General Psychiatry

Connectome-based predictive modelling can predict follow-up craving after abstinence in individuals with opioid use disorders

Wenhan Yang,[1] Jungong Han,[2] Jing Luo,[3] Fei Tang,[1] Li Fan,[3] Yanyao Du,[1] Longtao Yang,[1] Jun Zhang,[4] Huiting Zhang,[5] Jun Liu [3,6,7]

To cite: Yang W, Han J, Luo J, *et al*. Connectome-based predictive modelling can predict follow-up craving after abstinence in individuals with opioid use disorders. *General Psychiatry* 2023;**36**:e101304. doi:10.1136/gpsych-2023-101304

► Additional supplemental materials are published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101304).

Received 24 August 2023
Accepted 01 December 2023

For numbered affiliations see end of article.

Correspondence to
Dr Jun Liu;
junliu123@csu.edu.cn

ABSTRACT

Background Individual differences have been detected in individuals with opioid use disorders (OUD) in rehabilitation following protracted abstinence. Recent studies suggested that prediction models were effective for individual-level prognosis based on neuroimage data in substance use disorders (SUD).

Aims This prospective cohort study aimed to assess neuroimaging biomarkers for individual response to protracted abstinence in opioid users using connectome-based predictive modelling (CPM).

Methods One hundred and eight inpatients with OUD underwent structural and functional magnetic resonance imaging (fMRI) scans at baseline. The Heroin Craving Questionnaire (HCQ) was used to assess craving levels at baseline and at the 8-month follow-up of abstinence. CPM with leave-one-out cross-validation was used to identify baseline networks that could predict follow-up HCQ scores and changes in HCQ ($HCQ_{follow\text{-}up}$–$HCQ_{baseline}$). Then, the predictive ability of identified networks was tested in a separate, heterogeneous sample of methamphetamine individuals who underwent MRI scanning before abstinence for SUD.

Results CPM could predict craving changes induced by long-term abstinence, as shown by a significant correlation between predicted and actual $HCQ_{follow\text{-}up}$ ($r=0.417$, $p<0.001$) and changes in HCQ (negative: $r=0.334$, $p=0.002$; positive: $r=0.233$, $p=0.038$). Identified craving-related prediction networks included the somatomotor network (SMN), salience network (SALN), default mode network (DMN), medial frontal network, visual network and auditory network. In addition, decreased connectivity of frontal-parietal network (FPN)-SMN, FPN-DMN and FPN-SALN and increased connectivity of subcortical network (SCN)-DMN, SCN-SALN and SCN-SMN were positively correlated with craving levels.

Conclusions These findings highlight the potential applications of CPM to predict the craving level of individuals after protracted abstinence, as well as the generalisation ability; the identified brain networks might be the focus of innovative therapies in the future.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Associations between craving in opioid use disorders (OUD) and neuroimaging measures have been demonstrated, revealing potential brain recovery and differences in individual outcomes after protracted abstinence.

WHAT THIS STUDY ADDS

⇒ A connectome-based machine learning analysis of whole-brain data was used in this study to predict follow-up craving levels after protracted abstinence in individuals with OUD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The identified craving-related networks could be considered potential treatment targets in future studies, and the prediction model could help make individualised treatment decisions and improve treatment effects in individuals with OUD.

INTRODUCTION

Opioid use disorder (OUD) is a serious public health emergency that involves the misuse of prescribed opioid medications.[1] Craving, which is a key hallmark of addiction, is a strong incentive for a variety of appetitive behaviours that have a vital role during the processing of relapse.[2] Neuroimaging studies have shown that anatomical abnormalities and dysfunctions in some brain regions,[3–5] like the prefrontal cortex (PFC), striatum, insula and thalamus, are related to reward processing and impaired cognitive control[6] in patients and animals with OUD or substance use disorders (SUD). Moreover, associations between clinical outcomes (craving or behaviour improvement) and neuroimaging measures after protracted abstinence in OUD were demonstrated by recent longitudinal studies,[7] revealing potential brain recovery after protracted abstinence. However, these studies have mainly concentrated on brain abnormalities based on group-level differences (eg, OUD vs healthy controls (HCs) or preprotracted/postprotracted abstinence),

providing incomplete data since individual differences exist in symptomatic or behavioural improvement, especially in craving improvement during protracted abstinence in SUD.[8] Thus, searching for new neurobiological markers that may identify high craving traits might help pinpoint those at high risk of relapse for OUD after protracted abstinence.

Machine learning analysis of whole-brain data can predict individual responses to specific therapies, potentially assisting the development of individualised treatment decisions and improving treatment effects. For example, a machine learning study[9] established and validated a new prediction model based on whole-brain resting state functional connectivity (RSFC) data to predict relapse in patients with SUD; in addition, the authors demonstrated varied treatment outcomes depending on individual differences in large-scale brain networks for cocaine use disorder. Moreover, identifying individual-level brain predictors of craving may expand existing biological knowledge of addiction pathophysiology.[10] Meanwhile, studies have identified specific craving networks that may be targeted in novel interventions for individualised precision therapy in the future.[11] Thus, building a model based on individualised brain data to predict abstinence-induced outcomes more precisely for OUD is required.

Connectome-based predictive modelling (CPM) is a machine learning approach that builds brain connection and behaviour models using whole-brain functional connectivity data.[12] Known as 'neural fingerprints',[9] the built-in cross-validation in CPM protects against overfitting by assessing the strength of the association in a novel sample, which improves the possibility of replication in follow-up research and generality to different clinical samples and is superior to correlation or regression models.[13] Moreover, CPM is data-driven and requires no prior network selection before the analysis.[9]

This study applied the CPM approach to the whole-brain resting-state functional magnetic resonance imaging (RS-fMRI) baseline data to identify craving-related neural networks predictive of 8-month follow-up abstinence for OUD. In addition, we further explored the predictive ability of these identified craving-related networks for abstinent responses in an independent SUD sample. Based on a previous study,[9] we hypothesised that CPM might predict follow-up craving state (changes in craving scores or craving scores at follow-up) at the individual level. Furthermore, based on the neural mechanisms of the reward pathway,[14] we hypothesised that higher levels of connection within and between the prefrontal and limbic brain regions would positively predict follow-up craving after abstinence.

