HHS Public Access

Author manuscript

Mol Psychiatry. Author manuscript; available in PMC 2024 February 16.

Published in final edited form as:

Mol Psychiatry. 2023 August ; 28(8): 3365–3372. doi:10.1038/s41380-023-02120-0.

Distinct neural networks predict cocaine versus cannabis treatment outcomes

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Abstract

Treatment outcomes for individuals with substance use disorders (SUDs) are variable and more individualized approaches may be needed. Cross-validated, machine-learning methods are well-suited for probing neural mechanisms of treatment outcomes. Our prior work applied one such approach, connectome-based predictive modeling (CPM), to identify dissociable and substance-specific neural networks of cocaine and opioid abstinence. In Study 1, we aimed to replicate and extend prior work by testing the predictive ability of the cocaine network in an independent sample of 43 participants from a trial of cognitive behavioral therapy for SUD, and evaluating its ability to predict cannabis abstinence. In Study 2, CPM was applied to identify an independent cannabis abstinence network. Additional participants were identified for a combined sample of 33 with cannabis use disorder. Participants underwent fMRI scanning before and after treatment. Additional samples of 53 individuals with co-occurring cocaine and opioid use disorders and 38 comparison subjects were used to assess substance specificity and network strength relative to participants without SUDs. Results demonstrated a second external replication of the cocaine network predicting future cocaine abstinence, however it did not generalize to cannabis abstinence. An independent CPM identified a novel cannabis abstinence network, which was (i) anatomically distinct from the cocaine network, (ii) specific for predicting cannabis abstinence, and for which (iii) network strength was significantly stronger in treatment responders relative to control particpants. Results provide further evidence for substance-specificity of neural predictors of

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Author Contributions

SDL, BK, and SWY collaborated on conception and design of the current analyses. MNP and BK oversaw acquisition of the data. SDL, RK, FY, BK, and SWY contributed to analysis and interpretation of the data. SDL and FY drafted the article. All authors revised the article critically for important intellectual content and provided final approval fo the version to be published.

Supplementary information is available at MP's website.

abstinence and provide insight into neural mechanisms of successful cannabis treatment, thereby identifying novel treatment targets.

Introduction

Despite the availability of effective evidence-based treatment approaches, outcomes for individuals seeking treatment for substance use disorders (SUDs) remain variable across individuals and success rates are suboptimal (1, 2). There is a growing consensus that alterations in neural functioning contribute importantly to the pathophysiologies of SUDs, yet incorporation of neuroimaging into clinical addiction treatment remains rare (3) and findings have been inconsistent across studies, in part due to reliance on methods such as correlation and regression that may overfit models to small datasets (4). Nonetheless, when combined with robust, data-driven predictive modeling, neuroimaging may provide a powerful tool for elucidating neural bases of recovery and has the potential to uncover novel treatment targets to facilitate the development of more individualized treatment approaches (4, 5).

Accordingly, our prior work has identified dissociable neural networks of cocaine (6) and opioid (7) treatment outcomes using a whole-brain predictive modeling approach called connectome-based predictive modeling (CPM) (8, 9). CPM is a data-driven method for identifying brain-behavior relationships that incorporates cross-validation to protect against overfitting and improve the generalizability of identified models. Furthermore, this approach also allows for direct mapping back to brain anatomy to facilitate the interpretation of neural mechanisms underlying identified brain-behavior relationships (termed ‘neural fingerprinting’).

Although some neural substrates of SUDs may be shared across substances, using CPM we found cocaine and opioid abstinence networks to be anatomically distinct from one another and specific for predicting cocaine versus opioid abstinence, even within the same individuals (7). These results, which are consistent with preclinical work (10), suggest that there may be key differences in the neural factors linked to abstinence from different substances, which could have important implications for improving existing treatment approaches.

These findings align with prior work emphasizing the heterogeneity of SUDs and the need to develop more individually-tailored treatment approaches (11). Congruently, distinct personality features may give rise to vulnerability for misusing different drugs (12), and interventions that directly target patients’ individual personality profiles may be effective for preventing and reducing substance misuse (13, 14). These data highlight the utility of parsing some of the heterogeneity among individuals with SUDs to develop more individually-targeted interventions and improve treatment outcomes. Consistent with this, our prior CPM results provide preliminary evidence that the development of treatment approaches that target neural mechanisms specific to different substances could have promise for improving SUD treatment outcomes. Nonetheless, further replication and extension is needed to confirm the substance specificity of previously identified abstinence networks.

