Effects of retrieval-extinction training on internet gaming disorder

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FULL-LENGTH REPORT

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ABSTRACT

Background and aims: Internet gaming disorder (IGD) leads to serious impairments in cognitive functions, and lacks of effective treatments. Cue-induced craving is a hallmark feature of this disease and is associated with addictive memory elements. Memory retrieval-extinction manipulations could interfere with addictive memories and attenuate addictive syndromes, which might be a promising intervention for IGD. The aims of this study were to explore the effect of a memory retrieval-extinction manipulation on gaming cue-induced craving and reward processing in individuals with IGD. *Methods:* A total of 49 individuals (mean age: 20.52 ± 1.58) with IGD underwent a memory retrieval-extinction training (RET) with a 10-min interval (R-10min-E, $n = 24$) or a RET with a 6-h interval (R-6h-E, $n = 25$) for two consecutive days. We assessed cue-induced craving pre- and post-RET, and at the 1- and 3-month follow-ups. The neural activities during reward processing were also assessed pre- and post-RET. *Results:* Compared with the R-6h-E group, gaming cravings in individuals with IGD were significantly reduced after R-10min-E training at the 3-month follow-up ($P < 0.05$). Moreover, neural activities in the individuals with IGD were also altered after R-10min-E training, which was corroborated by enhanced reward processing, such as faster responses ($P < 0.05$) and stronger frontoparietal functional connectivity to monetary reward cues, while the R-6h-E training had no effects. *Discussion and Conclusions:* The two-day R-10min-E training reduced addicts' craving for Internet games, restored monetary reward processing in IGD individuals, and maintained long-term efficacy.

INTRODUCTION

Internet gaming disorder (IGD) is characterized by the excessive and repetitive use of Internet-based games that leads to serious impairments in psychological and social function (Petry et al., 2014). Due to its increasing harmfulness, the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) included IGD as a psychiatric disorder candidate, and the International Classification of Disease 11th Revision (ICD-11) included gaming disorder as a formal diagnosis of disorders due to addictive behaviors. Since the existing treatments for IGD, such as pharmacotherapy, cognitive-behavioral therapy, and other types of interventions, lack stable efficacy based on the peer-reviewed literature (Griffiths, Kuss, Billieux, & Pontes, 2016; Kaptsis, King, Delfabbro, & Gradisar, 2016; Torres-Rodríguez, Griffiths, Carbonell, & Oberst, 2018; Young, 2013; Zajac, Ginley, Chang, & Petry, 2017), more effective treatments are much in need. Craving is a hallmark feature of addictive disorders and one of the most frequent causes of relapse, even after long periods of abstinence (Courtney, Schacht, Hutchison, Roche, & Ray, 2016; Engelmann et al., 2012; Robinson & Berridge, 1993). It may shift attentional and monitoring processes toward gaming-related cues (Decker & Gay, 2011; Zhou, Yuan, & Yao, 2012), and it also reflects the "incentive salience" of gaming-related cues (Robinson & Berridge, 1993). Interventions aimed at reducing cue-induced craving might be a promising approach for IGD (Dong & Potenza, 2014; King & Delfabbro, 2014). Notably, reducing addictive memory elements, important drivers of addiction syndromes, including craving (Hyman, 2005; Hyman, Malenka, & Nestler, 2006), can greatly reduce the relapse risk (Monfils & Holmes, 2018) and has attracted growing attention.

Memory retrieval-extinction manipulations are nonpharmacological methods that interfere with pathological memories. Acute exposure to associative cues followed by repeated exposure to the same cues within the reconsolidation time window resulted in the updating of the original reward memory with new information that is incongruent with the established cue-drug contingency (drug cues no longer predict pharmacological reward). It can prevent the reinstatement, renewal, and spontaneous recovery of pathological memories, thereby reducing the addicts' craving and urge to use. Recent studies have shown that memory reconsolidation is a time-dependent process (<6 h), and memories can be rendered labile following retrieval and are susceptible to updating or disruption (Alberini, 2005; Dudai, 2006; Nader, Schafe, & Le Doux, 2000). The extinction manipulation is in the timeframe of the "reconsolidation time window" after cued retrieval of the memories, and researchers have found that the retrieval-extinction interval within the reconsolidation window (10 min) has a better performance on clinic patients by comparing with other intervals (e.g., 6 h) (Monfils, Cowansage, Klann, & LeDoux, 2009; Xue et al., 2012). These memory retrieval-extinction manipulations have been used to measure the efficacy of treatment for drug addiction in human and animal studies (Chen et al., 2019; Everitt, 2014; Everitt & Robbins, 2016; Germeroth et al., 2017; Liu et al., 2020; Luo et al., 2015; Ma, Zhang, & Yu, 2012; Millan, Milligan-Saville, & McNally, 2013; Milton & Everitt, 2012; Sartor & Aston-Jones, 2014; Xue et al., 2012). Xue et al. (2012) were the first to use this approach in humans with drug addiction. Their results showed that a retrieval-extinction manipulation with a 10-min interval caused a reduction in cue-induced craving compared to a 6-h interval, and this effect lasted for 6 months after intervention in humans with heroin addiction who had been abstinent from the drug (Xue et al., 2012). Similarly, another study showed that cue-induced cravings and smoking behaviors were significantly reduced in humans with nicotine addiction (Germeroth et al., 2017). These evidences support memory retrieval-extinction manipulations as a promising treatment for addiction (Monfils & Holmes, 2018). However, the efficacy of the memory retrieval-extinction manipulations for treating nondrug addictions, such as IGD, needs to be verified.

Furthermore, despite extensive studies of the efficacy of memory retrieval-extinction manipulations on addictions, little is known about their impact on cognitive function, such as reward processing. Models of addiction posit that alterations in reward processing are a key factor contributing to drug abuse and relapse (Bechara, 2005). Prolonged drug use impacts the mesolimbic dopamine system, resulting in addictive rewards gaining increased incentive salience, whereas the incentive salience of nonaddictive rewards (e.g., money) is reduced (Koob & Le Moal, 1997; Robinson & Berridge, 1993). Previous studies have revealed the effects of memory retrieval-extinction manipulations on reducing the incentive salience of addictive rewards by showing reduced drug-related craving (Germeroth et al., 2017; Xue et al., 2012). However, whether this manipulation could restore the incentive salience of nonaddictive rewards and the underlying mechanisms are poorly understood. Executive control over incentive salience is essential to maintain goal-directed behavior, and executive control deficits drive dysfunction in reward function, which plays a critical role in the development and maintenance of drug addiction (Bechara & Martin, 2004; Hinson, Jameson, & Whitney 2003). Working memory is a crucial component of cognitive control and is centrally involved in goal-directed behavior. Limited working memory could lead to abnormal reward evaluations, such as a poor ability at keeping information related to addictive rewards out and information related to nonaddictive rewards in (Bechara & Martin, 2004; Hinson, Jameson, & Paul, 2003), which reduces the effects of the incentive salience of nonaddictive rewards in drug addiction (Robinson & Berridge, 1993).

