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CLINICAL TRIAL

Emotional bias modification weakens game-related compulsivity and reshapes frontostriatal pathways

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Addiction is characterized by compulsive engagement despite adverse consequences. Psychobehavioural interventions targeting compulsivity in addictions are relatively rare, particularly for behavioural addictions like internet gaming disorder (IGD). Free from confounding drug-on-brain effects, IGD provides a promising model for understanding neuropsychological processes of addictions. IGD is a global concern in the setting of increasing internet use worldwide. Thus, developing interventions and understanding their mechanisms of action are important. Positive emotional association biases (EABs) towards addiction cues based on reward conditioning may underlie addiction-associated compulsivity. Here, we developed an EAB modification (EABM) protocol and examined whether modifying EABs via cognitive training would alter neurocognitive aspects of addiction-associated compulsivity in IGD.

We recruited 90 IGD participants who were randomly assigned to receive EABM or sham training in a 1:1 ratio (clinicaltrials.gov identifier: NCT04068064). The EABM intervention involved six consecutive days of exposure to negative emotional terms linked to gaming stimuli and positive terms linked to non-gaming healthy-alternative stimuli. The sham training involved similar stimuli linked to neutral words. Participants underwent event-related functional MRI while performing a regulation-of-craving task and received several behavioural assessments pre-training and post-training. Primary efficacy measures were changes in gaming-related positive EABs, and compulsive gaming thoughts and behaviours.

Behaviourally, EABM (versus sham) training decreased gaming-related positive EABs and compulsive gaming thoughts and behaviours. Neurally, EABM training involved decreased activation in the bilateral dorsal striatum in the regulation-of-craving task and altered left dorsal striatum-centric functional connectivity with ventral prefrontal cortical regions, which correlated with decreases in gaming-related EABs or compulsive gaming thoughts and behaviours. EABM training also implicated activation changes in the right medial frontal gyrus and posterior insula.

EABM may reduce compulsive gaming thoughts and behaviours via reshaping functional organization of frontostriatal pathways and insular activity in IGD. The therapeutic potential of EABM should be examined in larger, longer-term studies, as should its application to other addictive disorders.

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Introduction

Addiction is characterized by compulsive behavioural engagement despite adverse consequences.[1,2] Empirically validated psychobehavioural interventions targeting compulsive processes in addictions are relatively rare, particularly for behavioural addictions like internet gaming disorder (IGD). Sharing core neuropsychological processes with gambling and substance-use disorders,[3,4] IGD was included in *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5).[5] IGD represents a promising model free from confounding drug-on-brain effects for understanding neuropsychological processes of addictions.[6] As the most frequent subtype (57.5%) of internet addiction,[7] IGD represents a global public health concern,[4] which may be aggravated by the coronavirus disease 2019 (COVID-19) pandemic.[8,9] Intervention research targeting compulsive processes in IGD may promote public health efforts for this condition specifically and addictions broadly.

Multiple theories (e.g. the reinforcement theory, incentive sensitization theory and interaction of person–affect–cognition–execution model) and empirical evidence suggest that reward-conditioning may be an important contributor to the formation of compulsive addictive behaviours.[10–12] Via repetitive reinforcement from hedonic experiences, addiction cues may be preferentially associated with immediate reward feelings rather than long-term negative consequences/emotions associated with addictions; that is, positive emotional association biases (EABs) towards addiction cues.[13,14] Such biases may help maintain stimulus-–approach–response habits, accompanied with compulsivity-related neuroadaptations, making addiction cues 'automatically' elicit compulsive engagement in addictive behaviours.[15,16] Previous studies aiming to modify EABs suggest that pairing alcohol cues with negative pictures may increase negative emotions towards alcohol and reduce drinking,[17,18] but little research has examined whether EAB modification (EABM) may affect neurocognitive aspects of compulsive processes in addictions. Concerning addiction-associated compulsivity, animal research and cross-sectional studies implicate frontostriatal pathways as involved in habitual approach tendencies and weakened inhibitory control.[19–23] Specifically, as approach tendencies become more habitual, addiction-cue processing over time may shift to dorsal striatum (DS) from the ventral striatum,[23,24] leading to 'wanting-related' compulsive engagement rather than 'liking-related' impulsive engagement.[25] Abnormal activation of, and interactions within, frontostriatal circuitry may underlie addiction-related impairments in inhibitory control that may become more habitual over time.[2,21,22] However, few psychobehavioural intervention studies have examined whether such neuroadaptations can be reshaped via targeting addiction-related compulsivity in behavioural addictions.

The current study examined in IGD whether EABM would affect compulsive gaming and related neuroadaptations. Previous interventions for IGD have been mainly psychotherapies (e.g. cognitive behavioural therapy, family-based intervention and counselling programmes),[7,26] which required the participation of therapists, limiting widespread application. The current EABM simply involved completion of cognitive tasks, which would facilitate widespread use. This study also examined neural mechanisms underlying intervention effects, which may facilitate development of individualized treatments for IGD.

To enhance the robustness of the approach, the current EABM protocol optimized aversive-conditioning protocols used previously[17,18] by setting probabilistic reward learning and increasing training duration (see details in the 'Materials and methods' section). To examine intervention effects and neural mechanisms, this study used relevant behavioural assessments and a well-validated functional MRI regulation-of-craving task[27,28] with theoretical links to neuroadaptations of addiction-associated compulsivity.[10,11,18] During the gaming-related regulation-of-craving task, participants were instructed to react naturally to gaming images in the look condition and reduce cue-induced craving via cognitive reappraisal in the regulate condition, linking to learned approach tendencies and inhibitory control, respectively.[27,29] Given that neurocognitive aspects of compulsive processes in addictions may result from reward-conditioning,[10,11,24] we hypothesized that EABM training would reduce compulsive gaming thoughts and behaviours and other indicators including positive EABs, IGD severity and weekly gaming time, and alter neural correlates of regulation-of-craving task performance involving DS activity and frontostriatal functional connectivity. Given potential EABM contributions to making stimuli potentially more aversive, we hypothesized insular and amygdalar involvement.