MATERIALS AND METHODS

Subjects

A total of 108 inpatients aged 20–50 years with a history of opioid use were recruited from drug rehabilitation centres in Changsha, China, from September 2016 to December 2018 in this prospective cohort study. Inclusion criteria were the following: (1) a positive urine test for heroin; (2) met the diagnostic criteria for OUD according to the Diagnostic and Statistical Manual on Mental Disorders, Fifth Edition (DSM-V)[15]; (3) a negative urine test for methamphetamine and ketamine; (4) no history of methadone maintenance therapy; (5) Han Chinese and right-handed. Exclusion criteria were as follows: structural brain disease, seizures, head trauma, mental or behavioural disorders or MRI contraindications. All the participants were inpatients throughout the 8-month study at detoxification facilities that did not provide methadone or other drug maintenance treatment but offered education and physical exercise. At the start of the study, the abstinence median was 30 days. Baseline MRI scans and assessments by the Heroin Craving Questionnaire (HCQ)[16] were carried out. The HCQ includes 45 items and 5 theory-derived subscales that assess various aspects of craving; each is rated on a 7-point scale from strongly disagree to strongly agree.

MRI data acquisition

Neuroimaging data were collected using a 3 T MRI scanner (MAGNETOM Skyra, Siemens) with a 32-channel head receiving coil at the Second Xiangya Hospital of Central South University in Changsha, China. To obtain high-quality MRI data, participants were asked to remain motionless with their eyes open and their heads restrained by a padding and head restraint band. To exclude structural lesions in the brain, T1-weighted and T2-weighted imaging (T1/T2WI) scans were used. Parameters of resting-state fMRI were: repetition time (TR)=2000 ms, echo time (TE)=30 ms, field-of-view (FOV)=220×220 mm^2, flip angle=80°, slice thickness=4 mm, and axial slices=36. High-resolution T1-weighted MRI was obtained using a three-dimensional fast gradient echo sequence with the following parameters: TR=1450 ms, TE=2.0 ms, inversion time=900 ms, slice thickness=1 mm, FOV=256×256 mm^2, voxel size=1×1×1 mm^3, flip angle=12°, gap=0 mm and slices=176.

MRI data processing

Image data preprocessing was performed with Statistical Parametric Mapping 12 (SPM 12) (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and GRaph thEoreTical Network Analysis (GRETNA, https://www.nitrc.org/projects/gretna/). Participants with head movements or rotations of >3 mm or 3° were excluded. We first registered the resting state image with the T1 structure image. Then, after being reoriented into the anterior commissure (AC)-posterior commisure (PC) axis, all images were spatially normalised to the Montreal Neurological Institute space using the diffeomorphic anatomical registration technique using the Exponential Lie algebra registration method. All images were smoothed by a 6 mm half-height, full-width Gaussian kernel. Then, linear detrending eliminated variables, such as white matter, cerebrospinal fluid and 24 head movement parameters.

Finally, linear detrending was performed; white matter, cerebrospinal fluid and 24 head movement parameters were subsequently removed as covariates.

Functional connectivity

Whole-brain functional connectivity analyses were conducted using the GRETNA. The network nodes were defined in earlier CPM research[9 12] based on the Shen 268-node brain atlas, which comprises the cortex, subcortex and cerebellum (CBL).[17] The average time course from each voxel of the 268 nodes was calculated and then used in node-by-node pairwise Pearson's correlations. Next, Fisher's z-transformation was applied to the resultant r values to construct symmetric connectivity matrices, each of which provided a measure of the strength of a connection between two independent nodes.[9]

Connectome-based predictive modelling

CPM was conducted using previous custom Matrix Laboratory (MATLAB) scripts.[9 12] CPM performs a prediction model of the behavioural data from the group connection matrices using behavioural data and connectivity matrices as input. In this study, HCQ was scored at the 8-month follow-up time, and changes in HCQ scores during abstinence were separately input as behavioural data.[12] Data from the OUD group was divided into training and testing sets. Leave-one-out cross-validation (LOOCV) was used to assess the prediction performance of the model. For N individuals, N−1 individuals were used for the training set, and the remaining one was used for the testing set. The above process was repeated N times (where N=sample size), each time leaving out a different subject to use as a single test subject and to get a predicted $HCQ_{follow\text{-}up}$/change of HCQ ($HCQ_{follow\text{-}up}$–$HCQ_{baseline}$). From the training data, the connectivity of the edges from the training data set used Pearson's correlation to identify positive and negative predictive networks, that is, we used Pearson's correlation between the edges and the behavioural data set; a 268 by 268 connectivity matrix was input for each subject from the 'Functional connectivity' section. The Pearson's correlation coefficient r values between each edge connection and the HCQ score were computed and the associated significant threshold was set at $p<0.01$. Positive networks are edges for a positive correlation between connectivity and the craving score ($HCQ_{follow\text{-}up}$/$HCQ_{follow\text{-}up}$–$HCQ_{baseline}$), and negative networks are those for a negative correlation between connectivity and the craving score. The negative network, positive network and both negative and positive networks were used to predict craving measures, that is, changes in HCQ scores between baseline and the 8-month follow-up and the follow-up HCQ scores, separately. The importance of edge weights in each network was then added to provide single-individual summary statistics that were input into prediction models with linear correlations to behavioural data. The test data set was then used to apply the resultant polynomial coefficients, including slope and intercept, to predict behaviours. LOOCV was used in this study; the predicted value of the 'left-out' individual was generated by using other individuals' data as the training data set iteratively until each individual had a predicted value.

