Long-term abstinence reduces optimal energy required for transitions from the exogenous networks to the frontoparietal network in methamphetamine addicts

Authors: Yanyao Du[1#], Jiaqi Zhang[2,3#], Dan Cao[2], Wenhan Yang[1], Jin Li[4], Deying Li[2,3], Ming Song[2], Zhengyi Yang[2], Jun Zhang[5], Tianzi Jiang[2,3,6,7,8*], Jun Liu[1,9,10*]

Affiliations:

[1] Department of Radiology, Second Xiangya Hospital of Central South University, Changsha, Hunan, China

[2] Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

[3] School of Artificial Intelligence, University of Chinese Academy of Sciences, Beijing 100190, China

[4] School of Psychology, Capital Normal University, Beijing, China

[5] Hunan Judicial Police Academy, Changsha, Hunan, China

[6] Center for Excellence in Brain Science and Intelligence Technology, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

[7] Research Center for Augmented Intelligence, Zhejiang Lab, Hangzhou 311100, China

[8] Xiaoxiang Institute for Brain Health and Yongzhou Central Hospital, Yongzhou 425000, Hunan Province, China

[9] Clinical Research Center for Medical Imaging in Hunan Province, Changsha, Hunan, China

[10] Department of Radiology Quality Control Center, Changsha, Hunan, China

*** Corresponding Authors:** junliu123@csu.edu.cn (J. Liu), jiangtz@nlpr.ia.ac.cn (T. Jiang).

 # The authors contributed equally

Abstract

Methamphetamine (MA) addiction is a chronic neurotoxic brain disorder that places a significant burden on public health, with a high relapse risk. Long-term abstinence can significantly reduce craving, yet the potential alterations caused by long-term abstinence still remain unclear. In this study, a total of 62 MA users who underwent longitudinal follow-up during their period of long-term abstinence (duration of long-term abstinence: 347.52 ± 99.25 days) were enrolled. For the first time, we employed a promising framework known as network control theory to explore the impact of long-term abstinence on MA addicts. Our observations indicated that long-term abstinence led to a decline in the control energy required for transitions from the visual network, and somatomotor network to the frontoparietal network, suggesting a reduced barrier for triggering executive control response to the drug cues. Furthermore, we identified the orbitofrontal cortex and the dorsolateral prefrontal cortex as crucial regions involved in facilitating these transitions. Notably, we discovered significant associations between the influence of long-term abstinence on brain regions and the spatial distribution of key biological factors, such as DAT, 5HTT, D2, MOR, VAChT, and NET. Overall, our findings not only provide a novel perspective on understanding the impact of long-term abstinence in MA addicts but also link this process to biological factors.

1. Introduction

Methamphetamine (MA) is a profoundly addictive stimulant that exerts its effects on the central nervous system (Zhao et al. 2022). Presently, it stands as the primary globally illicitly manufactured synthetic drug (United Nations Office on Drugs and Crime 2023). Prolonged abuse of MA can result in severe consequences, such as psychosis, delusions, impulsivity, and various complications, including infections like hepatitis C virus and acquired immune deficiency syndrome (AIDS), which not only

pose a substantial burden on individual health but also contribute significantly to societal and public health challenges (Degenhardt et al. 2019; Compton and Manseau 2018). Hence, there exists an imperative to investigate more efficacious intervention and treatment strategies targeting MA addiction.

Long-term abstinence serves as a direct and effective therapeutic strategy that can significantly reduce craving, which is widely recognized as the central feature of drug addiction (O'Brien et al. 1998), involving interactions among distributed brain regions (Koban, Wager, and Kober 2023; Wilson, Sayette, and Fiez 2004). Investigating structural and functional alterations associated with craving resulting from long-term abstinence is highly beneficial for improving addiction treatment. Prior research has been limited by incomplete longitudinal data, small sample sizes, and short follow-up periods (Wang et al. 2013; Salo et al. 2009; Li et al. 2015). Complex brain function depends on dynamic state transitions supported by the underlying structural scaffold (Luppi et al. 2023). However, most previous studies have primarily focused on analyzing the difference in traditional average static or dynamic neuroimaging data (Owens et al. 2019), neglecting the crucial causal relationship between structure and function, which restricts our comprehensive understanding. MA-induced neurotoxic effects are closely tied to neurotransmitters including dopamine and serotonin (Jayanthi, Daiwile, and Cadet 2021), yet research linking system-level alterations to these biological factors remains sparse. Consequently, exploring the alterations in the causal connection between the structure and brain functional states of MA addicts after long-term abstinence and how these changes relate to specific biological factors remains a significant question to be addressed.

In order to solve these challenges, we expanded our sample size to 62 participants, implemented a comprehensive longitudinal follow-up for each subject, and gathered neuroimaging data both before (MA1) and after (MA2) their long-term abstinence. Subsequently, we need to study and quantify the causal relationship between structure

and brain functional states. Network control theory (NCT) (Gu et al. 2015; Gu et al. 2017) is a powerful computational framework to characterize how structural connectivity constrains the brain state transitions and has exhibited its utility in psychiatric diseases (Parkes et al. 2021; Hahn et al. 2023) and cognitive function (Cui et al. 2020; Stiso et al. 2019). Here, we applied NCT constrained by the Brainnetome atlas (Fan et al. 2016) to explore the impact of long-term abstinence on brain state transitions constrained by empirical structural connectome and explored the contribution of 19 receptors and transporters (Hansen et al. 2022) to the spatial distribution of influence on brain regions resulting from long-term abstinence. To the best of our knowledge, the application of this approach in the context of MA addiction is currently lacking in the existing studies.