Materials and methods

Participants

Young adults (n = 1085) were screened via online questionnaires and telephone interviews from universities in Beijing, China (Fig. 1). The desired sample was 66 [F-tests: $\alpha = 0.05$, power = 0.8, medium effect size (Cohen's f) = 0.25] using G*Power 3.1.9.2.[30] Given

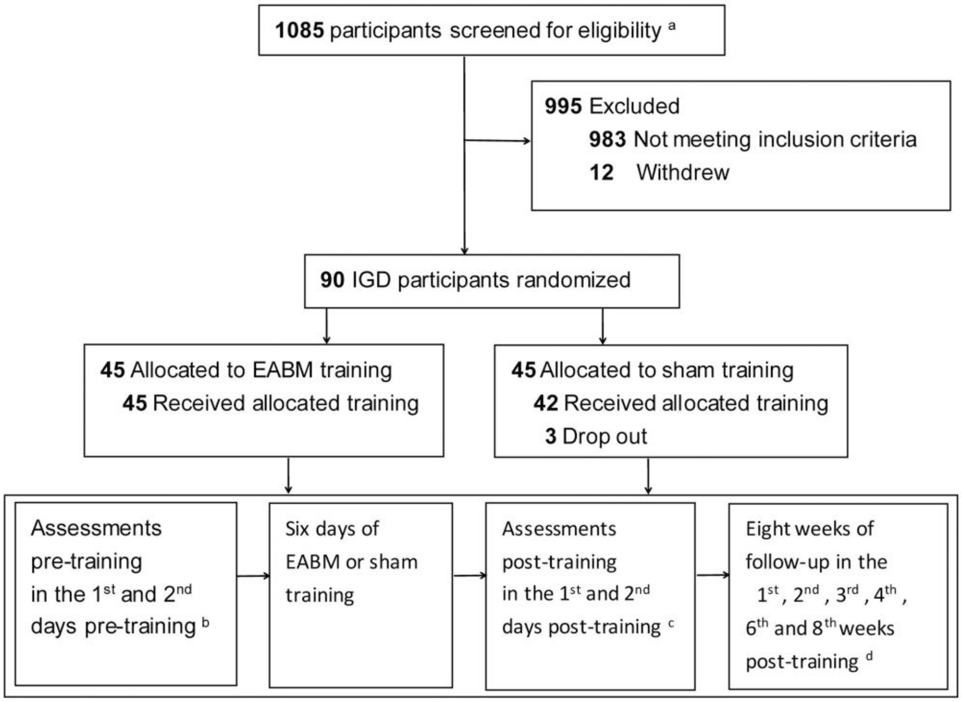

Figure 1 Study flow chart and design. Advertisements led to 1085 young adults from universities in Beijing being screened for eligibility. We recruited 90 IGD participants. Eighty-seven participants completed the EABM or sham training. The intervention included 6 days of training and assessments pretraining, post-training and during an 8-week follow-up. [a]The 1085 individuals who were screened included individuals with IGD and non-IGD gaming participants. [b]Assessments pretraining included compulsive gaming thoughts and behaviours, IAT-assessed severity of IGD, weekly gaming time, responses during a functional MRI regulation-of-craving task and gaming-related EABs. [c]Assessments post-training included responses in the functional MRI regulation-of-craving task and gaming-related EABs. [d]An 8-week follow-up included assessments of compulsive gaming thoughts and behaviours and weekly gaming time in Weeks 1, 2, 3, 4, 6 and 8 post-training and IAT-assessed severity of IGD in Weeks 4 and 8 post-training.

that previous research pairing alcohol cues with negative pictures showed increased negative emotions towards alcohol and reduced drinking behaviours with some medium effects,[29] we estimated a medium effect size here. Given possible drop-out, we recruited a larger sample of 90 participants. In accordance with higher prevalence of IGD in males,[31] most study participants were male. Inclusion criteria included endorsing ⩾5 items of the proposed DSM-5 criteria for IGD, scoring ⩾50 on Young's online internet addiction test (IAT),[32] spending more than 50% of online time gaming and playing internet games ⩾20 h/week for ⩾1 year.[33,34]

IGD participants endorsed one of three internet games popular among Chinese youth (i.e. League of Legends, King of Glory and Playerunknown's Battlegrounds) as their preference. Experimental tasks that included gaming picture were given in three versions based on the three types of internet games. Participants were assigned to the version in accordance with the preferred game. Potential participants were excluded for any of the following conditions: (i) risky drinking, as defined by scoring ⩾5 on the Alcohol Use Disorder Identification Test[35] and scoring ⩾ 6 on the Michigan Alcoholism Screening Test[36]; (ii) nicotine dependence, as defined by scoring ⩾6 on the Fagerström Test for Nicotine Dependence[37]; (iii) current or previous use of illegal drugs (any prior exposure); (iv) neurological or psychiatric disorders and use of psychotropic medications as assessed using the Chinese version of the Mini International Neuropsychiatric Interview[38]; (v) any history of head trauma, presence of metal in the body or other contraindication to functional MRI scanning; and (vi) left-handedness. To avoid confounding effects from recent gaming experience, we instructed all participants not to play any internet games for 3 days prior to assessments. To avoid confounding effects from substance use on imaging data, participants were asked not to smoke or drink for 3 days prior to scanning. All participants reported compliance with the abstinence requirements upon arrival.

The study was approved by a research ethics committee at the Beijing Normal University. All participants provided written informed consent and were paid for their participation.

Study design, intervention and assessments

The intervention was sham-controlled, between-subject, randomized and double-blind (trial registration: clinicaltrials.gov identifier: NCT04068064). IGD participants randomly received six consecutive days of EABM or sham training in a 1:1 ratio (see detailed randomization in Supplementary Table 1). Pretraining measures assessed compulsive gaming thoughts and behaviours (using the Yale–Brown Obsessive–Compulsive Scale modified for IGD (IGD-YBOCS), IGD severity (using the IAT), weekly gaming time and regulation-of-craving task-evoked blood oxygen level-dependent (BOLD)-functional MRI neural responses 2 days before training, and gaming-related EABs (assessed with a priming task) 1 day before training. Assessments post-training included functional MRI regulation of craving and priming tasks. Eighty-seven IGD participants completed EABM or sham training including assessments pre- and post-training, with three participants (in the sham group) discontinuing after assessments of

Table 1 Demographic and clinical characteristics of participants

	EABM (45)		Sham (42)			
	Mean	SD	Mean	SD	t	P
Age	20.56	1.42	20.57	1.45	−0.05	>0.1
Gender, male/female	35/10[a]	–	38/4[a]	–	2.60[b]	>0.1
IGD severity (IAT)	67.58	13.55	67.60	11.91	−0.006	>0.1
Weekly gaming time	25.24	5.40	26.24	7.23	−0.73	>0.1
Anxiety (BAI)	2.02	3.12	1.55	2.22	0.81	>0.1
Depression (BDI)	3.16	3.12	3.14	4.18	0.02	>0.1
Impulsivity (BIS-11)	76.07	8.88	72.63	8.50	1.81	=0.07
Self-control (DMSCS)	32.79	5.56	34.66	5.63	−1.53	>0.1
Sensation seeking (SSS)	26.49	5.18	28.05	5.53	−1.34	>0.1
Reward sensitivity (BIS/BAS)	36.49	4.87	38.02	3.73	−1.62	>0.1
Punishment sensitivity (BIS/BAS)	22.88	4.16	24.00	3.56	−1.32	>0.1
Alcohol using	11[a]	–	12[a]	–	0.19[b]	>0.1
Tobacco smoking	4[a]	–	1[a]	–	1.70[b]	>0.1

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BIS-11 = Barratt Impulsiveness Scale; BIS/BAS = Behavioural Inhibition System/Behavioural Approach System Scale; DMSCS = Dual-Mode of Self-Control Scale; EABM = Emotional Associative Bias Modification; IAT = Young's Online Internet Addiction Test; IGD = internet gaming disorder; SSS = Sensation Seeking Scale.
[a]Number of participants.
[b]Chi-square test.

