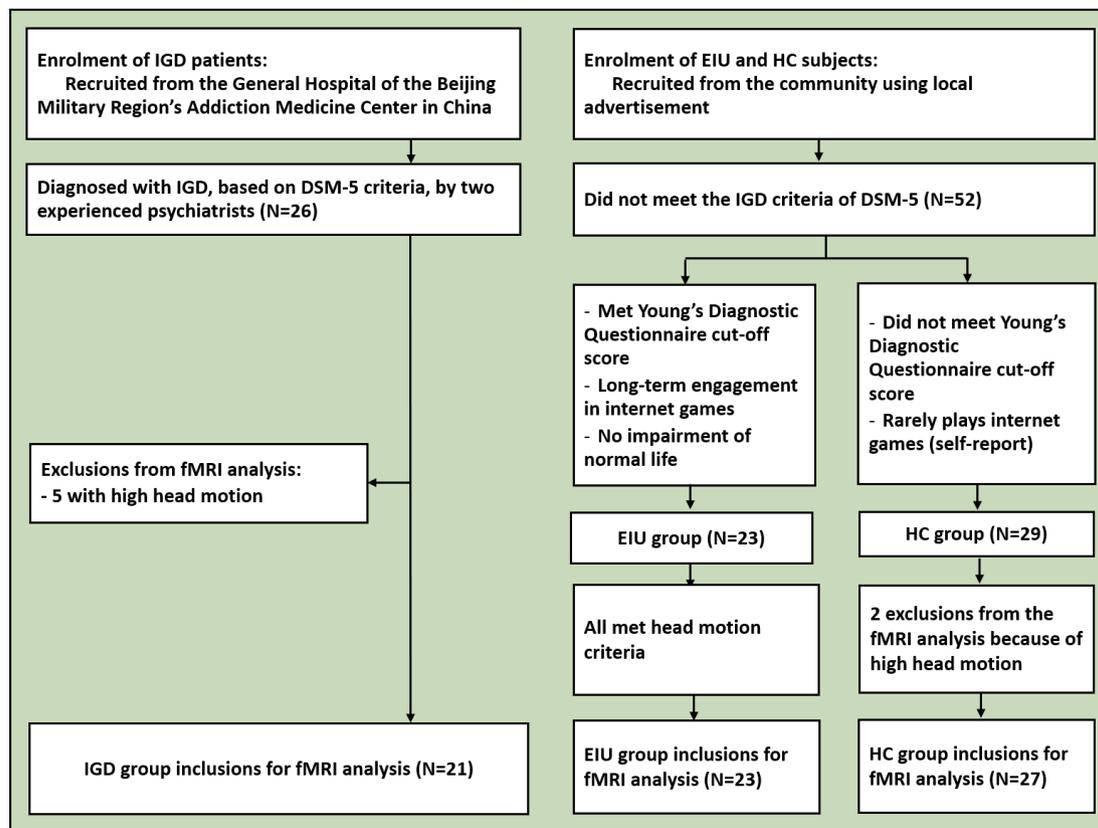


Figure 1 Enrolment of study participants. DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EIU, excessive internet game user; fMRI, functional magnetic resonance imaging; HC, healthy control; IGD, internet gaming disorder.

significant impact on normal life is the basic condition in the diagnosis of mental illness, so the Young's Diagnostic Questionnaire can only reflect the excessive use of the internet. Therefore, we grouped the subjects who met the Young's Diagnostic Questionnaire cut-off score but did not meet the IGD diagnostic criteria into the EIU group. Those who met neither of the two criteria were grouped into the HC group. In addition, all EIU subjects reported that they had been playing internet games for at least 12 months prior to the inclusion in the study, that their regular play did not interfere with school, work, family or social obligations and did not cause them distress, and that they do not need to seek treatment for prolonged internet gaming exposure. See [figure 1](#) for the detailed procedure of the enrolment of the subjects.

Questionnaires

To assess participants' excessive internet gaming degree (EIGD), we employed the problem internet game-playing questionnaire. The original questionnaire³² was translated into Chinese and modified by replacing the term 'videogame' with 'internet game'. This Chinese version of the problem internet game-playing questionnaire has been used and validated in a previous study.³³ Two EIGD scores were obtained for each participant: the highest EIGD score (HEIGD) during the year before the experiment and the current EIGD score (CEIGD). The scoring rules of HEIGD and CEIGD are provided in online supplemental file 1. Participants were also asked

to report the duration of internet gaming per week and the percentage of internet gaming time in leisure time based on their recall of the status when their excessive online gaming behaviour was most intense in the past year. Participants' age, education and gender information were also collected.

BEHAVIOUR TASKS

All of the participants performed DDT and IGT. These two tasks were used to assess impulsivity, a known risk factor for IGD.^{34,35}

We used the same DDT paradigm as we had in our previous study.³⁴ In each trial, two options of reward were presented to participants. One option is an immediate reward, which means participants can get the reward immediately after finishing the task. The other option is a delayed reward with a specified delay, which means participants can get the reward after the delay. Participants need to make a selection between an immediate reward option and a delayed reward option in each trial. The reward for the immediate option was always 50 Chinese yuan. Delayed reward options were combined with two sets of reward magnitudes (M1: 50 yuan, 55 yuan, 70 yuan, 90 yuan, 110 yuan, 140 yuan, 175 yuan; M2: 50 yuan, 60 yuan, 68 yuan, 75 yuan, 100 yuan, 125 yuan, 150 yuan) and two sets of delays (T1: 0 day, 7 days, 30 days, 60 days, 90 days, 180 days; T2: 0 day, 10 days, 28 days, 50 days, 100

days, 160 days). M1 was combined with T1 (such as 110 yuan with a delay of 30 days), and M2 was combined with T2 (such as 150 yuan with a delay of 10 days), yielding a total of 84 combinations of reward magnitudes and delays. Each combination occurred once during the task, so the entire task contained 84 trials. Participants were informed that they would obtain actual payment in cash on one randomly drawn trial of the task based on their choice. Participants received the payment at the end of the scanning if the outcome of the selected trial was an immediate reward; otherwise, payment was sent to participants with the specified delay. Before the task, a practice version of the DDT was provided for participants to familiarise them with the task.