In this study, we tested the following hypotheses: (I) alterations in structural brain networks resulted from the long-term abstinence may facilitate the transition from exogenous networks (related with receiving external information) to frontoparietal network (related with executive function) more efficiently, i.e., at a lower energetic cost. (II) the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC) may play a crucial role in facilitating these two state transitions. (III) the impact of long-term abstinence on brain regions was associated with specific biological factors, such as dopamine transporter (DAT) and serotonin transporter (5HTT).

2. Material and Methods

2.1 Participants

The experimental design is shown in **Fig. 1**. This research received approval from the ethics committee of the Second Xiangya Hospital of Central South University, Hunan, China. Informed written consent was obtained from all participants. MA-abstinent subjects were recruited from drug rehabilitation centers in Changsha, Zhuzhou, and

Yueyang (Hunan, China). During the abstinence period, participants received interventions solely comprising medication, education, and physical exercise. Inclusion criteria were as follows: (a) positive MA urine test and negative tests for other substances; (b) meeting addiction diagnosis criteria outlined in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); (c) possession of complete MR and scale data both before (MA1) and after long-term abstinence (MA2); (d) normal visual acuity, hearing, and right-handedness. Exclusion criteria for abstinent groups included: (a) MRI contraindications; (b) history of structural brain abnormalities (e.g., intracerebral hemorrhage, epilepsy, tumor) and psychiatric illness. Ultimately, our study included 124(62*2) participants for both MA1 and MA2 assessments. Following MR examinations, all individuals completed questionnaires, including the Fagerstrom Test for Nicotine Dependence, the Alcohol Use Disorder Identification Test, and the Methamphetamine Craving Questionnaire (MCQ).

2.2 MR Imaging Acquisition

All imaging acquisitions were performed using a 3T MRI scanner (MAGETOM Skyra, Siemens Healthcare, Erlangen, Germany) equipped with a 32-channel head coil. The MRI protocol comprised T1-weighted imaging, T2-weighted imaging, three-dimensional magnetically prepared rapid acquisition gradient echo (3D MPRAGE) sequences, and diffusion tensor imaging (DTI). The parameters for 3D MPRAGE scanning were set as follows: 176 sagittal slices, TR 1450 ms, TE 2.03 ms, flip angle 30°, voxel size 1×1×1mm^3, slice thickness 1 mm, and field of view 256 mm×256 mm^2. For DTI, the parameters were as follows: b values of 1000 mm/s^2 and 0 mm/s^2, 64 gradient directions, 60 axial slices, TR 9500 ms, TE 88 ms, voxel size 2×2×2 mm^3, slice thickness 2 mm, and field of view 256 mm×256 mm^2.

2.3 MR Imaging Processing

The structural preprocessing utilized the Brainnetome Atlas (Fan et al. 2016), comprising 246 brain regions. For DTI preprocessing, probabilistic tractography and network construction were conducted using PANDA, implemented in Matlab 2016b (Cui et al. 2013). The preprocessing steps included: (a) conversion from DICOM to compressed NIfTI; (b) brain mask estimation and raw image cropping; (c) correction for the eddy-current effect; (d) averaging of multiple acquisitions; (e) calculation of diffusion tensor metrics; and (f) execution of probabilistic tractography and network construction using BedpostX and probtrackx command.

2.4 Network Control Theory

To investigate the influence of long-term abstinence on brain network dynamics, we applied network control theory(Gu et al. 2015; Gu et al. 2017) to explore brain state transitions. This theory enables us to understand how empirical white matter architecture constrains brain state trajectories in response to external energy inputs. As in previous studies (Cui et al. 2020; He, Caciagli, et al. 2022; Parkes et al. 2022), the linear time-invariant model can be defined by the following equation:

$$\dot{x(t)} = Ax(t) + Bu(t) \tag{1}$$

where $x(t)$ is a $N \times 1$ vector $(N = 246)$ that represents the brain state at time point t, here we defined nine binary brain states including visual network (VIS), somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LIM), frontoparietal network (FPN), default network (DMN) (Thomas Yeo et al. 2011), subcortical network (SUB) **(Fig 1. B.1)**, and a baseline network (BASE), i.e., all element equals to 0. A is an $N \times N$ matrix representing the interactions between system elements, and in this context, A was

defined as the individual structural connectome. To prevent unbounded system growth(Karrer et al. 2020), A was normalized as follows:

$$A_{\text{norm}} = \frac{A}{|\lambda(A)|_{\max} + 1} - I \tag{2}$$

here, $|\lambda(A)|_{\max}$ denotes the largest absolute eigenvalue of the system, and I denotes an $N \times N$ identity matrix. B is an $N \times N$ diagonal matrix that defines control nodes, specifically, if brain region m is chosen to receive energy, then $B(m,m) = 1$; otherwise, $B(m,m) = 0$. Last, $u(t)$ represents the time-dependent input energy for each brain region.