IGD-YBOCS, IAT and weekly gaming time pretraining. Participants in the EABM and sham groups were comparable on demographic and clinical characteristics (Table 1). Imaging data from four IGD participants (two in the EABM group) were discarded for motion exceeding 2 mm in translation or 2° in rotation ($n = 2$)[39] or missing in-scanner data due to accidental failure during scanning ($n = 2$). An 8-week follow-up included assessments of compulsive gaming thoughts and behaviours and weekly gaming time at 1, 2, 3, 4, 6 and 8 weeks post-training, and IAT-assessed severity of IGD at 4 and 8 weeks post-training, with 87 participants (45 in the EABM group) having completed it in Weeks 1, 2, 3 and 4, 81 participants (42 in the EABM group) in Week 6 and 82 participants (41 in the EABM group) in Week 8. Overall, 77 participants (39 in the EABM group) completed the entire follow-up.

Prior EABM protocols[17,18] only included a 1-day training for building associations between addiction-cue and negative emotions. Associations were generated by presenting relevant stimuli together and instructing participants to conduct button-press responses irrelevant to the associations. The current EABM protocol optimized previous research by increasing training duration, expanding stimulus types and setting probabilistic reward learning. Specifically, it involved six consecutive days of exposure to negative emotional terms (e.g. frustrated, self-abased) linked to gaming stimuli and positive terms (e.g. successful, confident) linked to non-gaming healthy-alternative stimuli, aimed to reduce gaming-related positive EABs. During EABM training, gaming and healthy-activity (e.g. sporting, reading, playing an instrument) pictures were always presented with negative and positive word-pairs, respectively. We set probabilistic reward learning, in which participants might get monetary rewards via word selections, to facilitate acquisition of associations. Specifically, selecting a fixed word of the word-pair was associated with a high probability (80%) of getting monetary reward ('+25', equalling CN¥0.1) and a low probability (20%) of no reward ('+0'), and probabilities were reversed for the other word. Participants were instructed to select words via button-press to acquire as much monetary reward as possible. Participants were paid (CN¥560) for completion of the experiment and received additional money (CN¥120–240) for experimental rewards obtained. We set probabilistic monetary rewards in the current training for three reasons. First, monetary rewards, particularly probabilistic monetary rewards, might motivate participants to mobilize more cognitive resources to learn the current new associations, thus facilitating modification of positive EABs that existed towards gaming. Second, it helped conceal the real purpose of the training, thus facilitating participants to form adaptive emotional associations unconsciously. Third, it might make the training more interesting and reduce potential drop-out. The sham training was virtually identical to the EABM training except that words were neutral.

Each trial of the training (Supplementary Fig. 1A) started with a fixation cross for 600–800 ms, followed by a gaming or healthy-activity picture. Participants were required to carefully observe the picture. A pair of emotional words appeared on the picture after the picture was solely presented for 2000 ms. Each picture was paired with a fixed word-pair. Participants were asked to select one of the two words. Participants pressed the right button of the computer mouse to select the word on the right and the left button for the left word. The picture with the word pair disappeared upon button-press. They would also disappear if participants did not make a selection within 2000 ms. Afterwards, response feedback including reward acquired in the current trial ('+25' or '+0') and accumulated reward until the current trial was presented for 800 ms. Participants were told that they would get additional money based on the rewards won in the training apart from the base payment after completion of the study. We instructed participants to maximize their earnings via word selections, without informing them of rules for acquiring rewards.

The training task included 10 gaming pictures, 10 healthy-activity pictures, five pairs of negative words and five pairs of positive words in total. Every two pictures shared the same word-pair. Each training run comprised 100 gaming picture trials and 100 healthy-activity picture trials, presented in a pseudo-randomized order. Participants received two training runs every day, with 200 pairings of gaming and negative emotions and 200 pairings of healthy activities and positive emotions in total. The training lasted for six consecutive days. Apart from the implicit reward rules, participants needed to complete word selections within 2000 ms to get rewards in the first 2 days and complete them within 1000 ms, 900 ms, 800 ms, 700 ms, respectively, in the following 4 days. We employed such an approach to gradually facilitate the consolidation of new associations. The training took 25–40 min every day. Pictures in the training tasks were different but comparable to those in the priming task and fMRI regulation-of-craving task, so that we could test the generalized intervention effects on internet gaming rather than on specific gaming pictures.

The IGD-YBOCS is based on the YBOCS for heavy drinking, an instrument with good construct validity and internal consistency.[40,41] In the IGD-YBOCS, 'drinking' in the YBOCS for heavy drinking was replaced with 'playing internet games'. See a translated version of the IGD-YBOCS in the Supplementary material. A pilot cross-sectional study with 30 individuals with IGD and 30 gamers without IGD showed that scores of compulsive gaming thoughts and behaviours on IGD-YBOCS distinguished well individuals with and without IGD and that total scores of IGD-YBOCS positively correlated with those of IAT and DSM-5 criteria counts, suggesting validity of the IGD-YBOCS (Supplementary material).

The regulation-of-craving task is validated for assessing controlled and automatic processing of appetitive stimuli.[27,34] The current functional MRI-regulation-of-craving task included four conditions: gaming look, healthy-activity look, gaming regulate/decrease, and healthy-activity regulate/increase. Participants were instructed to observe pictures while maintaining craving for gaming or healthy activity in the look conditions, and decrease or increase their craving via cognitive reappraisal in the decrease or increase conditions. The task was block-designed. Each block (Supplementary Figure 1C) began with an instructional cue (look/decrease/increase) for 2000 ms, with 'look' instructions for gaming look and healthy-activity look blocks, 'decrease' instructions for gaming decrease blocks and 'increase' instructions for healthy-activity increase blocks. Afterwards, five gaming or healthy-activity pictures were successively presented, with each picture presented for 3700 ms following a 300 ms fixation cross. We required participants to naturally view or reappraise these stimuli according to the instructional cue. Participants were instructed to decrease their craving for gaming via considering negative consequences of excessive gaming (e.g. it harms physical health, psychosocial functioning and academic/work performance) in gaming-decrease blocks, and increase craving for healthy activities via considering positive effects of regular engagement in these activities (e.g. enjoyment, achievement) in healthy-activity increase blocks. Afterwards, a 5000 ms craving-rating phase ensued, during which participants rated craving levels for gaming or healthy-activity on a 9-point Likert scale (from 1 = 'not at all' to 9 = 'very much').