Model performance was assessed by Pearson's correlation coefficient (r) between predicted HCQ scores (changes in HCQ/follow-up HCQ) and actual HCQ scores for the positive model, the negative model and the combined positive and negative model, respectively. At the same time, to test the significance of parametric statistics (r value), we further performed non-parametric permutation tests and repeated the above CPM process through the permutation test (5000 times). The CPM analysis was rerun using the shuffled data after randomly shuffling the correspondence between behavioural measures and connectivity matrices 5000 times to produce null distributions for significance testing. The p values for leave-one-out predictions were generated based on these null distributions.[12] The statistical threshold was set at $p<0.05$.

Visualising network anatomy

Edges appearing in 100% of the LOOCV iterations across all subjects were defined as consensus edges. By dividing the edges into groups according to the macroscale brain areas, consensus edges were detected, thus making it easier to see how each region contributes to the models. Using circle plots, 268 regions of interest (ROIs) were organised into 10 different brain areas, including the prefrontal, motorstrip, insular, parietal, temporal, occipital, limbic, CBL, subcortical and brainstem areas.[17] Visualisation of the edges was conducted using BioImage Suite (https://www.nitrc.org/projects/bioimagesuite/).

External validation set

To determine the generalisability of our findings, we tested the ability of the identified networks to predict SUD craving outcomes in a heterogeneous sample of methamphetamine-dependent individuals (n=39). These patients were recruited from drug rehabilitation centres in Changsha; each participant had a positive urine test for methamphetamine and met the diagnostic criteria for methamphetamine use disorder according to the DSM-V. An additional inclusion criterion for the methamphetamine group was a negative urine test for heroin and ketamine. Also, all participants were admitted to the detoxification facility for abstinence and given 8 months of education and physical exercise. In addition, they all underwent an MRI scan and were evaluated by the methamphetamine craving score (Methamphetamine Craving Questionnaire) based on the HCQ[16] at baseline. After approximately 8 months, these participants were asked to participate in a follow-up craving interview to report craving scores. The predicted value of the follow-up methamphetamine craving score was calculated by the CPM model generated from the above step. Next, the

Table 1 Demographic and clinical characteristics of heroin users in a CPM study (n=108)*

	Total (n=108)		fMRI data included in CPM (n=69)†			
			Yes (n=69)		No (n=39)	
	N	%	N	%	N	%
Male	65	60.2	43	62.3	22	56.4
Completed high school	79	73.1	48	69.6	31	79.5
Nicotine	106	98.1	68	98.6	38	97.4
Alcohol	28	25.9	23	33.3	5	12.8
	Mean	SD	Mean	SD	Mean	SD
Age (years)	42.4	7.2	41.9	6.7	43.4	7.7
Years of drug use	15.4	7.1	14.7	7.1	16.5	6.9
Age at first drug use	26.9	9.3	26.2	9.7	28.1	8.7
Follow-up HCQ scores	–	–	29.4	18.1	–	–
Changes in HCQ scores	–	–	–25.1	13.3	–	–
	Median	Range	Median	Range	Median	Range
Dosage of former heroin use‡/per day	0.5	(0.01, 2)	0.5	(0.1, 1.5)	0.5	(0.01, 2)
Days of abstinence at MRI baseline	30	(9, 259)	30	(9, 194)	36	(10, 259)

*One-hundred and eight participants completed the baseline MRI scan.
†Seventy-five reported their follow-up HCQ, and six were excluded because of excessive motion during the MRI scanning.
‡Dosage of former heroin use before they came into the drug rehabilitation centres.
CPM, connectome-based predictive modelling; fMRI, functional MRI; HCQ, Heroin Craving Questionnaire; MRI, magnetic resonance imaging; SD, standard deviation.

correlation between the predicted and true values of this group was calculated using Pearson's correlation to further evaluate the CPM model.

RESULTS

Study

One-hundred and eight inpatients with OUD underwent MRI scans and were assessed by the HCQ at baseline. Six participants were excluded due to excessive head movements or poor-quality MRI data. After approximately 8 months, 69 of the original participants (33 were lost during the follow-up) were asked to participate in a follow-up interview and report a follow-up HCQ score. Finally, data from 69 participants with OUD (43 males and 26 females, age: 41.9 (6.7 years)) were included as a data set to construct the subsequent CPM model (table 1). Demographic characteristics are summarised in table 1. Figure 1 shows the flowchart.

Associations between clinical variables and craving

No significant associations between clinical variables (years of use, abstinence days, age at first drug use, age, education) and the $HCQ_{follow\text{-}up}$ (years of use: r=0.21, p=0.309; abstinence days: r=−0.19, p=0.414; age at first drug use: r=−0.06, p=0.601; age: r=0.14, p=0.292; education: r=0.16, p=0.176) or HCQ changes (years of use: r=0.15, p=0.264; abstinence days: r=0.19, p=0.132; age at first drug use: r=−0.11, p=0.263; age: r=−0.04, p=0.982; education: r=0.05, p=0.896) were found according to the Pearson's correlation analyses.

Predicting craving scores at the 8-month follow-up

The overall CPM model successfully predicted HCQ scores at 8-month follow-up (negative network: r=0.417, df=68, p<0.001) (figures 2A, 3A, 4A). Figure 3A summarises negative craving networks based on the connection between large-scale brain areas. In addition, connectivity was summarised in terms of the number of connections between neural networks like frontal-parietal network (FPN), motor, default mode (DMN) and salience (SALN) for the negative networks. The top 10 nodes of negative edges with the most connections in the OUD craving network (8-month follow-up HCQ scores) were located in the bilateral CBL, the left limbic region and the brainstem area (see online supplemental table 1).

There was no significant association between HCQ scores at the 8-month follow-up and the RSFC in the positive network (r=0.027, p=0.149) and both negative and positive networks (r=0.136, p=0.100).