To investigate the energetic efficiency of the structural connectome in facilitating the transitions between functional brain states, we employed the optimal control framework **(Fig 1. B.2)**, which allows us to estimate the control energy while taking into account both the length of the transition trajectory and the amount of energy cost required to transition from the initial brain state $x(0)$ to the target brain state $x(T)$. The optimal solution $u(t)^*$ to the cost function can be defined as follows:

$$u(t)^* = \arg\min_{u} \int_0^T \left(\mathrm{x}_T - \mathrm{x}(t)\right)^{\mathrm{T}} \left(\mathrm{x}_T - \mathrm{x}(t)\right) + \rho \mathrm{u}\,(t)^{\mathrm{T}} \mathrm{u}(t)\ dt \tag{3}$$

here, ρ determines the relative weighting of the amount of energy cost, and we utilized the default value of $\rho = 1$. By integrating the control energy for each control node over time, we defined the energy of each control node i as follows:

$$E_i^* = \int_{t=0}^{T} \|u_i^*(t)\|^2 dt \tag{4}$$

And the total optimal energy E_{opt}^* was defined as:

$$E_{\text{opt}}^{*} = \sum_{i=1}^{N} E_i^{*} \tag{5}$$

To assess the significance of each brain region in achieving the desired transitions, we defined the control impact I_i as follows, which is consistent with previous literature (Mahadevan et al. 2023):

$$I_i = \log \frac{E_{\text{opt}}^{*}(\mathrm{B}_i)}{E_{\text{opt}}^{*}(\mathrm{B}_0)} \tag{6}$$

where B_0 represents the control set including all brain regions and B_i represents the control set after the exclusion of brain region i.

2.5 PET Receptor Densities

To link the spatial distribution of influence on brain regions by long-term abstinence with biologically meaningful patterns, we estimated spatial densities for a total of 19 receptors and transporters using published PET maps (Hansen et al. 2022), including dopamine (D1, D2, and DAT), norepinephrine (NET), serotonin (5HT1a, 5HT1b, 5HT2a, 5HT4, 5HT6, and 5HTT), acetylcholine (A4B2, M1, and VAChT), glutamate (NMDA and mGluR5), GABA (GABAa), histamine (H3), cannabinoid (CB1), and opioid (MOR). Volumetric PET images were registered to the MNI-ICBM 152 non-linear 2009 (version c, asymmetric) template and subsequently parcellated into 246 regions according to the Brainnetome atlas (Fan et al. 2016). For each PET map, we z-scored the resulting receptor density (**Fig 4. A**).

2.6 Spatial Null Models

To illustrate that our results are specific to the spatial distribution of certain receptors, we implemented a spatial autocorrelation preserving null model, known as spin test

(Markello and Misic 2021; Váša and Mišić 2022). For each PET spatial map, we generated 5,000 surrogate maps using BrainSMASH (Burt et al. 2020), and $p-values$ were determined as the fraction of iterations in which the observed average correlation surpassed the randomized average correlation.

3. Results

3.1 Participant characteristics

The mean age of MA1 patients was 35.00±9.35 years, with 66.13% were men. Demographic characteristics are depicted in **Table 1**, including histories of nicotine, alcohol, and drug use, along with the duration of MA use and the dose consumed. The abstinence periods for MA1 and MA2 were 28.11±18.88 days and 347.52±99.25 days, respectively. The MCQ score exhibited a significant reduction (P<0.001) in MA2 (45.39±9.41) compared to MA1 (61.37±16.07) (**Table 1, Fig. 2. A**).

3.2 Decreased state transition energy after long-term abstinence

To investigate the impact of long-term abstinence on MA addicts, we initially quantified the energy required to facilitate state transitions between any two of the nine brain states, aiming to examine the impact on brain network dynamics. We observed that long-term abstinence led to a decrease in the energy required for transitions from VIS to FPN and SMN to FPN. In more comprehensive detail, the energy supporting transitions was significantly lower (VIS to FPN: $P_{Bonferroni}$ = 2.09e-04, T = -3.95 and SMN to FPN: $P_{Bonferroni}$ = 1.63e-05, T = -4.68, paired t test) in MA2 (VIS to FPN: 7.06e+04 $\pm$ 641.60, SMN to FPN: 7.01e+04 $\pm$ 456.22) than in MA1 (VIS to FPN: 7.10e+04 $\pm$ 800.45, SMN to FPN: 7.05e+04 $\pm$ 495.59) (**Fig 2. B**).

Furthermore, we performed a partial Spearman correlation to assess the association between the alterations of craving score and the alterations of transition energy while

accounting for the influence of group, sex, age, education, nicotine use, FTND, alcohol use and AUDI factors (**Table 1**). The results from both analyses revealed significant correlations (VIS to FPN: r = 0.3395, P = 0.012 and SMN to FPN: r = 0.2831, P = 0.0381 controlling for group, sex, age, education, nicotine use, FTND, alcohol use and AUDI) (**Fig 2. C**).

3.3 Control impact of each brain region in supporting state transitions

Once the significant state transitions related to craving score were identified, we proceeded to quantify the relative influence of each brain region in these transitions. For each state transition (i.e., VIS to FPN and SMN to FPN), we calculated the control impact I_i for each brain region i according to **Equation 6**. This metric indicated the increment in the total optimal energy E^*_{opt} resulting from the removal of each brain region.

First, we explore the important brain regions in the context of MA1. For each individual, we systematically computed the relative influence of each region, and then averaged the results across the group to obtain the average spatial map of control impact for both state transitions (**Fig 3. A**). In more detail, we identified the top 3% of brain regions that played a primary role in facilitating the transition from VIS to FPN. These regions included OrG_R_6_3 (I = 4.5048), MFG_R_7_7 (I = 4.2875), SFG_L_7_1 (I = 3.9393), MFG_L_7_3 (I = 3.7325), MFG_L_7_4 (I = 3.5753), MFG_R_7_3 (I = 3.5213), SFG_R_7_6 (I = 3.4977). Interestingly, the top 3% of brain regions contributing to the transition from SMN to FPN were the same as those for the transition from VIS to FPN, with only variations in the specific control impact values: OrG_R_6_3 (I = 4.5123), MFG_R_7_7 (I = 4.2966), SFG_L_7_1 (I = 3.9218), MFG_L_7_3 (I = 3.7396), MFG_L_7_4 (I = 3.5822), MFG_R_7_3 (I = 3.5284), SFG_R_7_6 (I = 3.5049).