We also used the same IGT paradigm as we had in our previous study.³⁶ Four decks of cards (decks A, B, C and D, presented from left to right) were presented to participants during the task. On the front of each card were gain points and possible loss points. Deck A gave 100 gain points for each card and -150, -200, -250, -300 and -350 loss points for 5 cards out of every 10. Deck B gave 100 gain points for each card and -1250 loss points once out of every 10 cards. On average, 10 choices of deck A or deck B resulted in -250 net points. So deck A and B were bad decks. Deck C gave 50 gain points for every card and -25, -40, -50, -60 and -75 loss points for 5 cards out of every 10. Deck D also gave 50 gain points for every card but -250 loss points once out of every 10 cards. On average, 10 choices of deck C or deck D resulted in 250 net points. So decks C and D were good decks. Participants were instructed to choose from the four decks in each trial. The entire task contained 180 trials. The initial score for each participant was 3000 points. Before the task, participants were told that some decks were advantageous and some decks were disadvantageous, and they needed to find the rule to maximise their total net score in the task. Payments for participants were based on their performance in the task, with 100 net points exchanged for one Chinese yuan.

For DDT, the averaged indifference point and discounting rate were estimated for each participant as the measures of impulsivity.³⁴ For IGT, four promising reinforcement learning models were used for the modelling of participants' performance: the prospect valence learning with decay reinforcement learning rule (PVL-Decay) model,²⁵ the prospect valence learning with delta reinforcement learning rule (PVL-Delta) model,³⁷ the value-plus-perseverance learning (VPP) model³⁸ and the outcome-representation learning (ORL) model.³⁹ The detailed procedure of the modelling analysis is provided in online supplemental file 1.

Scanning and preprocessing of fMRI

Resting-state fMRI data were acquired with 3.0 T Siemens scanners. Each fMRI scan consists of 240 volumes. For each volume, 33 slices (slice thickness=3.7 mm, repetition time (TR)=2s, echo time (TE)=30 ms) were acquired. During the scan, participants were asked to relax, close

their eyes and stay awake. Resting-state fMRI data were preprocessed using a toolbox for Data Processing & Analysis of Brain Imaging (DPABI)⁴⁰ based on functions in Statistical Parametric Mapping V.12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). The first 10 images of each run were discarded to allow for signal stabilisation. The remaining images were corrected for temporal shifts between slices, realigned, and spatially normalised to the Montreal Neuroimaging Institute (MNI) space by using echo planar imaging (EPI) templates⁴¹ and spatially smoothed (Gaussian kernel, 8mm full-width at half maximum). Nuisance regressors were then removed,⁴² including linear trends, motion parameters and their derivatives (Friston 24-parameter model⁴³), white matter, CSF time series and head motion scrubbing regressors (framewise displacement (FD) threshold for 'bad' time points=0.5 mm). The images were also band-pass filtered (0.008–0.08).⁴⁴ Two HCs and five subjects with IGD were excluded from the fMRI analysis because of high head motion (translation >2.5 mm or rotation >2.5°). Automated anatomical labelling (AAL) atlas⁴⁵ was applied to the preprocessed fMRI data to construct functional brain networks. The hubness of nodes in the brain network was measured by five measures: closeness centrality, degree centrality, betweenness centrality, eigenvector centrality and nodal efficiency. These measures were estimated for each graph at each connection density. An R graph analysis package called *igraph* V.1.2.6 (<https://igraph.org/r/>) was used to estimate these measures. The detailed methods of brain network construction and hubness estimations are provided in online supplemental file 1.

Statistical analysis

For each hubness measure, the estimations at different connection densities were first averaged to generate a single estimate of one hubness measure for one subject. We then compared these averaged values among the three groups using analysis of covariance (ANCOVA) with age and years of education as covariates on all of the 90 AAL regions. We adopted the most stringent multiple comparison correction method, the Bonferroni correction, to prevent false-positive results and ensure the statistical results were stable and sufficiently robust.

RESULTS

Demographics and internet game use

The basic demographics of the IGD, EIU and HC groups are shown in [table 1](#). There was no significant difference in the distribution of sexes among the three groups ($\chi^2=3.33$, $p=0.190$). However, statistically significant differences were found among the three groups regarding age and education (both p values<0.05). Therefore, we included age and years of education as covariates in the subsequent statistical analysis to exclude the interference of these factors on the statistical results. We compared the IGD and EIU on the HEIGD score, the percentage

Table 1 Sample demographics

Sample group	IGD (n=26)	EIU (n=23)	HC (n=29)
Age (year), mean (SD)	20.15 (3.33)	24.52 (1.78)	20.17 (1.67)
Gender (M/F), n	24/2	18/5	27/2
Education (year), mean (SD)	12.50 (2.58)	17.09 (1.16)	14.21 (1.84)

EIU, excessive internet game user; HC, healthy control; IGD, internet gaming disorder; M/F, male/female; SD, standard deviation.

of internet gaming time in leisure time and the duration of internet gaming in the week with the most intense internet gaming in the past year. The results showed no statistically significant between-group difference between the IGD and EIU groups in the use of internet games (the smallest $p=0.710$, online supplemental figure S1).