Predicting changes in the craving score

The overall CPM model successfully predicted changes in HCQ scores ($HCQ_{follow\text{-}up}$–$HCQ_{baseline}$) between the baseline time and the time of the 8-month follow-up (positive network: r=0.233, p=0.038 negative network: r=0.334, p=0.002) (figure 4B,C). Positive and negative craving networks based on the connection between large-scale brain areas are summarised in figure 2B,C. The connectivity was summarised in terms of the number of connections between or within neural networks like FPN, DMN, motor and SALN for the positive (figure 3B) and negative

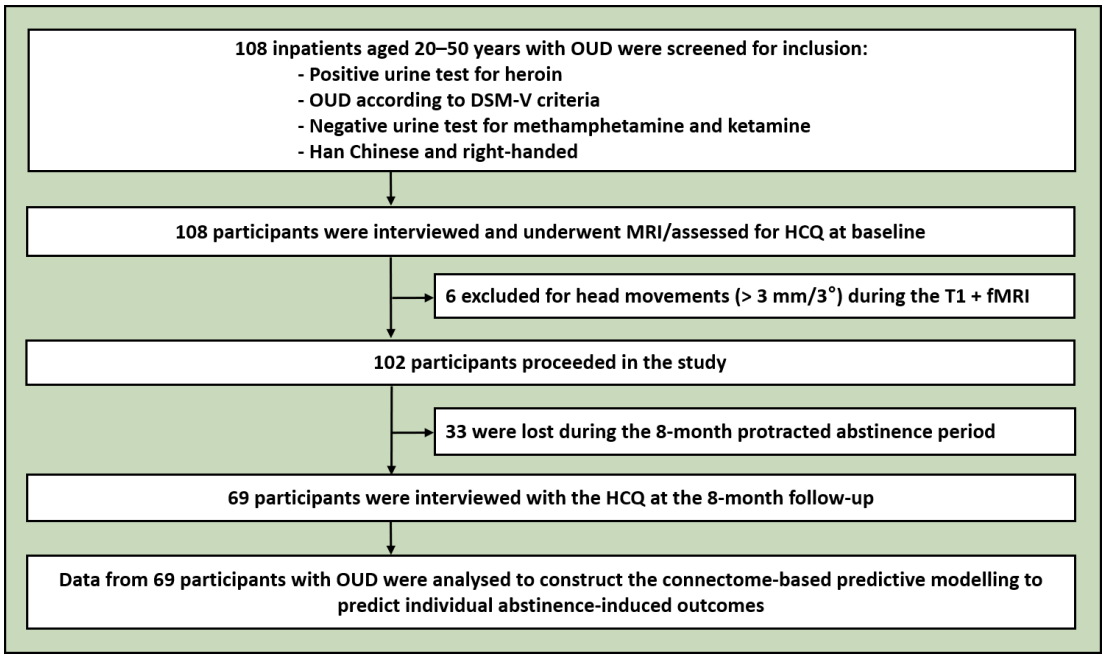

Figure 1 The flowchart of the study. DSM-V, Diagnostic and Statistical Manual on Mental Disorders, Fifth Edition; fMRI, functional MRI; HCQ, Heroin Craving Questionnaire; MRI, magnetic resonance imaging; OUD, opioid use disorders; T1, T1-weighted.

(figure 3C) networks. The top 10 nodes of positive edges with the most connections in the OUD craving changes-related network ($HCQ_{follow\text{-}up}$–$HCQ_{baseline}$) were located in the bilateral limbic and parietal, the left motorstrip and prefrontal regions (see online supplemental table 2). In addition, the top 10 nodes of negative edges with the most connections in the OUD craving changes-related network were located in the bilateral subcortical, the right prefrontal, the left limbic, the brainstem and the CBL areas (see online supplemental table 3).

There was no significant association between HCQ score changes and the RSFC in the model of either a negative or positive network (r=0.146, p=0.124).

External validation

The negative prediction network, which was applied to an independent set of 39 individuals with SUD (methamphetamine), could successfully predict follow-up craving (r=0.432, p=0.006). The positive and negative networks failed to predict craving changes among these

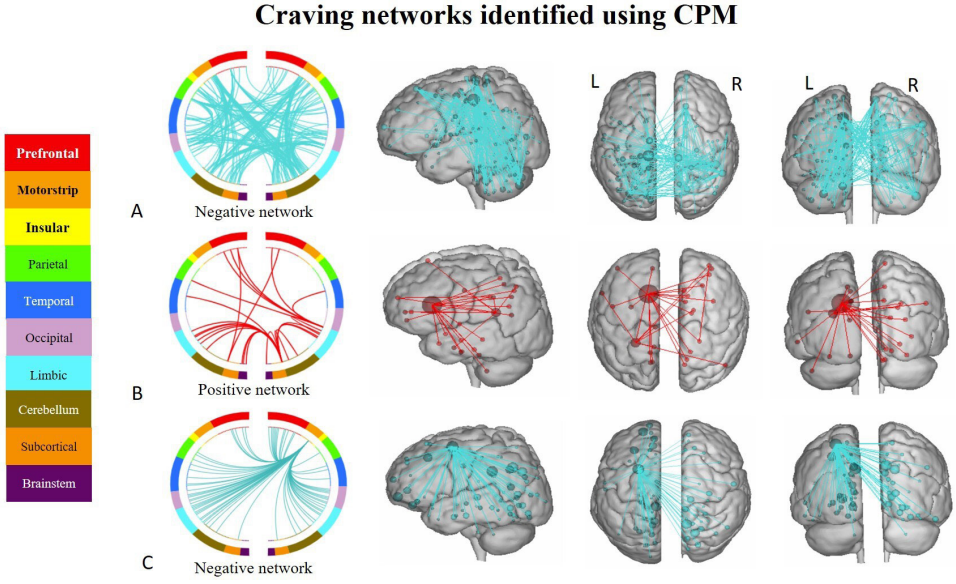

Figure 2 Panel A shows negative craving ($HCQ_{follow\text{-}up}$) networks; Panel B shows positive craving changes related ($HCQ_{follow\text{-}up}$-$HCQ_{baseline}$) networks; Panel C shows negative craving changes related networks. Larger spheres indicate nodes with more edges, and smaller spheres indicate fewer edges. HCQ: Heroin Craving Questionnaire. Positive network: positive correlation between edges and craving scores; Negative network: negative edges between edges and craving scores.