The current functional MRI regulation-of-craving task included two runs with 60 gaming pictures and 60 healthy-activity pictures in total. Each run included 12 blocks with three blocks per condition. Blocks were presented in a pseudo-randomized order with a 10 s interblock interval. Gaming and healthy-activity pictures for the look and decrease/increase conditions were comparable on self-reported craving levels and arousal from a separate sample of 30 internet-game players in a pilot test (P's > 0.1), respectively. Participants practiced prior to scanning. Functional MRI data acquisition of the regulation-of-craving task was conducted on a 3 T Siemens Prisma scanner. See more details in the Supplementary material.

The priming task is validated for assessing EABs towards stimuli.[42] Participants were instructed to judge the emotional valence of positive or negative words following priming pictures in the task. Taking gaming-related stimuli as an example, faster responses to positive words than to negative words following gaming pictures indicates positive EABs towards gaming. The current priming task included two types of runs: gaming picture and healthy-activity picture runs. Each run included two types of trials: positive and negative word trials. Each trial (Supplementary Fig. 1B) started with a fixation cross for 600–800 ms. Afterwards, a gaming picture or healthy-activity picture in accordance with the type of the current run appeared for 200 ms and participants were instructed to observe the picture. Following each picture, a positive or negative word was presented for 300 ms. Participants were instructed to indicate the emotional valence of the word via button response as quickly and accurately as possible. The assignment of response buttons was counterbalanced across participants—for half of the participants, pressing the left button of the computer mouse for positive words and the right for negative words was done, and vice versa for the other half. Upon termination of the target stimulus, the fixation cross reappeared for 1500 ms. Gaming-related positive EABs could be calculated by determining differences in reaction times [RTs; $RTs_{(negative-word)}$ minus $RTs_{(positive-word)}$] in response to words following gaming pictures. Analogous calculations were applied to healthy-activity-related positive EABs. Larger scores reflect larger positive EABs.

The current task included 20 gaming pictures, 20 healthy-activity pictures, 10 positive words and 10 negative words. Each gaming or healthy-activity picture constituted one negative-word trial and one positive-word trial within one run, so that crucial features (e.g. craving and arousal levels) of pictures for the positive-word and negative-word conditions were comparable. Forty positive-word trials and 40 negative-word trials were presented in a pseudo-randomized order within each run, with the restriction that no more than three trials from the same condition were presented consecutively. The task included two gaming picture runs and two healthy-activity picture runs. Participants practiced prior to the formal experiment.

Blinding and adverse events

The study was double-blind. IGD participants were blind to both the purpose of training and training condition. Experimenters were blind to the training condition. All IGD participants were randomly assigned to training type 1 or 2 in a 1:1 ratio and double-blind fashion. All IGD participants were not told the study was investigating an intervention targeting gaming behaviour. Instead, they were told it was an experiment examining behaviours involving maximizing monetary bonuses. After completion of the study, participants were informed that the study was an intervention on gaming behaviour and they might have received real or sham training. Moreover, they were instructed to guess their training condition by choosing one of the following answers: 'Strong belief that I received real training'; 'Moderate belief that I received real training'; 'I do not know'; 'Moderate belief that I received sham training'; 'Strong belief that I received sham training'. After study completion, participants rated potential adverse events (negative feelings, mental disorder and physical harm) associated with the training via 'yes' or 'no' responses.

Statistical analyses

Primary efficacy measures were changes in gaming-related positive EABs and compulsive gaming thoughts and behaviours. Secondary outcomes were changes in healthy-activity-related positive EABs, IAT-assessed IGD severity, weekly gaming time and craving during the regulation-of-craving task. We conducted Group (EABM, sham) × Time (pretraining, post-training/follow-up) ANOVAs supplemented by simple effects analyses where appropriate. Considering that there were multiple measures, primary and secondary outcomes were, respectively, corrected for multiple comparisons using false discovery rate (FDR) correction. Corrected P-values are reported. See details in the Supplementary material.

As with neural changes, during whole-brain univariate activation analyses, in first-level analyses, a general linear model including four regressors of task conditions (i.e. gaming look, gaming decrease, healthy-activity look and healthy-activity increase) during picture presentation and the regressors of instruction and craving-rating phase were built for each participant and convolved with the canonical haemodynamic response function, with six realignment parameters included as regressors of no interest. In second-level analyses, we first conducted two-sample t-tests for each task condition with imaging data of pretraining to detect whether EABM and sham groups were comparable on baseline regulation-of-craving task neural responses. Next, intervention effects on BOLD signal for each task condition were assessed using Group (EABM, sham) × Time (pretraining, post-training) ANOVAs. We calculated EABM (post-training > pretraining) > sham (post-training > pretraining) contrasts for each task condition to indicate intervention-elicited increases or decreases in brain activation. The whole-brain activation analysis was conducted with a threshold of voxel-level $P < 0.001$ prior to cluster-level family-wise error (FWE) correction ($P_{FWE} < 0.05$).[33] Considering that we tested intervention effects on neural responses of four different conditions during the regulation-of-craving task, neural results were corrected for multiple comparisons using FDR correction. For regions showing significant intervention effects, parametric estimates in the identified regions (10 mm spheres centred at peak coordinates) were extracted. Pearson correlation analyses were used to examine relationships between neural responses and behavioural indicators.

Given the role of the DS in addiction-related compulsivity[25,43] and that training-related attenuation of DS activation positively related to decreases in gaming-related EABs in the current study (see 'Results' section), we examined whether and how the EABM intervention would relate to functional connectivity between the DS and other brain regions in four different conditions during the regulation-of-craving task, using a generalized form of task-dependent psychophysiological interaction (gPPI) analyses.[44] See details in the Supplementary material.