Subsequently, we repeated the same calculation process in the context of MA2, and the resulting average spatial maps of control impact for both transitions were displayed in **Fig 3. B**. The outcome regarding the top 3% crucial brain regions remained consistent with MA1, except for changes in control impact values. Control impact in transition from VIS to FPN: OrG_R_6_3 (I = 4.2643), MFG_R_7_7 (I = 4.1464), SFG_L_7_1 (I = 3.8249), MFG_L_7_3 (I = 3.6273), MFG_L_7_4 (I = 3.4658), MFG_R_7_3 (I = 3.3835), SFG_R_7_6 (I = 3.3337). Control impact in transition from SMN to FPN: OrG_R_6_3 (I = 4.2644), MFG_R_7_7 (I = 4.1499), SFG_L_7_1 (I = 3.7997), MFG_L_7_3 (I = 3.6319), MFG_L_7_4 (I = 3.4622), MFG_R_7_3 (I = 3.3884), SFG_R_7_6 (I = 3.3381).

3.4 Influence on brain regions by long-term abstinence associated with the distribution of neurotransmitter densities

While we have quantified the control impact for both state transitions in the context of MA1 and MA2, we continued to explore whether the spatial distribution of influence due to long-term abstinence exhibited randomness, uniformity, or any associations with specific biological factors.

Here, we defined the influence on brain regions as the difference in regional control impact between MA1 and MA2. The average spatial maps of the difference in control impact for both transitions were presented in **Fig 4. B**. These maps revealed that the effects of long-term abstinence were primarily concentrated in *A39rd* and *A7m*. Subsequently, we assessed the correlations between the maps of differences in regional control impact and PET receptor densities (described in detail in Section *Spatial Null Models*). We observed a significant correlation between the influence of long-term abstinence and the spatial distribution of 5HTT (P_{spin} = 0.0032), D2 (P_{spin} = 0.0108), DAT (P_{spin} = 0.0370), MOR (P_{spin} = 0.0166), and VAChT (P_{spin} < 0.001) in the context of the transition from VIS to FPN. Additionally, in the context of the transition from

SMN to FPN, we found significant correlations between the influence of long-term abstinence and the spatial distribution of DAT ($P_{spin} = 0.0346$) and NET ($P_{spin} = 0.0022$).

4. Discussion

In this work, we applied an intriguing approach known as the network control theory to explore the impact of long-term abstinence on MA addicts. Initially, we quantified the optimal energy across 81 state transitions, observing that long-term abstinence led to a decline in the optimal control energy required from transitions from the exogenous networks to the frontoparietal network. Importantly, these alterations were found to be closely linked to changes in craving scores. Subsequent systematic evaluations of the control impact of each brain region underscored the pivotal roles played by the OFC and DLPFC in facilitating these two state transitions. Furthermore, we delved into the contribution of 19 receptors and transporters to the spatial distribution of influence on brain regions resulting from long-term abstinence.

Compared to MA1, there was a significant reduction in the energy required for transitions from the VIS and SMN to the FPN in MA2. Moreover, the difference in craving between MA1 and MA2 showed a positive correlation with the difference in the transition capabilities from VIS to FPN and SMN to FPN. The FPN plays a crucial role in supporting the advanced cognitive abilities necessary for self-regulation in the brain, such as response inhibition, working memory, decision-making, and planning (Miller and Cohen 2001; Tranel 1994). In other words, individuals who exhibited a significant reduction in craving after long-term abstinence also experienced a notable decrease in the energy cost of transitioning from VIS and SMN to FPN, suggesting a reduced barrier for triggering executive control response to the drug cues. A multifaceted investigation into substance abuse and relapse, considering various cues and craving indicators, has indicated that the response to drug-associated cues serve as an important metric for predicting drug use and craving changes (Vafaie and Kober

2022). Studies on brain self-regulation suggest an imbalance between the intensity of addiction and impulsivity and an individual's capacity for self-restraint or the implementation of restraint on desires (Kelley, Wagner, and Heatherton 2015). Additionally, following prolonged abstinence, external stimuli activating the exogenous networks could more easily mobilize the FPN, thereby suppressing craving. These results align with a recent publication that noted the response of certain regions, including those in the FPN, partially mediated the impact of visual craving features on craving ratings (Koban, Wager, and Kober 2023).

Reasonably, we found that the OFC and DLPFC play key roles in these two state transitions. Whether it is research on addiction mechanisms (Huang et al. 2023) or exploration of addiction treatment targets (Yuen et al. 2022), the OFC and DLPFC have always been areas of great concern. Increased activation of the OFC and DLPFC in response to cues signaling anticipated drug use may indicate the explicit representation of this expectancy by the OFC, and the generation and sustenance of behavioral goals directed towards acquiring drug rewards by the DLPFC (Goldstein and Volkow 2002; Bonson et al. 2002). During the delay period, OFC neurons showed higher activity in anticipation of reward (Schultz, Tremblay, and Hollerman 2000), while DLPFC neurons encoding reward anticipation also showed higher activity (Wallis and Miller 2003). Activation of these two areas was found to be consistently reliable in cue-exposure studies involving drug addicts who were still actively using (Wilson, Sayette, and Fiez 2004). Our results also prove the important role of OFC and DLPFC in abstinence from addiction in another perspective.

