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A multi-scale, circuit-to-gene signature of approach-bias modification in internet gaming disorder

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ABSTRACT

Background: Approach-bias modification (ApBM) is a cognitive training intervention with potential therapeutic value for internet gaming disorder (IGD). However, its clinical efficacy and the underlying neural mechanisms remain to be systematically investigated. This study aimed to evaluate the effectiveness of ApBM for IGD and to identify the associated multi-scale neurobiological signatures, from brain connectivity to gene expression. *Methods:* We conducted a randomized controlled trial involving individuals with IGD assigned to either an ApBM ($N = 30$) or a control group ($N = 27$). Resting-state functional magnetic resonance imaging data were collected pre- and post-intervention. We applied non-negative matrix factorization and a machine learning framework to identify intervention-related functional connectivity patterns. Imaging-transcriptomic analysis was then used to explore the molecular foundations of the identified neural signature. *Results:* The ApBM intervention led to a reduction in IGD symptoms and craving. A specific functional connectivity pattern, characterized by anti-connectivity between the visual and ventral attention network (VAN), was identified via machine learning as a potential neural marker of the intervention. This pattern's statistical significance under conservative permutation test was ($p = 0.06$–0.08). It was spatially coupled to genes enriched in neurodevelopmental and synaptic transmission processes. *Conclusions:* This study provides multi-scale evidence supporting ApBM as an intervention for IGD. The remodeling between vision and the VAN may reflect a mechanism that interrupts the automatic capture of attention by gaming cues, a process regulated by genes associated with neuroplasticity. We propose a circuit-to-gene framework for understanding ApBM in IGD, though the identified neural signature warrants further independent validation.

KEYWORDS

internet gaming disorder, approach-bias modification, ventral attention network, visual network, functional connectivity

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INTRODUCTION

Internet gaming disorder (IGD) is conceptualized as a behavioral addiction characterized by impaired control over gaming, an increasing prioritization of gaming over other life activities, and continued engagement despite negative consequences (King & Delfabbro, 2014). While

the World Health Organization's ICD-11 officially recognizes gaming disorder (WHO, 2022), it remains listed in the DSM-5 as a condition requiring further research, reflecting an evolving clinical landscape (APA, 2013). IGD has been linked to a range of cognitive impairments, involving heightened cue reactivity and craving, the development of compulsive habits, and deficits in executive functions, particularly poor inhibitory control (Brand, Antons, et al., 2025). Furthermore, IGD frequently co-occurs with other psychiatric conditions such as depression, anxiety, and ADHD, compounding its clinical severity (Falcione & Weber, 2025). Given its prevalence and the significant functional impairments it causes, there is a clear need to develop and validate targeted interventions that can effectively address the core mechanisms of the disorder.

A variety of interventions have been developed to address IGD, broadly categorized into psychological therapies, pharmacotherapy, and non-invasive brain stimulation. Pharmacological approaches have explored medications like bupropion and escitalopram (Brand, Antons, et al., 2025), while non-invasive brain stimulation has utilized techniques such as transcranial direct current stimulation (Dong, Dai, & Potenza, 2024). Among these, cognitive behavioral therapy (CBT) is the most widely studied and established psychological treatment for IGD (Zhang et al., 2022). The core mechanism of CBT involves cognitive restructuring to challenge maladaptive beliefs about gaming, alongside teaching practical skills for managing addictive thoughts and preventing relapse (Reangsing, Wongchan, Trakooltorwong, Thaibandit, & Oerther, 2025). This approach is actually a general term for a range of cognitive training techniques, which can be further differentiated to address different cognitive intervention goals. For instance, a study has focused on emotional association bias modification, which aims to alter the positive emotional valence linked to gaming cues (Wu et al., 2022). Other approaches include mindfulness-oriented therapies designed to reduce craving and enhance cognitive control (Lindenberg, Kindt, & Szász-Janocha, 2022; Ni et al., 2024). Meanwhile these interventions appear to rely on distinct neural underpinnings; The emotional association bias modification has been shown to enhance negative emotional evaluations of gaming cues by increasing activity in posterior insula (Wu et al., 2022), whereas the mindfulness targets awareness of internal sensations and modulates connectivity between the default mode network and the fronto-parietal/subcortical networks (Ma et al., 2024; Xu et al., 2024). Therefore, the diversity of cognitive targets and neural pathways highlights the importance of dissecting the brain-behavior connection mechanisms of promising interventions to optimize and personalize IGD treatment options.

