

Research Paper

Amygdala Network Dynamics During Drug Cue Processing in Methamphetamine Use Disorder



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ABSTRACT

Introduction: Methamphetamine use disorder (MUD) has substantial societal and individual implications, necessitating a comprehensive understanding of its neural underpinnings for effective intervention. Key to addiction is the amygdala, implicated in emotion processing and reward systems, which interacts with the prefrontal cortex in addictive behaviors.

Methods: We conducted a study involving 54 male individuals with MUD (age range: 22–44 years) to examine amygdala-cortical connectivity during methamphetamine cue reactivity, aiming to uncover effective neural pathways. We combined generalized psychophysiological interaction (gPPI) analysis and dynamic causal modeling (DCM) to elucidate connectivity dynamics and effective neural pathways. We delved deeper into neuro-behavioral connections using the Pearson correlation and group factor analysis (GFA).

Results: Our findings revealed increased functional connectivity within the amygdala-posterior cingulate cortex (PCC) and amygdala-dorsolateral prefrontal cortex (dlPFC) networks during methamphetamine cue reactivity. DCM revealed a neural network characterized by positive bidirectional connections among the amygdala, dlPFC, and PCC, along with negative intrinsic connections. Interestingly, we observed that the intrinsic self-inhibition of the dlPFC was negatively correlated with post-task positive affect, suggesting its role in emotional regulation. Nonetheless, utilizing GFA, we did not discover any noteworthy cross-unit latent factors between the neural group and variables related to behavior, psychology, or demographics.

Conclusion: These discoveries enrich our comprehension of the neural mechanisms at play in methamphetamine cue reactivity and addiction-related processes. The increased amygdala-cortical connectivity underscores the role of these networks in drug cue processing, potentially contributing to craving and relapse. Effective connectivity analysis highlights the interconnectedness of the amygdala, dlPFC, and PCC, revealing potential pathways for neural signaling during cue reactivity. Our results contribute to the growing body of knowledge about addiction’s neurobiological basis, offering insights that may inform targeted interventions to mitigate the impact of methamphetamine cue reactivity on addiction progression.

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Highlights

- Task-based functional magnetic resonance imaging combined with generalized psychophysiological interactions analysis and dynamic causal modeling revealed increased connectivity in the amygdala-dorsolateral prefrontal cortex and amygdala-posterior cingulate cortex networks during cue reactivity.
- Dynamic causal modeling identified neural networks with positive amygdala-dorsolateral prefrontal cortex-posterior cingulate cortex connections and negative intrinsic connections, shedding light on complex interactions.
- Intrinsic self-inhibition of the dorsolateral prefrontal cortex negatively correlated with post-task positive affect, suggesting its role in emotional regulation.
- Increased amygdala-cortical connectivity emphasizes networks' role in drug cue processing, with implications for craving and relapse.

Plain Language Summary

Methamphetamine use disorder (MUD) is a serious problem that affects individuals and society. We wanted to understand how the brain is involved in this addiction so that we can help people better. We focused on a part of the brain called the amygdala, which is important for emotions and rewards, and how it works with another part called the prefrontal cortex during addiction. We studied 54 men with MUD to see how these brain parts are connected when they are shown cues related to methamphetamine. We used brain scans and special analysis techniques and found that when people with MUD see cues related to the drug, the amygdala and the prefrontal cortex become more connected. This finding suggests that these brain parts work together when the person is exposed to drug-related cues. We also looked at how these brain parts communicate with each other. We found connections between the amygdala, prefrontal cortex, and another brain part called the posterior cingulate cortex. These connections help the brain process cues related to the drug. We also found that the prefrontal cortex can control emotions, essential in addiction. Although we did not find strong connections between the brain and behavior, our study helps us understand how the brain is involved in addiction. These findings could help us develop better ways to help people with MUD by targeting the brain's responses to drug cues.

1. Introduction

Methamphetamine use disorder (MUD) continues to be a substantial public health concern, with its profound impact on individuals' physical, psychological, and social well-being (Courtney & Ray, 2014; Hedegaard et al., 2018; Paulus & Stewart, 2020a). Understanding the neural mechanisms that underlie the complex process of addiction is paramount for developing targeted interventions and treatment strategies (Paulus & Stewart, 2020b; Soleimani et al., 2023; Soleimani et al., 2023). Neuroimaging methods, including functional magnetic resonance imaging (fMRI), provide a distinct perspective on the complex operations of the addicted brain, offering insights into the neural networks and pathways that influence drug-related behaviors (Ekhtiari et al., 2022; Jan et al., 2012; Koob & Volkow, 2016; Parvaz et al., 2011; Stewart et al., 2014).

Amygdala, a crucial node in the brain's emotion processing and reward systems, plays a central role in the addiction process (Everitt et al., 1999; Phelps & LeDoux, 2005). Its interactions with various cortical regions, particularly the prefrontal cortex, are instrumental in the emergence of addictive behaviors, including craving and cue reactivity (Goldstein & Volkow, 2011; Zilverstand et al., 2018). Given the amygdala's involvement in processing emotionally salient stimuli and its established relevance to addiction, investigating its connectivity with cortical regions during methamphetamine cue exposure is of paramount importance (Soleimani et al., 2023).

The present study seeks to address this crucial gap in knowledge by utilizing an fMRI approach to explore amygdala-cortical connectivity and effective neural pathways involved in methamphetamine cue reactivity. By employing a combination of task-based fMRI paradigms and advanced connectivity analyses, we aim to shed light on how neural networks interplay in

response to methamphetamine cues, providing a more comprehensive understanding of addiction's neurobiological underpinnings.

Our primary objective is to investigate the modulation of amygdala-cortical connectivity during methamphetamine cue exposure compared to neutral cues. Our hypothesis posits that exposure to drug-related cues will increase connectivity between the amygdala and regions associated with reward processing and cognitive control, such as the prefrontal cortex. This investigation will offer valuable insights into the brain's dynamic response to cues that trigger drug craving, unraveling the mechanisms that facilitate the transition from cue exposure to craving and potential relapse.

Furthermore, this study seeks to delve beyond functional connectivity by exploring effective neural pathways using dynamic causal modeling (DCM). This modeling enables the investigation of directed interactions between brain regions, shedding light on the neural network's causal relationships and information flow. By applying DCM to our multimodal fMRI data, we aim to uncover the directional influences and effective pathways that underlie amygdala-cortical interactions during methamphetamine cue reactivity.

In addition to the neural perspectives, this study will explore potential correlations between neural connectivity patterns and psychological variables. We will utilize the Pearson correlation and group factor analysis (GFA) to elucidate potential neuro-behavioral relationships, bridging the gap between brain connectivity and the subjective experiences associated with drug cue reactivity.

In the subsequent sections, we will comprehensively overview the research methodology, findings, and implications. This study aims to contribute to the growing body of knowledge concerning addiction's neurobiological underpinnings by integrating advanced neuroimaging techniques, connectivity analyses, and psychological assessments. Ultimately, our findings may pave the way for more targeted interventions that address the neural circuitry involved in methamphetamine cue reactivity and addiction-related processes.