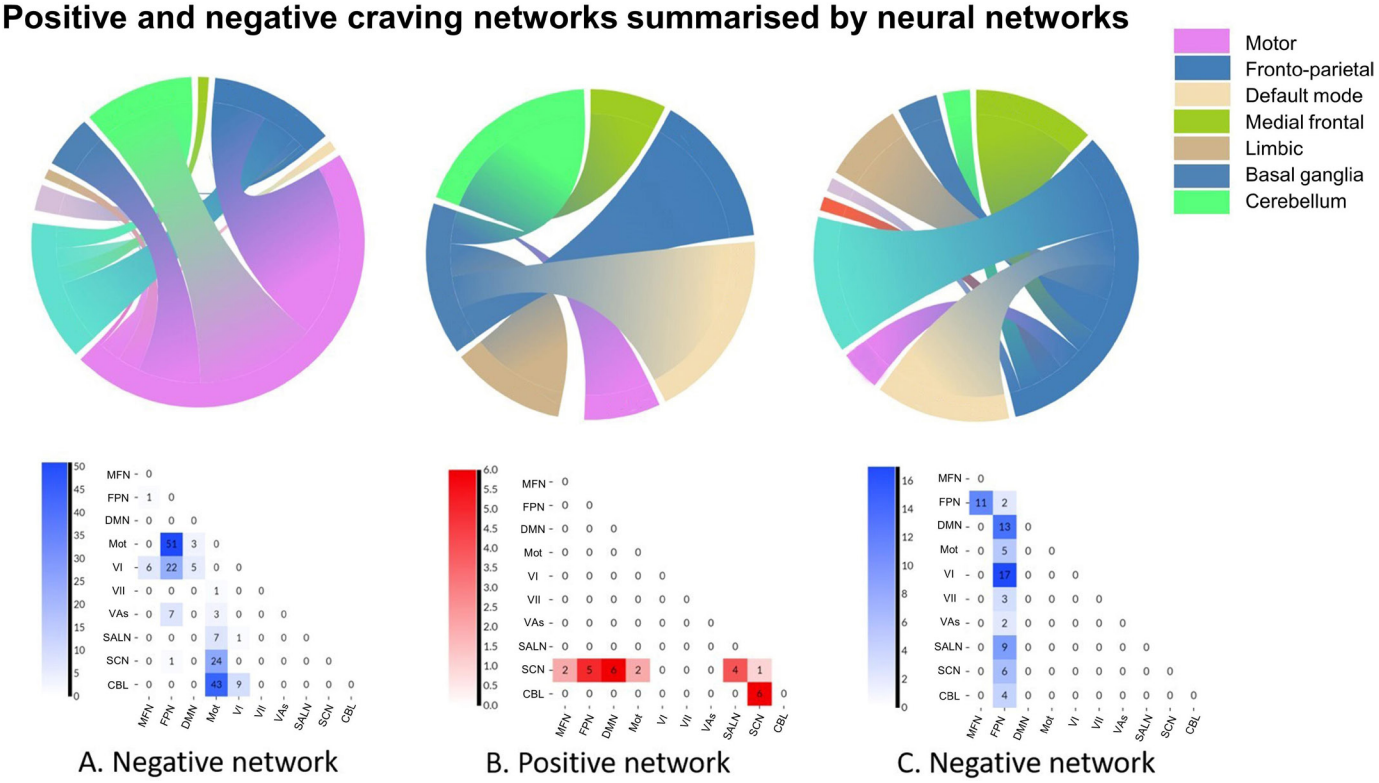

Figure 3 Positive and negative craving networks summarized by neural networks. Panel A shows negative craving ($HCQ_{follow-up}$) networks; Panel B shows positive craving changes related ($HCQ_{follow-up}$-$HCQ_{baseline}$) networks; Panel C shows negative craving changes related networks. MF: Medial frontal; FP: Frontal parietal; DMN: Default mode; Mot: Motor/sensory; VI: Visual a; VII: Visual b; Vas: Visual assoc.; SAL: Salience; SC: Subcortical; CBL: Cerebellum/brainstem.Positive and negative craving networks summarized by neural networks.

independent individuals (positive: r=0.17, p=0.097; negative: r=0.13, p=0.360).

DISCUSSION

Main findings

In this study, we demonstrated that a connectome-based machine learning technique could predict follow-up craving after abstinence in individuals with OUD and could also be transferred to an independent SUD sample. The key findings of the study are the following: (1) follow-up craving was positively predicted by the decreased connection of somato-motor network (SMN), FPN, subcortical network (SCN), CBL, DMN and visual network; (2) craving changes related to the network were positively predicted by the increased connection of SCN, DMN, FPN, SALN and auditory network; (3) a decrease in the connection of FPN, DMN and SMN was seen in the patients with OUD. Our study has provided novel insights into the neuropsychological pathway underlying neural mechanisms of addiction by revealing the potential functional brain biomarkers of craving changes after prolonged abstinence. The identified craving-related networks could be considered potential treatment targets in future studies, while further replication is warranted.

Implications

In the current study, we found decreased connectivity of FPN-SMN, FPN-DMN and FPN-SALN and increased connectivity of SCN-DMN, SCN-SALN and SCN-SMN, which were all positively correlated to the changes in craving scores; these data are partially consistent with Yip *et al*.[9] Yet, the results of our study implicated stronger network segregation (decreased connectivity) between attention and executive control systems (FPN, medial frontal network (MFN)) and salience encoding and the responding reward system (SMN, SALN, DMN); stronger network integration within salience encoding and the responding reward system (increased connectivity between the SCN, SMN, SALN, DMN) at baseline positively predicted higher follow-up craving levels after abstinence.