Cannabis is the most widely used illicit drug worldwide with global rates of use increasing steadily over the past decade (15). Recent estimates suggest that 22.1 million people met criteria for cannabis use disorder (CUD) in 2016 (16), and CUD has been linked to poor mental health, psychosis, and bronchitis (17). Notably, the prevalence of CUD has increased as rates of use have risen, particularly among more vulnerable populations (18), spurring increased demand for effective CUD treatments (19). Nonetheless, there are currently no efficacious pharmacological treatments for CUD, although several medications appear to be effective for symptoms of cannabis withdrawal (e.g., sleep disturbance, loss of appetite) (20). There are several psychosocial treatment options for CUD, with cognitive behavioral therapy, motivational enhancement therapy, relapse prevention, and contingency management showing an overall moderate effect size in the short-term, yet there is little evidence for longer term efficacy of any available interventions (17, 21). Therefore, elucidating neural features predicting successful CUD treatment has the potential to identify promising new treatment targets (3, 4, 5, 22).

Here we seek to replicate and extend our prior work by analyzing neuroimaging data from a heterogeneous sample of individuals with cocaine and cannabis use disorders. Aims were threefold: In Study 1, we sought to (i) test the replicability of the cocaine network in another external sample and (ii) to determine whether the cocaine abstinence network would generalize to predict cannabis abstinence. Based on our earlier work indicating substance specificity of abstinence networks, we anticipated that the cocaine abstinence network would replicate in an external sample, but that it would not generalize to predict cannabis abstinence. Thus, in Study 2, we further aimed to (iii) conduct an independent CPM analysis to identify separate neural substrates as predictive of cannabis abstinence. Based on extant literature on neural correlates of cannabis use (23), we hypothesized that cannabis abstinence networks would be characterized by connections within and between frontoparietal, frontostriatal, and cerebellar regions.

Notably, our prior work found that when comparing treatment responders and non-responders (defined based on their pattern of abstinence during treatment) to healthy control participants, treatment responders were characterized by significantly greater cocaine and opioid abstinence network strength relative to control participants, suggesting that the achievement of abstinence may require ‘hyper-functioning’ of abstinence networks to above the level observed in non-substance-using individuals (7, 24). Therefore, here we also compared network strength of the newly identified cannabis abstinence network among treatment responders, non-responders, and healthy comparison subjects to assess whether individuals who are successful in treatment would again be characterized by ‘hyper-functioning’ network strength relative to comparison subjects.

Subjects and Methods

Participants

Participants for the cocaine network replication and initial application to cannabis abstinence (Study 1) were drawn from a randomized clinical trial (RCT) of cognitive-behavioral treatments for SUDs (NCT01442597; 25). The trial included a heterogeneous polysubstance-using sample of outpatient treatment-seeking individuals. A majority of these

individuals met criteria for multiple lifetime substance use disorders, and participants were included in the current analysis if they had lifetime cocaine and/or cannabis use disorder, as well as usable pre-treatment fMRI reward task data (motion <.3mm), resulting in a sample of 43 individuals (see Table 1 for subject characteristics). Within this sample, 18 individuals met criteria for cocaine use disorder and 39 individuals met criteria for lifetime cannabis use disorder; 14 of these participants met criteria for both lifetime cocaine and cannabis use disorders.

Following this, a separate CPM was conducted to test whether an independent network might predict cannabis abstinence (Study 2). Although most participants met criteria for multiple lifetime substance use disorders, they also indicated their primary drug of choice at the time of treatment entry, and only participants who reported cannabis as their primary drug were included in the second analysis. Additionally, data from another 16 individuals from two separate RCTs (NCT00350649, NCT01406899; 26, 27) were also included for a combined sample size of 33 individuals entering treatment for CUD with usable pretreatment fMRI data.

All parent RCTs monitored abstinence via weekly urine toxicology screens during the study treatment period, as well as at 1-, 3-, and 6-month post-treatment follow-up visits. All participants provided written informed consent approved by the Yale School of Medicine IRB following description of study procedures, and all experiments were performed in accordance with relevant guidelines and regulations.

Finally, to facilitate follow-up analyses addressing substance specificity and comparison with control participants, additional samples of individuals with co-occurring cocaine- and opioid-use disorders (n=53) and healthy comparison subjects (n=38) were also included (see Supplement for subject characteristics) (details on these samples have also been described previously, see 6, 7).

Neuroimaging data acquisition and preprocessing

fMRI data were acquired during the Monetary Incentive Delay task (reward processing) and the Stroop task (cognitive control) at baseline and following treatment. Neuroimaging data were preprocessed using SPM8 and the Bioimage Suite (28), as described previously (6, 29), and runs with motion exceeding .3mm were excluded. Consistent with our prior work (6, 29), data were parcellated into 268 nodes defined using the Shen brain atlas (30), and mean time courses for each node were used to compute pairwise Pearson correlations between every node pair. Fisher's r-to-z-transformation was applied to create symmetric 268×268 matrices, also known as 'connectomes', which summarize the connection strength between every pair of nodes throughout the brain and serve as the input for CPM (8, 31) (see Supplement for additional details). Reward task matrices were generated for participants with at least one usable run (out of two, i.e., ≥50% acceptable data), and average cognitive control matrices were generated for participants with at least three usable runs (out of six, i.e., ≥50% acceptable data).