2. Materials and Methods

Study participants

The present study involved 62 male volunteers diagnosed with MUD. Thirteen subjects were excluded from the study due to non-compliance with the inclusion in-

structions, as revealed in their screening assessments. The participants were sourced from addiction treatment centers. The exclusion criteria included current or previous comorbid axis I-disorders other than drug dependence, as outlined by the diagnostic and statistical manual of mental disorders, the fourth edition, text revision (DSM-IV-TR) (APA, 2000), psychiatric or neurological disorders, including head trauma, as well as MR-specific exclusion criteria. The inclusion criteria stipulated a diagnosis of methamphetamine dependence for a minimum of 6 months in accordance with DSM-IV-TR criteria. Additionally, participants were required to self-report and test negative for all drugs (except nicotine) in both urine and self-reports for a minimum of one week. Participants' right-handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971), and inclusion criteria also specified an age range of 20 to 45 years. The visual acuity of each participant was normal or corrected to normal.

Sixty-two subjects met all the inclusion and exclusion criteria. Nevertheless, 8 participants were excluded from the data analysis due to excessive head motion during scanning. Consequently, the final sample for the analyses comprised 54 male participants diagnosed with MUD, aged 22 to 44 years (Mean±SD 32.02±5.09). Comprehensive behavioral and demographic information about methamphetamine users is provided in Table 1.

Experimental procedures

During the screening session, participants diagnosed with MUD underwent a series of baseline assessments. These assessments encompassed demographic information (Ranaei et al., 2022), substance use patterns, mental health evaluations, treatment history, and a risky behaviors profile. This profile included a history of drug injection, engagement in high-risk sexual activities, prior incarcerations, participation in drug sales, and a record of violent altercations. Furthermore, participants completed the Barratt impulsiveness scales-11 (BIS-11) (Barratt, 1994) and the depression anxiety stress scales-21 (DASS-21) (Hosseini et al., 2023; Hosseini & Modarresi Chahardehi, 2021; Osman et al., 2012). They also underwent a training session to familiarize themselves with the drug cue reactivity task before the MRI scan day (Figure 1A).

After successful screening, participants underwent a single fMRI session. Participants arrived for the MRI scans between 8:30 and 10:30 AM on the designated day after abstaining from all drugs (except nicotine) for at least one week. After participants finished self-assess-

Table 1. Sample characteristics (n=54)

Variables		Mean±SD
	Age (y)	32.02±5.09
	Education (y)	10.19±2.82
DASS	Depression (0-21)	8.87±5.28
	Anxiety (0-21)	7.74±4.47
	Stress (0-21)	11.67±5
BIS	Attention impulsiveness score (0-100)	20.19±4.54
	Motor impulsiveness score (0-100)	27.31±6.44
	Non-planning impulsiveness score (0-100)	28.35±5.65
Drug abuse profile	Age of Meth use onset (y)	24.66±5.67
	Duration of Meth abuse (m)	64.8±29.8
	Duration of Meth dependence (m)	64.14±30.6
	Duration of Meth abstinence (d)	103.1±182.67
	Dosage of Meth (g/d)	1.21±1.08

Abbreviations: DASS: Depression anxiety stress scales; BIS: Barratt impulsiveness scale; Meth, Methamphetamine.

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ments of their current drug craving using a 0–100 visual analog scale (VAS) and evaluations of positive and negative emotional states using the positive and negative affect schedule (PANAS) (Crawford & Henry, 2004), they proceeded to engage in the methamphetamine cue-reactivity paradigm within the fMRI scanner. After the scans were concluded, the participants were asked to provide another round of ratings for their level of drug craving and assess their positive and negative emotional states (Figure 1A). To reduce the likelihood of post-scanning drug use, participants were recommended to stay at the imaging center for at least one hour for recovery.

Functional methamphetamine cue reactivity paradigm

The methamphetamine cue reactivity paradigm was developed to investigate the brain's functional responses to methamphetamine compared to neutral stimuli (Dakhili et al., 2022; Ekhtiari et al., 2022; Jafakesh et al., 2022). The experiment comprised four runs of the fMRI drug cue reactivity task, with intervals of rest blocks featuring a fixation point. Each run had four blocks lasting 36 seconds each, and each block contained 24 images. The images included blank screens, negative cues, methamphetamine cues, and neutral cues. The stimuli were displayed for 1000 ms, followed by an average inter-stimulus in-

terval of 500 ms. The order of block presentations was pseudo-randomized across the four runs, and after each block, there was a 12-second inter-block interval. Each run lasted approximately 198 s, with 18-s fixation intervals separating the runs. In these fixation periods, a white cross was shown on a black background (Figure 1B). Before the scanning session, participants received training to acquaint themselves with the fMRI environment and the cue reactivity paradigm. The negative and neutral cues were selected from the international affective picture system database (Lang et al., 1997). In contrast, the drug-related cues were sourced from a publicly available and validated cue database (Ekhtiari et al., 2020).

MRI data acquisition

We used a SIEMENS 3.0T scanner (MAGNETOM Trio, SIEMENS, Germany) with a 64-channel head coil to acquire T1 and fMRI sequences. fMRI images were obtained from a T2*-weighted gradient-echo echoplanar imaging (EPI) sequence. Each volume of functional data comprised 40 slices, featuring a repetition time (TR) of 2200 ms, an echo time (TE) of 30 ms, and a flip angle of 90°. The field of view (FOV) was configured to 192×192 mm, and the voxel dimensions were 3×3×3 mm. A total of 367 T2*-weighted functional images were obtained in an interleaved slice acquisition order.