In the context of transition from VIS to FPN, the impacts of long-term abstinence exhibited a significant correlation with the spatial distribution of neurotransmitters, including 5HTT, D2, DAT, MOR, and VAChT. Similarly, a notable correlation was observed between the effects of long-term abstinence and the spatial distribution of DAT and NET in the context of transition from SMN to FPN. These findings indicate

that the consequences of prolonged abstinence on various brain regions were not uniform or random; rather, they demonstrated a significant association with the spatial distribution of specific neurotransmitters. Dysfunctions in both dopamine transmission and reuptake have long been considered the foundation of addictive behavior and play a crucial role in the molecular biological mechanism of addiction (Kohno et al. 2022; Keiflin and Janak 2015). Consistent with these findings, we observed the correlation between the effects of long-term abstinence and the spatial distribution of DAT was evident in both state transitions. Furthermore, serotonin, norepinephrine, and acetylcholine were also key neurotransmitters linked to addiction. Serotonin regulated neuroplasticity, hedonic and motivational processes, as well as reinforcement mechanisms and cognitive function (Müller and Homberg 2015; Howell and Cunningham 2015). Norepinephrine triggered stress responses during addiction (Sharp 2017; Weinshenker and Schroeder 2007), and acetylcholine regulation played a crucial role in the treatment of drug addiction, particularly in the learning and memory processes (He, Chen, et al. 2022; Williams and Adinoff 2008). Interestingly, the influence maps exhibited a negative correlation with DAT, 5HTT, D2, MOR, and VAChT, however, the trend was positive in the context of NET, indicating the intricate nature of multiple interacting neurotransmitter systems (Shine 2019, 2023).

In conclusion, our work link the impact of long-term abstinence to the energy required for brain state transitions, biological factors, and craving scales, providing a novel insight into the underlying neural mechanisms of long-term abstinence in MA addicts.

Figures Legends

Fig.1 Schematic description of the study framework

A) **Recruit MA users (N = 62)**. In this study, we recruited a total of 62 MA addicts who were longitudinally followed up during their period of long-term abstinence (duration of long-term abstinence: 347.52±99.25 days). All participants underwent neuroimaging data acquisition and questionnaires.

B) **Quantify state transition energy. B.1 Define brain states.** We identified seven functional brain states based on the known resting-state networks (Thomas Yeo et al. 2011) for cortical regions, while the remaining subcortical regions were categorized as the eighth brain state for further analysis. **B.2 Network control theory.** Initially, we defined the initial brain state $x(0)$ at $t = 0$ and the target brain state $x(T)$ at $t = T$. Subsequently, we computed the optimal control energy $u(t)$ required to facilitate the state transition, taking into account constraints imposed by the individual's empirical structural connectome. Lastly, we aimed to associate the energy with craving scores, thereby endowing the observed energy variations with biological significance.

C) **Explore underlying biological factors.** To achieve a comprehensive understanding, we explored the underlying biological factors associated with the regional impact of long-term abstinence.

Fig.2 Alterations observed after long-term abstinence

A) **Decreased craving score after abstinence.** A paired t-test was conducted to assess the statistical differences in craving score between MA1 and MA2.

B) **Transition energy matrix.** We applied network control theory to analyze the energy necessary for transitions between different brain states. Paired t-tests were performed to evaluate the statistical differences following long-term abstinence. The p-values were computed and adjusted for multiple comparisons using Bonferroni correction.

C) **Relationship between energy and craving score.** We conducted a partial correlation analysis between alterations in craving scores and alterations in transition energy used for transitioning from VIS to FPN and from SMN to the FPN.

Asterisks indicate the presence of statistically significant differences (*<0.05; **<0.01; ***<0.001).

Fig.3 Control impact of brain regions in transitions from exogenous networks to the frontoparietal network

A) **Control impact of brain regions in MA1.** We evaluated the relative importance of each brain region within the Brainnetome atlas in the transitions from exogenous networks to the frontoparietal network in the context of MA1.

B) **Control impact of brain regions in MA2.** We evaluated the relative importance of each brain region within the Brainnetome atlas in the transitions from exogenous networks to the frontoparietal network in the context of MA2.

The results were visualized with the BrainSpace (Vos de Wael et al. 2020) and code is available at https://github.com/MICA-MNI/BrainSpace.

Fig.4 Underlying biological factors influencing brain regions by long-term abstinence

A) **PET receptor densities.** A total of 19 receptors and transporters density values were extracted from publicly available datasets (Hansen et al. 2022).

B) **Alterations in control impact.** We computed the mean differences in control impact between each pair of brain regions across all individuals.

C) **Relationship between receptor density and alterations in control impact**. To investigate the non-uniform impact on brain regions after long-term abstinence, we computed individual-level Spearman correlation coefficients between the distribution of 19 receptors and the changes in control impact. We repeated these calculations using 5,000 spin-permuted receptor maps.

Tables

Table 1. Demographic characteristics.

Characteristic	MA1 (N=62)	MA2 (N=62)	Z	*P*
Age (years)	35.00±9.35	-	-	-
Gender (male/female)	41/21	-	-	-
Education (years)	9.39±2.63	-	-	-
Nicotine use (yes/no)	56/6	-	-	-
FTND	5.00(3.00, 6.00)	-	-	-
Alcohol use (yes/no)	35/27	-	-	-
AUDI	2.00(0.00, 7.25)	-	-	-
Handedness	62R	-	-	-
Age of first use (years)	27.27±7.48	-	-	-
Duration of MA use (years)	4.53±3.92	-	-	-
Dosage of MA use (g/day)	0.44±0.35	-	-	-
Abstinence period (days)	28.11±18.88	347.52±99.25	-	-
MCQ score [a]	61.37±16.07	45.39±9.41	9.525	**<0.001***

[a] Paired sample t-test. MA1, before long-term abstinence. MA2, after long-term abstinence. N, number of subjects. FTND, Fagerstrom Test for Nicotine Dependence. AUDIT, Alcohol Use Disorders Identification Test. MCQ, Methamphetamine Craving Questionnaire. A significant level was set at $P<0.05$. Data were superscripted with asterisks (*) indicates significant differences between groups.