Nodal hubness comparison

We found that the three groups produced significantly different closeness centrality ($F(66)=8.65$, $p<0.001$, uncorrected; $p=0.041$ corrected) and nodal efficiency ($F(66)=8.65$, $p<0.001$, uncorrected; $p=0.041$ corrected) in the right medial orbital part of the superior frontal gyrus (ORBsupmed, figure 2A). A post hoc test revealed that the EIU and HC groups showed significantly higher closeness centrality and nodal efficiency (in average) in the right ORBsupmed than the IGD group, and the EIU group also exhibited slightly higher closeness centrality and nodal efficiency (in average) than the HCs in this node (figure 2B–C).

No significant difference was found among the three groups in degree centrality, eigenvector centrality or betweenness centrality after Bonferroni correction. Nevertheless, we found that the three groups showed significant differences in degree centrality ($F(66) = 7.25$, $p=0.001$, uncorrected) and eigenvector centrality ($F(66) = 5.14$, $p=0.008$, uncorrected) at the right ORBsupmed node before multiple comparison correction. The post hoc tests also revealed the same difference pattern (figure 2D–E).

Relationship between the hubness of the right ORBsupmed and the degree of excessive internet gaming

Further correlation analysis revealed that both closeness centrality ($r=0.43$, $p=0.043$, figure 2F) and nodal efficiency ($r=0.41$, $p=0.050$, figure 2G) of the right ORBsupmed were significantly and positively correlated with the HEIGD score in the EIU group. No significant correlation was found between closeness centrality ($r=0.12$, $p=0.610$) or nodal efficiency ($r=0.16$, $p=0.490$) and HEIGD score in the IGD group. In addition, we also tested the other two hubness measures that showed significant differences among the three groups before Bonferroni correction, degree centrality and eigenvector centrality. These two hubness measures also significantly correlated with the

HEIGD score in the EIU group (both p values <0.05 , one side, figure 2H–I) but not in the IGD group.

The unique positive correlation found between the hubness of the right ORBsupmed and the highest degree of excessive internet gaming in the EIU group could be the underlying mechanism of the fact that those with IGD exhibited lower hubness in the right ORBsupmed compared with the EIUs, even though both showed excessive engagement in internet games. To make this clearer, we built a predictive linear model based on EIU data with the HEIGD score as the predictor (gender, age and education were also included in the linear model to remove the effect of these covariates) and hubness of the right ORBsupmed as the variable to be predicted. Based on this model, we predicted IGD hubness at the right ORBsupmed node (online supplemental figure S2). The predictions were higher than the true values in most subjects with IGD, especially those with lower hubness at the right ORBsupmed node. This result further illustrates the bias of hubness at the right ORBsupmed node in those with IGD compared with EIUs.

Moreover, we found that CEIGD scores of the IGD group were significantly and negatively correlated with both closeness centrality ($r=-0.57$, $p=0.007$, figure 2J) and nodal efficiency ($r=-0.55$, $p=0.009$, figure 2K) of the right ORBsupmed. In addition, a similar pattern was also found in the relationship between CEIGD scores of the IGD group and degree centrality ($r=-0.55$, $p=0.005$, one side, figure 2L) or eigenvector centrality ($r=-0.46$, $p=0.017$, one side, figure 2M) of the right ORBsupmed. Subjects with IGD were recruited from the hospital's addiction medicine centre and had been in an abstinent state for the week before the experiment. This result illustrates that the hubness of the right ORBsupmed affects the relief of internet game addiction symptoms in hospitalised subjects with IGD. As expected, there was no significant correlation between the CEIGD score and any hubness measure of the right ORBsupmed in the EIU group (the smallest $p=0.720$).

Cognitive significance of the hubness of the right ORBsupmed

The results above indicate that higher hubness of the right ORBsupmed might be a potential protective factor for not becoming addicted to internet games. The question remained what the cognitive significance of the hubness of right ORBsupmed was and why it could play a protective role. We then explored the data from the DDT to answer these questions.

For each subject, we estimated their impulsivity in decision-making by calculating three measures based on their performance in the DDT: the number of delayed choices, the average indifference point and the discounting rate. Each subject's indifference point at a specific delay was estimated using logistic regression (see figure 3A for an example from one subject in the IGD group). Each subject's discounting rate was estimated via hyperbolic fitting (see figure 3B for an example from one subject in the IGD group). We found that the