Interestingly, as for the negative craving changes network (figure 3C), the left motorstrip showed the greatest predictive value as a brain connection node; networks included DMN and SMN. Evidence from resting-state connectivity analysis suggests that FPN includes the rostrolateral and dorsolateral prefrontal cortices, anterior frontal operculum, dorsal anterior cingulate cortex, precuneus and anterior inferior parietal lobule.[18] The FPN constitutes a fundamental substrate of executive functions at the network level, including the control of

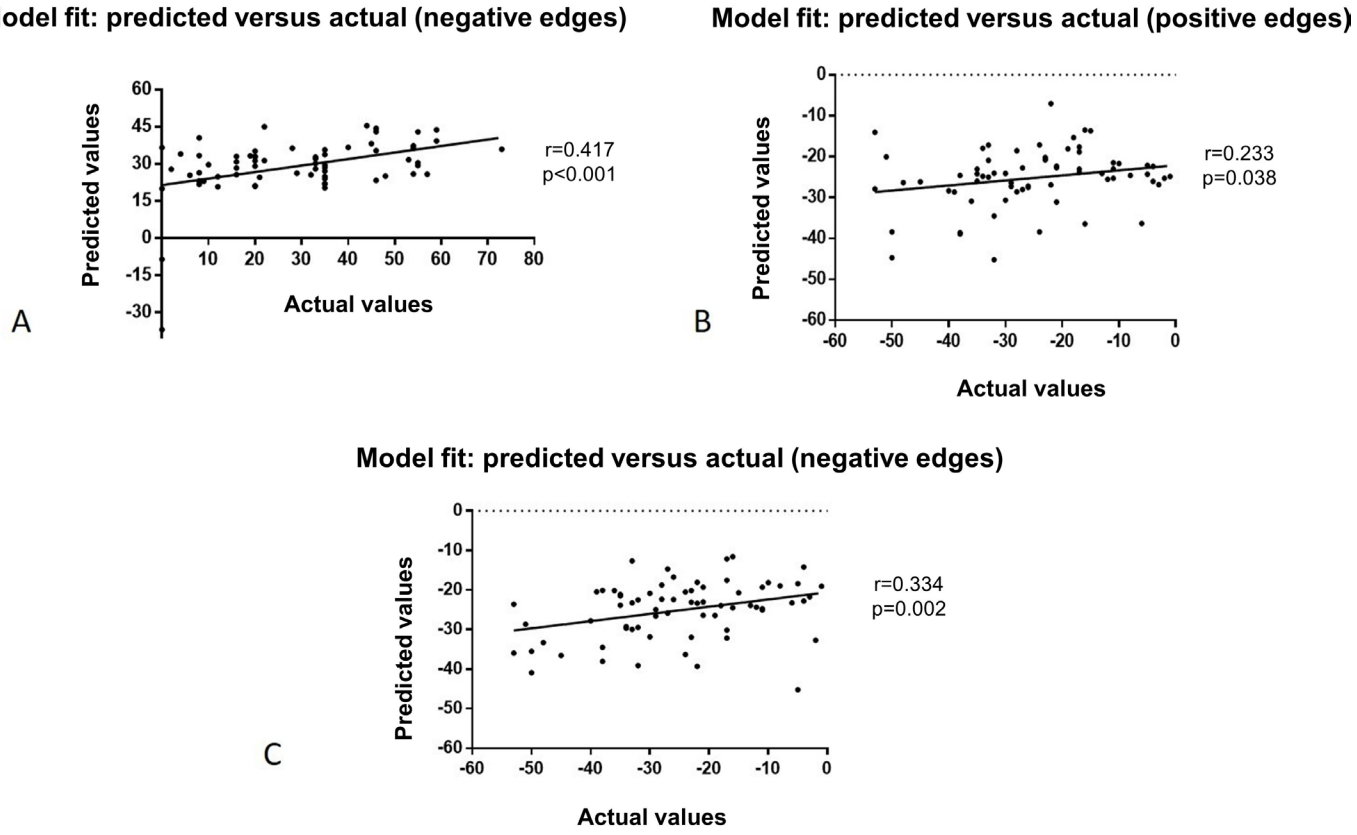

Figure 4 Panel A illustrates the correspondence between actual (x-axis) and predicted (y-axis) follow-up craving scores ($HCQ_{follow\text{-}up}$) from negative and positive edges generated using CPM. Panel B and C illustrates the correspondence between actual (x-axis) and predicted (y-axis) changes of craving scores ($HCQ_{follow\text{-}up}$-$HCQ_{baseline}$) from positive and negative edges generated using CPM. CPM successfully predicted within-abstinent follow-up craving scores (r=0.417, p<0.001) and changes of craving scores (negative: r=0.334, p=0.002, positive: r=0.233, p=0.038). $HCQ_{follow\text{-}up}$: HCQ score of 8-month follow-up abstinent heroin users; $HCQ_{baseline}$: HCQ score of baseline time abstinent heroin user.

SUD. Besides, FPN can help shift the focus of interest and attention transfer, which may improve self-control during abstinence in individuals with OUD. A cocaine study demonstrated reduced FPN functions in individuals with cocaine use disorder and HCs.[19] Holla *et al* found that high-risk boys from families with alcohol use disorder have reduced functional segregation of the FPN.[20]

The DMN is a network that controls thinking processes, which is deactivated during task performance and activated during rest; it includes the cingulate, medial prefrontal and inferior parietal cortices. Functional abnormalities of DMN were found in patients with mental disorders, including SUD. Studies have found that a disrupted connection between the DMN and the cortical areas concerned with executive function/memory might increase the craving and cause compulsive drug seeking, thus causing relapse.[21] During abstinence, the DMN is significantly activated while the executive control network (FPN) is disrupted.[22] Therefore, we hypothesised that the abnormal resting-state functional connectivity of DMN was a factor in diminished self-awareness and increased negative feelings during abstinence, and disrupted FPN-DMN was related to a high craving state during abstinence.