Data Availability

The data supporting this study's findings are available from the corresponding authors on reasonable request.

Code Availability

Codes for network control theory is available at https://github.com/BassettLab/nctpy.

Acknowledgments

This work was supported by STI2030-Major Projects 2021ZD0200201; National Science Foundation of China 82151307 and 62327805; Innovative Province special construction foundation of Hunan Province 2020SK4001; National Natural Science Foundation of China 61971451; Innovative Province special construction foundation of Hunan Province 2019SK2131; Neurobiological mechanism of drug addiction and prediction model of relapse U22A20303; Scientific Project of Zhejiang Lab (No. 2022ND0AN01, No. 2022KI0AC02).

Conflict of Interests

All authors declare no competing interests.

References

Bonson, Katherine R, Steven J Grant, Carlo S Contoreggi, Jonathan M Links, Janet Metcalfe, H Lloyd Weyl, Varughese Kurian, Monique Ernst, and Edythe D London. 2002. 'Neural systems and cue-induced cocaine craving', Neuropsychopharmacology, 26: 376-86.

Burt, Joshua B, Markus Helmer, Maxwell Shinn, Alan Anticevic, and John D Murray. 2020. 'Generative modeling of brain maps with spatial autocorrelation', Neuroimage, 220: 117038.

Compton, Michael T, and Marc W Manseau. 2018. The American opioid epidemic: from patient care to public health (American Psychiatric Pub).

Cui, Zaixu, Jennifer Stiso, Graham L Baum, Jason Z Kim, David R Roalf, Richard F Betzel, Shi Gu, Zhixin Lu, Cedric H Xia, and Xiaosong He. 2020. 'Optimization of energy state transition trajectory supports the development of executive function during youth', elife, 9: e53060.

Cui, Zaixu, Suyu Zhong, Pengfei Xu, Yong He, and Gaolang Gong. 2013. 'PANDA: a pipeline toolbox for analyzing brain diffusion images', Frontiers in human neuroscience, 7: 42.

Degenhardt, Louisa, Jason Grebely, Jack Stone, Matthew Hickman, Peter Vickerman, Brandon DL Marshall, Julie Bruneau, Frederick L Altice, Graeme Henderson, and Afarin Rahimi-Movaghar. 2019. 'Global patterns of opioid use and dependence: harms to populations, interventions, and future action', The Lancet, 394: 1560-79.

Fan, Lingzhong, Hai Li, Junjie Zhuo, Yu Zhang, Jiaojian Wang, Liangfu Chen, Zhengyi Yang, Congying Chu, Sangma Xie, and Angela R Laird. 2016. 'The human brainnetome atlas: a new brain atlas based on connectional architecture', Cerebral cortex, 26: 3508-26.

Goldstein, Rita Z, and Nora D Volkow. 2002. 'Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex', American Journal of Psychiatry, 159: 1642-52.

Gu, Shi, Richard F Betzel, Marcelo G Mattar, Matthew Cieslak, Philip R Delio, Scott T Grafton, Fabio Pasqualetti, and Danielle S Bassett. 2017. 'Optimal trajectories of brain state transitions', Neuroimage, 148: 305-17.

Gu, Shi, Fabio Pasqualetti, Matthew Cieslak, Qawi K Telesford, Alfred B Yu, Ari E Kahn, John D Medaglia, Jean M Vettel, Michael B Miller, and Scott T Grafton. 2015. 'Controllability of structural brain networks', Nature communications, 6: 8414.

Hahn, Tim, Nils R Winter, Jan Ernsting, Marius Gruber, Marco J Mauritz, Lukas Fisch, Ramona Leenings, Kelvin Sarink, Julian Blanke, and Vincent Holstein. 2023.

'Genetic, individual, and familial risk correlates of brain network controllability in major depressive disorder', Molecular Psychiatry, 28: 1057-63.

Hansen, Justine Y, Golia Shafiei, Ross D Markello, Kelly Smart, Sylvia ML Cox, Martin Nørgaard, Vincent Beliveau, Yanjun Wu, Jean-Dominique Gallezot, and Étienne Aumont. 2022. 'Mapping neurotransmitter systems to the structural and functional organization of the human neocortex', Nature neuroscience, 25: 1569-81.

He, Teng, Wenwen Chen, Yu Fan, Xing Xu, Hao Guo, Nanqin Li, Xue Lu, Feifei Ge, and Xiaowei Guan. 2022. 'A novel cholinergic projection from the lateral parabrachial nucleus and its role in methamphetamine-primed conditioned place preference', Brain Communications, 4: fcac219.

He, Xiaosong, Lorenzo Caciagli, Linden Parkes, Jennifer Stiso, Teresa M Karrer, Jason Z Kim, Zhixin Lu, Tommaso Menara, Fabio Pasqualetti, and Michael R Sperling. 2022. 'Uncovering the biological basis of control energy: structural and metabolic correlates of energy inefficiency in temporal lobe epilepsy', Science Advances, 8: eabn2293.

Howell, Leonard L, and Kathryn A Cunningham. 2015. 'Serotonin 5-HT2 receptor interactions with dopamine function: implications for therapeutics in cocaine use disorder', Pharmacological reviews, 67: 176-97.