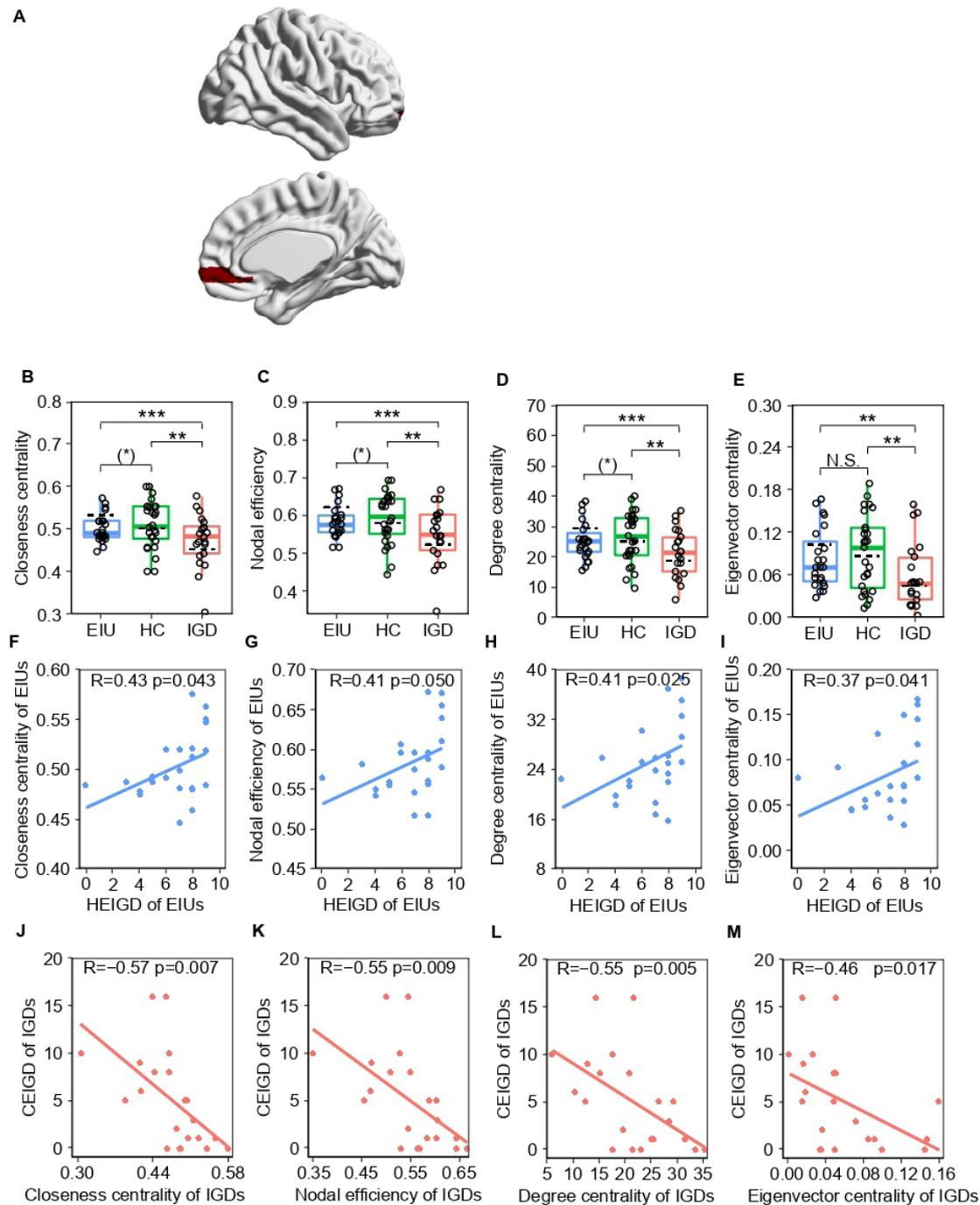


Figure 2 Relationship between the hubness of the right ORBsupmed and the degree of excessive internet gaming. (A) Position of the right ORBsupmed (red area). Only the right hemisphere was plotted. (B) Distributions of closeness centrality in each group and the statistical results. (C) Distributions of nodal efficiency in each group and the statistical results. (D) Distributions of degree centrality in each group and the statistical results. (E) Distributions of eigenvector centrality in each group and the statistical results. The solid line within the boxplot represents the sample median, and the dashed line represents the covariate-adjusted sample mean. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; (*) represents $p < 0.1$; and N.S. represents no significance. (F) Closeness centrality of the right ORBsupmed was plotted against the HEIGD score in EIU subjects. (G) Nodal efficiency of the right ORBsupmed was plotted against the HEIGD score in EIU subjects. The p value was from one-side test. (H) Degree centrality of the right ORBsupmed was plotted against the HEIGD score in EIU subjects. The p value was from one-side test. (I) Eigenvector centrality of the right ORBsupmed was plotted against the HEIGD score in EIU subjects. The p value was from one-side test. (J) The CEIGD score was plotted against the closeness centrality of the right ORBsupmed in subjects with IGD. (K) The CEIGD score was plotted against the nodal efficiency of the right ORBsupmed in subjects with IGD. (L) The CEIGD score was plotted against the degree centrality of the right ORBsupmed in subjects with IGD. The p value was from one-side test. (M) The CEIGD score was plotted against the eigenvector centrality of the right ORBsupmed in subjects with IGD. The p value was from one-side test. CEIGD, the current excessive internet gaming degree; EIU, excessive internet game user; HC, healthy control; HEIGD, the highest excessive internet gaming degree during the past year; IGD, internet gaming disorder.