In CBT, approach-bias modification (ApBM) is an intervention designed to redirect individuals' attention away from negative stimuli related to their disorder and toward neutral or positive stimuli through repeated training (Fodor et al., 2020). As a mechanized and cost-effective training paradigm, this approach has been widely used in clinical research for a variety of psychiatric disorders, including anxiety, depression, and substance use disorder (SUD) (Gober, Lazarov, & Bar-Haim, 2021). In neuroimaging studies of SUD, while there is no consensus on the direct effects of ApBM on activation in specific brain regions, studies have found that baseline activation levels in reward- and cognitive control-related brain regions, such as the insula and anterior cingulate cortex, can predict intervention efficacy (Dean et al., 2019; Mayer et al., 2020). This suggests that ApBM may work by modulating the function of these key brain regions. A recent pilot study explored brain activation patterns in individuals with IGD while performing an attention bias task and found that insula activity tracked dynamic attention bias states associated with gaming cues (Oka et al., 2024). However, the effectiveness of ApBM intervention for IGD required further evaluation, and existing neuroimaging findings showed significant heterogeneity. We speculate that the neuroplastic changes induced by this intervention may not manifest as activation of isolated brain regions, but rather be characterized by a remodeling of global brain network connectivity patterns. Thus, based on the framework of network neuroscience, this study will examine the effects of ApBM intervention on the global functional connectivity network in people with IGD.

The present study reports on a randomized controlled trial of an ApBM intervention for IGD, employing an integrated behavior-brain-gene model to examine treatment efficacy and its underlying neural mechanisms. At the behavioral level, we compared the clinical outcomes of the ApBM intervention relative to a control group. At the neural level, we utilized non-negative matrix factorization and a machine learning framework to identify functional connectivity patterns distinctive of the ApBM intervention and to link these neural changes with clinical variables. Finally, an imaging-transcriptomic analysis was conducted to explore the gene expression profiles associated with this neural signature. We hypothesized that: 1) ApBM training would ameliorate IGD-related symptoms; 2) the intervention would be associated with a unique connectivity signature, characterized by a spatial pattern involving the insula-led salience network; and 3) this neural pattern would be constrained by a genetic architecture involving pathways implicated in the neurobiology of addiction.

METHODS

Participants

Participants were recruited through advertisements placed at local universities. The recruitment and screening process involved multiple stages to ensure the eligibility of the final sample. Initially, interested individuals completed an online screening questionnaire, which included the internet addiction test (IAT) (Widyanto & McMurran, 2004). Those who scored 50 or higher were invited for a follow-up telephone interview. The interview process was a structured clinical assessment, with the following inclusion criteria for the study (Fu, Chen, Wang, Dong, & Dong, 2025; Zhang et al., 2025): (1) aged between 18 and 30 years; (2) an IAT score of 50 or higher; (3) met at least five of the nine

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for IGD (APA, 2013); (4) a history of online gaming for at least two years, with an average of over 14 h per week in the past year; and (5) self-expressed a desire to reduce their gaming time.

Participants were excluded if they had: (1) a history of any other psychiatric disorders or were currently receiving psychological or pharmacological treatment; (2) a history of substance abuse or dependence, including nicotine and alcohol; (3) any contraindications for MRI scanning, such as a history of brain surgery, claustrophobia, or metal implants; or (4) a score greater than 50 on the Beck depression inventory (BDI).

Initially, 1,103 individuals completed an online screening questionnaire. Following telephone interviews and assessment against strict inclusion/exclusion criteria, an initial cohort of 51 eligible participants was randomized into the ApBM group ($n = 26$) and the control group ($n = 25$). To achieve the preregistered sample size (30) and increase statistical power, a supplementary recruitment wave was conducted using identical criteria, yielding an additional 6 eligible participants. These individuals were also randomized, with 4 allocated to the ApBM group and 2 to the control group. The final sample for analysis thus consisted of 30 participants in the ApBM group and 27 participants in the control group. The two groups were well-matched at baseline and did not differ significantly in age, gender, DSM scores, or other game-related variables.

Procedure

This study followed RCT procedures, with participants enrolled in the different intervention settings and behavioral and neuroimaging data collected at baseline and on the day of the last intervention. Participants were asked to get adequate sleep and avoid stimulants like coffee or alcohol for three days before fMRI scan.

Approach-bias modification training

The intervention was administered using a modified Approach-Avoidance Task (AAT) that required participants to respond to images using a push-pull joystick (Wei et al., 2025). The task was programmed such that participants responded to an irrelevant feature of the stimulus (i.e., the shape of the image frame) rather than its content. A square frame required a "push" action away from the body, causing the image to shrink, while a circular frame required a "pull" action toward the body, causing the image to enlarge. This zooming function visually reinforced the concepts of avoidance and approach.

The stimuli consisted of 10 game-related images and 10 neutral images. Each training session consisted of 200 trials and lasted approximately 20 min. The ApBM group was asked to undergo five training sessions over ten days. Upon completion of the training, participants were briefly interviewed regarding their perception of the study's purpose and whether they detected specific rules governing the image-action associations. Participants in both groups predominantly reported believing the cover story (i.e., that the task measured reaction time to geometrical shapes), and sham group did not report awareness of the random contingency. All participants completed five training sessions over ten days.

ApBM group

Participants in the ApBM group received genuine game-avoidance training. A strong contingency was established: 90% of game-related images were presented with a square frame, requiring a push (avoidance) response, while 90% of neutral images were presented with a circular frame, requiring a pull (approach) response. This protocol was designed to retrain the automatic tendency, creating a new association between gaming cues and avoidance.