The primary goal of the present study was to extend the findings derived from drug addiction to nondrug addiction by examining the effect of a memory retrieval-extinction manipulation on cue-induced gaming craving and cognitive functions in IGD individuals. The first hypothesis was that compared to the memory retrieval extinction manipulation with a 6-h interval (R-6h-E), the memory retrieval-extinction manipulation with a 10-min interval (R-10min-E) would reduce cue-induced gaming craving immediately, and/or maintain a long-term

effect on IGD individuals. The second hypothesis was that the R-10min-E treatment effects would generalize to improvements in reward processing. We tested the second hypothesis by using the monetary incentive delay task (MIDT) combined with Electroencephalogram (EEG) recording.

METHODS

This study was registered in the Chinese Clinical Trial Registry (ChiCTR-IPR-17012886, http://www.chictr.org.cn/showproj.aspx?proj=21961).

Participants

We conducted eligibility screening of 403 young adults from universities in Hefei, China via online or offline advertisements and posters. The sample size calculation was performed with the G*Power program. Assuming a moderate effect size of 0.25, with 95% power and an alpha of 5%, the required number of participants in this study was 44 (Cohen, 2013). To account for possible dropouts, 60 IGD individuals (18–23 years old) were recruited, and they were not simultaneously involved in other gaming disorder intervention plans.

Participants who met the following criteria joined in the experiment: 1) they played an Internet game named League of Legends (LOL, one of the most popular massively multiplayer online role-playing games among Chinese college students) for more than 21 h per week; 2) they met 5 or more out of 9 criteria for Internet Gaming Disorder in the DSM-5. The exclusion criteria were as follows: 1) chronic neurological, psychological, or physical diseases; 2) treatment with any drugs during the previous 3 months; 3) diagnosis of depression or anxiety by the Beck Depression Inventory and Beck Anxiety Inventory, respectively; 4) generally ill-suited to perform EEG; 5) other drug dependence including nicotine and alcohol or nonsubstance use disorders; or 6) being left-handed. During the experiment, 2 participants were lost to the two-day intervention, 4 participants were lost to the 1-month follow-up, and 5 participants were removed due to low EEG data quality. The data of the remaining 49 participants were used for analysis. A CONSORT flow diagram is shown in Fig. 1.

All participants provided written informed consent before the study and were paid 240 RMB (~USD 35) after completing four experimental visits. The participants were randomly assigned to either the experimental group (10-min time window; $n = 24$, including 2 females and 22 males; mean age: 20.56 ± 1.63) or the control group (6-h time window; $n = 25$, including 1 female and 24 males; mean age: 20.48 ± 1.53).
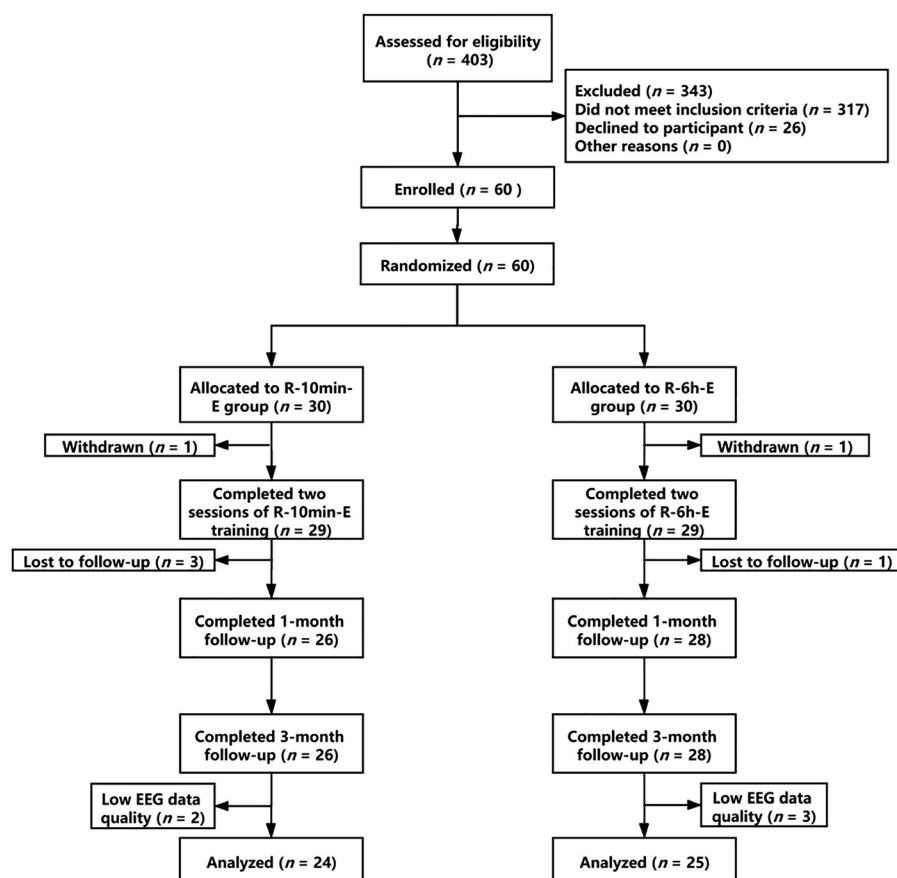

Fig. 1. **CONSORT Flow Diagram**. R-10min-E indicates memory retrieval-extinction training with 10-min interval; R-6h-E indicates memory retrieval-extinction training with 6-h interval

Procedure

This was a randomized single-blind study comparing two different intervals within the RET for IGD. We informed the participants that we were conducting a study on the craving mechanism of Internet gaming disorder. After admittance, participants were randomized using a computer-generated random number sequence in a 1:1 ratio into one of the two treatment groups R-10min-E training and R-6h-E training. Randomization was concealed for participants, and the participants in either the control or the experimental group did not know the experimental time interval of the other group. The study blinding was successfully maintained to the end of the study, and no one reported being treated. Follow-up measures were conducted at RET completion and 1 and 3 months post RET. The experimental procedure consisted of four stages: (i) baseline session; (ii) retrieval-extinction training (RET) sessions; (iii) posttraining session; and (iv) follow-up session. Figure 2A provides a diagrammatic summary of the study design and procedures.