The SALN is another rewarding-related network involved in stimulus-independent thought processes. SALN is essential for cognitive control and response inhibition. The salient network is involved in salience attribution, interoceptive awareness and the reward system, whose components include the supragenual anterior cingulate cortex, amygdala, nucleus accumbens, dorsomedial thalamus, insula and ventrolateral PFC. SALN aids in attentional allocation and direction to external versus internal stimuli. Abnormal connectivity in SALN is related to networks associated with dysregulated cognitive and emotional regulation, such as deficiencies in regulation and increased susceptibility to drug stimuli.[23] A cocaine study[24] found significant differences in the structural and functional salience regions between chronic cocaine users and HCs. Moreover, the researchers further found that dysregulation of SALN in chronic cocaine users could predict relapse in an independent sample. The negative networks, including SMN, also showed a promising prediction of follow-up craving scores. Moreover, the SMN is an important connection node in predicting craving. Core areas of the SMN are structurally and functionally linked to the dopaminergic substantia nigra-related nigrostriatal circuit. The relationship between the

regulation of FPN-SMN and craving remains to be further investigated.

In this study, the follow-up craving network (figure 3A) and the craving changes network (figure 3C) identified FPN as a critical brain region, yet there are differences between the two networks. Thus, we concluded that the follow-up craving-related network and the craving change network might show different neural mechanisms. The identified prediction of follow-up craving negative network mainly included connectivity between the FPN-SMN, CBL-SMN and SCN-SMN circuits. It has been suggested that the CBL has a specific role in learning SMN patterns, initially in developing conventional motor abilities and, subsequently, in learning voluntary movements, Pavlovian conditioning and operant conditioning.[25] A previous study showed abnormal connectivity between SCN-SMN circuits involving drug use in individuals with SUD.[26] Individuals with OUD experience severe sensorimotor deficits and aberrant functional brain activity in cortical and subcortical regions involved in motor control. In this study, changes in craving were more involved in the craving state at baseline in individuals with OUD but not at the 8-month follow-up. Changes in craving implied the sensitivity of OUD to protracted abstinence therapy; greater changes might mean more sensitivity to prolonged withdrawal therapy in individuals with OUD, showing that these individuals are more suitable to receive protracted abstinence while others should be treated by other more precise and curative treatments.

As shown in figure 3B, the increased connectivity of SCN-DMN, SCN-SALN and SCN-SMN was positively correlated to the changes in craving scores. According to a 7 T fMRI study, many interconnections exist between the subcortical DMN, including the basal forebrain and thalamus, brainstem, basal ganglia and ventral tegmental areas.[27] Recent research revealed that the basal forebrain and other subcortical areas are physically and functionally crucial for controlling and regulating the function of DMN.[28] Thus, the increased connectivity of SCN-DMN at baseline in individuals with OUD might reveal the integration of a reward-related system and the prediction of higher cravings after abstinence in this study. As for SCN-SALN, the core region of SALN is thought to be related to the ventral tegmental area (subcortical regions) mesocorticolimbic pathway in SUD. A previous study suggested that SMN is structurally and functionally related to the dopaminergic nigrostriatal circuit[29]; however, the relationship between the regulation of SCN-SMN and craving requires further investigation. Additionally, the change in the craving level (change of HCQ) also involves the craving level at baseline, which may be related to the congenital complex network within individuals before they ever used opioids.

Limitations

There are several limitations in the present study. First, the sample is relatively small due to the relative specialisation of the population studied. Although we tested the ability of the identified networks to predict SUD craving outcomes in a heterogeneous sample of methamphetamine-dependent individuals, the number of subjects is still small. Thus, to improve the reproducibility of the predictive model—also for validation and replication—future work using baseline resting-state fMRI data with larger samples is needed to help elucidate the optimum edges that successfully predict craving levels in individuals with OUD after protracted abstinence. Second, imaging data and craving measures were only collected at baseline and the 8-month follow-up. Longitudinal follow-up studies with multiple time points are needed to validate the CPM model further. Third, according to previous evidence, resting-state fMRI data are restricted by structural connectivity.[30] Future integrated analyses of multimodal neuroimaging might extend our knowledge of the neuronal mechanisms underlying craving changes during protracted abstinence. Fourth, only the negative network model successfully predicted individuals' craving scores at the 8-month follow-up. Given the relative specialisation of the population studied, it would be challenging to increase the sample size. As the sample size was relatively limited in the current study, the stability of the predictive model might be influenced by a larger number of subjects. Last, the sample of the independent external validation set was limited. In the current study, the present negative follow-up craving prediction network was successfully applied to an independent individual with substance (methamphetamine) use disorder, indicating that the generalised application of the prediction model and different SUDs may share a common loop of neuro-mechanisms. The current findings require further validation using an independent, larger and demographically matched OUD sample in future studies.

CONCLUSION

These findings highlight the potential applications of CPM to predict the craving level of individuals after protracted abstinence. The identified brain networks should be considered the focus of innovative therapies.

Author affiliations
[1]The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[2]Department of Computer Science, Aberystwyth University, Aberystwyth, UK
[3]Department of Radiology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[4]Hunan Judicial Police Academy, Changsha, Hunan, China
[5]Siemens Healthineers Ltd, Wuhan, Hubei, China
[6]Clinical Research Center for Medical Imaging in Hunan Province, Changsha, Hunan, China
[7]Department of Radiology Quality Control Center in Hunan Province, Changsha, Hunan, China

Acknowledgements The authors express their appreciation to the participants in this study.

Contributors WY, JLuo conceived and designed the study. WY, JH, JLiu, FT, LF, LY and YD conducted the behavioural and imaging analyses. JZ, HZ and YD conducted the assessments. JLuo revised the manuscript and supervised the study. WY wrote the first draft and all authors provided input on the final version of the manuscript. JLuo is responsible for the overall content as the guarantor.