Control group

Participants in the Control group underwent an identical procedure, but without the specific training contingency. For this group, both game-related and neutral images were presented with square and circular frames with equal probability (50%). This design served as an active control, matching the experimental group for time, motor activity, and exposure to stimuli, but without aiming to modify any underlying cognitive bias.

Measurement of self-report questionnaires

The following self-report measures were administered at both pre-test and post-test: (1) DSM-5 criteria; (2) IAT score and (3) Game Craving Questionnaire: Adapted from the Tiffany Questionnaire for Smoking Urges (TQSU), this scale was modified to measure the intensity of participants' cravings for online gaming (Xu, Yang, Zheng, Ni, & Dong, 2025).

fMRI acquisition and preprocessing

Data preprocessing followed the standard processing pipeline of fMRIPrep and XCP-D (Esteban et al., 2019; Mehta et al., 2024). Detailed information on fMRI acquisition and preprocessing is provided in the Supplementary Materials.

Data-driven identification of connectivity patterns

The construction of whole-brain functional connectivity matrices began with time-series signals from 246 regions defined by the Brainnetome Atlas (BNA) (Fan et al., 2016). We calculated Pearson correlations between all pairs of regions to create a functional connectivity matrix for each subject, which was then separated into positive and negative connectivity matrices. To extract meaningful brain network patterns from this high-dimensional data, we employed a data-driven approach using Non-negative Matrix Factorization (NMF) (Lee & Seung, 1999). By evaluating component stability and reconstruction error (Wang et al., 2025), we determined the optimal number of components ($k = 20$), which decomposed the complex individual connectivity data into a series of interpretable, parts-based network components and their

corresponding expression weights for each subject. Detailed technical procedures for matrix construction and NMF analysis are provided in the Supplementary Materials.

Identifying intervention-specific connectivity patterns

To identify the functional connectivity patterns most sensitive to the ApBM intervention, we implemented a multivariate classification analysis. The goal was to predict group membership (ApBM vs. Control) using the intervention-induced change in NMF component weights (ΔW) as features. We evaluated several machine learning algorithms within a nested cross-validation framework and selected the best-performing linear discriminant model. To interpret the model and rank the importance of each connectivity pattern, we applied the SHAP (Shapley Additive Explanations) algorithm (Mangalathu, Hwang, & Jeon, 2020), which allowed us to identify the neural signatures most robustly modulated by the ApBM training. Full technical details, including algorithm comparisons and validation procedures, are available in the Supplementary Materials.

Neuroimaging transcriptomic analysis

To explore the potential molecular underpinnings of our neuroimaging findings, we integrated the key functional connectivity pattern (Neg15) with whole-brain gene expression data from the Allen Human Brain Atlas (AHBA) (Hawrylycz et al., 2012). We used Partial Least Squares (PLS) regression to map the spatial topology of the intervention-related connectivity network onto brain-wide transcriptomic profiles, with significance validated through spin-based permutation tests (Xie et al., 2022). To understand the biological meaning of the resulting transcriptomic signature, we performed a functional enrichment analysis on the top-ranking genes (Zhou et al., 2019). A detailed description of the data processing, PLS regression, and enrichment analysis is provided in the Supplementary Materials.

Statistical analysis

To evaluate the intervention, we performed repeated-measures analyses of variance (ANOVAs) to test for Group × Time interaction effects on both clinical scores and the NMF-derived neural connectivity patterns, with Bonferroni correction applied for the neural data. We then used Pearson correlations and a moderation analysis to investigate the relationship between changes in neural patterns and clinical improvement. For the imaging-transcriptomic analysis, we used Partial Least Squares (PLS) regression to link the intervention-related connectivity pattern to brain-wide gene expression, with significance assessed via 5,000 spin-based permutations. The biological relevance of the identified gene signature was then explored using a functional enrichment analysis. A full description of all statistical methods is provided in the Supplementary Materials.

Ethics

The study protocol was approved by the Yunnan Normal University Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent before the experiment commenced. The trial was pre-registered at the Chinese Clinical Trial Registry (ChiCTR2300077831).

RESULTS

Behavioral measurement

Table 1 shows the demographic and behavioral measures for the two groups. We found that ApBM demonstrated good intervention effectiveness, with significant reductions in DSM ($F = 8.507$, $p = .005$), IAT ($F = 7.233$, $p = .009$), and craving scores ($F = 4.349$, $p = .042$). We also analyzed the remission rate for each group and defined clinical remission as a post-intervention score of <5 (i.e., no longer meeting the diagnostic criteria for IGD). The analysis revealed a significant difference in outcomes ($\chi^2 = 5.643$, $p = .018$) (Table 1).