Intervention

The RET included retrieval and extinction sessions separated by different intervals, i.e., 1) R-10min-E and 2) R-6h-E. All

participants were randomly assigned to 1 of the 2 groups who received R-10min-E training or R-6h-E training for 2 consecutive days. Regarding the second group, the participants could do their routine work. However, they could not play LOL or get exposed to game-related materials within the 6-h interval. During the retrieval session, the participants were exposed to the 5-min game-related video; during the extinction sessions, the participants were given 4 consecutive sessions of repeated exposures to different types of game-related cues, each session consisting of 5-min game-related words (100 words, 3,000 ms for each word), 5-min game-related pictures (100 pictures, 3,000 ms for each picture), and 5-min game-related video. All the cues were selected from 300 words, 300 pictures, and 10 video clips based on the scores given by excessive Internet gamers (score ≥8 with a maximal score of 10). All participants were required to not play LOL during the whole experiment and to be supervised by their roommates or friends.

Measures

Baseline characteristics. Each participant received a baseline assessment of demographic and clinical characteristics and completed the Beck Anxiety Inventory (BAI) (Fydrich, Dowdall, & Chambless,1992), Beck Depression Inventory (BDI)
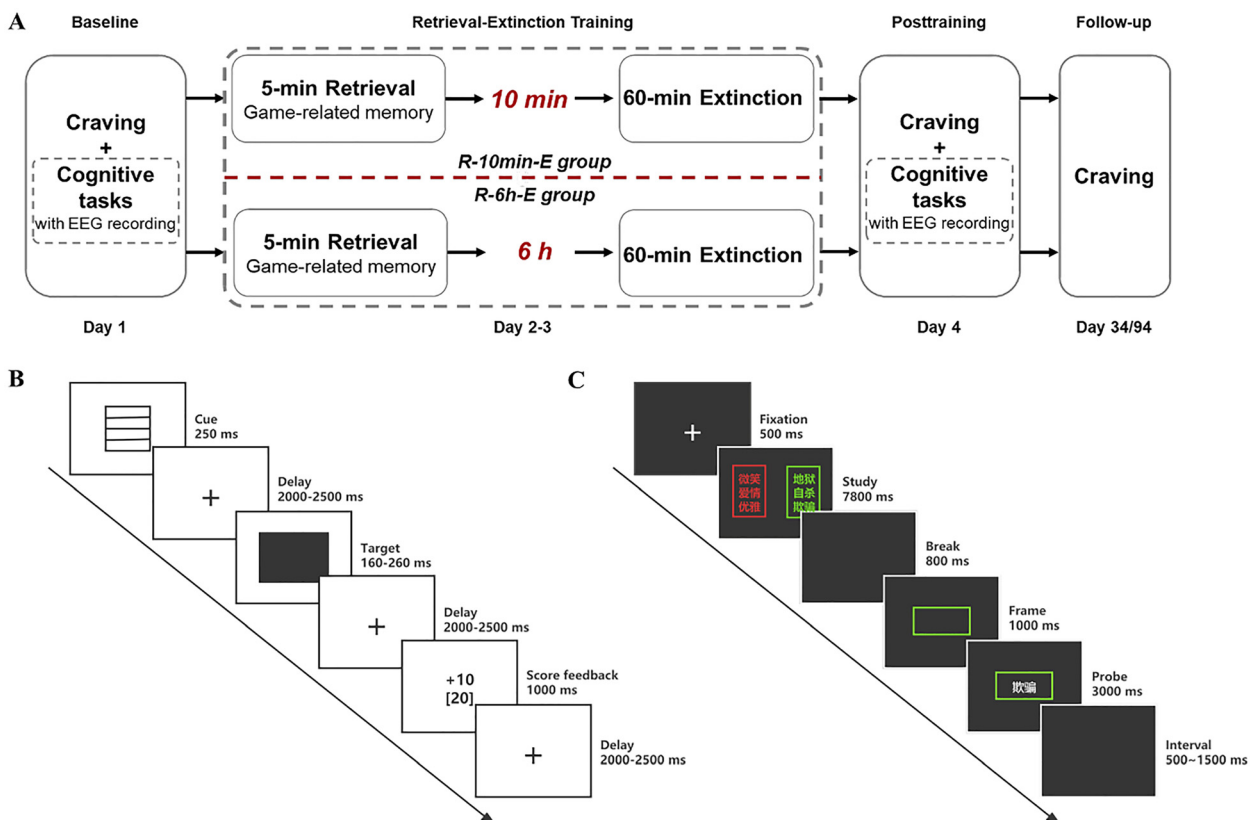

Fig. 2. **Experimental design**. (A) A timeline of the experiment. On day 1, participants received baseline assessments; on days 2–3, the participants were divided into two groups and trained in the retrieval-6 h-extinction (R-6h-E group) context or retrieval-10 min-extinction (R-10min-E group) context for two days; on day 4, the participants received the same assessment on day 1; on day 34/94, participants' craving levels were tested. (B) MIDT procedure. Structure of the task for a gain trial (Knutson et al., 2003). (C) MST procedure. Structure of the task for a relevant trial (Joormann & Gotlib, 2008)

(Dozois, Dobson, & Ahnberg, 1998), Raven's Intelligence Test (Raven, 2000), Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987), and Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998). Internet gaming craving was induced by a 5-min game-related video clip showing a real gaming scenario. Internet gaming craving was assessed using a visual analog scale (VAS) (Dong et al., 2017; Zhang et al., 2016), i.e., an undivided line marked at the left and right ends with 0 ("not at all") and 10 ("extremely high"), on which the participants rated and self-reported their craving level for the Internet game before and immediately after exposure to the game-related video clip.

After receiving an assessment of the change in scores related to gaming craving, the participants were instructed to complete 2 behavioral tasks, i.e., a modified monetary incentive delay task (based on Knutson, Fong, Bennett, Adams, & Hommer, 2003) and a modified Sternberg task (Joormann & Gotlib, 2008). The subjects sat in a chair at an eye distance of 100 cm from a 21-inch monitor. All subjects were asked to focus on the center of the monitor and to try to avoid blinking and head movement during the experiment. Electroencephalogram (EEG) activities were recorded.

Monetary incentive delay task (MIDT). In the MIDT (Fig. 2B, adopted from Knutson et al., 2003) each of the two task sessions consisted of 75 trials presented in a pseudo-randomized order, yielding a total of 150 trials. During each trial, the participants saw one of five cue shapes (cue: 250 ms), fixed on a crosshair as they waited for a variable interval (delay: 2,000–2,500 ms), and then responded to a solid black target square that appeared for a variable length of time (target: 160–260 ms) by pressing the "1" button as quickly as possible. Following target disappearance, feedback (feedback: 1,000 ms) notified participants whether they had won or lost money during that trial and indicated total money that had accumulated up to that point. On incentive trials, the participants could win or avoid losing money by pressing the button during the target presentation. EEG acquisitions were time-locked to the offset of each cue and thus were acquired during the anticipatory period.