Cocaine abstinence network replication

Network strength of the cocaine abstinence network, previously identified and validated using CPM (6), was extracted from reward and cognitive control matrices. Predictive accuracy (i.e., association between cocaine abstinence network strength and actual observed abstinence during treatment) was assessed using Spearman's rank order correlation, as in our prior work (6, 29). As only a positive association between network strength and abstinence indicates accuracy (i.e., a negative correlation between observed and predicted values constitutes a model failure), results were considered significant at one-tailed $\alpha<.05$ (32).

Cannabis abstinence network identification

As described above, CPM is a cross-validated machine-learning approach that takes whole-brain connectomes and a behavioral variable of interest as inputs and identifies positive and negative features that are predictive of the given behavioral variable (8), such as abstinence (6, 29). CPM analyses were conducted using custom scripts in Python, based on Shen et al. (8), and available on GitHub (https://github.com/fye92/abcd_fy/tree/main/CPM_code). A 5-fold cross-validation (CV) CPM was adopted for all analyses: for each fold, 80% of participants were randomly assigned as training data and the remaining 20% were assigned as testing data. During training, Pearson correlation coefficients (r) were calculated across participants between edge weights in the input matrices and cannabis abstinence (i.e., the percentage of cannabis-negative urines provided during treatment). Edges that positively correlated with cannabis abstinence with ($p<0.01$) were identified as the positive features ("positive edges"), whereas edges that negatively correlated with cannabis abstinence were identified as the negative features ("negative edges"). A summary statistic was then calculated for each individual by subtracting the sum of negative edge weights from the sum of positive edge weights, and a linear regression model was trained on this statistic to predict abstinence. The predictive features identified in the training data were then extracted from the task-based matrices from the testing data, and the trained models were applied to the summary statistic of the testing data to generate predictions, as in prior work (6, 7, 8, 9, 31, 33, 34, 35).

Model performance was quantified as the Spearman correlation (*rho*) between the testing-data predictions and actual values across the whole sample. To further improve the reliability of our results and to prevent over-fitting to a random split of the data, models using 5-fold CV were repeated 100 times to generate 100 Spearman *rho* values, consistent with current recommendations (33). Only features present in 100% of iterations were included in the final cannabis abstinence network.

Permutation testing was adopted to evaluate the significance of the observed Spearman *rho* values. For 1,000 iterations, abstinence values were randomly permuted and then fed into CPMs. The resulting 1,000 Spearman *rho* values formed a null distribution and a one-tailed p-value was calculated by contrasting the actual Spearman *rho* against the null distribution:

$$p = \frac{\text{Number of null } rho > rho_{\text{actual}}}{\text{Number of null } rho \text{ available}}$$

Again, one-tailed *p*-values were chosen over two-tailed *p*-value because rho_{actual} was expected to be positive (i.e., a negative *rho* indicates model failure) (32).

Post-hoc sensitivity testing

Assessing relationship with pre-treatment cannabis use—To determine the specificity of the identified cannabis abstinence network for predicting *future* abstinence during treatment (i.e., versus a more general marker of current/ongoing use), we computed a Pearson correlation (*r*) between cannabis abstinence network strength and cannabis use frequency during the 28 days *prior* to treatment.

Cannabis abstinence network strength across substance use outcomes—To assess substance specificity of the cannabis abstinence network, we extracted the cannabis network from an independent sample of methadone-maintained individuals with co-occurring opioid and cocaine use disorders (details on this sample have been described previously, see 6, 7, 36; also see Supplement for Subject Characteristics and recruitment information). Spearman correlations were computed to assess whether cannabis abstinence network strength would predict cocaine or opioid abstinence in this independent sample.

Application to post-treatment data—Consistent with prior work (6, 7), we also sought to assess whether the strength and predictive ability of the cannabis abstinence network would be stable across pre- and post-treatment data. Therefore, a Pearson correlation (*r*) was calculated between baseline network strength and post-treatment network strength (n=21), a paired t-test was adopted to compare pre- and post-treatment connectivity strengths, and a Spearman correlation (*rho*) was calculated between post-treatment network strength and the post-treatment abstinence data (n=15; see Supplement for additional details).

Cannabis abstinence network strength relative to heathy comparison participants—Finally, to assess how cannabis abstinence network strength varies between individuals with CUD and comparison participants, the cannabis network was extracted from a healthy comparison sample. Network strength was compared between control participants, treatment responders, and non-responders, and independent samples t-tests were used to compare network strength between groups. Patients were classified as treatment responders if they had a minimum of 75% cannabis-negative urines during treatment, consistent with recent literature (37)— and also consistent with the bimodal distribution of cannabis-negative urines in this dataset (see Supplemental Figure 1 for the distribution of cannabis abstinence)—resulting in 16 participants (48.5%) being classified as treatment responders and 17 participants (51.5%) classified as treatment non-responders. Although these subsamples are small, it is important to note that this analysis is not designed to compare treatment responders to non-responders, but rather to assess how healthy comparison subjects' network strength compares to individuals with CUD who have and have not achieved ≥75% abstinence in treatment. Findings from this analysis should nonetheless be considered exploratory.