Data availability

Data are available when required by contacting zhangjintao@bnu.edu.cn

Results

Primary efficacy: intervention effects on gaming-related positive EABs, compulsive gaming thoughts and behaviours

Analyses for gaming-related positive EABs [$RTs_{(gaming-negative-word)} - RTs_{(gaming-positive-word)}$; Fig. 2A and Supplementary Table 2] revealed a significant group-by-time interaction [$F(1,85) = 4.50$, $P_{uncorrected} = 0.037$, $P_{corrected} = 0.037$, $\eta_p^2 = 0.05$], with the EABM (versus sham) group showing no significant difference pretraining [$P > 0.1$, 19.26 (32.42) versus 22.82 (27.98)] and showing a larger decrease post-training (pretraining minus post-training) [$t(85) = 2.12$, $P = 0.037$, 17.95 (22.49) versus 7.29 (24.37)].

Analyses of compulsive gaming thoughts scores (Fig. 2B and Supplementary Table 3) showed a significant group-by-time interaction [$F(6,450) = 2.70$, $P_{uncorrected} = 0.014$, $P_{corrected} = 0.021$, $\eta_p^2 = 0.04$], with the EABM (versus sham) group showing no significant differences pretraining [$P < 0.1$, 12.21 (2.42) versus 11.89 (2.95)], showing no significantly larger decreases, respectively, in Weeks 1, 2 and 3 post-training [P's < 0.1; 3.21 (3.60) versus 2.08 (2.87); 3.13 (3.97) versus 1.89 (2.98); 3.05 (4.77) versus 1.58 (3.22)], and showing larger decreases, respectively, in Weeks 4, 6 and 8 post-training [$t(75) = 2.36$, $P = 0.021$, 3.54 (3.83) versus 1.68 (3.01); $t(75) = 2.36$, $P = 0.021$, 3.72 (3.59) versus 1.82 (3.47); $t(75) = 2.93$, $P = 0.004$, 4.26 (4.01) versus 1.66 (3.75)].

Analyses of compulsive gaming behaviour scores (Fig. 2C and Supplementary Table 3) showed a significant Group × Time interaction [$F(6,450) = 2.83$, $P_{uncorrected} = 0.01$, $P_{corrected} = 0.021$, $\eta_p^2 = 0.04$], with the EABM (versus sham) group showing no significant difference pretraining [$P > 0.1$, 13.64 (1.86) versus 14.03 (2.55)], showing no significantly larger decreases, respectively, in Weeks 1 and 2 post-training [P's > 0.1; 3.62 (3.35) versus 2.66 (2.86); 3.54 (2.63) versus 2.79 (3.35)] and showing larger decreases, respectively, in Weeks 3,4, 6 and 8 post-training (versus pretraining) [$t(75) = 2.41$, $P = 0.019$, 3.82 (3.64) versus 2.11 (2.49); $t(75) = 3.89$, $P < 0.001$, 4.49 (3.03) versus 2.16 (2.14); $t(75) = 2.28$, $P = 0.026$, 4.62 (3.31) versus 3.00 (2.90); $t(75) = 2.51$, $P = 0.014$, 2.92 (3.99) versus 0.84 (3.23)].

Taken together, the EABM and sham groups were comparable on primary outcome measures of gaming-related positive EABs, compulsive gaming thoughts and behaviours pretraining, and the EABM relative to sham training decreased these measures.

Secondary efficacy: intervention effects on healthy-activity-related positive EABs, severity of IGD, weekly gaming time and craving during the regulation-of-craving task

Analyses for healthy-activity-related positive EABs (Supplementary Table 2) revealed no significant results [P's > 0.1; pretraining (EABM versus sham): 14.02 (22.65) versus 15.38 (23.72); post-training (EABM versus sham): 17.22 (24.32) versus 19.08 (17.22)]. However, increases in healthy-activity-related positive EABs correlated with decreases in those towards gaming for the EABM group ($r = 0.43$; $P = 0.003$).

Analyses of scores of severity of IGD (Supplementary Fig. 2A and Supplementary Table 4) showed a significant uncorrected Group × Time interaction [$F(2,150) = 3.73$, $P_{uncorrected} = 0.026$, $P_{corrected} > 0.1$, $\eta_p^2 = 0.05$], with the EABM (versus sham) group showing no significant differences pretraining [$P > 0.1$, 66.44 (12.96) versus 67.39 (12.41)], showing no significantly larger decrease in Week 4 post-training [$t(75) = 1.72$, $P = 0.09$, 21.95 (19.08) versus 14.68 (18.00)], and showing a larger decrease in Week 8 post-training [$t(75) = 2.52$, $P = 0.014$, 24.72 (22.34) versus 13.29 (17.05)].

We observed no significant Group × Time interaction on weekly gaming time ($P > 0.1$); however, planned comparisons showed that the EABM (versus sham) training decreased weekly gaming time in Weeks 2, 3, 4, 6 and 8 post-training (Supplementary Fig. 2B and Supplementary Table 5). We observed no significant Group × Time interactions involving craving during the regulation-of-craving task (Supplementary Fig. 2C–F and Supplementary Table 6). See details in the Supplementary material.

In addition to results from 77 participants who completed the EABM or sham training including assessments pre- and post-