The cues signaled potential reward outcomes ($n = 60$, denoted by open squares), potential loss outcomes ($n = 60$, denoted by open circles), or no money outcomes ($n = 30$, denoted by open triangles). Gain cues signaled the possibility of winning either ¥1 ($n = 30$, a square with one horizontal line) or ¥10 ($n = 30$, a square with three horizontal lines). Similarly, loss cues signaled the possibility of losing either ¥1 ($n = 30$, a circle with one horizontal line) or ¥10 ($n = 30$, a circle with three horizontal lines).

Modified sternberg task (MST). The MST (Fig. 2C, adopted from Joormann & Gotlib, 2008) assessed how individuals store and retrieve random information from short-term memory. In the MST, the participants completed a total of 96 trials, which were divided into three blocks and preceded by three practice trials. Each trial had three separate displays: a learning display, a cue display, and a probe display. In the learning display, two lists of three words in red and green

were simultaneously presented, and participants were instructed to memorize all six words. Next, a red or green frame was presented in the cue display. The color of the frame indicated which of the two lists just presented would be relevant regarding a decision about the upcoming probe. Finally, a single word in black appeared in the red or green frame, which was the probe display. The participants' task was to indicate as quickly and accurately as possible by pressing the appropriate keys on the keyboard whether the word came from the relevant list (press "J") or not (press "K") (see details in the supplementary material).

Cue-induced craving. Internet gaming craving was assessed on days 1, 4, 34, and 94. The cue-induced craving score was the difference between the craving test scores before and immediately after exposure to the game-related video clip.

Neural activities of reward processing. The neural activities during cognitive tasks after the RET were measured by reaction times, P3 amplitudes, and functional connectivity associated with each type of cue in the MIDT and MST. The relationships between these outcomes were analyzed by correlations between these results (e.g., craving scores and functional connectivity value of gain cues during the MIDT).

Physiological recording

EEG data were recorded using a SynAmps amplifier (NeuroScan, Charlotte, NC, USA) with an elastic cap incorporating 64 Ag/AgCl electrodes that are placed on the scalp at specific locations based on the extended international 10–20 system. The electrical activities were recorded over the left and right mastoids. Horizontal electrooculography (EOG) was recorded using a bipolar channel placed lateral to the outer canthus of each eye, and vertical EOG was recorded using a bipolar channel placed above and below the left eye. The reference electrode was attached to the tip of the nose, and the ground electrode was attached to AFz. The impedance between the reference electrode and any recording electrode was kept under 5 kΩ. Alternating current signals (0.03–100 Hz) were continuously recorded and digitized with a 24-bit resolution at a sampling rate of 500 Hz during data collection. Electrocardiography (ECG) and Skin Conductance Response (SCR) data were recorded with BIOPAC MP150 system (Goleta, CA, USA). ECG was assessed using 3 ECG clamps connected to the BioPac System's ECG module. The 3 clamps were attached to both legs and left wrist of the participants. SCR was assessed using 2 Ag–AgCl electrodes, which were connected to the BioPac System's skin conductance module. The electrodes were attached to the first and second fingers of the left hand, between the first and second phalanges (ECG and SCR data will be reported elsewhere).

EEG data analysis

Preprocessing. Offline analyses in the 2 behavioral tasks were conducted using MATLAB (2016a). EEG data were preprocessed using EEGLab toolbox (Delorme & Makeig, 2004).
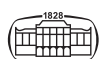
The preprocessing steps for each participant were as follows: We resampled the signal at 500 Hz, and bandpass (1–50 Hz) filtered the data with a finite impulse response (FIR) filter. Electrodes with excessively noisy signals were interpolated from neighboring electrodes using spherical spline interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989). Continuous EEG data were segmented into 2,000 ms epochs, beginning at 500 ms prior to stimulus onset. Independent component analysis was used to correct for ocular and muscle artifacts. Each epoch was visually inspected for remaining artifacts, which were removed from subsequent analyses.

Event-related potentials (ERPs). For stimulus-evoked activity, we examined the P3 component in a time window immediately following stimulus onset. ERPs were grand averaged based on each cue in different tasks across participants (in the MIDT, we combined the two kinds of gain cues for these analyses). EEG signals were bandpass-filtered at 1–30 Hz. Only artifact-free and correct trials were included in the analysis. All ERPs were quantified by the mean amplitude measure relative to the −200 to 0 ms prestimulus baseline. We compared the P3 component at electrode site Pz (the most frequently reported electrode site for analysis in previous studies). The P3 amplitude was obtained by calculating the average amplitude of the selected group peak time window (300–600 ms).

Functional connectivity. The EEG datasets were divided into nonoverlapping 1-s epochs, including a 100 ms prestimulus baseline. Time-frequency domain features were calculated by short-time Fourier transform. We compared the features under different conditions and found areas with significant differences (400–500 ms time range, 8–13 Hz frequency range). Then, functional connectivity was computed for each epoch and pair of electrodes. Analyses were focused on the 400–500 ms time range and 8–13 Hz frequency range. Before computing connectivity measures, a current-source-density transform was applied to the EEG data, as in previous studies. This method provides a reference-independent signal and acts as a spatial filter, leading to a relatively improved spatial resolution. The wPLI measures the extent to which phase angle differences between two time series x(t) and y(t) are distributed toward positive or negative parts of the imaginary axis in the complex plane (Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011).

Statistical analysis

The variance analysis on the measured variables was conducted by two-way mixed-design repeated measures analysis of variance (ANOVA), using the RET (group) as a between-subjects factor, time as a within-subjects factor, and gender, age, BDI score, BAI score, and TPQ score as covariates. Significant effects from the ANOVA were followed by Bonferroni correction. Student's t-tests were performed to compare conditions. Pearson's correlation analysis was conducted to analyze correlations between two variables. All reported P-values were two-tailed, and a P-value below 0.05 was considered to indicate statistical significance. The false discovery rate (FDR) approach was applied for the correction for multiple comparisons in

functional connectivity analyses, and the corrected threshold was set at $P < 0.05$. All analyses were performed using SPSS 24 and MATLAB (2016a).

Ethics

The study procedures were carried out in accordance with the Declaration of Helsinki. The Institutional Review Board of the Biomedical Ethics Committee of University of Science and Technology of China approved the study. All subjects were informed about the study and all provided informed consent.

RESULTS

Demographic and clinical characteristics

We found no differences in the baseline demographic and clinical characteristics between the R-10min-E group and the R-6h-E group by using independent sample t-tests (Table 1).