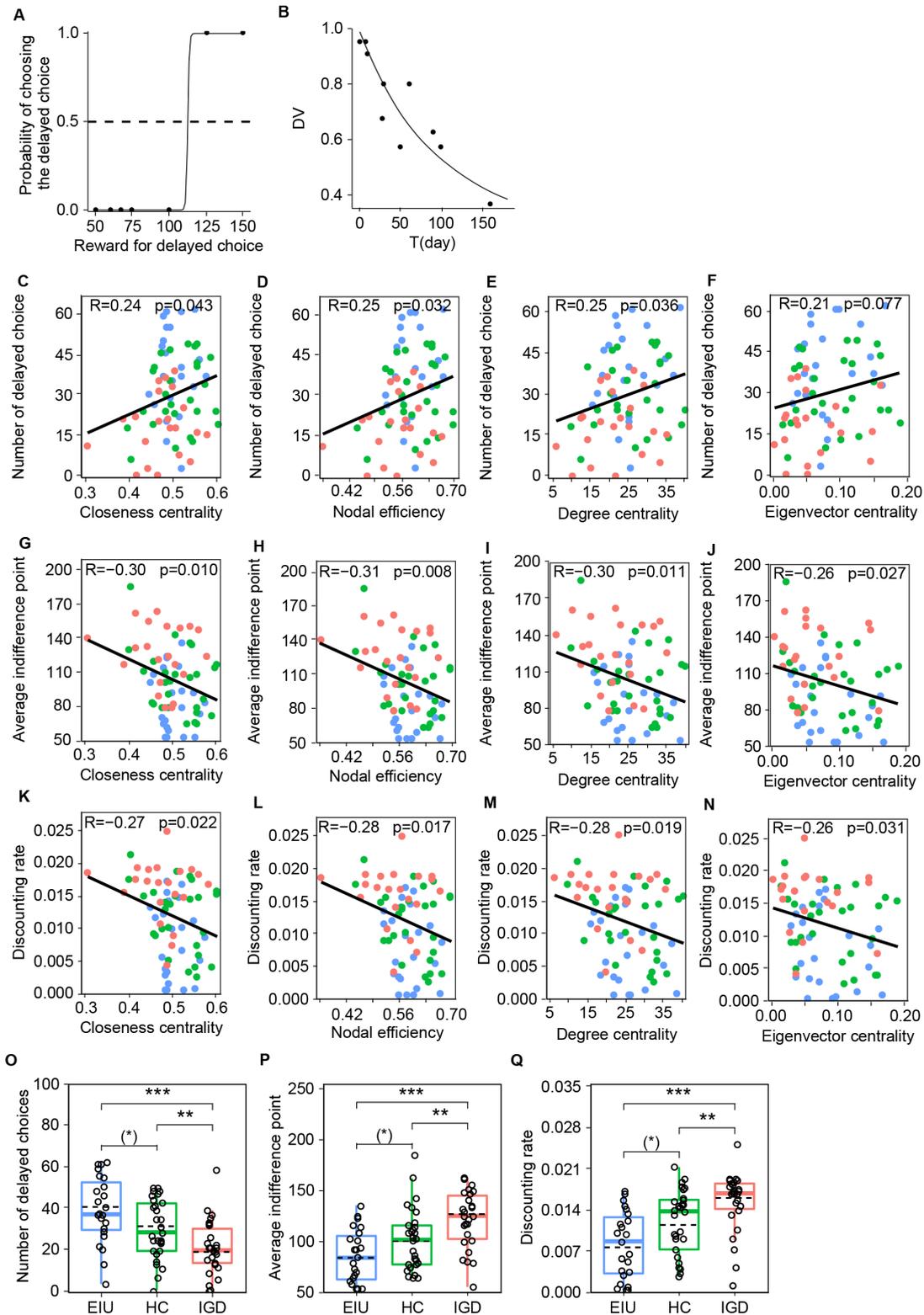


Figure 3 Relationship between closeness centrality or nodal efficiency of the right ORBsupmed and impulsivity in decision-making. (A) Illustration of the logistic regression from one participant. (B) Illustration of the hyperbolic discounting curve from one participant. A steeper discounting curve indicates higher impulsivity for the individual. (C–F) The number of delayed choices was plotted against the hubness of the right ORBsupmed. (G–J) The averaged indifference point was plotted against the hubness of the right ORBsupmed. (K–N) The discounting rate was plotted against the hubness of the right ORBsupmed. (O) Distributions of the number of delayed choices in each group and the statistical results. (P) Distributions of the average indifference point in each group and the statistical results. (Q) Distributions of the discounting rate in each group and the statistical results. The solid line within the boxplot represents the sample median, and the dashed line represents the covariate-adjusted sample mean. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; and (*) represents $p < 0.1$. DV, discounted value; EIU, excessive internet game user; HC, healthy control; IGD, internet gaming disorder.

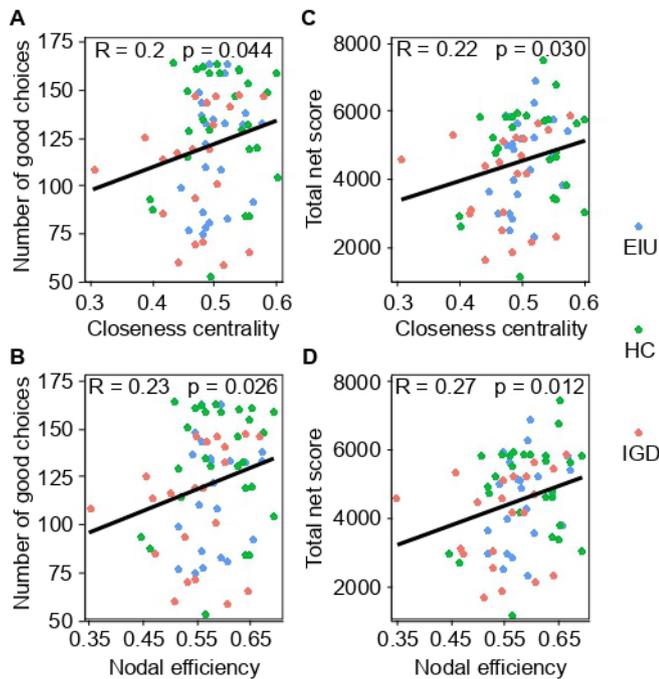


Figure 4 Relationship between performance in the Iowa gambling task (IGT) and closeness centrality or nodal efficiency of the right ORBsupmed. (A) The number of good choices was plotted against the closeness centrality of the right ORBsupmed. (B) The number of good choices was plotted against the nodal efficiency of the right ORBsupmed. (C) Total net score was plotted against closeness centrality of the right ORBsupmed. (D) Total net score was plotted against nodal efficiency of the right ORBsupmed.

number of delayed choices was significantly and positively correlated with closeness centrality and nodal efficiency of the right ORBsupmed (p values < 0.05 , [figure 3C–D](#)). Both the average indifference point and the discounting rate were significantly and negatively correlated with closeness centrality and nodal efficiency (p values < 0.05 , [figure 3G–H and K–L](#)). We also tested these relationships in each group, and the results produced the same pattern ([online supplemental figure S3–4](#)). In addition, the relationship between degree centrality or eigenvector centrality of the right ORBsupmed and impulsivity in decision-making also showed the same pattern ([figure 3E–F, I–J and M–N](#)).