Classification performance and feature screening

The individual FC matrix was summarized into 20 positive and 20 negative typical components by NMF. We first asked whether these components can correctly identify the subject's category label. We observed that the linear discriminant function showed the best classification performance compared with other algorithms (accuracy: 77.2%, Fig. 1A). Figure 1B and C show the confusion matrix and ROC curve results of this function, respectively. The permutation test showed that the model fit was significant ($p < 0.001$, Fig. S1 in Supplementary Materials). We then examined the top 10

Table 1. Demographic information in this study

	ApBM	Controls	F/χ^2/t	*p*	η^2
Age (Mean ± SD)	20.367 ± 3.737	21.519 ± 2.155	−1.404	.166	–
Sex (M/F)	17/13	15/12	.007	.933	–
Remission rate	30(8)	27(1)	5.643	.018	.315
DSM (pre/post)	7.400 ± 1.221 6.267 ± 2.572	7.037 ± 1.315 7.185 ± 1.360	8.507	.005	.134
IAT (pre/post)	70.233 ± 10.874 64.667 ± 16.462	67.481 ± 8.911 69.370 ± 12.163	7.233	.009	.116
Craving (pre/post)	61.766 ± 16.786 54.300 ± 20.856	56.000 ± 14.142 55.148 ± 16.762	4.349	.042	.073

Note: Remission rate: The number in parentheses indicates the number of subjects who no longer meet the diagnostic criteria (DSM-5 score ≤4) for IGD after intervention. ApBM: Approach bias modification; IAT: Internet Addiction Test; DSM: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Internet Gaming Disorder criteria count.

components ranked by SHAP global importance in classification, including 5 components each of positive and negative connections (Fig. 1D). The SHAP summary plot (Fig. 1E) shows the directionality of each component's contribution to the classification. We found that the higher the Δweight (post-pre) of the positive connection component, the more likely the subject was to be classified as the control group. Conversely, the higher the Δ weight of the negative connection component, the more likely the subject was to be classified as the ApBM group. Thus, the positive and negative connectivity components remain consistent internally, while showing opposite explanatory trends externally.

Associations between the NMF weights and intervention

We next asked which components were statistically significantly associated with the intervention. Repeated-measures ANOVA identified a significant interaction effect for the 15th negatively connected component (Neg15, $F = 9.249$, $p_{Bonferroni} = .036$, partial $\eta^2 = 0.14$, Cohen's $f = 0.41$, Fig. 2A). The main effects of group ($F = 1.253$, $p = .268$) and time ($F = 0.888$, $p = .350$) were not significant. Simple effects analysis showed that there was no difference in NMF weights between the two groups at baseline ($t = -0.609$, $p = .545$), but after intervention, the weights of the ApBM group were significantly higher than those of the control group ($t = 2.645$, $p = .012$). Also, we observed that the Neg15 weight of the ApBM group was significantly increased compared with baseline ($t = 2.725$, $p = .011$). No significant interactions were found for the remaining components.

We examined the spatial connectivity pattern of Neg15, and Fig. 2B shows the top 1% of the strongest connected edges. Figure 2C summarizes the relationships between these connections at the network level by averaging the edges within the network. We found that these edges mainly involved the visual network, especially the negative connections between the visual and ventral attention networks (VAN). Correlation analysis showed that the ΔNeg15 weight was significantly negatively correlated with the change rate of DSM ($r = -.296$, $p = .025$, Fig. 2D), but not significantly so in IAT and craving measures. Furthermore, we found that the ΔNeg15 weight moderated the effect of interventions on the change rate of DSM ($F = 4.056$, $p = .049$). Simple slope analysis showed that as the Δweight increased, the DSM change rate in the ApBM group significantly decreased compared to the control group. These results confirmed that