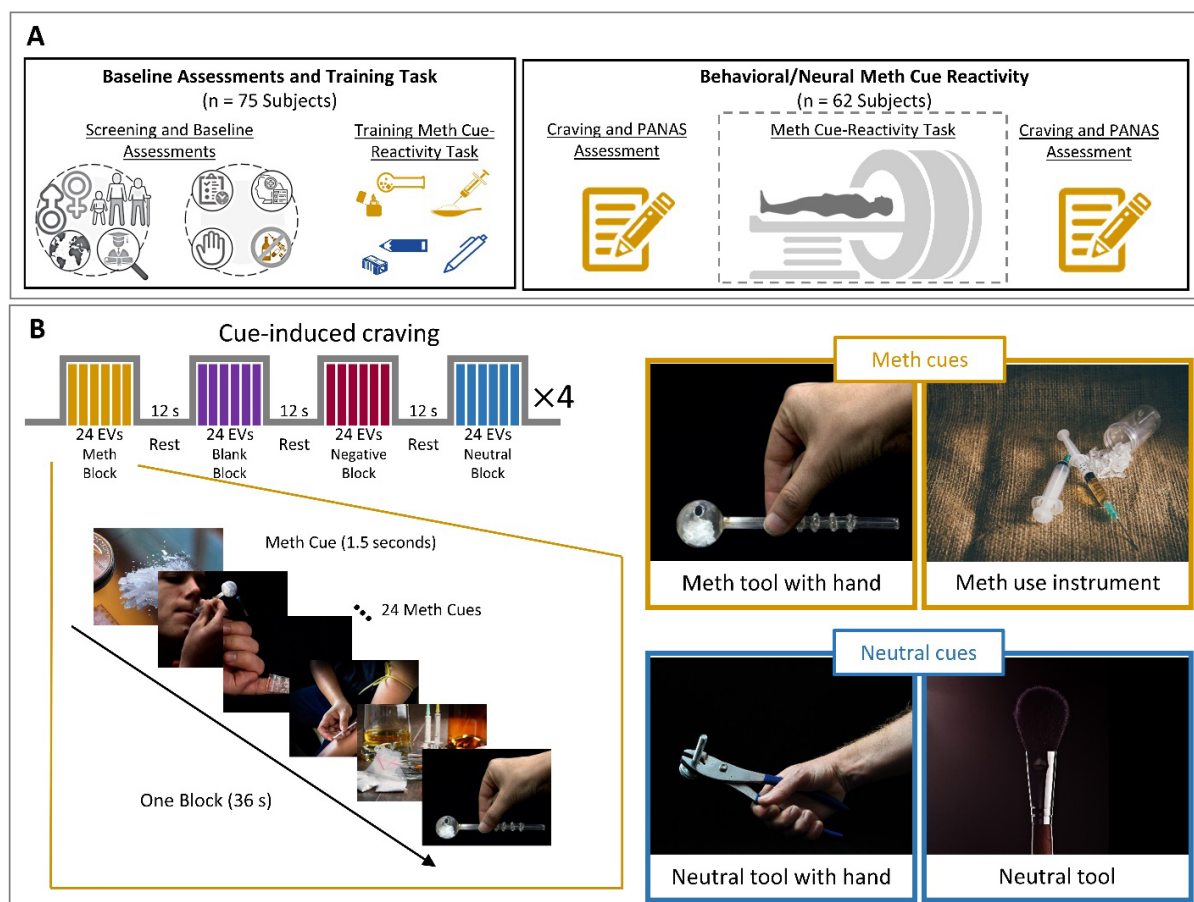


Figure 1. Study design and methamphetamine cue reactivity task

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Meth: Methamphetamine; PANAS: Positive and negative affect schedule.

Notes: The procedure of the experiment: Initially, participants underwent assessments to evaluate their neuropsychological functioning. Subsequently, each participant completed a training task involving methamphetamine cue reactivity. During the experimental session, the subjects underwent a magnetic resonance (MR) scan while performing the methamphetamine cue-reactivity task. Before and after the MR scan, the participants self-reported ratings for their craving level and positive and negative emotional states.

Methamphetamine cue-reactivity task: During the methamphetamine cue-reactivity task, participants were presented with a total of 16 blocks, each containing 24 pictures. These blocks consisted of 4 sets with methamphetamine cues, 4 with blank cues, 4 with negative cues, and 4 with neutral cues. Following each block, there was an inter-block interval lasting 12 seconds.

Furthermore, a structural image was obtained using the magnetization-prepared rapid acquisition gradient echo sequence. This sequence parameters were set as follows: TR=1800 ms, TE=3.44 ms, flip angle=7°, FOV=256×256 mm, and voxel size=1×1×1 mm.

warp, slice-timing correction, outlier identification, direct segmentation, and normalization into the standard Montreal Neurological Institute (MNI) space. Additionally, functional smoothing was applied using an 8 mm full-width at half-maximum Gaussian kernel.

Functional MRI data preprocessing

The fMRI data was subjected to preprocessing through the utilization of the CONN toolbox (version 20.b) (Whitfield-Gabrieli & Nieto-Castanon, 2012) in SPM12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). The standard preprocessing pipeline involved several steps: functional realignment and un-

Task-based functional brain activity analysis

The preprocessed fMRI data underwent a general linear model (GLM) analysis. This model was constructed by modeling onset times for the methamphetamine, neutral, negative, and blank conditions using a 36-second block function. These onset times were convolved with a canonical hemodynamic response function to gener-

ate the corresponding regressors of interest. Moreover, the six individual motion correction parameters were included as nuisance regressors in the first-level model.

In each participant's case, contrast images illustrating the comparison between the methamphetamine and neutral conditions were subsequently incorporated into second-level one-sample t-test models, all of which were executed using SPM12. The individual contrast maps were initially thresholded at $P < 0.05$ (uncorrected). On the other hand, the whole-brain statistical group maps underwent correction for family-wise error (FWE) to address multiple comparisons. This correction was accomplished using Gaussian random field theory (Nichols & Hayasaka, 2003; Worsley et al., 1996). Furthermore, Brainnetome atlas parcellation was applied to each subject's data. This allowed for the estimation of the average BOLD signal change across the 246 sub-regions present in the atlas. Notably, the specific sub-region of the right medial amygdala, identified through the Brainnetome atlas-based parcellation of the fMRI data, was chosen as the seed region for the ensuing seed-to-whole brain generalized psychophysiological interaction (gPPI) analysis. This analysis aimed to uncover modulations in connectivity influenced by drug cue reactivity.

Task-based functional brain connectivity analysis

The task-based functional brain connectivity analysis was conducted using the CONN toolbox (version 20.b) (Whitfield-Gabrieli & Nieto-Castanon, 2012) integrated within SPM12. A seed-to-whole brain approach was employed in this analytical framework, utilizing gPPI analysis. In this context, the right medial amygdala was chosen as the specified seed region. The primary objective of the PPI analysis was to reveal specific brain regions exhibiting connectivity patterns that demonstrated variability based on the psychological context, with a specific focus on the differential response to methamphetamine stimuli in comparison to neutral stimuli.

At the first level of the gPPI analysis, the psychological regressors of interest encompassed the timing of both methamphetamine and neutral blocks. These timings were convolved with a hemodynamic response function. The physiological regressor was then computed using the average time series derived from the designated seed region, specifically the right medial amygdala, as outlined in the Brainnetome mask. The PPI regressors were constructed as interaction terms involving psychological and physiological regressors. Through this approach, we contrasted the PPI regressors, identifying brain regions where connectivity with the medial amygdala demon-

strated significant differences between the methamphetamine and neutral conditions. These PPI regressors were computed for each participant, revealing the voxel-level interaction with the seed region while comparing the methamphetamine and neutral conditions.

Subsequently, a second-level gPPI analysis was conducted to detect significant clusters. This analysis utilized voxel-wise and cluster-extent thresholds, where clusters were deemed active if they exceeded a voxel-level threshold of uncorrected $P < 0.001$ and a cluster-size threshold corrected for false discovery rate (FDR) at $P < 0.05$. The regions demonstrating the most robust PPI connectivity with the amygdala region were subsequently selected as regions of interest for the parametric empirical Bayes (PEB)-DCM analysis. To this end, functional regions of interest (ROIs) with 8 mm spheres were centered on the peak voxels within the amygdala (coordinates: 19, -2, -19), the dlPFC (coordinates: 16, 34, 44), and the PCC (coordinates: -4, -40, 34). These coordinates were derived from our gPPI outcomes concerning cue-reactivity processing.