The above results demonstrate that impulsivity in decision-making decreased with the increase in the hubness of the right ORBsupmed. Based on this, we can speculate that individuals with IGD should show higher decision-making impulsivity than EIUs and HCs. Therefore, we further compared these impulsivity indices among the three groups, and the results were consistent with our speculation. Subjects with IGD chose significantly less delayed choice than EIU and HC subjects (ANCOVA: $F(73) = 7.42$, $p = 0.001$; IGD vs EIU: $p < 0.001$; IGD vs HC: $p = 0.007$; [figure 3O](#)). Subjects with IGD showed a higher average indifference point than EIU and HC subjects (ANCOVA: $F(73) = 8.21$, $p < 0.001$; IGD vs EIU: $p < 0.001$; IGD vs HC: $p = 0.003$; [figure 3P](#)). In addition, subjects with

IGD showed a higher discounting rate than EIU and HC subjects (ANCOVA: $F(73) = 8.31$, $p < 0.001$; IGD vs EIU: $p < 0.001$; IGD vs HC: $p = 0.004$; [figure 3Q](#)). Moreover, we also found that those in the EIU group showed slightly lower impulsivity than the HCs (p values < 0.1).

Further validation of the cognitive significance of the right ORBsupmed hubness in IGT

The above results have clarified the relationship between the hubness of the right ORBsupmed and impulsivity in decision-making. Based on this finding, we can infer that those with higher hubness in the right ORBsupmed, which is associated with lower impulsivity in decision-making, should perform better in IGT. To test this inference, we analysed the relationship between subjects' performance in IGT and hubness at the right ORBsupmed node. Consistent with our hypothesis, the subjects' performance indices, number of good choices and total net scores were positively correlated with closeness centrality and nodal efficiency of the right ORBsupmed (all p values < 0.05 , one side, [figure 4](#)). We also tested these relationships in each group, and the results produced the same pattern ([online supplemental figure S5](#)). In addition, the relationship between degree centrality or eigenvector centrality of the right ORBsupmed and impulsivity in decision-making also showed the same pattern ([online supplemental figure S6](#)).

To obtain a more refined parametric measure of subjects' underlying behavioural characteristics in the IGT decision-making process, we then modelled subjects' behavioural data via reinforcement learning models. Based on previous literature, four models were used: the PVL-Decay model, the PVL-Delta model, the VPP model and the ORL model. Hierarchical Bayesian analysis was used to estimate parameters, and the Gelman-Rubin statistic (R) was used to test the convergence of sampling chains. As shown in [online supplemental Table S1](#), the R of the sampling chains of each model was approximately 1, and the maximum value did not exceed 1.1, indicating that the variance between sampling chains was not greater than the variance within the sampling chain. Therefore, the sampling process reached a state of convergence. We also visually diagnosed the sampling chain performance by plotting the trace of the sampling chains to ensure that the chains converged. For reference, we provided the trace plot of the sampling chains of the VPP model (see [figure 5A](#) and [online supplemental figure S7–8](#)).

We then checked which model provided the best predictive accuracy, as measured by the leave-one-out information criterion (LOOIC) and widely applicable information criterion (WAIC). Note that the smaller a model's values of LOOIC or WAIC scores are, the better its model fits are. As noted in [figure 5B](#), the VPP model provided the best model fit relative to the other models in all groups. These results are consistent with several previous reports.^{25 36} We further validated the VPP model through simulations ([figure 5C](#)). The predictions for each group's average choice sequences exhibited high