Huang, Yuefeng, Ahmet O Ceceli, Greg Kronberg, Sarah King, Pias Malaker, Muhammad A Parvaz, Nelly Alia-Klein, Eric L Garland, and Rita Z Goldstein. 2023. 'Association of Cortico-Striatal Engagement During Cue Reactivity, Reappraisal, and Savoring of Drug and Non-Drug Stimuli With Craving in Heroin Addiction', American Journal of Psychiatry: appi. ajp. 20220759.

Jayanthi, Subramaniam, Atul P Daiwile, and Jean Lud Cadet. 2021. 'Neurotoxicity of methamphetamine: Main effects and mechanisms', Experimental neurology, 344: 113795.

Karrer, Teresa M, Jason Z Kim, Jennifer Stiso, Ari E Kahn, Fabio Pasqualetti, Ute Habel, and Danielle S Bassett. 2020. 'A practical guide to methodological considerations in the controllability of structural brain networks', Journal of neural engineering, 17: 026031.

Keiflin, Ronald, and Patricia H Janak. 2015. 'Dopamine prediction errors in reward learning and addiction: from theory to neural circuitry', Neuron, 88: 247-63.

Kelley, William M, Dylan D Wagner, and Todd F Heatherton. 2015. 'In search of a human self-regulation system', Annual review of neuroscience, 38: 389-411.

Koban, Leonie, Tor D Wager, and Hedy Kober. 2023. 'A neuromarker for drug and food craving distinguishes drug users from non-users', Nature neuroscience, 26: 316-25.

Kohno, Milky, Laura E Dennis, Holly McCready, and William F Hoffman. 2022. 'Dopamine dysfunction in stimulant use disorders: Mechanistic comparisons and implications for treatment', Molecular Psychiatry, 27: 220-29.

Li, Qiang, Wei Li, Hanyue Wang, Yarong Wang, Yi Zhang, Jia Zhu, Ying Zheng, Dongsheng Zhang, Lina Wang, and Yongbin Li. 2015. 'Predicting subsequent relapse by drug-related cue-induced brain activation in heroin addiction: an event-related functional magnetic resonance imaging study', Addiction biology, 20: 968-78.

Luppi, Andrea I, S Parker Singleton, Justine Y Hansen, Danilo Bzdok, Amy Kuceyeski, Richard F Betzel, and Bratislav Misic. 2023. 'Transitions between cognitive topographies: contributions of network structure, neuromodulation, and disease', bioRxiv.

Mahadevan, Arun S, Eli J Cornblath, David M Lydon-Staley, Dale Zhou, Linden Parkes, Bart Larsen, Azeez Adebimpe, Ari E Kahn, Ruben C Gur, and Raquel E Gur. 2023. 'Alprazolam modulates persistence energy during emotion processing in first-degree relatives of individuals with schizophrenia: a network control study', Molecular Psychiatry: 1-10.

Markello, Ross D, and Bratislav Misic. 2021. 'Comparing spatial null models for brain maps', Neuroimage, 236: 118052.

Miller, Earl K, and Jonathan D Cohen. 2001. 'An integrative theory of prefrontal cortex function', Annual review of neuroscience, 24: 167-202.

Müller, Christian P, and Judith R Homberg. 2015. 'The role of serotonin in drug use and addiction', Behavioural brain research, 277: 146-92.

O'Brien, Charles P, Anna Rose Childress, Ronald Ehrman, and Steven J Robbins. 1998. 'Conditioning factors in drug abuse: can they explain compulsion?', Journal of psychopharmacology, 12: 15-22.

Owens, Max M, Sabrina K Syan, Michael Amlung, Steven RH Beach, Lawrence H Sweet, and James MacKillop. 2019. 'Functional and structural neuroimaging studies of delayed reward discounting in addiction: A systematic review', Psychological Bulletin, 145: 141.

Parkes, Linden, Jason Z Kim, Jennifer Stiso, Monica E Calkins, Matthew Cieslak, Raquel E Gur, Ruben C Gur, Tyler M Moore, Mathieu Ouellet, and David R Roalf. 2022. 'Asymmetric signaling across the hierarchy of cytoarchitecture within the human connectome', Science Advances, 8: eadd2185.

Parkes, Linden, Tyler M Moore, Monica E Calkins, Matthew Cieslak, David R Roalf, Daniel H Wolf, Ruben C Gur, Raquel E Gur, Theodore D Satterthwaite, and Danielle S Bassett. 2021. 'Network controllability in transmodal cortex predicts positive psychosis spectrum symptoms', Biological Psychiatry, 90: 409-18.

Salo, Ruth, Stefan Ursu, Michael H Buonocore, Martin H Leamon, and Cameron Carter. 2009. 'Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study', Biological Psychiatry, 65: 706-09.

Schultz, Wolfram, Léon Tremblay, and Jeffrey R Hollerman. 2000. 'Reward processing in primate orbitofrontal cortex and basal ganglia', Cerebral cortex, 10: 272-83.

Sharp, BM. 2017. 'Basolateral amygdala and stress-induced hyperexcitability affect motivated behaviors and addiction', Translational psychiatry, 7: e1194-e94.

Shine, James M. 2019. 'Neuromodulatory influences on integration and segregation in the brain', Trends in cognitive sciences, 23: 572-83.

———. 2023. 'Neuromodulatory control of complex adaptive dynamics in the brain', Interface focus, 13: 20220079.