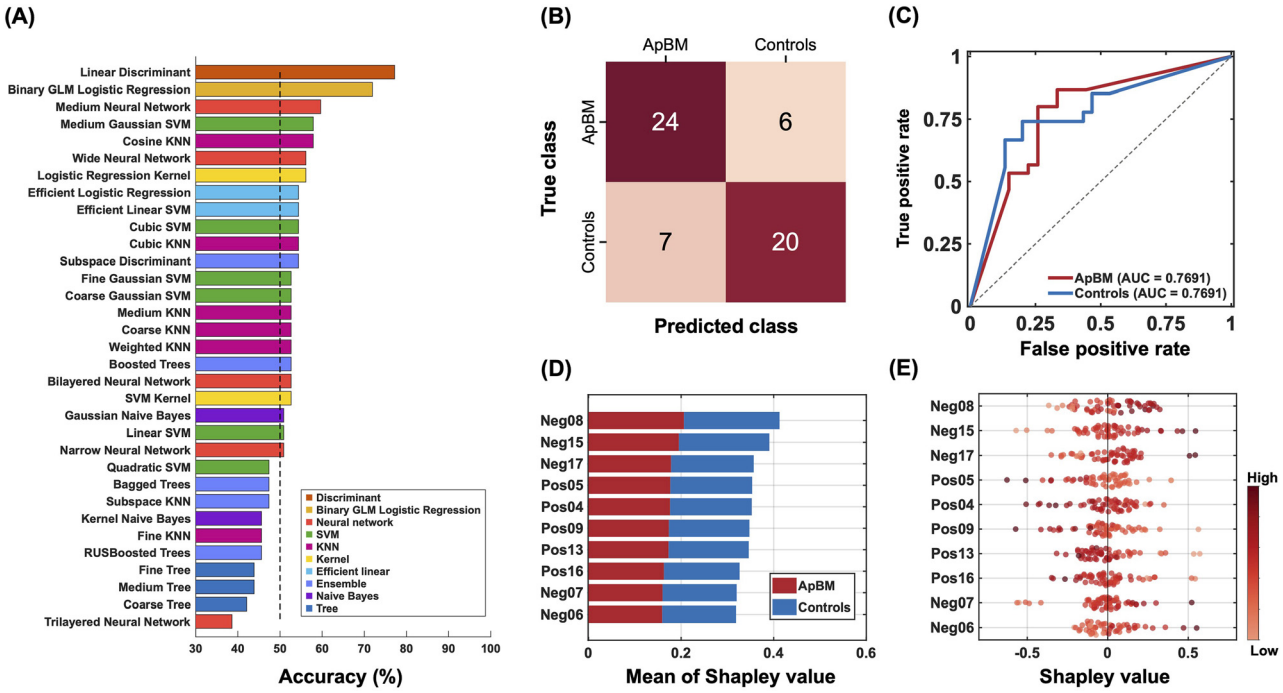

Fig. 1. Classification performance and feature importance based on NMF component weights

(A) Performance comparison of various machine learning algorithms used to classify participants into ApBM and control groups based on the change in NMF weights (Δweight). The linear discriminant model achieved the highest accuracy. (B) Confusion matrix for the linear discriminant model, displaying the number of true and predicted classifications for each group. (C) Receiver Operating Characteristic (ROC) curve for the linear discriminant model, with an Area Under the Curve (AUC) of 0.7691. (D) The top 10 most important NMF components (5 positive, 5 negative) ranked by their mean absolute SHAP (Shapley Additive Explanations) value. (E) SHAP summary plot showing the distribution and impact of each feature on the model's output. Each dot represents a subject, with its color indicating the feature value (Δweight) and its position on the *x*-axis representing its impact on the prediction. An increase in the Δweight of negative components predicted classification into the ApBM group, whereas an increase in the Δweight of positive components predicted classification into the control group

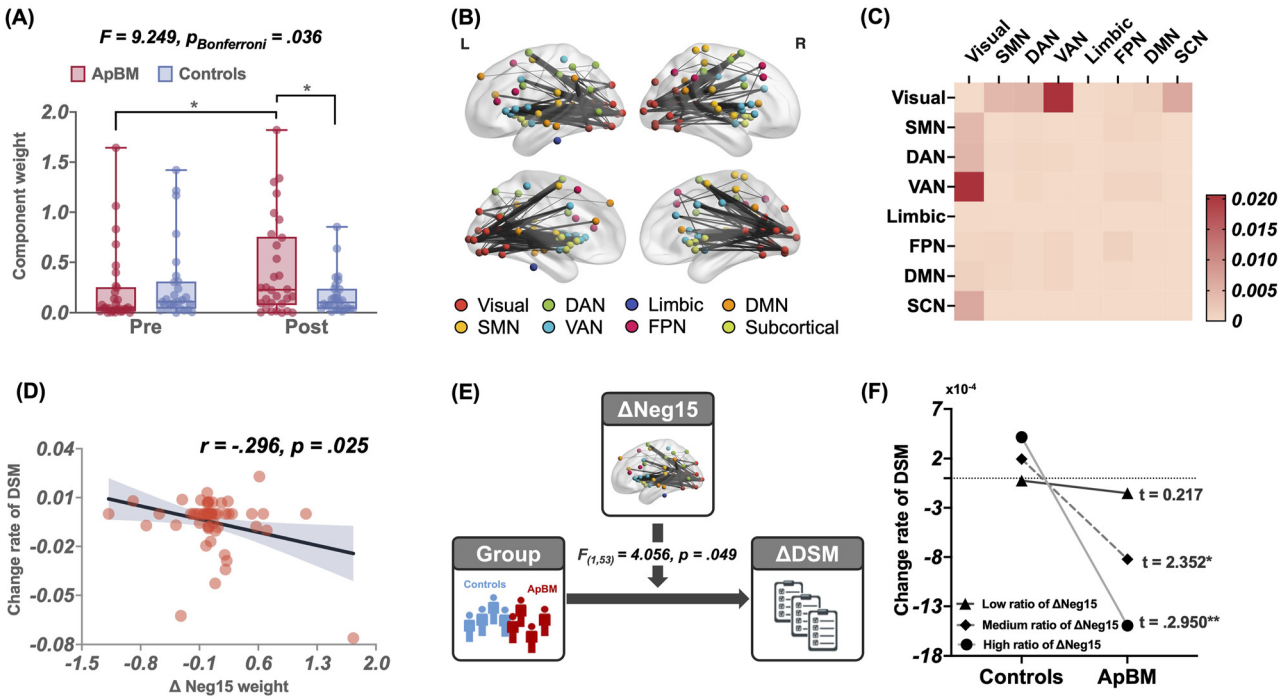

Fig. 2. The Neg15 connectivity pattern is modulated by ApBM and associated with clinical improvement