Results

Cocaine abstinence network replication and application to cannabis abstinence (Study 1)

Consistent with prior work (6), connectivity within the previously established cocaine abstinence network, as assessed during reward task performance, was significantly associated with subsequent within-treatment abstinence from cocaine both among individuals with lifetime cocaine use disorder (n=18; *rho*=.44, *p*=.033), as well as across the entire poly-substance-using sample more generally (n=43; *rho*=.28, *p*=.034). Follow-up analysis indicated that this effect did not generalize to cognitive task data (full sample, n=40: *rho*=.22, *p*=.083; cocaine sample, n=16: *rho*=.23, *p*=.20).

In contrast, baseline cocaine network strength was not related to subsequent within-treatment cannabis abstinence, neither across the entire sample (reward: n=43, *rho*=−.14, *p*=.183; cognitive: n=40, *rho*=−.19, *p*=.122) nor when constrained only to individuals with primary cannabis use disorder (reward task: n=39, *rho*=−.13, *p*=.221; cognitive: n=36, *rho*=−.13, *p*=.230).

Independent Cannabis Abstinence Network Identification (Study 2)

Across 100 iterations, connectome-based models run with 5-fold cross-validation and generated from both types of task data each successfully predicted cannabis abstinence during treatment (reward: rho=0.67, p<0.001; cognitive: rho=0.69, p<0.001), indicating relevance of both cognitive control and reward-related processes in cannabis treatment outcomes. While not identical, network comparisons indicated significant anatomical overlap between networks (see Supplement for details). Given the similarities in both predictive accuracy and anatomical features, we next combined the cognitive control and reward task matrices to test the predictive accuracy of a multi-task model. This combined model (also run with 100 iterations and 5-fold cross-validation; *rho*=0.69, *p*<0.001; see Figure 1a) had comparable predictive accuracy and captured relevant features from both reward-related and cognitive control-related brain states. Therefore, the combined model was used as the primary cannabis model for all subsequent analyses (described below).

Network Anatomy—Similar to previously identified cocaine and opioid abstinence networks (6, 7), the cannabis abstinence network was complex and included connections within and between multiple brain regions and networks. Nonetheless, the network contained only 2% of all possible connections (786 total edges; 307 positive, 479 negative). Therefore, despite its complexity, the connections included were also quite specific. Figure 1b summarizes cannabis network anatomy based on overlap with macroscale brain regions, including connections between frontal, parietal, temporal, occipital, limbic, and subcortical regions. The highest degree nodes (i.e., nodes with the greatest number of network connections) of the positive network (i.e., nodes for which increased connectivity is predictive of cannabis abstinence) were in the dorsolateral prefrontal cortex, premotor/supplementary motor area, and parietal regions, whereas the highest degree nodes of the negative network (i.e., nodes for which decreased connectivity is predictive of cannabis abstinence) were in the bilateral insula and caudate.

Figure 1c summarizes cannabis abstinence network anatomy based on overlap with canonical networks (e.g., default mode, frontoparietal). The positive network was predominantly characterized by connections between the motorsensory network and frontoparietal, medial frontal, and salience networks. The negative network was largely comprised of within-network connections of the motorsensory network.

Comparison between cocaine and cannabis abstinence network anatomy— Cannabis and cocaine abstinence networks showed very distinct patterns of network anatomy (Figure 2a). Whereas the positive cocaine abstinence network was characterized by connections between the motorsensory network and salience and cerebellar networks, as well as between the frontoparietal and medial frontal network, the positive cannabis abstinence network was dominated by connections between the motorsensory network and frontoparietal and medial frontal networks. Furthermore, there were no overlapping edges between the positive cocaine abstinence and positive cannabis abstinence networks. Similarly, whereas the negative cocaine abstinence network was comprised of connections between the salience, medial frontal, frontoparietal, default mode, visual, visual association, motorsensory, and cerebellar networks, the negative cannabis abstinence network was characterized by a much more focal pattern of within-network motorsensory connectivity. Furthermore, the negative cocaine and negative cannabis abstinence networks shared only 5 edges, connecting nodes within the subcortical network to the medial frontal and visual networks, as well as connecting nodes between the salience and default mode networks.

Assessing relationship with pre-treatment cannabis use—Pre-treatment cannabis use frequency was not associated with cannabis abstinence network strength (r=.021, p=.907), suggesting that cannabis abstinence network strength is uniquely predictive of *future* cannabis abstinence during treatment (e.g., versus a general marker of current use patterns).