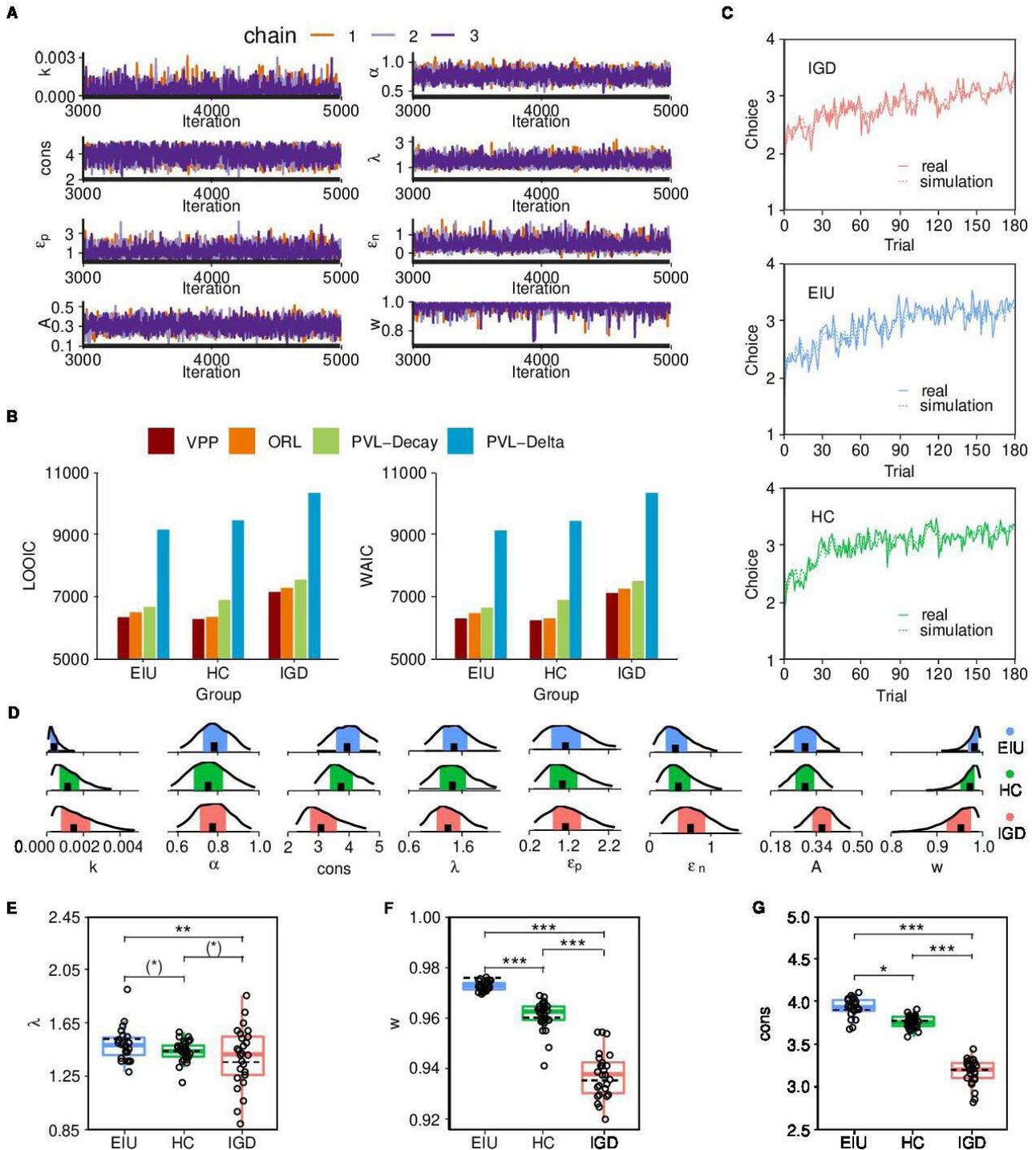


Figure 5 Modelling analysis of behaviour data in the Iowa gambling task (IGT). (A) Trace plot of the MCMC samples of the EIU group-level parameters in the VPP model. The first 3000 iterations were not plotted since they were burn-in samples. MCMC samples were well mixed and converged, which was consistent with their R values. The trace plot of the HC and IGD subjects are provided in online supplemental figures S10-11. (B) The LOOIC and WAIC of each model, computed separately for each group. (C) Simulations of the VPP model in each group. (D) Posterior distributions of group-level parameters in the VPP model. The black bar represents the median of the distribution. The coloured area represents the 50% CI, and the range of the distribution curve represents the 95% CI. (E) Distributions of the loss aversion parameter in each group and the statistical results. (F) Distributions of the reinforcement learning weight in each group and the statistical results. (G) Distributions of the consistency parameter in each group and the statistical results. The solid line within the boxplot represents the sample median, and the dashed line represents the covariate-adjusted sample mean. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; and (*) represents $p < 0.1$. CI, confidence interval; EIU, excessive internet game user; HC, healthy control; IGD, internet gaming disorder; LOOIC, leave-one-out information criterion; MCMC, Markov chain Monte Carlo; ORL, outcome-representation learning model; PVL-Decay, prospect valence learning with decay reinforcement learning rule model; PVL-Delta, prospect valence learning with delta reinforcement learning rule model; VPP, value-plus-perseverance learning model; WAIC, widely applicable information criterion.

accuracy. Additional checks of the simulation accuracy of each single subject are presented in online supplemental figures S9-11.

Next, we used the best-fitting model (VPP) to compare the three groups. For reference, we provided the posterior distributions of the group-level parameters of the VPP model (see [figure 5D](#)). The three groups showed significant differences in loss aversion (λ , $F(73) = 4.21$, $p=0.019$, [figure 5E](#)), reinforcement learning weight (w , $F(73) = 154.74$, $p<0.001$, [figure 5F](#)) and consistency parameter ($cons$, $F(73) = 179.34$, $p<0.001$, [figure 5G](#)). Specifically, the IGD group displayed lower loss aversion (IGD vs EIU: $p=0.005$; IGD vs HC: $p=0.082$), reinforcement learning weight (IGD vs EIU: $p<0.001$; IGD vs HC: $p<0.001$) and consistency parameter (IGD vs EIU: $p<0.001$; IGD vs HC: $p<0.001$) than the other two groups.

DISCUSSION

Main findings

In this study, we found that compared with both EIU and HC groups, the IGD group displayed decreased hubness in the right ORBsupmed. The hubness of this area was significantly and positively correlated with the HEIGD score of EIUs, while it was significantly and negatively correlated with the CEIGD score of subjects with IGD. These results indicate that the higher hubness of the right ORBsupmed may be a protective factor in preventing internet gaming addiction. Further modelling analysis of DDT and IGT revealed the cognitive significance of the hubness of the right ORBsupmed and linked it to impulsivity in decision-making. Combining all the results, we conclude that the lower hubness of the right ORBsupmed is a biomarker of IGD and is also associated with higher impulsivity in decision-making.