(A) Repeated-measures ANOVA revealed a significant Group × Time interaction for the weight of the Neg15 component. Post-hoc tests showed that the Neg15 weight in the ApBM group was significantly increased after the intervention compared to baseline and was also significantly higher than the control group post-intervention. (B) The spatial pattern of Neg15, displaying the top 1% of edges with the strongest negative connectivity. Nodes are color-coded by their respective functional networks. (C) A matrix summarizing the connectivity pattern at the network level, showing that connections primarily involve the visual network and its interaction with the ventral attention network (VAN). (D) Scatter plot showing a significant negative correlation between the change in ΔNeg15 weight and the rate of change in DSM scores. (E) Diagram of the moderation analysis, which found that ΔNeg15 weight significantly moderated the intervention's effect on the change in DSM scores. (F) Simple slopes plot visualizing the moderation effect, indicating that as the ΔNeg15 weight increases, the reduction in DSM scores becomes more pronounced in the ApBM group compared to the control group

Abbreviations: Visual, Visual Network; SMN, Somatomotor Network; DAN, Dorsal Attention Network; VAN, Ventral Attention Network; Limbic, Limbic Network; FPN, Frontoparietal Network; DMN, Default Mode Network; SCN, Subcortical Network.

*: $p < 0.05$, **: $p < 0.01$.

Neg15 weight increased in the ApBM group after intervention and that this result was associated with clinical improvement.

Enrichment analysis

We next sought to identify the molecular signatures associated with the Neg15 connectivity pattern. The gene expression profile derived from the first PLS component (PLS1) showed a significant spatial correlation with this shared connectivity phenotype ($r = .124$, $p_{perm} < .001$, Fig. 3A). Figure 3B displays the genes with the highest positive and negative weights from this analysis. An enrichment analysis of the top-ranking (positively-weighted) genes revealed a strong association with fundamental neurodevelopmental processes. The most statistically significant terms were related to brain development, indicating that genes associated with brain maturation are spatially associated with this connectivity pattern (Fig. 3C). This finding was further supported by the enrichment of related pathways such as neuron projection development, sensory organ development, and the broader Neuronal System term. In contrast, the analysis of bottom-ranking (negatively-weighted) genes highlighted processes related to the refinement and function of neural circuits. These terms related to the neural communication, including 'modulation of chemical synaptic transmission', 'inorganic ion transmembrane transport' and 'synapse organization', indicated a collective enrichment for genes that govern how neurons form connections and communicate with each other (Fig. 3D).

Sensitivity analysis

We performed repeated-measures ANOVA with age and sex as covariates for the weights of Neg15, and the results repeated the findings above ($F = 9.489$, $p_{Bonferroni} = .032$). Given that the current Bonferroni correction is a post-hoc correction based on feature selection, we performed a nonparametric permutation test on all components (5,000 iterations) to further verify the robustness of the Neg15 results. The results showed a marginal significance for the Group × Time interaction (permutation $p = .08$). Furthermore, when controlling for age and gender as covariates, the significance level approached the threshold (permutation $p = .06$). These results suggest that while the finding is