R-10min-E training decreased IGD individuals' gaming cravings

The RET (R-6h-E, R-10min-E) * time (Pre-RET, 1-month, 3-month) interaction on gaming craving was significant in long-term, $F_{2, 39} = 3.546$, $P = 0.037$, $d = 0.430$ (Fig. 3). At the 3-month follow-up, the R-10min-E group showed significant decreased gaming craving compared to R-6h-E group ($t_{47} = -2.385$, $P = 0.042$, Bonferroni correction, $d = 0.634$, $\Delta = -0.847$ [95% CI, $-1.562 – -0.133$]). However, there is no significant RET (R-6h-E, R-10min-E) * time (Pre-RET, Post-RET) interaction on gaming craving after the intervention immediately, $F_{1, 40} = 0.738$, $P = 0.395$, $d = 0.135$. Our results indicated that IGD individuals' craving for Internet games significantly decreased after R-10min-E training, although no significant main effect of RET on the number of DSM-5 criteria met was found (Figure S1).

Table 1. Baseline demographic and clinical characteristics in the two groups

Characteristic	R-10min-E($n = 24$)	R-6h-E($n = 25$)	P-value
Age, years	20.56 ± 1.63	20.48 ± 1.53	0.852
SPM Score	89.03 ± 8.68	91.00 ± 8.35	0.764
TPQ			
NS	15.39 ± 0.94	16.57 ± 0.59	0.57
HA	15.66 ± 1.40	16.2 ± 1.25	0.77
RD	16.62 ± 0.89	17.63 ± 0.65	0.36
BDI	5.36 ± 0.90	4.53 ± 0.65	0.46
BAI	6.41 ± 1.01	7.75 ± 1.50	0.49
HVLT-R			
HVLT-R-1	28.59 ± 0.95	28.41 ± 0.93	0.89
HVLT-R-2	10.11 ± 0.32	9.7 ± 0.45	0.47
HVLT-R-3	11.11 ± 0.23	11 ± 031	0.77

Data are presented as means±standard deviations.
BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; SPM = Raven's Intelligence Test; TPQ = Tridimensional Personality Questionnaire; HVLT-R = Hopkins Verbal Learning Test-revised.
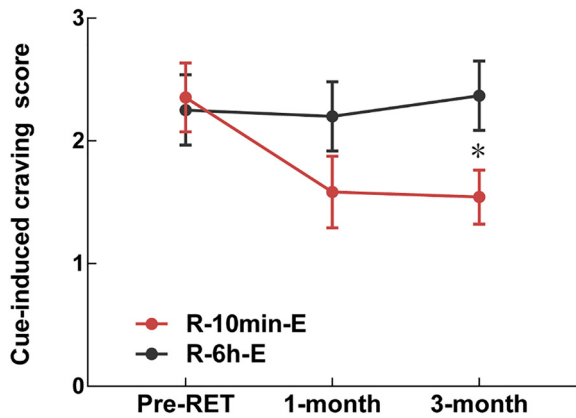
Fig. 3. **R-E training effects on gaming craving**. The effect of R-10min-E and R-6h-E trainings on IGD individuals' gaming craving. Error bars indicate standard errors (SEs). "Pre-RET" was defined as before the R-E intervention. * $P < 0.05$

R-10min-E training accelerated IGD individuals' reaction to monetary rewards

The RET (R-6h-E, R-10min-E) * time (pre-RET, post-RET) interaction on reaction time (RT) with gain cues on the MIDT was marginally significant, $F_{1, 40} = 3.000$, $P = 0.091$, $d = 0.304$. There was a marginally significant main effect of

RET on the RT with gain cues on the MIDT, $F_{1, 40} = 3.716$, $P = 0.061$, $d = 0.305$, $\Delta = -26.864$ [95% CI, $-55.029 – 1.302$], with a faster response to gain cues in the R-10min-E group than in the R-6h-E group, $t_{47} = -2.276$, $P = 0.028$, $d = 0.620$, $\Delta = -37.685$ [95% CI, $-71.175 – -4.194$] after training (Fig. 4A). However, there was no main effect of RET on the RT with neutral cues in the MIDT (Figure S2).

R-10min-E training impacted IGD individuals' P3 amplitude evoked by monetary reward cues

In the MIDT, we compared P3 components evoked by gain cues between RET groups from Pre-RET to Post-RET (Fig. 4B and C). Regarding P3 amplitudes, no significant RET (R-6h-E, R-10min-E) * time (pre-RET, post-RET) interaction was found, $F_{1, 40} = 1.630$, $P = 0.209$. The main effect of the RET was also not significant, $F_{1, 40} = 0.470$, $P = 0.497$, although the R-10min-E group exhibited a significantly increased P300 amplitude, $t_{23} = -2.194$, $P = 0.039$, $d = 0.456$ (Fig. 4B), while the R-6h-E group did not exhibit an effect, $t_{24} = -1.351$, $P = 0.189$ (Fig. 4C). However, there was no significant correlation between P3 amplitudes and RTs with gain cues in the R-10min-E group ($r = 0.056$, $P = 0.794$) after RET, and P3 amplitudes were not correlated with craving scores ($r = -0.049$, $P = 0.820$). P3 amplitudes evoked by the neutral cues also showed no significant difference between pre- and post-RET (Figure S3).
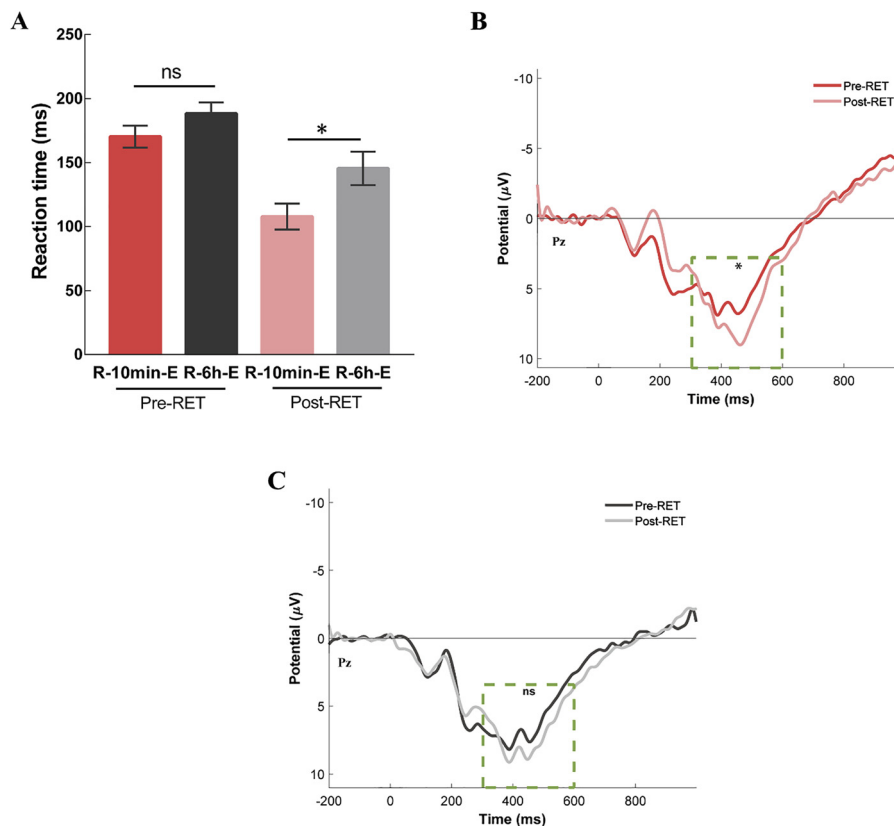