Task-based dynamic causal modelling

The analysis of task-based effective brain connectivity over the amygdala, dlPFC, and PCC brain regions was conducted utilizing the DCM toolbox integrated within SPM12. The principal eigenvariate time series were derived from predefined unilateral masks of these regions, with adjustments for effects of interest. To explore the effective functional connectivity between these regions, we employed the bilinear DCM approach (Friston et al., 2003), incorporating the stochastic option (Daunizeau et al., 2012; Friston et al., 2011; Li et al., 2011). A full DCM model was constructed, encompassing three components: 1) Fixed connections encompass the extrinsic forward and backward connections between the amygdala and dlPFC, amygdala and PCC, and dlPFC and PCC, as well as intrinsic self-connections within each region, 2) Contextual modulation involves the adjustment of intrinsic self-connections influenced by craving, and 3) exogenous inputs refer to the introduction of methamphetamine and neutral stimuli as driving inputs into the respective nodes. Bayesian model inversion was carried out for each subject, entailing the establishment and inversion of this parent DCM model.

In the group-level DCM analysis, we performed a linear PEB analysis on a fully connected model estimated across all participants. By utilizing a post hoc model selection approach that entailed an extensive exploration of the model space, we ascertained the network struc-

ture at the group level. This process involved employing Bayesian model reduction to assess nested PEB models. Using Bayesian parameter averaging, we estimated the probabilities and magnitudes associated with each connectivity parameter. Additionally, we determined the magnitudes and effects related to the modulated connections. We established significant connectivity parameters in the current study using a posterior probability threshold of $P_p > 0.99$.

GFA

We applied the GFA method to uncover latent variables that reveal relationships among distinct variable groups while adhering to a sparsity constraint (Klami et al., 2015). GFA relies on sparse Bayesian estimation to pinpoint latent factors that either expound upon group-specific variations or outline a robust relationship among different groups. In this study, we defined four variable groups: 1) Neural measures, 2) Psychologic measures, 3) Behavioral measures, and 4) Demographic measures. For the neural measures, significant effective connectivity parameters derived from the DCM analysis within three identified regions of interest (amygdala, dlPFC, PCC) were used as constituents of the neural GFA group. Six subscale scores across two self-report questionnaires (DASS subscales encompassing depression, anxiety, stress, and BIS subscales encapsulating attention, motor, and non-planning) were entered as a group for psychological measures.

In contrast, the behavioral group consisted of measurements taken before and after fMRI, encompassing craving intensity and positive and negative scores on the PANAS. Finally, demographic measures were represented by three scores (age, education, and marital status), forming a distinct GFA group. To ensure compatibility with GFA, all variables underwent z-normalization, thereby attaining a mean of zero and a variance of one. This standardized format aligns with the requirements of GFA. We conducted the sparse Bayesian estimation process in ten iterations to mitigate the potential of identifying spurious latent factors. Only the factors that displayed robustness across all ten replicates of GFA were then extracted and deemed suitable for subsequent analysis (Ghobadi-Azbari et al., 2022; Peng et al., 2021; White et al., 2021).

We utilized the Pearson correlation to assess the bivariate relationships between behavioral and neural variables as an additional approach to exploring neurobehavioral associations. The GFA and Pearson correlation were conducted using the statistical software R. The GFA

analysis was executed using the 'gfa' function within the R software, specifically with the R package GFA (Lepäaho et al., 2017; Team, 2020).

3. Results

Behavioral data

To investigate the behavioral effect of cue reactivity on positive and negative emotional states, as assessed by the PANAS scale and craving intensity, we conducted a comparative analysis by directly comparing data collected before and after the fMRI session. After the completion of the fMRI session, participants did not exhibit a statistically significant reduction in self-reported craving intensity ($t_{33} = -0.54$, $P = 0.592$; Figure 2A), and there was no notable increase observed in PANAS-PA scores ($t_{33} = 0.51$, $P = 0.615$; Figure 2B) when compared to their pre-scanner state. Nevertheless, a substantial and statistically significant alteration emerged in PANAS-NA scores following the cue-reactivity paradigm ($t_{33} = -4.37$, $P < 0.0001$) (Figure 2C).

Functional activity analysis of methamphetamine cue reactivity

A whole-brain GLM analysis was performed as a quality control measure to validate the activation pattern linked to methamphetamine cue reactivity. This analysis included methamphetamine and neutral cues as fixed regressors, as depicted in Figure 3A. The main effect of cue reactivity (methamphetamine > neutral contrast) yielded significance in multiple clusters, employing a voxel-wise P threshold of $P < 0.001$ and a minimum cluster size of $k = 40$. These clusters included regions in the middle orbital gyrus, superior medial gyrus, posterior cingulate cortex, caudal lingual gyrus, and cerebellum cortex. Furthermore, we presented the brain activation findings across the 246 subregions outlined in the human Brainnetome atlas, as illustrated in Figure 3B.

Functional connectivity analysis of methamphetamine cue reactivity

We utilized seed-to-whole brain gPPI analysis to pinpoint target regions exhibiting functional connectivity with the source region, specifically the right medial amygdala (coordinates: $X = 19$, $y = -2$, $z = -19$; Figure 4A). In fact, we examined how this connectivity was modulated by drug cue reactivity during the methamphetamine > neutral condition. The gPPI analysis unveiled that task-modulated connectivity was statistically significant in two clusters. This outcome was determined

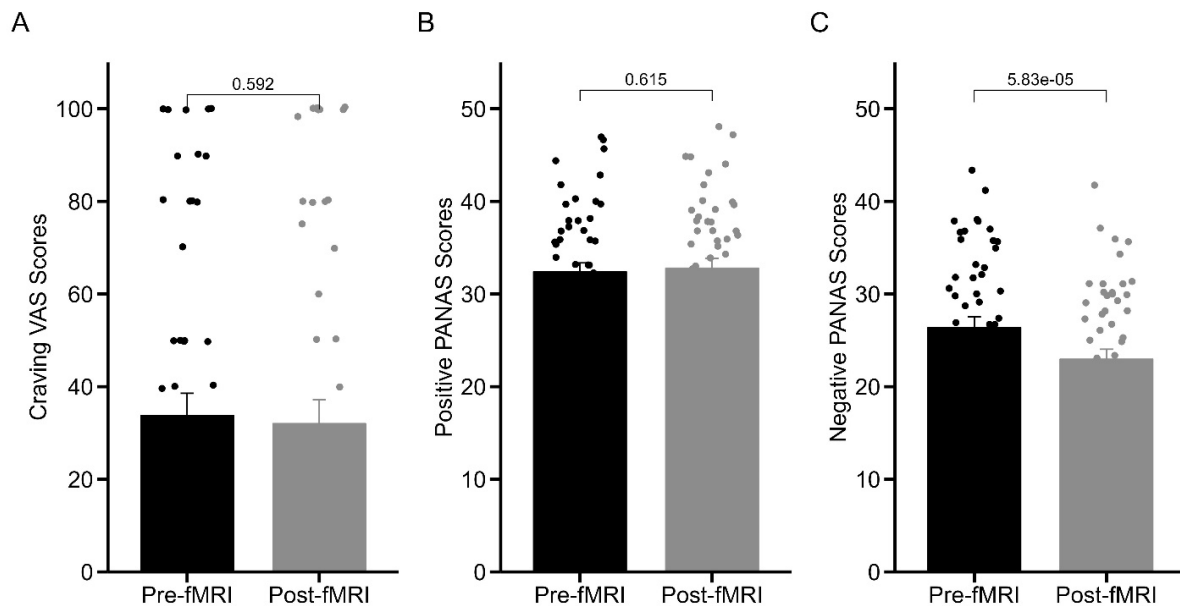


Figure 2. Behavioral cue reactivity effects on methamphetamine users

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PANAS: Positive and negative affect schedule.