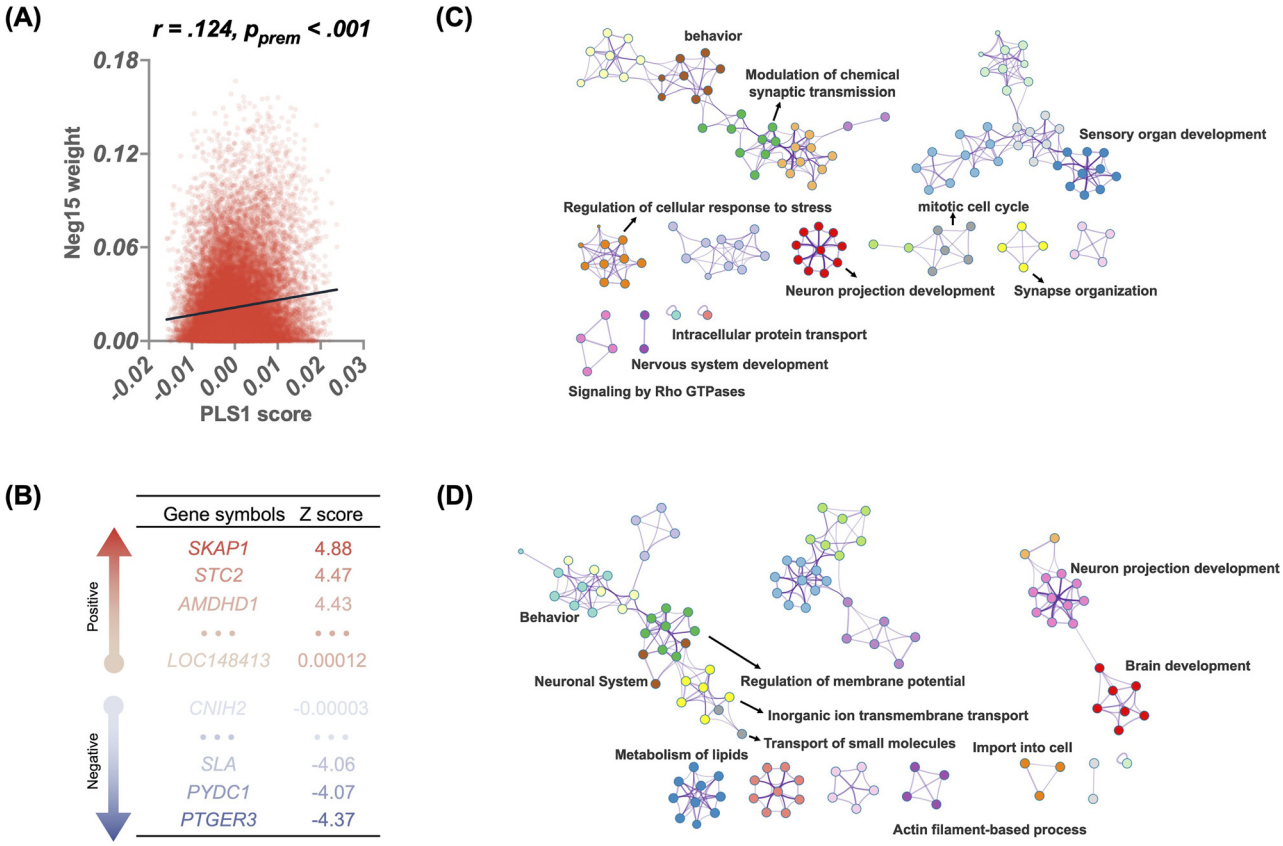

Fig. 3. Transcriptomic signatures of the Neg15 connectivity pattern
(A) Scatter plot showing the significant spatial correlation between the Neg15 component weight and the first partial least squares (PLS1) component score derived from whole-brain gene expression data. (B) A list of the top- and bottom-ranked genes based on their Z-scored weights from the PLS analysis, indicating their positive or negative contribution to the PLS1 component. (C) Gene set enrichment analysis of the top-ranking (positively-weighted) genes. The network plot visualizes enriched biological processes, which are related to fundamental neurodevelopment. (D) Gene set enrichment analysis of the bottom-ranking (negatively-weighted) genes. The network plot visualizes enriched biological processes, which are related to synaptic function and neural communication

sensitive to statistical conservatism, the underlying signal remains consistent across methods.

DISCUSSION

Our study identified a multi-scale neurobiological signature that underlies the clinical efficacy of ApBM in individuals with IGD. We first confirmed that the ApBM intervention effectively reduced addiction severity and craving. Using a data-driven NMF approach combined with machine learning, we isolated a specific negative functional connectivity pattern, Neg15, whose weight increase was predictive of assignment to the ApBM group. Crucially, the magnitude of this increase in Neg15 weight was associated with clinical improvement, as evidenced by its correlation with reduced DSM scores and its role in moderating the intervention's therapeutic effect. Spatially, this key connectivity pattern was characterized by hypoconnectivity between the visual and ventral attention networks. Furthermore, we found that the topology of this intervention-sensitive network was constrained by genes involved in fundamental neural development and synaptic communication processes. Taken together, these findings provide a comprehensive, circuit-to-gene pathway that elucidates how this behavioral training reshapes brain connectivity, which may underlie the therapeutic outcomes in IGD.

ApBM improves IGD by reshaping basic functions

Cognitive bias modification, a form of computerized cognitive training, aims to target and retrain the automatic, implicit cognitive processes believed to maintain addictive behaviors. Although the effectiveness of such measures in SUD remains controversial (Boffo et al., 2019), IGD provides a unique context for such training. IGD does not involve direct pharmacological effects of exogenous substances on the brain, and its addiction mechanism may be more purely driven by cognitive and behavioral patterns (Brand, Müller, et al., 2025; Dong & Potenza, 2014, 2022). This makes its potential cognitive biases particularly prominent and more easily modified through cognitive training. Unlike previously reported associative bias modification that utilizes negative emotional associations (Wu et al., 2022), ApBM retrains automatic motor processes by reinforcing avoidance

responses. The significance of this approach lies in its ability to achieve clinical symptom improvement by targeting a foundational aspect of behavior. In other words, disrupting the basic physiological links in the addictive behavior chain (e.g., automatic approach tendencies) may also have cascading positive effects on more complex IGD symptoms.