Specificity of cannabis abstinence network across substance use outcomes— In an independent sample of 53 individuals entering treatment for cocaine use disorder (see Supplement for subject characteristics; this sample has also been described previously, see 6, 7), there were no significant associations between within-treatment cocaine abstinence and cannabis abstinence network strength extracted from combined cognitive control and reward task matrices (*rho*=−.09, p=.256; see Figure 2b). Given that this sample was characterized by co-occurring cocaine and opioid use disorders, we also assessed whether cannabis abstinence network strength would relate to opioid abstinence. Similarly, there were no significant associations between within-treatment opioid abstinence and cannabis abstinence network strength (*rho*=−.145, p=.151).

Post-Treatment Replication—Cannabis abstinence network strength was stable across treatment (n=21 with pre- and post-treatment cognitive control and reward task data; r=0.8, p<.001; paired t=−0.495, p=.626). Additionally, when applying the cannabis abstinence network to post-treatment fMRI and cannabis abstinence data (n=15), a comparable effect size was observed, although the association was not statistically significant in the smaller sample (*rho*=.34, p=.10).

Comparison with Healthy Control Participants—On average, cannabis abstinence network strength was not significantly different between CUD and control participants (extracted from combined cognitive control and reward task matrices; t=−.577, p=.567). However, when comparing control participants to treatment responders and non-responders, we found that control participants displayed an intermediate level of network strength, consistent with our prior work in other, non-cannabis SUDs (7). Specifically, relative to control participants, cannabis abstinence network strength was significantly increased in treatment responders (t=−9.597, p<.001), and significantly decreased among non-responders (t=7.784, p<.001).

Discussion

Here we demonstrate that a previously identified cocaine abstinence network (6) successfully predicted cocaine abstinence during treatment in a third independent sample. Consistent with our earlier work identifying substance-specific networks predicting cocaine and opioid abstinence (7), the cocaine abstinence network was also found to be specific for predicting cocaine, but not cannabis abstinence. Accordingly, we applied CPM to test for a separate cannabis abstinence network in a sample of individuals entering treatment for CUD. This independent CPM was successful and identified a network that was anatomically distinct from the cocaine abstinence network, and specific for predicting cannabis (versus other substance) use.

The current finding that the cocaine abstinence network generalizes to a third independent sample supports the utility of CPM for identifying neural substrates of addiction recovery that generalize across individuals and settings and may therefore represent useful treatment targets. Indeed, we are currently investigating whether directly targeting CPM-derived networks via real-time connectome-based neurofeedback may improve outcomes for individuals engaged in treatment for opioid use disorder. Furthermore, despite recent evidence that reliable brain-behavior correlations in heterogenous, normative populations may require very large sample sizes (n≈2000) (38), the current results demonstrate that replicable and generalizable brain-behavior relationships can be identified in clinical populations using smaller samples, so long as these are combined with machine learning techniques and appropriately stringent cross-validation approaches (39).

Given that the cocaine abstinence network was found to be specific for predicting cocaine, but not cannabis abstinence, we also applied CPM to identify a novel cannabis abstinence network. Cannabis abstinence was primarily associated with increased connectivity between the motorsensory network and frontoparietal, medial frontal, and salience networks, as well as decreased within-network connectivity of the motor sensory network. Within these larger canonical networks, increased connectivity of regions of the dorsolateral prefrontal cortex, premotor/supplementary motor area, and parietal cortex and decreased connectivity of the caudate and bilateral insula were found to be central to predicting cannabis abstinence during treatment.

The current finding that sensorimotor connections played a key role in predicting cannabis abstinence is consistent with prior data-driven work identifying neural features predictive

of chronic cannabis use (40), as well as opioid abstinence during treatment (7). This is hypothesized to relate to the automatization of drug use behaviors with extended substance use (7, 41). Accordingly, increased connectivity between frontoparietal, medial frontal, and motorsensory networks may facilitate greater top-down control over automatized drug use behaviors, rendering these individuals less vulnerable to relapse. Additionally, the insula has been associated with drug craving and may promote drug seeking behavior in the face of conflicting goals/negative consequences (42). Therefore, reduced insula connectivity may also facilitate success in treatment via reduced cannabis craving and drug-seeking.

These results have implications for informing the development of improved treatments for CUD. For instance, it may be possible to directly target this neurocircuitry using neuromodulatory approaches, such as real-time connectome-based neurofeedback (43). Alternatively, this pattern of results can also inform the development of behavioral treatment approaches. For example, existing treatments rarely consider or target acquired automaticity of drug use behaviors. The observed anatomy of the cannabis abstinence network suggests that developing behavioral strategies to improve top-down control over these automatized behaviors may help to improve individuals' success in treatment, as well as specifically strategizing around managing cannabis craving.