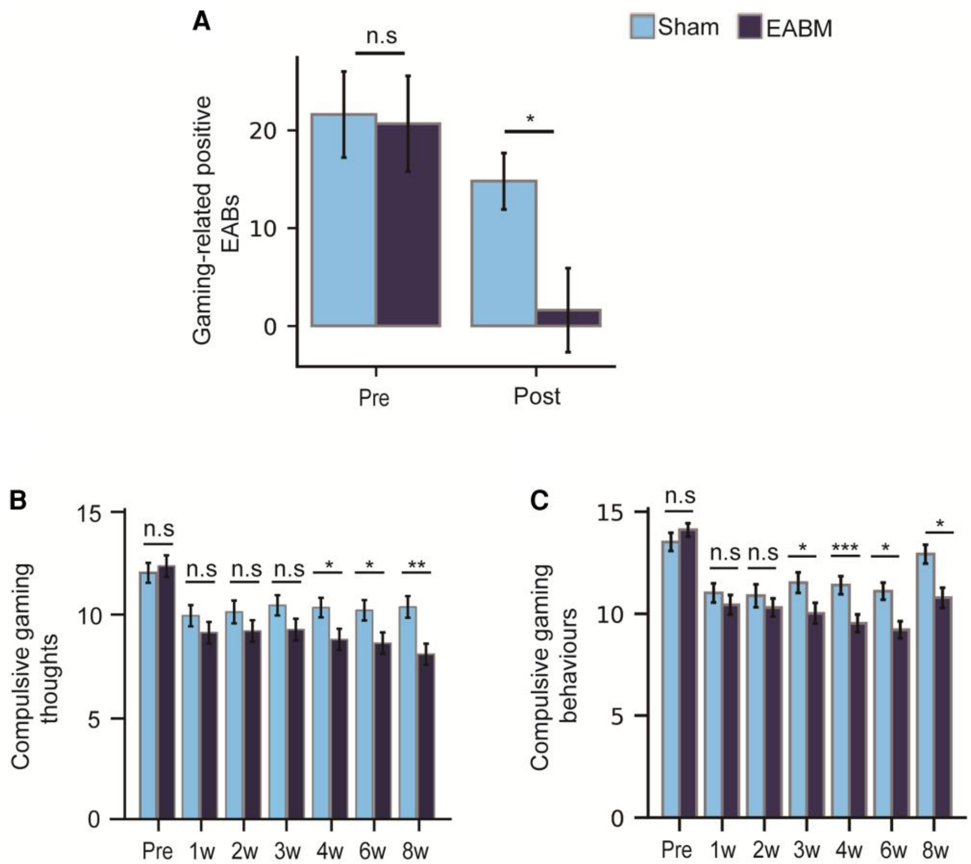

Figure 2 Primary efficacy results of intervention. (**A**) The EABM (versus sham) training decreased gaming-related positive EABs. (**B**) The EABM (versus sham) training decreased compulsive gaming thoughts in Weeks 4, 6 and 8 post-training. (**C**) The EABM (versus sham) training decreased compulsive gaming behaviours in Weeks 3, 4, 6 and 8 post-training. $^{*}P<0.05$, $^{**}P<0.01$, and $^{***}P<0.001$; n.s. = not significant.

training, and during the entire follow-up (above), we also analysed data from all 90 participants using mixed models with respect to intervention effects on compulsive gaming thoughts and behaviours, IAT-assessed severity of IGD and weekly gaming time. The results exhibited similar significant patterns. See details in Supplementary material.

Imaging results

Whole-brain univariate activation analyses revealed no significant results concerning between-group differences pretraining. Regarding intervention effects [EABM (post-training > pretraining) > sham (post-training > pretraining)], whole-brain univariate activation analyses for the gaming-look condition revealed that EABM (versus sham) training increased activation of the right medial frontal gyrus (MeFG) and posterior insula (Table 2 and Supplementary Fig. 3A and B). Analyses for the gaming decrease condition revealed that EABM (versus sham) training attenuated activation of the bilateral DS (Table 2 and Fig. 3A). Analyses for healthy-activity look and healthy-activity increase conditions revealed no significant intervention effects.

Analyses using gPPI revealed no significant results concerning between-group differences pretraining. Left DS-centric gPPI analyses revealed that EABM versus sham training decreased left DS–ventrolateral prefrontal cortex/orbitofrontal cortex (lDS-vlPFC/OFC) functional connectivity (Table 2 and Fig. 3B) in the gaming-look condition and increased lDS-vPFC functional connectivity (Table 2 and Fig. 3C) in the gaming decrease condition. Analyses for healthy-activity look and healthy-activity increase conditions

Table 2 Intervention effects on whole-brain activation (voxel-level $P<0.001$ prior to cluster-level $P_{FWE}<0.05$) and functional connectivity (voxel-level $P<0.001$, cluster size >30)

Regions	Laterality	MNI coordinates			t-value	Cluster size
Whole-brain univariate activation						
Gaming look						
MeFG	R	8	−18	54	5.47	583
Posterior insula	R	34	−28	20	4.68	482
Gaming decrease						
DS	L	−18	12	−2	−5.29	647
	R	16	8	6	−5.13	539
Functional connectivity						
Gaming look						
vlPFC/OFC	L	−42	46	−4	−4.00	83
Gaming decrease						
vPFC	R	26	52	−6	4.37	83
Vermis	L	−2	−70	−20	5.44	535
Declive	L	−28	−68	−30	4.15	108

DS = dorsal striatum; MeFG = medial frontal gyrus; OFC = orbital frontal cortex; vlPFC = ventrolateral prefrontal cortex; vPFC = ventral prefrontal cortex.