Notes: (A-C) Bar charts that provide a visual representation of the main effects of cue-reactivity on (A) craving intensity, (B) positive PANAS scores, and (C) negative PANAS scores before and after the methamphetamine cue-reactivity paradigm. The data displayed in the bar charts are presented as Mean±SEM.

using a voxel-level threshold of uncorrected $P < 0.001$ and a cluster-size threshold of FDR-corrected $P < 0.05$, as depicted in [Figure 4B](#). These clusters are located in the dlPFC (peak at MNI coordinate: -16, 34, 44; 122 voxels; $p\text{-FWE}=0.01$) and the PCC (peak at MNI coordinate: -4, -40, 34; 90 voxels; $p\text{-FWE}=0.05$) ([Figure 4C](#) and [supplementary Table 1](#)). Our results showed increased PPI strength within the amygdala-dlPFC and amygdala-PCC functional networks during the cue reactivity task in the methamphetamine condition (amygdala-dlPFC: 0.042 ± 0.009 ; amygdala-PCC: 0.035 ± 0.008 ; Mean±SE) compared to the neutral condition (amygdala-dlPFC: -0.005 ± 0.011 , amygdala-PCC: -0.004 ± 0.009 ; Mean±SE) ([Figures 4D](#) and [4E](#)).

Next, we tested for bivariate correlations between behavioral effects (self-reported craving and positive and negative emotional states) and neural response (amygdala-dlPFC and amygdala-PCC PPI connectivity during cue exposure). Therefore, we tested whether individual estimated functional connectivity parameters are directly associated with behavioral cue-reactivity effects ([post-pre] craving and [post-pre] positive/negative PANAS). Interestingly, behavioral findings did not correlate with functional connectivity on amygdala-dlPFC and amygdala-PCC connections ([Figures 4F](#) and [4-G](#)). For

example, the individual functional connectivity in the amygdala-dlPFC did not correlate with craving intensity ($R=0.13$; $P=0.35$; [Figure 4F](#)) and negative PANAS changes ($R=0.12$; $P=0.41$; [Figure 4G](#)).

Effective connectivity of methamphetamine cue reactivity

Building upon these results, we aimed to examine whether the observed changes in functional connectivity could be validated through effective connectivity analysis. Our functional connectivity analysis determined whether cue reactivity influences forward, backward, or bidirectional projections between the amygdala, dlPFC, and PCC. For this purpose, we applied dynamic causal modeling to the adjusted BOLD time series data originating from the amygdala, dlPFC, and PCC. Using model selection, we established a full model for each participant ([Friston et al., 2016](#)). This model encompassed all conceivable modulatory inputs from craving on intrinsic self-connections and visual stimuli acting as driving inputs into the nodes ([Figure 5A](#)).

Regarding the Bayesian model selection ([Friston et al., 2016](#)) dynamic causal models – and linear models at subsequent (between-subject, we determined the model

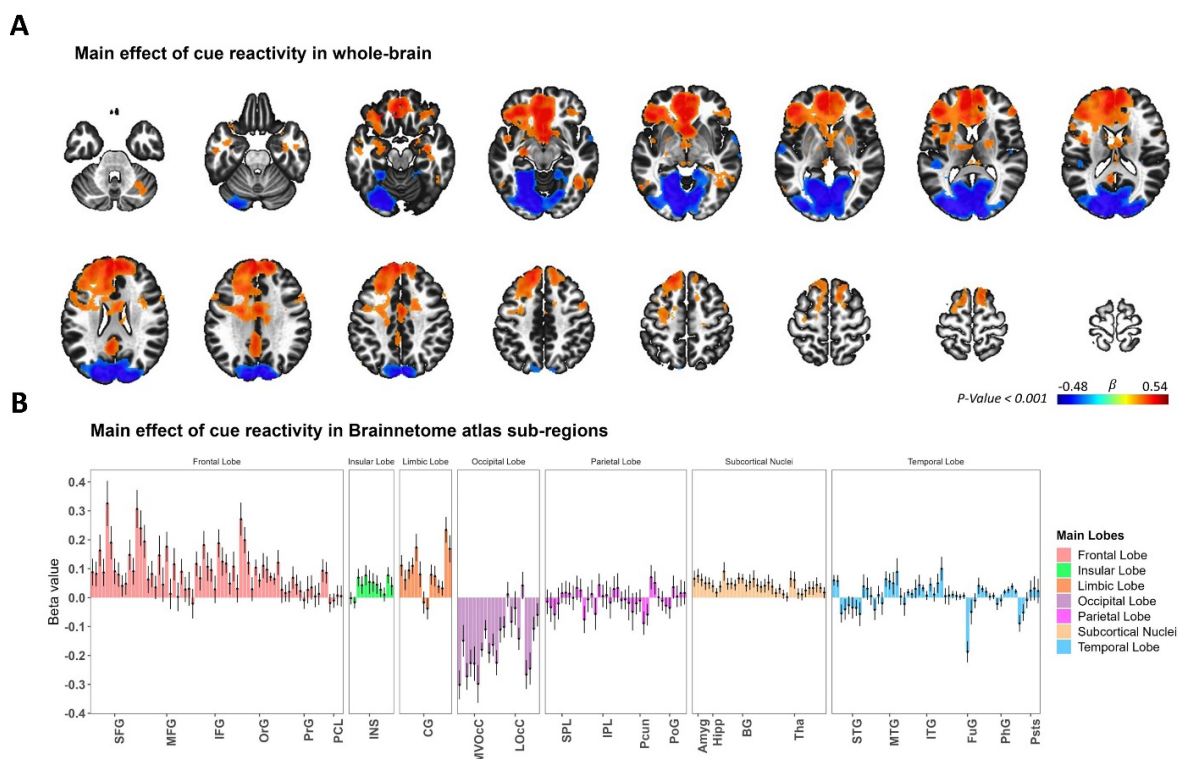


Figure 3. Whole-brain neural response during the task-based fMRI when comparing the conditions of Meth and neutral stimuli

Abbreviations: Meth: Methamphetamine; Amyg: Amygdala; BG: Basal ganglia; CG: Cingulate gyrus; FuG: Fusiform gyrus; Hipp: hippocampus; IFG: Inferior frontal gyrus; IPL: Inferior parietal lobule; INS: Insular gyrus; ITG: Inferior temporal gyrus; LOcc: Lateral occipital cortex; MFG: Middle frontal gyrus; MITG: Middle temporal gyrus; MVOcc: Medioventral occipital cortex; OrG: Orbital gyrus; PCun: Precuneus; PCL: Paracentral lobule; PhG: Parahippocampal gyrus; PoG: Postcentral gyrus; pSTS: Posterior superior temporal sulcus; PrG: Precentral gyrus; SFG: Superior frontal gyrus; SPL: Superior parietal lobule; STG: Superior temporal gyrus; Tha: Thalamus.

Notes: Whole-brain activation pattern related to drug craving during the Meth cue-reactivity task and (B) alterations in brain activation pattern within Brainnetome (BNA) sub-regions. The data in the bar charts are presented as Mean±SEM.