Fig. 4. **R-E training effects on behavioral performance and P3 amplitudes during MIDT**. (A) Effect of R-E training on reaction times with gain cues between the R-6h-E and R-10min-E groups. Grand-averaged ERP evoked by gain cues from pre-RET and post-RET in the (B) R-10min-E group and (B) R-6h-E group. P3 (Pz) amplitudes were calculated by averaging the amplitudes between 300-600 ms and circled by the green dotted line. * $P < 0.05$; ns: not significant

R-10min-E training enhanced IGD individuals' frontoparietal connectivity to monetary reward

The functional connectivity of gain cues in the MIDT was significantly increased between several pairs of frontoparietal lobe electrodes ($P < 0.05$, FDR correction) after RET relative to values observed in time-point shuffled data in the R-10min-E group but not in the R-6h-E group (400–500 ms time range, 8–13 Hz frequency range; Fig. 5A and B). Further analysis revealed that functional connectivity between P6-F2, P8-F2, PO4-FC4, PO6-F2, PO6-FCz, and PO8-F2 was

specifically enhanced after training in the R-10min-E group. The wPLI values for these electrode pairs in the ROI (400–500 ms time range, 8–13 Hz frequency range) showed significant RET (R-6h-E, R-10min-E) * time (pre-RET, post-RET) interactions and were mainly positioned on the frontoparietal lobe (Fig. 6). Additionally, the participants in the R-10min-E group with greater decreases in the wPLI values exhibited greater decreases in craving scores in P6-F2 ($r = -0.410$, $P = 0.046$), P8-F2 ($r = -0.596$, $P = 0.002$), PO4-FC4 ($r = -0.617$, $P = 0.001$), PO6-F2 ($r = -0.512$, $P = 0.011$), PO6-FCz ($r = -0.562$, $P = 0.004$), and PO8-F2 ($r = -0.495$, $P =$
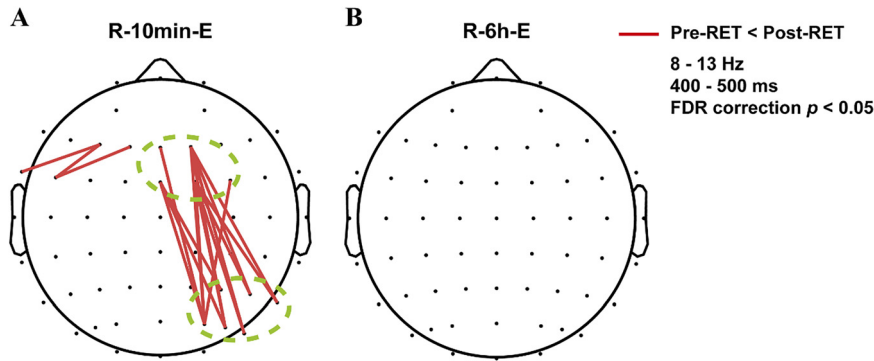

Fig. 5. **R-E training effects on functional connectivity during the MIDT**. Electrode pairs with significantly changed wPLI values in the ROI with gain cues in the (A) R-10min-E group and (B) R-6h-E group. ROI: 8–13 Hz range, 400–500 ms range. The red lines represent the electrode pairs with significantly enhanced connections (Pre-RET < Post-RET); the green dotted line circles the areas where these electrodes were mainly located
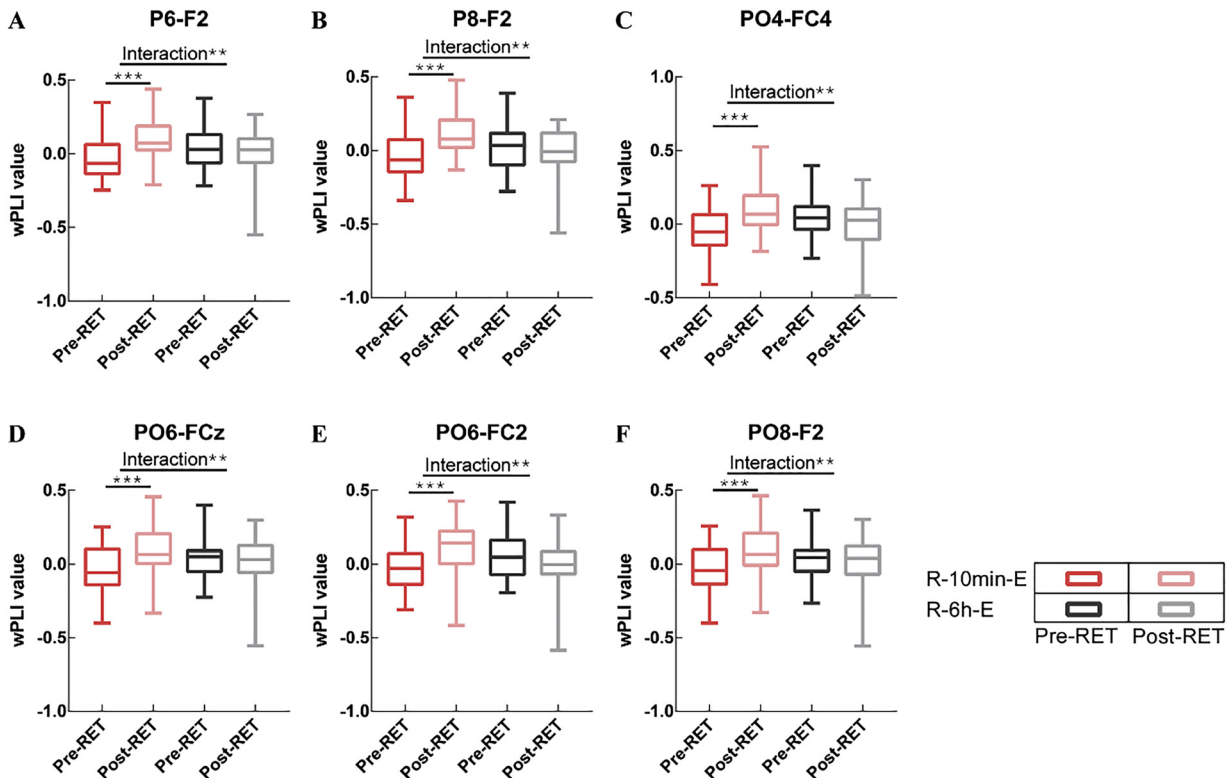

Fig. 6. **R-E training effects on functional connectivity between paired electrodes**. Effects of R-E training on electrode pairs' wPLI values with gain cues in pre-RET and post-RET in the R-6h-E group and R-10min-E group. Two-way ANOVA was performed. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

0.014) (FDR correction) (Fig. 7). No significant correlations were observed in the changed wPLI values and gaming craving scores in either group (all $P > 0.05$) (Figure S4). We also compared functional connectivity to neutral cues before and after RET in the R-10min-E group and R-6h-E group, and there were no significant changes in functional connectivity of the electrode pairs (Figure S5).