Funding This study was supported by grants from the National Natural Science Foundation of China (grant number: U22A20303, 61971451), Clinical Research Center for Medical Imaging in Hunan Province (grant number: 2020SK4001), Leading Talents of Scientific and Technological Innovation in Hunan Province in 2021 (grant number: 2021RC4016).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The Institutional Review Board of the Second Xiangya Hospital, Central South University, approved the protocol (8167071216). Written informed consent was obtained from participants after the experimental procedure was explained and after they read the consent form.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD

Jun Liu http://orcid.org/0000-0002-7851-6782

REFERENCES

1 Strigo IA, Murphy E, Mitchell JM, *et al*. Learning from addiction: craving of prescription opioids in chronic pain sufferers. *Neurosci Biobehav Rev* 2022;142:104904.
2 Ceceli AO, Huang Y, Kronberg G, *et al*. Common and distinct cortico-striatal volumetric changes in heroin and cocaine use disorders. *Brain* 2022;146:1662–71.
3 Zhao D, Zeng N, Zhang H-B, *et al*. Deep magnetic stimulation targeting the medial prefrontal and anterior cingulate cortices for methamphetamine use disorder: a randomised, double-blind, sham-controlled study. *Gen Psych* 2023;36:e101149.
4 Qin M, Guan J, Huang Y, *et al*. A novel model of drug cue-induced behaviours in rhesus macaque subjected to chronic ketamine exposure. *Gen Psych* 2023;36:e100902.
5 Li W, Zhang S, He X, *et al*. High-definition transcranial direct current stimulation over the right dorsolateral prefrontal cortex reduces risk-taking. *Gen Psych* 2023;36:e101182.
6 Mistler CB, Shrestha R, Gunstad J, *et al*. Adapting behavioural interventions to compensate for cognitive dysfunction in persons with opioid use disorder. *Gen Psych* 2021;34:e100412.
7 Yang W, Zhang M, Tang F, *et al*. Recovery of superior frontal gyrus cortical thickness and resting-state functional connectivity in abstinent heroin users after 8 months of follow-up. *Hum Brain Mapp* 2022;43:3164–75.
8 Moningka H, Lichenstein S, Worhunsky PD, *et al*. Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research. *Neuropsychopharmacology* 2019;44:259–73.
9 Yip SW, Scheinost D, Potenza MN, *et al*. Connectome-based prediction of cocaine abstinence. *Am J Psychiatry* 2019;176:156–64.
10 Nutt D, Hayes A, Fonville L, *et al*. Alcohol and the brain. *Nutrients* 2021;13:3938.
11 Tisdall L, MacNiven KH, Padula CB, *et al*. Brain tract structure predicts relapse to stimulant drug use. *Proc Natl Acad Sci U S A* 2022;119:e2116703119.
12 Shen X, Finn ES, Scheinost D, *et al*. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. *Nat Protoc* 2017;12:506–18.
13 Finn ES, Shen X, Scheinost D, *et al*. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci* 2015;18:1664–71.
14 Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 2016;3:760–73.
15 Hasin DS, O'Brien CP, Auriacombe M, *et al*. Dsm-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 2013;170:834–51.
16 Tiffany ST, Carter BL, Singleton EG. Challenges in the manipulation, assessment and interpretation of craving relevant variables. *Addiction* 2000;95 Suppl 2:S177–87.
17 Shen X, Tokoglu F, Papademetris X, *et al*. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *Neuroimage* 2013;82:403–15.
18 Spreng RN, Stevens WD, Chamberlain JP, *et al*. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage* 2010;53:303–17.
19 Worhunsky PD, Stevens MC, Carroll KM, *et al*. Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome. *Psychol Addict Behav* 2013;27:477–88.
20 Holla B, Panda R, Venkatasubramanian G, *et al*. Disrupted resting brain graph measures in individuals at high risk for alcoholism. *Psychiatry Res Neuroimaging* 2017;265:54–64.
21 Zhang R, Volkow ND. Brain default-mode network dysfunction in addiction. *Neuroimage* 2019;200:313–31.
22 Volkow N, Li TK. The neuroscience of addiction. *Nat Neurosci* 2005;8:1429–30.
23 Tolomeo S, Yu R. Brain network dysfunctions in addiction: a meta-analysis of resting-state functional connectivity. *Transl Psychiatry* 2022;12:41.
24 Geng X, Hu Y, Gu H, *et al*. Salience and default mode network dysregulation in chronic cocaine users predict treatment outcome. *Brain* 2017;140:1513–24.
25 Miquel M, Toledo R, García LI, *et al*. Why should we keep the cerebellum in mind when thinking about addiction *Curr Drug Abuse Rev* 2009;2:26–40.
26 Ersche KD, Meng C, Ziauddeen H, *et al*. Brain networks underlying vulnerability and resilience to drug addiction. *Proc Natl Acad Sci U S A* 2020;117:15253–61.
27 Li J, Curley WH, Guerin B, *et al*. Mapping the subcortical Connectivity of the human default mode network. *Neuroimage* 2021;245:118758.
28 Harrison BJ, Davey CG, Savage HS, *et al*. Dynamic subcortical modulators of human default mode network function. *Cereb Cortex* 2022;32:4345–55.
29 Conio B, Martino M, Magioncalda P, *et al*. Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. *Mol Psychiatry* 2020;25:82–93.
30 Honey CJ, Sporns O, Cammoun L, *et al*. Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A* 2009;106:2035–40.

Wenhan Yang obtained her bachelor's degree in medical imaging in 2016 from Hainan Medical University, Haikou, China. She obtained her master's degree and PhD in imaging and nuclear medicine from Second Xiangya Hospital, Central South University, Changsha, China, in 2019 and 2023, respectively. She is currently working in Imaging and Nuclear Medicine within the Department of Radiology at Second Xiangya Hospital, Central South University. Her main research interests include structural and functional magnetic resonance imaging biomarkers and predictors of behaviours in individuals with opioid or methamphetamine use disorder.