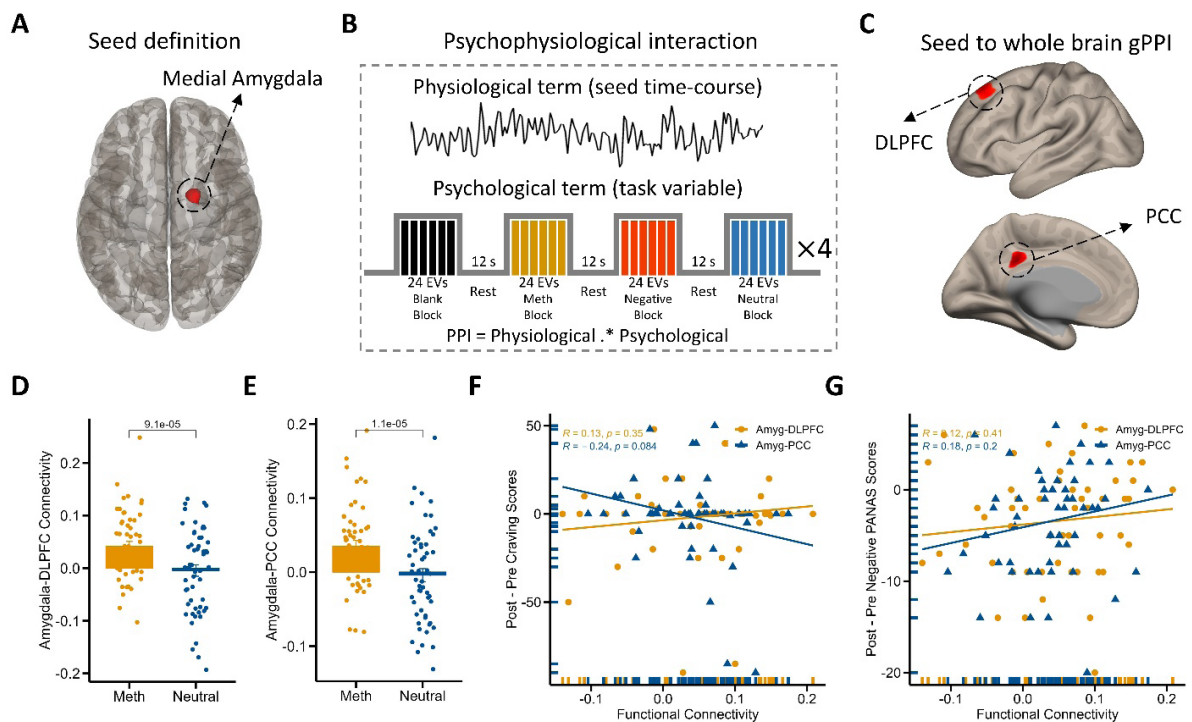
with the strongest evidence by assessing the data for all potential nested PEB models (Figures 5B, 5C and 5D). The winning model featured an effective neural network characterized by reciprocal positive connections between the amygdala and dlPFC, amygdala, and PCC, as well as dlPFC and PCC. Additionally, it included negative intrinsic connections within the three nodes (Figure 5B and Supplementary Table 2).

We tested whether behavioral effects (craving and positive and negative emotional states) are mediated by estimated significant effective connectivity. Hence, we examined whether the individual effective connectivity parameters from the winning model were directly correlated with behavioral cue reactivity effects, specifically the differences between post- and pre-measurements of craving and positive/negative PANAS scores. The correlational analyses unveiled a noteworthy negative association ($R=-0.28$; $P=0.041$, $n=54$, the Pearson correla-

tion). This finding suggests that the inhibitory intrinsic connection of the dlPFC was predictive of an increase in PANAS positive affect values during cue reactivity (Figure 5E). It is worth noting that behavioral findings did not exhibit any correlation with cue reactivity effects on other intrinsic and extrinsic connections.

Relationships between neural, psychological, behavioral, and demographic variables

The GFA extracted 9 sturdy latent variables (Figure 6), collectively accounting for roughly 38.53% of the variance across variable groups. Notably, no robust cross-unit latent factors were discerned between the neural, psychological, behavioral, and demographic variable groups. In simpler terms, the GFA did not reveal any meaningful association or alignment between the neural group and the behavioral, psychological, and demographic variable groups within the latent variable space.



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Figure 4. Seed-to-whole brain functional connectivity analysis during the task-based fMRI when comparing the conditions of Meth and neutral stimuli

Abbreviations: gPPI: Generalized psychophysiological interaction; Amyg: Amygdala; dIPFC: Dorsolateral prefrontal cortex; Meth: Methamphetamine; PCC: Posterior cingulate cortex; EVs: Events; PANAS: Positive and negative affect schedule.

Notes: The sub-region of the right medial amygdala, as defined in the Brainnetome atlas, was selected as a seed region for gPPI analysis. (B) In the Meth > neutral condition, the BOLD signal was derived from the seed region. Clusters demonstrating significant interaction are represented in red over a 3D brain (C). (D, E) The mean values, accompanied by error bars, depict the connectivity between the amygdala and dIPFC, as well as amygdala and PCC, during the task-based fMRI when comparing the conditions of Meth and neutral stimuli. (F, G) Correlations between functional connectivity and behavioral findings. The results show no significant relationship between amyg-DLPFC and amyg-PCC with craving and PANAS scores.

On the contrary, the GFA detected a robust latent factor that exhibited loadings across units of analysis in behavioral, psychological, and demographic domains. Nevertheless, the explained mean-variance differed at 20.05%, 30.88%, and 4.32% within the behavioral, psychological, and demographic variable groups, respectively. Hence, although this latent factor technically encompassed loadings across behavioral, psychological, and demographic levels of analysis, it was primarily influenced by the behavioral and psychological variables, accounting for most of the explained variance.