Prior literature demonstrates that different brain states are optimal for revealing different brain-behavior relationships using functional connectivity data (44). Congruently, our prior work revealed that identification of both the cocaine and opioid abstinence networks was brain-state specific, such that a cocaine abstinence network could be identified using reward but not cognitive control data and the opposite was found for the opioid abstinence network (7). The current analyses revealed that both reward and cognitive control brain states were relevant for predicting cannabis abstinence in treatment. Therefore, data from both brain states were combined to generate the cannabis abstinence network. Nonetheless, future work using data acquired during brain states more closely related to CUD treatment (e.g., exposure to cannabis cues) may further improve our CPM model performance, as well as potentially uncovering additional neural connections relevant to achieving abstinence in treatment.

The current results also demonstrate that comparison subjects displayed intermediate network strength relative to treatment responders and non-responders, consistent with our prior work (7). Furthermore, we also observed that network strength remained consistent from pre- to post-treatment among the CUD group. Collectively, this pattern of results suggests that the features identified in the model are present prior to treatment and have a meaningful impact on individuals' likelihoods of achieving abstinence. Therefore, this pattern of results further supports the idea that targeting these connections directly may help improve treatment outcomes for individuals entering treatment for cannabis use.

The current study has several limitations. The present sample of individuals entering treatment for CUD was characterized by a very small proportion of female individuals, precluding exploration of sex-/gender-related differences in neural features underlying cannabis abstinence. Future studies with larger samples of females are essential (23). The sample is also characterized by multiple lifetime substance use and other diagnoses. While

this is typical of real-world treatment settings and may improve the external validity of our results, it is also important to acknowledge that it is not a “pure” CUD sample. Therefore, co-occurring disorders may have impacted results. Additionally, although we used a rigorous cross-validation approach (5-fold cross-validation across 100 iterations), we did not include an external validation sample. Nonetheless, the current finding of a third independent replication of the cocaine abstinence network supports the utility of applying CPM to identify networks in modest samples that do ultimately generalize across different samples. Future work is needed to assess whether the cannabis network also replicates to predict cannabis treatment outcomes in independent samples of treatment-seeking individuals. Furthermore, analyses applying CPM to data acquired during brain states specific to cannabis use and treatment (e.g., cannabis cue-reactivity tasks) will be useful to assess for additional connections relevant to achieving abstinence in treatment. Related, it is critical that future research assess whether directly targeting the cannabis abstinence network via neurofeedback, neuromodulation, or other novel therapeutic approaches may improve treatment outcomes for individuals seeking treatment for CUD.

The current study sought to replicate our earlier work CPM to identify a neural network predictive of cocaine abstinence in treatment. We further aimed to extend these findings by assessing whether the cocaine abstinence network would extend to also predict cannabis abstinence in treatment. The present findings demonstrate that the cocaine abstinence network generalized to predict cocaine treatment outcome in a third independent sample, supporting the utility of CPM for identifying robust, reproducible, and clinically relevant neural networks. Consistent with prior work demonstrating the substance specificity of CPM-derived cocaine and opioid abstinence networks, we found that the cocaine abstinence network was specific for predicting cocaine, but not cannabis abstinence. Accordingly, we then applied CPM to identify a novel cannabis abstinence network, characterized by increased connectivity between the motorsensory network and frontoparietal, medial frontal, and salience networks, as well as decreased within-network connectivity of the motor sensory network. These results have implications for elucidating the neural mechanisms underlying successful cannabis-use treatment, as well as potentially uncovering novel treatment targets to improve treatment outcomes for this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The current work was supported by K08DA051667 (SL), Women’s Health Research at Yale (SL), T32DA007238 (RK), R01DA039136 (MNP), K02AA027300 (BK), and YSM Office of Team Science (SWY, SL). Data collection was supported by P50DA09241 (MNP, BK), R01DA020908 (MNP), R01DA035058 (MNP) and R01DA019039 (MNP).

Clinical Trials Registation: “Computer Based Training in Cognitive Behavioral Therapy Web-based (Man VS Machine)”, https://www.clinicaltrials.gov/ct2/show/NCT01442597, registration number: NCT01442597. “Maximizing the Efficacy of Cognitive Behavior Therapy and Contingency Management”, https://www.clinicaltrials.gov/ct2/show/NCT00350649, registration number: NCT00350649. “Computer-Based Training in Cognitive Behavior Therapy (CBT4CBT)”, https://www.clinicaltrials.gov/ct2/show/NCT01406899, registration number: NCT01406899.

Preliminary data on the cannabis abstinence network were presented at the Society for Biological Psychiatry's 2022 Annual Scientific Meeting, New Orleans, LA.