R-10min-E training failed to affect IGD individuals' working memory

We calculated the difference in RT (intrusion-new) as a measure of working memory. There was no significant RET (R-6h-E, R-10min-E) * time (pre-RET, post-RET) interaction on RT differences, $F_{1, 40} = 0.519$, $P = 0.476$ (Figure S6). We compared P3 amplitudes evoked by the intrusion and new cues, and no difference was found between pre-RET and post-RET in either group (all $P > 0.05$) (Figure S7). We also compared functional connectivity to intrusion and new cues before and after RET in the R-10min-E group and R-6h-E group, and there were no significant changes in functional connectivity of the electrode pairs (Figure S8).

DISCUSSION

The primary findings in this study were that R-10min-E training, relative to the ineffective R-6h-E training,

significantly reduced IGD individuals' gaming craving in long-term but not immediately. Moreover, the R-10min-E training also restored IGD individuals' monetary reward processing, which was corroborated by the assessment of gain cues in the MIDT, such as faster responses and stronger frontoparietal functional connectivity related to monetary reward. These findings are consistent with the reconsolidation hypothesis, namely, that game-related memory retrieval-extinction manipulations within the reconsolidation window would result in the updating of the game-reward contingency in memory and produce the observed behavioral outcomes. In summary, to our knowledge, this is the first study that applied a manipulation of memory retrieval and extinction in the treatment of IGD, leading to promising efficacy in those IGD individuals who completed a two-day R-10min-E training reported significant gaming craving reductions up to 3 months post-intervention and recovered from monetary reward processing dysfunction.

The present study extended the application range of memory retrieval-extinction manipulations from drug addictions (Xue et al., 2012) to nondrug addictions, such as IGD. This study revealed the effects of a brief R-10min-E training intervention on craving reduction in individuals with IGD. For the R-6h-E group, no significant reductions in craving were found on days 1, 4, 34, and 94 after training, which was consistent with the study conducted by Xue et al. (2012). Xue et al. found that retrieval of drug-associated
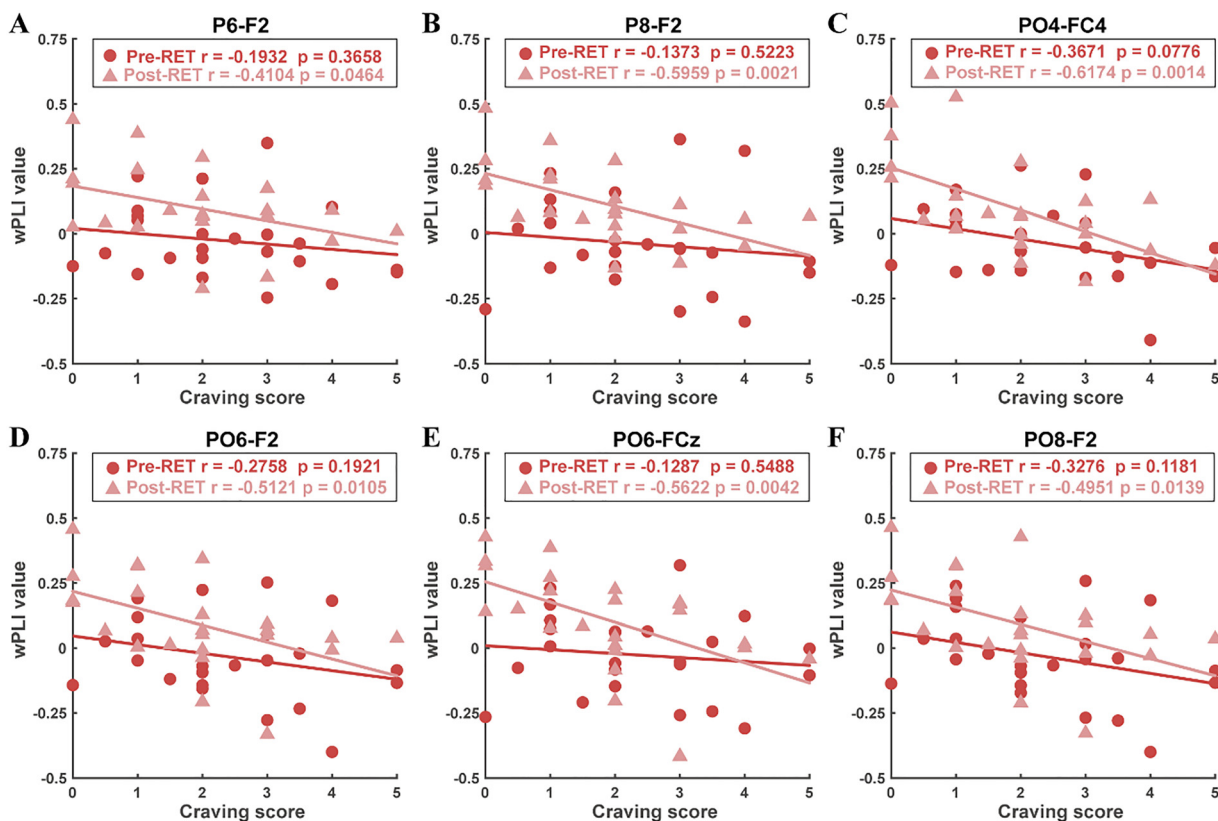

Fig. 7. **R-E training effects on functional connectivity correlate with gaming craving**. Correlations between the wPLI values with gain cues in the MIDT and craving scores in pre-RET and post-RET in the R-10min-E group. The wPLI values were between the electrode pairs with significantly changed functional connectivity

memories 10 min rather than 6 h before extinction sessions attenuated cue-induced drug craving in drug addicts. The consistent results indicated that the 10-min time window is crucial in the R-E training paradigm to reduce drug and gaming cravings.