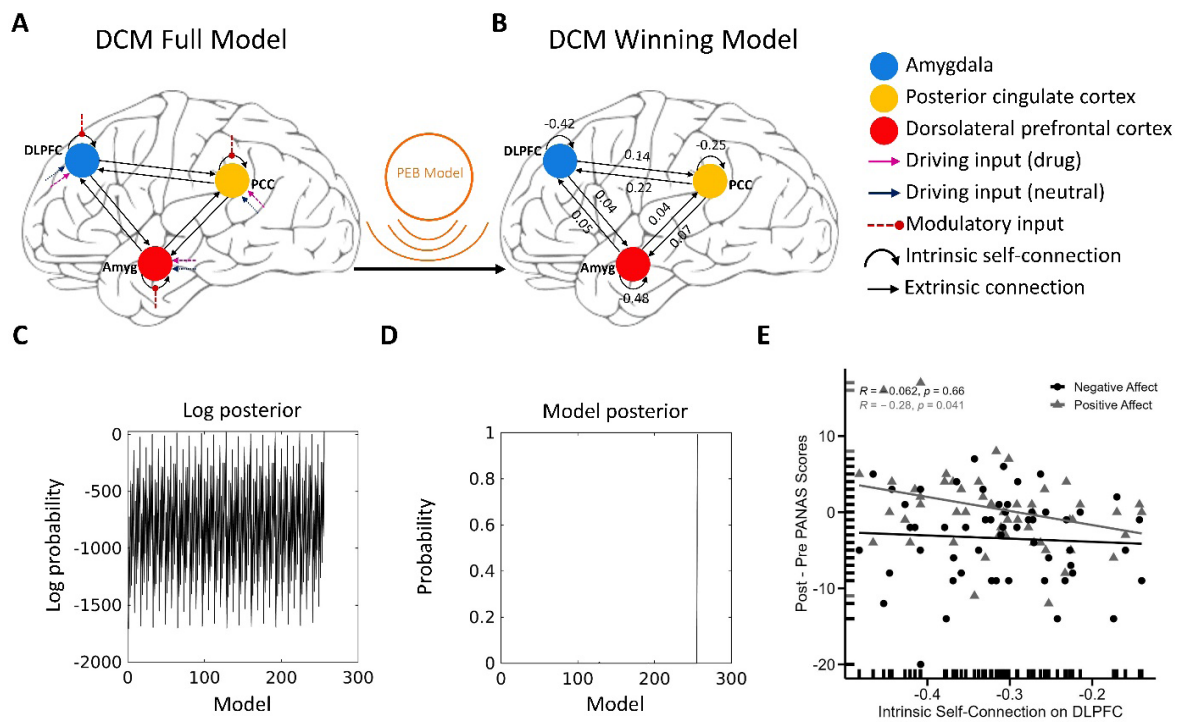
4. Discussion

The current study delved into the intricate neural mechanisms underlying methamphetamine cue reactivity by examining functional and effective connectivity in the amygdala-cortical pathways. The research aimed to uncover the underlying neural dynamics contributing to

drug craving and addiction-related processes in individuals with MUD (Grodin et al., 2019). Our discussion will focus on the implications of the findings, their alignment with existing literature, and their potential contributions to understanding addiction and informing interventions.

Functional connectivity and methamphetamine cue reactivity

The application of seed-to-whole brain gPPI analysis offered valuable insights into the functional interactions between the amygdala and other brain regions when exposed to drug cues. The observed increase in task-modulated connectivity within the amygdala-dIPFC and amygdala-PCC functional networks during methamphetamine cue reactivity supports the notion that these regions play a pivotal role in processing drug-related stimuli. These results are in line with prior research indicating that the dIPFC and PCC play a crucial role in



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Figure 5. Examining effective connectivity in methamphetamine cue reactivity through dynamic causal modeling

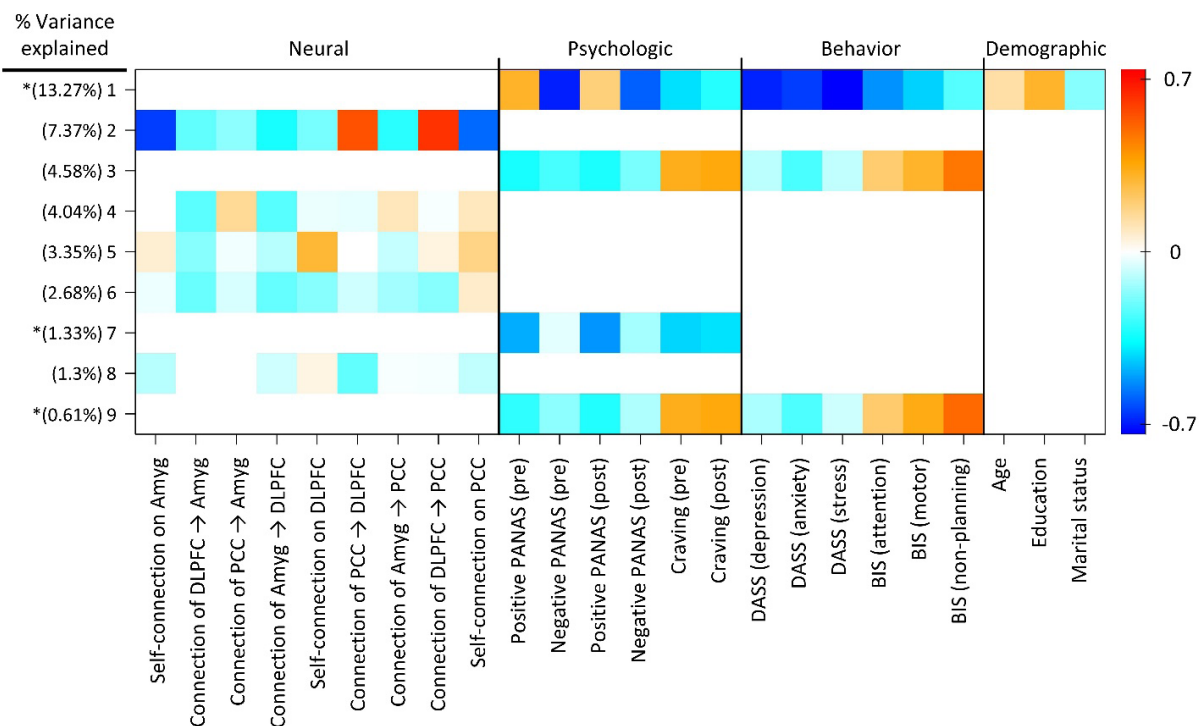
Abbreviations: Meth: Methamphetamine; DCM: dynamic causal modeling; dlPFC: Dorsolateral prefrontal cortex; PCC: Posterior cingulate cortex; PANAS: Positive and negative affect schedule.

Notes: For each subject, the full DCM model was specified and inverted. This model encompassed intrinsic self-connections and extrinsic forward and backward connections, with drug and neutral stimuli acting as driving inputs. Additionally, it accounted for drug-induced modulation of all intrinsic self-connections. (B) The winning DCM model, determined via post hoc Bayesian model selection, is a streamlined version with the most substantial supporting evidence across all subjects. This model encompasses the extrinsic forward and backward connections between the amygdala, dlPFC, and PCC. The parameters suggest a positive connection strength for extrinsic forward and backward connections while indicating negative self-connection strength within the amygdala, dlPFC, and PCC. (D) The panel illustrates the posterior probabilities for all the possible models. This finding indicates that the winning model had a posterior probability of 0.98, signifying it possessed more substantial evidence than any other model. (E) Correlations between behavioral and neural results revealed that individual parameter estimates of intrinsic self-connection on the DLDPFC were associated with PANAS-positive emotional state ($R=-0.28$; $P=0.041$; the Pearson correlation).

cognitive control processes, emotional regulation, and cue-induced craving in addiction contexts (Goldstein & Volkow, 2002, 2011; Jia et al., 2011; Sinha, 2001). The observed heightened connectivity within the amygdala-dlPFC and amygdala-PCC functional networks during methamphetamine cue reactivity tasks supports the engagement of these regions in the processing of drug-related cues. This engagement potentially contributes to the escalation of craving and the risk of relapse, aligning with the idea that the amygdala holds a central role in encoding emotional significance (Janak & Tye, 2015; Luo et al., 2013; Šimić et al., 2021).