Conflict of Interest

Drs. Lichenstein, Kohler and Ye report no competing financial interests in relation to the work described. Dr. Potenza has consulted for Opiant Therapeutics, Game Day Data, Baria-Tek, the Addiction Policy Forum, AXA and Idorsia Pharmaceuticals; has been involved in a patent application with Yale University and Novartis; has received research support from Mohegan Sun Casino and the Connecticut Council on Problem Gambling; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulse-control/addictive disorders; has provided clinical care in a problem gambling services program; has performed grant reviews for research-funding agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. Dr. Kiluk is a consultant to CBT4CBT LLC, which makes versions of CBT4CBT (one of the treatments evaluated in the parent RCTs included in this study) available to qualified clinical providers and organizations on a commercial basis. Dr. Yip is a consultant for Sparian Biosciences.

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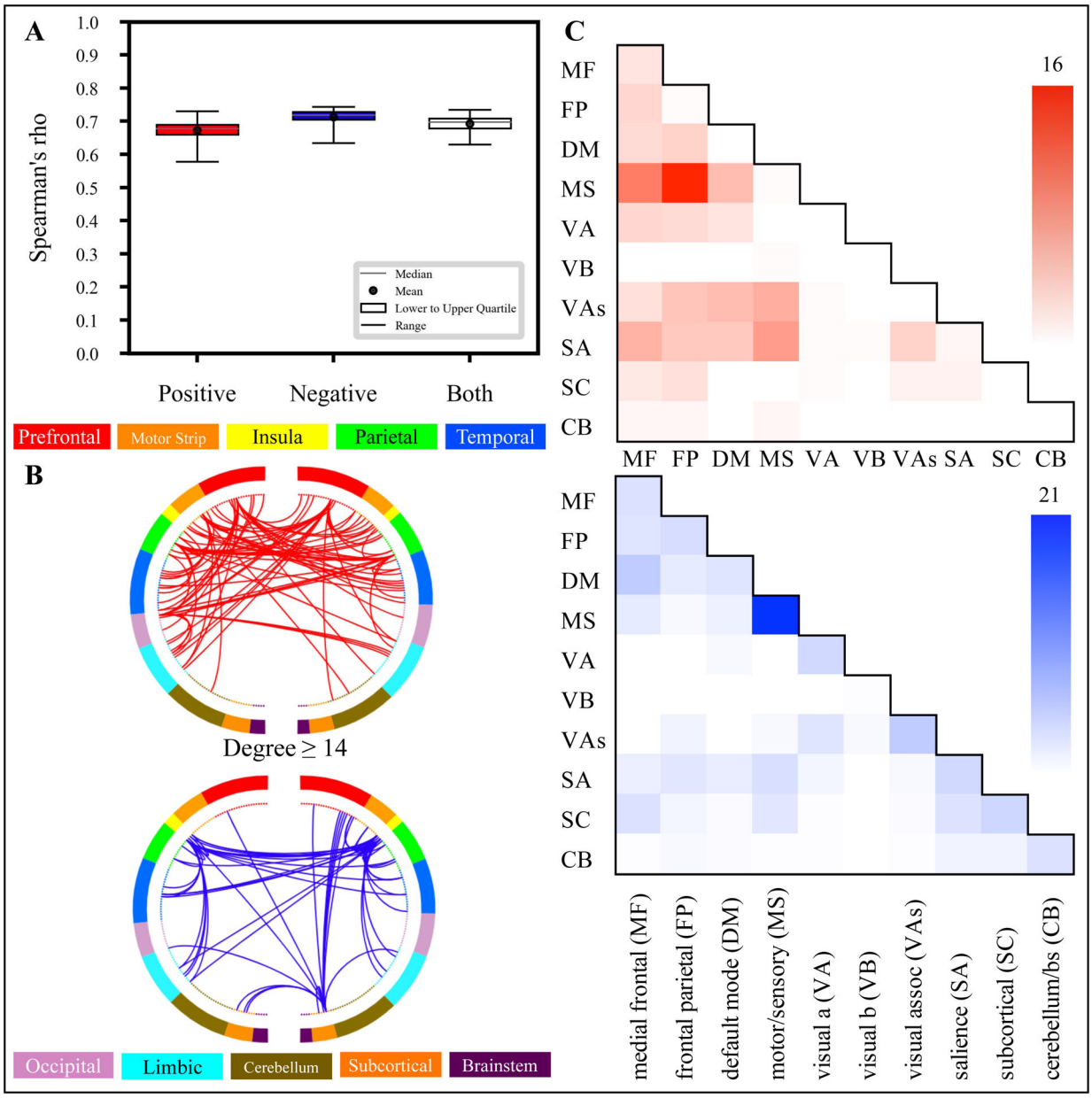

Figure 1. Cannabis Abstinence Network.