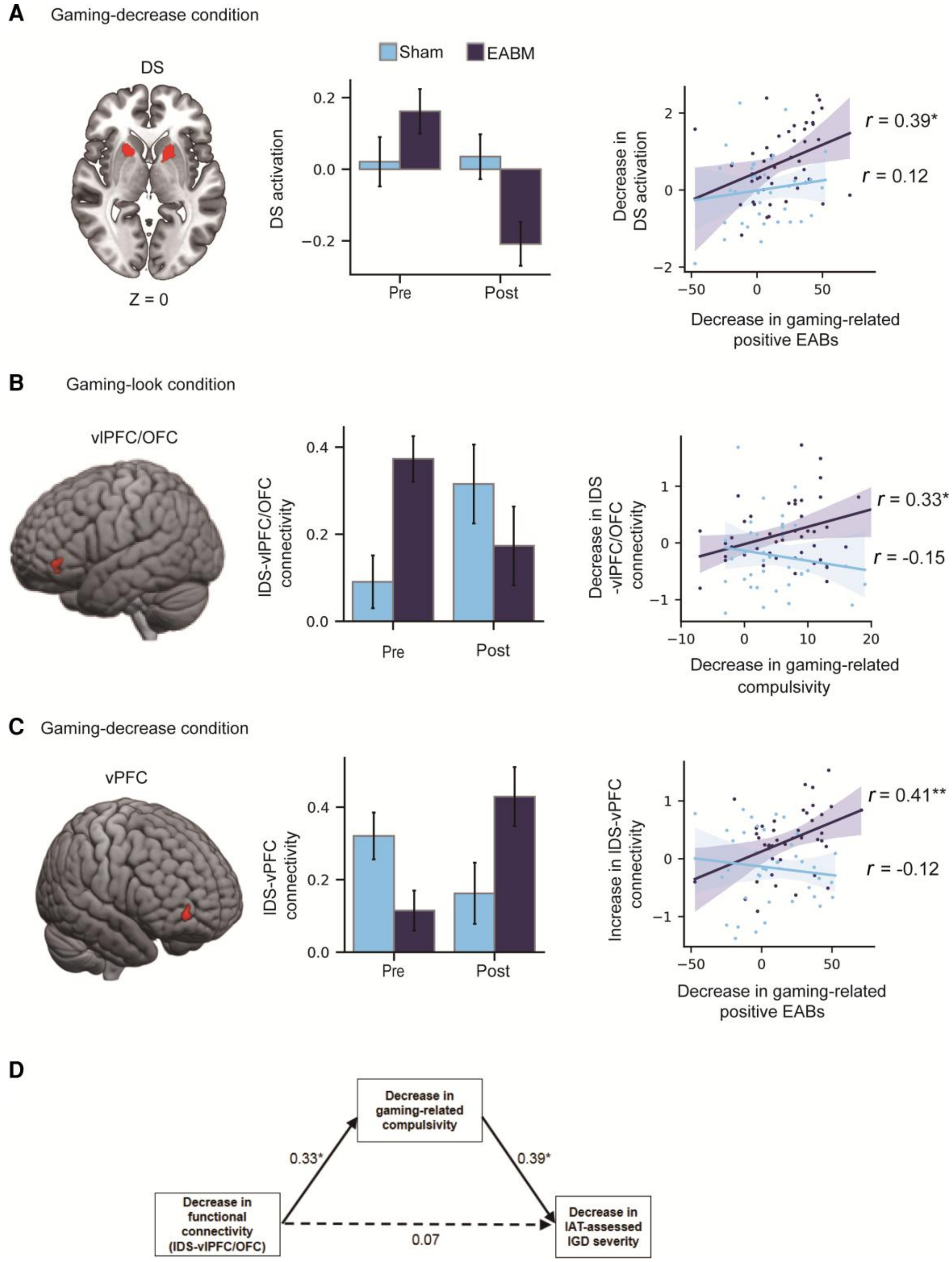

Figure 3 Intervention effects on neural responses relating to the DS in the regulation-of-craving task. (**A**) The EABM (versus sham) training decreased activation of bilateral DS in the gaming decrease condition. Furthermore, EABM-related decreases in activity in the DS bilaterally associated with decreases in gaming-related positive EABs. (**B**) The EABM (versus sham) training decreased left DS-ventrolateral prefrontal cortex/orbital frontal cortex (lDS-vlPFC/OFC) functional connectivity in the gaming look condition. Furthermore, EABM-related decreases in lDS-vlPFC/OFC functional connectivity correlated with decreases in compulsive gaming thoughts and behaviours. (**C**) The EABM (versus sham) training increased lDS-vPFC functional connectivity in the gaming decrease condition. Furthermore, EABM-related increases in the lDS-vPFC functional connectivity correlated with decreases in gaming-related positive EABs. (**D**) EABM-related decreases in compulsive gaming thoughts and behaviours in Week 1 post-training mediated decreases between lDS-vlPFC/OFC functional connectivity post-training and IAT-assessed IGD severity in Week 8 post-training [indirect effect: b = 4.83, 95% CI = (0.20–15.16), β = 0.13; medium to large effect size].

revealed no significant intervention effects. Analogous analyses for the right DS revealed no significant intervention effects.

Brain–behavioural relationships

Given the important role of the DS-centric frontostriatal circuits in compulsive addictive behaviours, Pearson correlation analyses between training-related changes in DS-centric signals (DS activation, lDS-vlPFC/OFC and lDS-vPFC connectivity) and important behavioural indicators (gaming-related positive EABs, total score of compulsive gaming thoughts and behaviours, and IAT-assessed severity of IGD) were separately conducted in EABM and sham groups. In the EABM group, the training-related decrease in DS activity (average signal of bilateral DS) and increase in lDS-vPFC functional connectivity in the gaming-decrease condition, respectively, positively correlated with decreases in gaming-related positive EABs ($r = 0.39$, $P = 0.011$; $r = 0.41$, $P = 0.006$; Fig. 3A and C). Decrease in the lDS-vlPFC/OFC connectivity in the gaming look condition positively correlated with decrease in total score of compulsive gaming thoughts and behaviours in Week 1 post-training ($r = 0.33$, $P = 0.029$; Fig. 3B) that also correlated with decrease in IAT-assessed severity of IGD in Week 8 post-training ($r = 0.41$, $P = 0.01$). In the sham group, the above correlations were not significant ($r = 0.12$; $r = -0.12$; $r = -0.15$; $r = 0.13$; P's > 0.1). Additionally, correlations between changes in lDS-vPFC functional connectivity and gaming-related positive EABs and between changes in lDS-vlPFC/OFC functional connectivity and compulsive gaming thoughts and behaviours were significantly larger in the EABM (versus sham) group ($z = 2.44$, $P = 0.015$; $z = 2.17$, $P = 0.03$).

Given the aforementioned correlations among decreases in lDS-vlPFC/OFC functional connectivity, compulsive gaming thoughts and behaviours and IAT-assessed severity of IGD in the EABM group, we tested a mediation model (Supplementary material) in which decreases in lDS-vlPFC/OFC functional connectivity indirectly related to decreases in IAT-assessed severity of IGD by way of changes in compulsive gaming thoughts and behaviours [indirect effect: $b = 4.83$, 95% CI = (0.20–15.16, $\beta = 0.13$; medium to large effect size]. The results suggest that EABM-related decreases in compulsive gaming thoughts and behaviours in Week 1 post-training mediated decreases between lDS-vlPFC/OFC functional connectivity post-training and IAT-assessed IGD severity in Week 8 post-training (Fig. 3D).

Blinding and adverse events

This intervention was well-blinded and well-tolerated. Specifically, 40% of the EABM group and 50% of the sham group incorrectly guessed (moderate or strong belief) their assigned training. Sixteen percent of the EABM group and 24% of the sham group were not sure about their assigned training. Forty-four per cent of the EABM group and 26% of the sham group correctly guessed (moderate or strong belief) their assigned training. The chi-square test revealed the two groups showed no significant difference in the three types of guessing ($\chi^2 = 2.14$, $P > 0.1$). These data support the efficacy of the blinding.

Ninety-seven per cent of participants reported no negative feelings associated with the training, and all participants reported no mental disorders or physical harm associated with the training. Thus, the EABM intervention was well-tolerated.

Discussion

This first investigation of EABM for IGD is important for multiple reasons. Behaviourally, EABM versus sham training decreased gaming-related positive EABs and compulsive gaming thoughts and behaviours, demonstrating important clinical effects. Neurally, EABM altered brain systems implicated in addiction-related compulsivity,[19,23,43,45] involving habitual reward processing, inhibitory control and negative-emotion processing networks. EABM training generated decreased DS activation bilaterally in the gaming decrease condition of the regulation-of-craving task and attenuated lDS-vlPFC/OFC and increased lDS-vPFC functional connectivities, respectively, in the gaming look and gaming decrease conditions. These changes in functional connectivity correlated with decreases in gaming-related EABs or compulsive gaming thoughts and behaviours. EABM training also increased activation in the right MeFG and posterior insula in the gaming look condition. Additionally, EABM-related decreases in compulsive gaming thoughts and behaviours mediated the positive relationship between decreases in lDS-vlPFC/OFC functional connectivity and IAT-assessed IGD severity. Together, results suggest that EABM training may alter gaming-related compulsivity via reshaping frontostriatal connectivity and insular activation, consistent with models of IGD, substance-use disorders and addictions broadly.