Effective neural pathways and methamphetamine cue reactivity

Dynamic causal modeling offers a more profound comprehension of the effective neural pathways that underlie methamphetamine cue reactivity. The established effective neural network, including reciprocal positive connections between the amygdala-dlPFC, amygdala-PCC, and dlPFC-PCC, aligns with theories highlighting the interplay between emotional processing and cognitive control systems in addiction. The existence of negative intrinsic connections among these nodes further highlights the complexity of the neural network involved in processing drug cues, potentially reflecting an intricate modulatory mechanism to counteract excessive responses to drug cues



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Figure 6. Exploring the associations among neural, psychological, behavioral, and demographic variables utilizing GFA

Abbreviations: Amyg: Amygdala; dLPFC: dorsolateral prefrontal cortex; PCC: Posterior cingulate cortex; PANAS: Positive and negative affect schedule; BIS: Barratt impulsiveness scale; DASS: Depression anxiety stress scales.

Notes: The heatmap illustrates the loading weight of each variable through different colors. The x-axis provides a view of the variables included in each group. The y-axis shows the extracted robust group factors and the respective percentage of explained variance. Group factors marked with asterisks signify at least one loading weight within them, and this weight's 95% credible interval does not include 0.

(Rolls, 2019). These results align with existing literature emphasizing the coordinated activity between the prefrontal cortex, cingulate cortex, and amygdala, mediating cue-induced responses and cognitive control (Etkin et al., 2015; Sotres-Bayon & Quirk, 2010).

Neurobehavioral relationships

The correlation analysis revealed a negative association between intrinsic self-inhibition in the dLPFC and PANAS-positive emotional state. This finding suggests a potential role for dLPFC inhibitory processes in modulating positive affect during methamphetamine cue reactivity. This finding aligns with theories emphasizing the interplay between cognitive control mechanisms and emotional regulation in substance use disorders (Lan-teaume et al., 2007; Ochsner & Gross, 2005; Volkow et al., 2016). While this result contributes to our understanding of the intricate relationship between neural connectivity and emotional responses, further research

is necessary to elucidate the underlying mechanisms and potential clinical implications.

In contrast to the robust neural connectivity findings, the absence of significant cross-unit latent factors between the functional connectivity patterns and behavioral, psychological, or demographic variables in the GFA analysis is intriguing. This outcome might indicate that the observed alterations in neural connectivity do not have straightforward translations into measurable relationships with these external factors. This discrepancy could be attributed to the multifaceted nature of substance use disorders, which are influenced by a myriad of interacting factors.

Integration with previous research

The present study builds upon a growing body of research that highlights the intricate interplay between brain regions in addiction. The observed connectivity changes in response to methamphetamine cues resonate

with previous studies investigating cue reactivity across different substances of abuse. The convergence of findings regarding the involvement of the amygdala, dlPFC, and PCC underscores their roles as core components in the addiction process, supporting the notion of a broader addiction-related neural network.

Clinical implications

Understanding the neural mechanisms underpinning methamphetamine cue reactivity holds significant clinical implications. The identified networks and connections offer potential targets for intervention strategies to mitigate craving and prevent relapse. Interventions targeting the amygdala-cortical circuitry could be designed to enhance cognitive control (Sadeghi et al., 2023) over drug-related cues and emotions, potentially aiding in the management of addiction (Soleimani et al., 2023).

5. Conclusion

In summary, this research enriches our understanding of addiction by investigating the amygdala-cortical connectivity and effective neural pathways associated with methamphetamine cue reactivity. Integrating functional and effective connectivity analyses and neurobehavioral assessments provides a comprehensive picture of the underlying neural dynamics. These findings offer insights into the mechanisms driving addiction-related processes and potential avenues for targeted interventions. As addiction continues to pose a significant public health challenge, these insights may pave the way for innovative strategies aimed at improving treatment outcomes and reducing the burden of addiction on affected individuals and society.

Limitations and future studies

Although the study offers valuable insights, it is essential to acknowledge its limitations. The sample consisted solely of male participants with MUD, potentially limiting the generalizability of the findings. Future studies could include diverse samples and consider the impact of gender and other demographic variables. Additionally, the study's cross-sectional nature restricts our capacity to establish causal relationships between functional connectivity patterns and addiction-related outcomes. Longitudinal studies could shed light on the trajectory of neural changes and their predictive value.

Ethical Considerations

Compliance with ethical guidelines

The Declaration of Helsinki was followed in the design and execution of the study procedure. This study was reviewed and approved by the Ethics Committee of Research at [Tehran University of Medical Science](#), Tehran, Iran (IR.TUMS.REC.93-02-98-23869). Participants in this study provided their written informed consent to participate.

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Authors' contributions

Conceptualization and methodology: Peyman Ghobadi-Azbari, and Yasaman Hosseini; Investigation: All authors; Formal analysis, and visualization: Peyman Ghobadi-Azbari; Writing the original draft: Peyman Ghobadi-Azbari; Review, and editing: Yasaman Hosseini, Hossein Moslemi, and Mitra Yousefpour; Supervision: Yasaman Hosseini and Hossein Moslemi.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Table 1. The results of the task-modulated connectivity obtained from the seed-to-whole brain gPPI analysis for two clusters

Seed	Cluster Location	Cluster Size	Peak Coordinate			T-value in Peak	p-FWE	p-FDR	P-un-corrected
			X	Y	Z				
R-mAmyg	Left dlPFC	122	-16	+34	+44	4.23	0.0108	0.0105	0.0003
R-mAmyg	Left PCC	90	-4	-40	+34	4.86	0.0472	0.0234	0.0013

Abbreviations: dlPFC: Dorsolateral prefrontal cortex; PCC: Posterior cingulate cortex; mAmyg: Medial amygdala; gPPI: Generalized psychophysiological interaction; FDR: False discovery rate; FWE: Family wise error.

Supplementary Table 2. The results of the DCM-PEB analyses for Meth cue-reactivity paradigm

Parameter*	Description	Units	Expectation	Variance	Posterior Probability
	Self-connection on mAmyg	None	-0.4771	0.0375	1
	mAmyg → dlPFC	Hz	0.0486	0.024	0.999987
	mAmyg → PCC	Hz	0.0358	0.0215	0.994482
	dlPFC → mAmyg	Hz	0.0414	0.0249	0.999385
	Self-connection on dlPFC	None	-0.4245	0.035	1
	dlPFC → PCC	Hz	0.1401	0.0219	1
	PCC → mAmyg	Hz	0.0699	0.0312	1
	PCC → dlPFC	Hz	0.2210	0.03	1
	Self-connection on PCC	None	-0.2476	0.0506	1
	Meth on mAmyg self-connection	None	0.0053	0.9035	0
	Meth on dlPFC self-connection	None	0.0365	0.9755	0
	Meth on PCC self-connection	None	0.0135	0.9778	0
	Driving: Meth on mAmyg	None	0.0016	0.8875	0
	Driving: Meth on dlPFC	None	0.0020	0.885	0
	Driving: Meth on PCC	None	-0.0004	0.8329	0
	Driving: Neutral on mAmyg	None	-0.0014	0.8407	0
	Driving: Neutral on dlPFC	None	0.0014	0.865	0
	Driving: Neutral on PCC	None	0.0003	0.8898	0

Abbreviations: mAmyg: Medial Amygdala; dlPFC: Dorsolateral Prefrontal Cortex; PCC: Posterior Cingulate Cortex; Meth: Methamphetamine.