Dissecting core biomarkers of addiction-related disorders is especially challenging because it is difficult to determine whether the findings obtained are associated with the development of addiction or just the consequences of long-term recurrent addictive behaviour.¹⁶ To address this issue, we included EIU as a control group in this study. There was no significant difference between the EIU and IGD groups in the degree of internet game use. Thus, the lower hubness of the right ORBsupmed found in individuals with IGD compared with those in the EIU group was not caused by recurrent excessive internet gaming behaviour and can serve as a biomarker of IGD. Abnormal activity in the ORBsupmed area was also found in patients with IGD compared with HCs in previous studies,^{13 46 47} which was consistent with our findings. In addition to the right ORBsupmed, a previous study found several other brain areas also showed significantly altered hubness in individuals with IGD,¹³ and the alterations in those areas might result from recurrent excessive internet gaming behaviour.

What could be the mechanism underlying EIUs' display of higher hubness in the right ORBsupmed, while those with IGD display lower hubness in this region? The

significant positive correlation between the hubness of the right ORBsupmed and the HEIGD in EIU individuals but not in those with IGD could answer this question. HEIGD measures the highest degree of excessive internet games played the year before the experiment. Therefore, the positive correlation indicates that EIUs possess the ability to develop higher hubness in the right ORBsupmed when their engagement in internet games reaches a higher degree to prevent them from becoming addicted to internet games. The finding that the hubness of this region was not correlated with the CEIGD in the EIU group was also consistent with this explanation. Possibly due to differences in neuroplasticity, individuals with IGD do not possess this efficient protective mechanism and thus develop lower hubness in the right ORBsupmed compared with EIUs. Interestingly, we also found that the CEIGD of IGDs exhibited a significant negative correlation with the hubness of the right ORBsupmed. Considering that IGDs in this study were recruited from the hospital and were in a state of forced abstinence from internet games in the week before the experiment, this negative correlation indicates that higher hubness of the right ORBsupmed cannot only prevent EIU from being addicted to internet games but may also promote IGDs' recovery when they were undergoing forced abstinence.

The findings from the modelling analysis of DDT and IGT explained why the hubness of the right ORBsupmed is so important in the development and recovery of IGD. We found that higher hubness of the right ORBsupmed was associated with lower impulsivity in decision-making measured by DDT. Consistent with our findings, previous studies have also found that higher impulsivity and abnormal executive control-related circuitry are risk factors in the development of IGD.⁴⁸⁻⁵⁹ And the abnormal impulsivity in addicted patients was also found to be associated with altered functional connectivity in prefrontal areas,^{50-52 54} providing further supportive evidence for the association between lower hubness of the right ORBsupmed and higher impulsivity in decision-making. We also validated this finding in IGT. Since the hubness of the right ORBsupmed is related to impulsivity, we can naturally infer that the lower the hubness of this region, the worse the subjects' performance on IGT. Consistent with our inference, we found that participants' performance on IGT was associated with the hubness of the right ORBsupmed. Further comparison of parameters from modelling analysis of IGT revealed that the IGD group exhibited lower λ , w and $cons$ than the EIU and HC groups. λ is the loss aversion parameter and determines the sensitivity to loss compared with gains.²⁵ w is the reinforcement learning weight, and a low value of w indicates that the subject relies less on reinforcement learning.²⁵ $cons$ determines whether the choice is more random or deterministic.²⁵ Therefore, the smaller fitted values of IGD subjects on the three parameters reflect the impulsivity of their decision-making process, consistent with our findings in the DDT.

In summary, this study revealed that the hubness of the right ORBsupmed, which is associated with impulsivity in decision-making, plays a key role in whether individuals are addicted to internet games and can serve as a potential biomarker of IGD.

LIMITATIONS

Because of the effect of IGDs' internet gaming behaviour on education, an important limitation of the present study is the confounding influence of age and education level. However, the effects of these confounding variables can be removed by including them as covariates in the statistical analysis. Additionally, there was no significant difference in age between the IGD and HC groups. The pattern of the difference between the IGD and HC subjects was the same as that between the IGD and EIU subjects. Thus, the influence of age can be ruled out. Considering the potential gender differences,^{60,61} another limitation is that males dominated the participants in the current investigation. But this will not affect the importance of our findings in the present study, given that gaming disorder rates were approximately 2.5:1 in favour of males compared with females.⁶² Even so, future studies may consider employing a gender-balanced sample. The relatively small sample size is also a potential limitation of the present study. But this does not affect our conclusions, considering that the sample size of each group meets the required minimum size estimated based on a priori power analysis. Future studies may consider validating the findings in large samples. Another limitation to be noted is that even though considerable evidence in the present study supports the protective role of higher hubness of the right ORBsupmed in preventing internet gaming addiction, direct evidence from cohort studies is still needed in the future to validate the causal relationship between the hubness of the right ORBsupmed and IGD.

IMPLICATIONS

Our findings provide both theoretical and practical implications for the investigation of IGD. Hubness of the right ORBsupmed, which characterises the functional connectivity of the right ORBsupmed, plays a key role in the development of IGD. Future studies could focus on the genes and environments associated with the connectivity of this area to search for genome-wide associations of IGD, thereby providing more informative insights about the causation of this addiction disorder. The hubness of the right ORBsupmed highlighted in our data also provides clues for the diagnosis and treatment of IGD. Future research on the treatment of IGD should consider developing treatment plans that target the right ORBsupmed. Non-invasive stimulation protocols could be designed to strengthen the functional connections of the ORBsupmed and serve as potential treatments for IGD and other impulsivity-related disorders.

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