Panel A displays model performance for positive, negative, and combined cannabis abstinence network CPM models. Panel B illustrates network anatomy based on overlap with macroscale brain regions; edges of the positive network are depicted with red lines and edges of the negative network are depicted with blue lines. Panel C illustrates network anatomy based on overlap with canonical neural networks. Darker shading indicates that network connections account for a greater percentage of the total network.

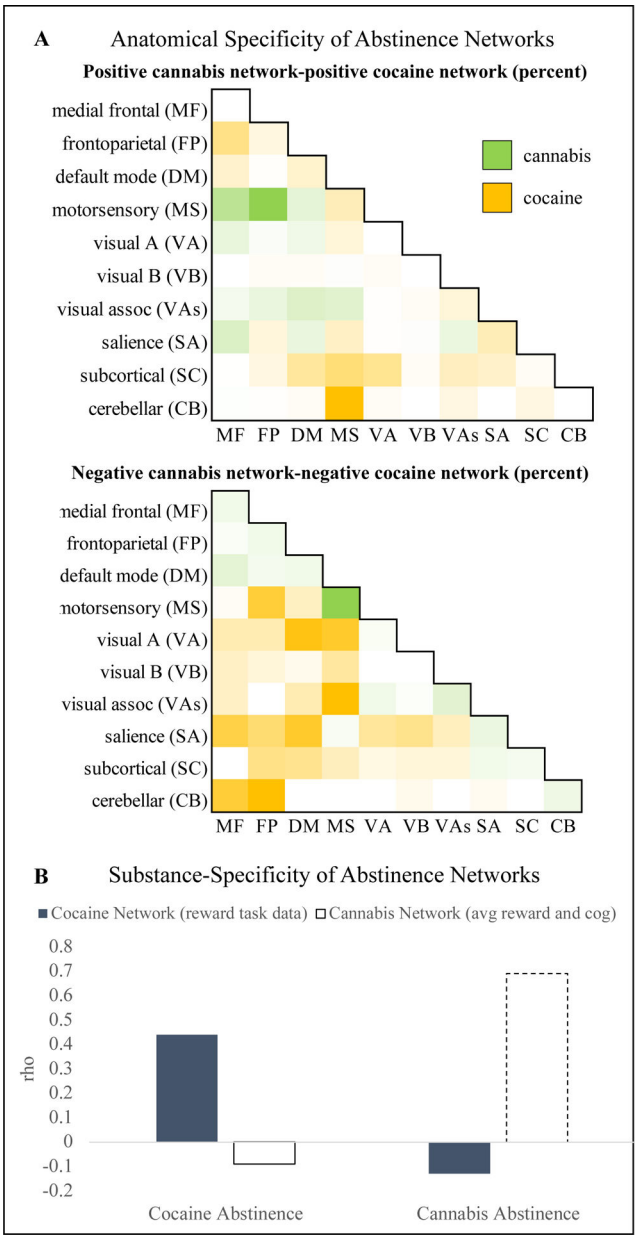

Figure 2. Specificity of Cannabis and Cocaine Abstinence Networks.

Panel A illustrates the anatomical specificity of cocaine and cannabis abstinence networks. Cells shaded in green represent network connections that are more characteristic of the cannabis versus cocaine abstinence network and cells shaded in orange represent network connections that are more characteristic of the cocaine versus cannabis abstinence networks. Panel B illustrates the substance specificity of abstinence networks by depicting the effect size for each network for predicting cocaine and cannabis abstinence.

Table 1.

Demographic and clinical characteristics

	Cocaine Abstinence Network Replication Sample* n=43	Cannabis Abstinence Network Identification Sample* n=33	Group Comparison $\chi^{2/t}$ (*p*)
Female, No. (%)	9 (20.9)	3 (9.1)	1.97 (.161)
Age, mean (SD)	36.3 (11.3)	27.6 (8.4)	**3.87 (<.001)**
Educational attainment (completed high school or above, %)	32 (74.4)	22 (66.7)	0.55 (.460)
Race, No. (%)			2.68 (.612)
White	10 (23.3)	9 (27.3)	
Black	23 (53.5)	17 (51.5)	
Hispanic	6 (14.0)	2 (6.1)	
Other	4 (9.3)	5 (15.1)	
Currently employed, No. (%)	12 (27.9)	12 (36.4)	0.62 (.432)
Currently married/cohabitating, No. (%)	6 (14.0)	3 (9.1)	0.42 (.516)
Years of regular cocaine use, mean (SD)	5.1 (9.3)	1.8 (7.5)	1.74 (.086)
Years of regular cannabis use, mean (SD)	12.5 (11.2)	10.3 (9.5)	0.88 (.381)
Lifetime alcohol use disorder, No. (%)	38 (88.4)	21 (63.6)	**6.58 (.010)**
Lifetime No. of arrests, mean (SD)	9.4 (10.5)	7.6 (9.6)	0.73 (.466)

**Note.* N=17 individuals with lifetime cannabis use disorder are included in both samples