The different findings between long-term and immediate effects of RET on craving were somewhat unexpected. One possibility is that for the R-6h-E group, though with no updating of gaming-related memory, extinction-related inhibition may be produced by extensive massed cue exposure (Chandler & Gass, 2013; Myers & Carlezon, 2010; Quirk & Mueller, 2008; Self, Choi, Simmons, Walker, & Smagula, 2004; Sutton et al., 2003). The extinction inhibition effect was getting weaker as time passed by, leading to reductions of the craving after the intervention immediately and at the 1-month follow-up assessment but a rebound at the 3-month follow-up assessment. For the R-10min-E group, it was the memory updated that produces persisted decreasing effect all the time, which was suggested to resist spontaneous recovery and drug-primed reinstatement. Due to the differences between extinction-related inhibition and memory reconsolidation, a significant difference in cravings emerged at the 3-month follow-up assessment.

The present study demonstrated that R-10min-E training can enhance the monetary reward processing in IGD individuals. The reward processing patterns of addictive individuals have been reported to be abnormal, including decreased incentive salience of nonaddictive rewards (Nestor, Hester, & Garavan, 2010; Robinson & Berridge, 1993) and reduced sensitivity to changes in the magnitude of rewards when processing monetary rewards (Goldstein et al., 2007, 2008). In the MIDT, the IGD individuals responded faster to monetary reward cues after R-10min-E training. Faster RTs were the direct outcomes of higher sensitivity and faster monetary reward processing. In the ERP analysis, a significant increase in P3 amplitudes at Pz evoked by the gain cues after R-10min-E training was found in the IGD individuals. P3 is elicited by monetary incentive cues and generally increased following exposure to salient stimuli. Reward cues that signal the possibility of receiving reward also lead to a more positive cue-induced P3 amplitude (Broyd et al., 2012; Goldstein et al., 2006; Polich & Kok, 1995; Pornpattananangkul & Nusslock, 2015; Ramsey & Finn, 1997). P3 amplitudes can also reflect neural activation levels during reward processing, supported by the observation that P3 amplitudes at Pz are positively correlated with neural activation in the ventral striatum, an important brain area related to reward processing for gain anticipation induced by gain cues (Novak & Foti, 2015; Pfabigan et al., 2014). Our findings may suggest that IGD individuals' incentive salience and sensitivity to monetary reward, to some extent, were restored after R-10min-E training. However, we didn't find significant changes in the stimulus-preceding negativity (SPN) amplitudes before the feedback onset after the intervention in the MIDT (see details in supplementary material). The SPN reflects the feedback-anticipation during reward processing, which can be interpreted as an anticipation of the motivational valence of the

reward cues (Brunia, 1988; Brunia, Hackley, van Boxtel, Kotani, & Yoshimi, 2011; Walentowska, Paul, Carlo Severo, Moors, & Pourtois, 2018). The insular cortex, which is thought to be involved in the processing of motivational input, has been identified as the main generator of the SPN component (Böcker, Brunia, & van den Berg-Lenssen, 1994; Brunia et al., 2011; Kotani et al., 2003). Some studies showed that IGD individuals have less impaired brain functions than drug addicts, and the brain regions related to the reward circuit were also less impaired (Kuss, Pontes, & Griffiths 2018; Yao et al., 2017). Combined with our negative result of the SPN after R-10min-E training, these findings may suggest that the IGD's motivational function at feedback-anticipation stage is plausibly intact during reward processing.

Importantly, our study found that alpha-band fronto-parietal connectivity during monetary reward processing was enhanced in IGD individuals after R-10min-E training, and the wPLI value for this connectivity was negatively correlated with gaming craving scores. Frontoparietal connectivity has been related to executive control function, and executive control function over incentive salience was shown to be impaired in IGD individuals (Cheng et al., 2020; Dong & Potenza, 2014; Koob & Volkow, 2016; Li et al., 2020; Love, Laier, Brand, Hatch, & Raju, 2015; Yuan et al., 2016). Our findings suggested that lower gaming craving for Internet games contributes to more executive control resources for monetary rewards, which was reflected by enhanced frontoparietal connectivity in the MIDT. The increased distribution of executive control resources to monetary rewards may weaken the interference of addictive rewards on nonaddictive reward processing. However, the relationship between recovered reward processing and redistribution of executive control resources in addiction needs further causal research in the future. Meanwhile, the cue-induced P3 amplitudes in MST can reflect neural activities related to working memory processing, and the parietal P3 amplitude has been validated to associate with the allocation of attentional resources for updating of working memory contents (Ford, Roth, Mohs, Hopkins, & Kopell, 1979; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Polich & Kok, 1995; Verleger, 1988). Previous studies also revealed that people with IGD present deficiencies in working memory and have higher cue-induced P3 amplitude than healthy people in working memory tasks (Nie, Zhang, Jia, & Li, 2016; Zhou, Zhu, Li, & Wang, 2014; Zhou, Zhou, & Zhu, 2016). But no direct evidence supports the relationship between restored reward processing and recovered working memory since the IGD individuals showed no differences in working memory performance or the ERP analysis during the MST after R-10min-E training.

The first limitation of the present study was that it is difficult to generalize the conclusions of this study to female addicts since only a few female subjects were recruited. The proportion of female addicts among those with IGD is very small (Fam 2018; Mihara & Higuchi 2017). Although a gender-unbiased recruitment advertisement was used in the recruitment process, only a few female participants were

recruited in our study. In future research, it is necessary to recruit more female subjects to explore the degree of generalization of the conclusions. The second limitation was that our research was a single-blind design: given that it was a pilot study, our results need to be confirmed using a double-blind design. The third limitation was that we used the same gaming-related stimuli on the 4 craving tests. Though a practice effect might exist due to the same stimuli, the claim of craving decrease by the effective intervention was evidenced by a comparison between the effective and ineffective intervention, which could control the impact of practice effect. It is certainly valuable to use novel stimuli to assess whether the effects of the effective intervention (RET with 10 min interval) can be generalized to novel gaming-related stimuli. The final limitation was that the improvement in reward processing in the IGD individuals was relatively weak (e.g. Weak effects on RTs and P3 amplitudes in the MIDT). There was also no improvement in working memory. The possible explanations of these results were that 1) the retrieval-extinction training was specific for the manipulation of gaming-related memory but not reward processing or working memory, and; 2) the additional effects on these two cognitive functions were difficult to amplify through only 2 days of training; 3) IGD participants have less impaired cognitive functions compared with drug addicts, and their relatively intact cognitive functions may be more difficult to be improved due to the ceiling effect. However, our study provided convergent evidence of behavioral and EEG results that contribute to improvements in reward processing in IGD individuals. In future work, an extended training procedure is needed to confirm the retrieval-extinction training effect on addicts' reward processing and other cognitive functions.

CONCLUSION

In conclusion, we applied R-10min-E training to the treatment of IGD for the first time. The two-day R-10min-E training intervention reduced addicts' craving for Internet games and restored monetary reward processing in IGD individuals. These results suggest that retrieval-extinction manipulations may have great potential to be utilized for clinical use to treat IGD.

SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2022.00006.

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