ApBM-related neural connectivity patterns

Consistent with our hypothesis targeting the insula-led salience network, we found that the ApBM intervention significantly modulated the VAN. Given that the anterior insula constitutes the core hub of the VAN (Vossel, Geng, & Fink, 2014), this finding highlights the potential involvement of this salience-processing system in the mechanism of ApBM. However, a novel feature of this signature was its specific interaction with the visual system: an induced functional antagonism between the VAN and the Visual Network. This distinguishes ApBM from other cognitive interventions. While CBT typically rely on enhancing top-down regulation via the frontoparietal or default mode networks (Zhang et al., 2022), our results suggest that ApBM operates through a unique bottom-up gating mechanism.

The engagement of visual network has been shown to be a frequently observed but often overlooked phenomenon in SUD field. This network reflects not only basic sensory processing but also attentional biases and the manifestation of enhanced incentive salience (Cooke & Bear, 2012). In the cue-craving paradigm, the learned association between cues and rewards makes it easier for individuals with SUD to automatically capture relevant visual cues and activate the visual cortex (Hanlon, Dowdle, Naselaris, Canterberry, & Cortese, 2014). Interacting with this sensory processing is the VAN, a neural system that acts as a "circuit breaker" for attention. The VAN has the primary function of detecting unexpected but behaviorally relevant stimuli and initiating bottom-up attentional redirection, thereby interrupting the current cognitive focus (Corbetta & Shulman, 2002; Vossel et al., 2014). In untreated IGD, visual gaming cues capture the VAN, triggering automatic incentive salience (Cooke & Bear, 2012). The increased anti-connectivity observed here may suggest a functional uncoupling, where the brain is retrained to block the transmission of bottom-up sensory information to the salience network. This interpretation is supported by our active control comparison, where participants exposed to the same stimuli without the avoidance contingency showed no such connectivity changes. Thus, rather than reflecting a generic improvement in attention, this Visual-VAN remodeling may represent an intervention-specific mechanism: the interruption of the automatic neural cascade from visual perception to craving.

Genetic context of the connectivity pattern

We found that the intervention-related connectivity pattern was spatially correlated with the expression maps of genes enriched in brain development and neuron projection. Rather than implying that the intervention alters gene expression (which cannot be determined from the static AHBA atlas) this finding suggests a spatial congruence. SUD is characterized by a pathological "rewiring" of neural circuits due to long-term drug-induced changes in gene expression, which is more pronounced during adolescence (Baratta, Rathod, Plasil, Seth, & Homanics, 2021; Renard et al., 2017). Our results indicate that ApBM-induced remodeling locates to regions with a genetic profile supporting high structural plasticity. This spatial alignment implies that the intervention may engage neural circuits that possess high intrinsic potential for reorganization, as indicated by their baseline genetic architecture. Neuroimaging studies have shown that the ventral attention network is activated by drug cues, mediating attentional bias, while the visual cortex shows heightened reactivity (Hanlon et al., 2014; Zeng, Han, Gao, Sun, & Yuan, 2023). The inverse relationship with synaptic transmission genes may reflect a normalization of regional activity. The intervention effects are topologically coupled to the molecular systems that regulate synaptic signaling, potentially stabilizing the hyper-reactive cue response within these plasticity-preferring circuits.

LIMITATIONS

Several limitations of the present study warrant consideration. First, this study assessed the effects of ApBM immediately following the intervention period. The absence of a long-term follow-up means that the durability of the observed behavioral and neural changes remains unknown. Also, the study design assessed at only two time points. Consequently, we cannot determine the temporal precedence of the observed changes. Second, the neuroimaging transcriptomic analysis is inherently correlational. It links functional connectivity patterns to a static, post-mortem atlas of gene expression and does not measure gene expression changes within the participants themselves. Third, the generalizability of our findings may be constrained, as the sample consisted of university students. Fourth, A methodological trade-off was made by using concatenated data for NMF decomposition. While this ensures a unified spatial framework and prevents mismatch between time points, it theoretically limits statistical independence. However, given that NMF is an unsupervised technique, we prioritized the spatial stability provided by this approach. Finally, we explored the associations between neural changes and clinical improvements. It is important to note that these correlation analyses were exploratory in nature and were not corrected for multiple comparisons. The above limitations require further improvement and exploration in future research.

CONCLUSIONS

This study provides multi-scale evidence supporting ApBM as an effective intervention for IGD. We suggest that this targeted cognitive training reduces clinical symptoms by reshaping a specific functional connectivity pattern between

the visual and ventral attention networks. Moreover, the spatial coupling between the network's topology and genes related to neurodevelopment and synaptic communication offers a potential molecular-level explanation for the intervention's effects, suggesting the intervention may leverage fundamental pathways of adaptive plasticity within the brain. These findings provide new insights into IGD treatment and propose a neural circuit assessment framework for ApBM. However, given the potential circularity inherent in the concatenated NMF derivation approach, independent replication with a separate component derivation step is needed before these findings can be considered definitive.

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SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2025.00434.

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