EABM-elicited alterations in functional organization of frontostriatal pathways and insular activity

Resonating with prior craving and compulsivity findings in substance-use disorders and IGD implicating the DS,[23–25,43] attenuated DS activation and gaming-related positive EABs following EABM training, and correlations between training-elicited attenuation in the DS activity and decreases in gaming-related positive EABs suggest that EABM reduces compulsive reward-processing. DS activity may be reshaped or potentially normalized by newly learned associations,[46] and positive EABs may be an objective behavioural index of compulsive 'wanting' that parallels DS activity.

EABM's alteration of DS-related frontostriatal circuits included decreased unregulated and increased regulated gaming-cue-related functional connectivity. With respect to the former, compulsivity in murine addiction models has been associated with approach-related striatum–OFC functional connectivity and strengthening or weakening DS–OFC synaptic connections may increase or reduce compulsive drug-taking, respectively.[19,20] Here, EABM-related increases in DS–vPFC functional connectivity were associated with decreases in gaming-related EABs. Consistent with other findings in substance-use disorders and IGD,[27,28,47] increased frontostriatal functional connectivity during inhibitory control may reduce addiction-related compulsivity. Thus, EABM may impact both seemingly automatic and controlled aspects of compulsive features of IGD. Moreover, the mediating role of EABM-related decreases in compulsive gaming thoughts and behaviours in the relationship between decreases in lDS-vlPFC/OFC connectivity and IAT-assessed IGD severity suggests that EABM-related reduction of compulsive aspects of IGD elicited by reshaped compulsivity-related circuits may contribute to decreases in severity of IGD over time.

EABM augmented MeFG activation in the gaming-look condition. Larger MeFG activation has been proposed to enhanced implicit and explicit executive control over motivational and emotional states,[48] suggesting another mechanism for EABM's enhancement of addiction-related inhibitory control.

EABM increased gaming look-related posterior insula activation. The insula has been implicated in evaluative and affective processes,[49] with increased activation towards both positive and negative (versus neutral) stimuli. As EABM aimed to build associations between gaming cue and long-term negative consequences of excessive gaming and related negative feelings, the increased insula activation may indicate processing of increased negative emotions towards gaming.

Clinical and theoretical implications

This study has important clinical and theoretical implications. Given that EABM alleviated addiction-associated compulsivity in IGD and that compulsive engagement in internet-related activities may be a common feature of internet addiction,[7] EABM may be a potentially effective treatment for internet addiction broadly, although this notion is currently speculative. Furthermore, EABM was well tolerated and easy to administer, which could promote widespread use and dissemination. Regarding theoretical implications, intervention-elicited neural alterations support addiction theories emphasizing roles of frontostriatal and insular pathways. Addiction theories, such as the incentive sensitization and interaction of person–affect–cognition–execution models,[10,12] emphasize the transition from impulsive, reward-driven to compulsive, habitual states based on the reward-conditioning process in addictions.[50] Extending cross-sectional findings,[23,24] the study also provides support for reversing reward conditioning underlying addictions.

Limitations

Several limitations should be discussed. First, while the EABM (versus sham) training exhibited significant larger short-term (alterations in gaming-related EABs and neural responses) and longer-term effects (alterations in compulsive gaming thoughts and behaviours which lasted nearly 2 months), the longer-term effects began to emerge several weeks after training. Based on the main effects of time on behavioural indicators in the sham group (see Supplementary material), the sham training also decreased gaming-related compulsivity, IAT-assessed IGD severity, weekly gaming time and craving. While the strict experimental design involving matched sham and EABM training except for emotional valence of words was good for excluding potentially confounding effects, the effects of EABM training may have been partly concealed as healthy-activity stimuli in the sham condition may have generated some effect, consistent with prior data suggesting repeated exposure to healthy non-addiction-related cues may mitigate against addictions.[51] This feature of sham training may also underlie the non-intervention effects on craving during the regulation-of-craving task assessed immediately post-training, although other possibilities (e.g. placebo effects) exist. Future studies may consider including a wait-list control group. Another possibility is that it took time for participants to implicitly consolidate learned new associations into actual gaming experiences. Second, while healthy-activity responses did not show group differences, increases in healthy-activity-related positive EABs correlated with decreases in gaming-related positive EABs, suggesting that building new positive associations may facilitate attenuation of addiction-related positive EABs, although this possibility requires further investigation. Third, the restrictive exclusion criteria of the current IGD sample, which excluded participants with other psychiatric disorders such as depression and substance-use disorders, may make the sample unrepresentative of community or clinical IGD samples. Nevertheless, considering that the current study is the first examining both clinical and neural effects of EABM training in individuals with IGD specifically and with an addictive disorder more generally, the more restrictive focus on IGD is important for examining the intervention effects of EABM among individuals with IGD by excluding potentially confounding effects related to other psychiatric conditions. This approach accords with most research investigating IGD and substance-use disorders. However, future studies are warranted to examine intervention effects in other IGD samples, including those with co-occurring disorders and in representative community samples. Fourth, although the current IGD-YBOCS was modified from the YBOCS for heavy drinking that has demonstrated good construct validity and internal consistency,[40,41] it was only validated in 60 participants with and without IGD (30 IGD). Future studies involving larger sample sizes are warranted to further validate the IGD-YBOCS. Given compulsivity's relationship to treatment outcomes in gambling disorder[52] and differences related to self-report and behavioural measures of compulsivity, a broader range of compulsivity measures warrants consideration in future IGD studies. We asked participants to refrain from playing games, smoking and drinking 3 days prior to the study to make the EABM and sham groups comparable in gaming cue-elicited behavioural and neural indicators pretraining. Although participants reported compliance upon arrival, we cannot be sure that all participants followed instructions. Nevertheless, statistical results revealed that the two groups were comparable in gaming cue-elicited behavioural and neural indicators pretraining. Moreover, future studies may optimize EABM designs via setting different durations of intervention and follow-up, examining intervention effects of EABM protocols with different emotional stimuli and alternating functional MRI measures in order to understand more fully the mechanisms of actions of EABM and its components and to optimize outcomes. Additionally, assessing effects of EABM on recreational gaming could be of value for prevention of IGD. Thus, future research examining effects of EABM in individuals with recreational gaming is warranted. Nonetheless, the investigation provides important insight into a possible new therapy for helping people with IGD.

Conclusions

EABM may reduce compulsive gaming thoughts and behaviours via reshaping functional organization of frontostriatal and insular pathways in IGD. The therapeutic potential of EABM should be examined in larger, longer-term studies, as should its application to other addictive disorders.

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mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; and has consulted for law offices and gambling entities on issues related to impulse control or addictive disorders.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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