Stiso, Jennifer, Ankit N Khambhati, Tommaso Menara, Ari E Kahn, Joel M Stein, Sandihitsu R Das, Richard Gorniak, Joseph Tracy, Brian Litt, and Kathryn A Davis. 2019. 'White matter network architecture guides direct electrical stimulation through optimal state transitions', Cell reports, 28: 2554-66. e7.

Thomas Yeo, BT, Fenna M Krienen, Jorge Sepulcre, Mert R Sabuncu, Danial Lashkari, Marisa Hollinshead, Joshua L Roffman, Jordan W Smoller, Lilla Zöllei, and Jonathan R Polimeni. 2011. 'The organization of the human cerebral cortex estimated by intrinsic functional connectivity', Journal of neurophysiology, 106: 1125-65.

Tranel, Daniel. 1994. 'Development of the concept of'executive function'and its relationship to the frontal lobes', Handbook of neuropsychology.

United Nations Office on Drugs and Crime. 2023. 'United Nations Office on Drugs and Crime. World drug report'. https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2023.html.

Vafaie, Nilofar, and Hedy Kober. 2022. 'Association of drug cues and craving with drug use and relapse: a systematic review and meta-analysis', JAMA psychiatry.

Váša, František, and Bratislav Mišić. 2022. 'Null models in network neuroscience', Nature Reviews Neuroscience, 23: 493-504.

Vos de Wael, Reinder, Oualid Benkarim, Casey Paquola, Sara Lariviere, Jessica Royer, Shahin Tavakol, Ting Xu, Seok-Jun Hong, Georg Langs, and Sofie Valk. 2020. 'BrainSpace: a toolbox for the analysis of macroscale gradients in neuroimaging and connectomics datasets', Communications biology, 3: 103.

Wallis, Jonathan D, and Earl K Miller. 2003. 'Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task', European Journal of Neuroscience, 18: 2069-81.

Wang, Yarong, Jia Zhu, Qiang Li, Wei Li, Ning Wu, Ying Zheng, Haifeng Chang, Jiajie Chen, and Wei Wang. 2013. 'Altered fronto-striatal and fronto-cerebellar circuits in heroin-dependent individuals: a resting-state FMRI study', PloS one, 8: e58098.

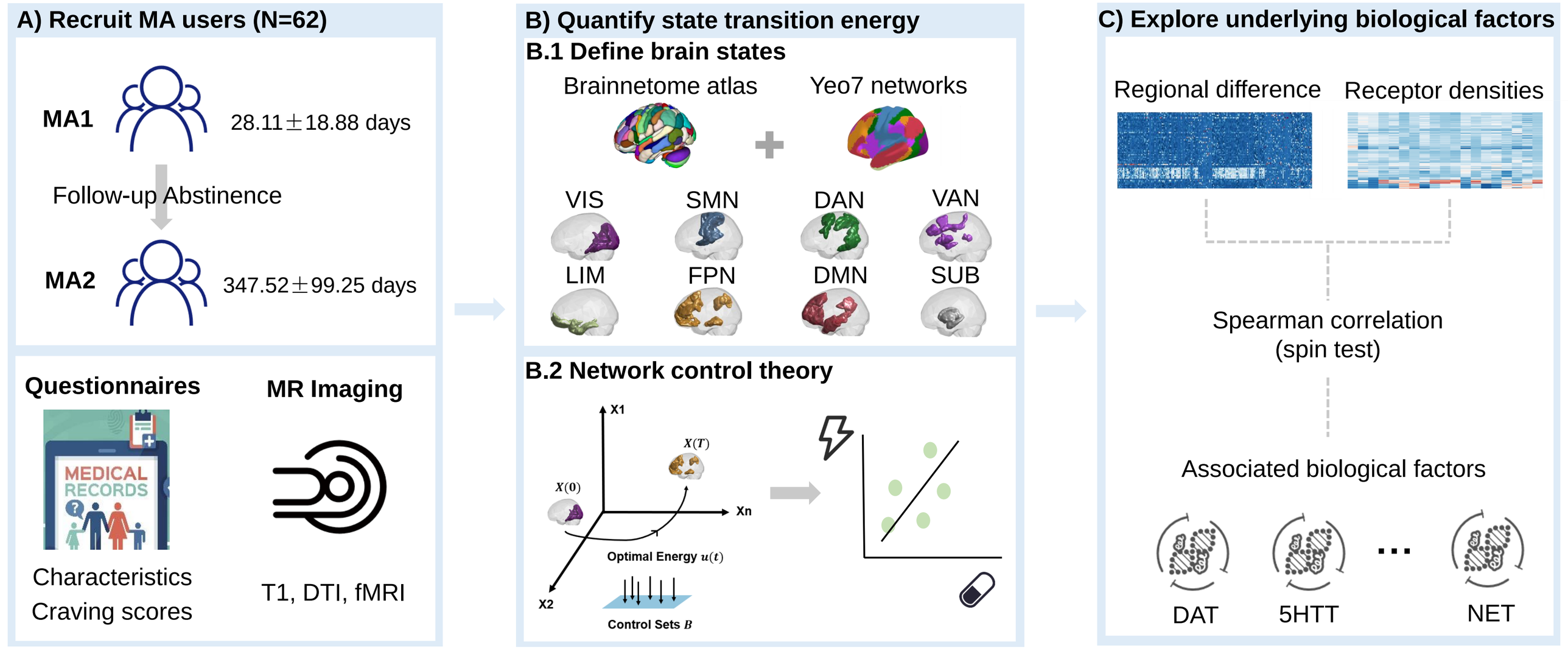
Weinshenker, David, and Jason P Schroeder. 2007. 'There and back again: a tale of norepinephrine and drug addiction', Neuropsychopharmacology, 32: 1433-51.

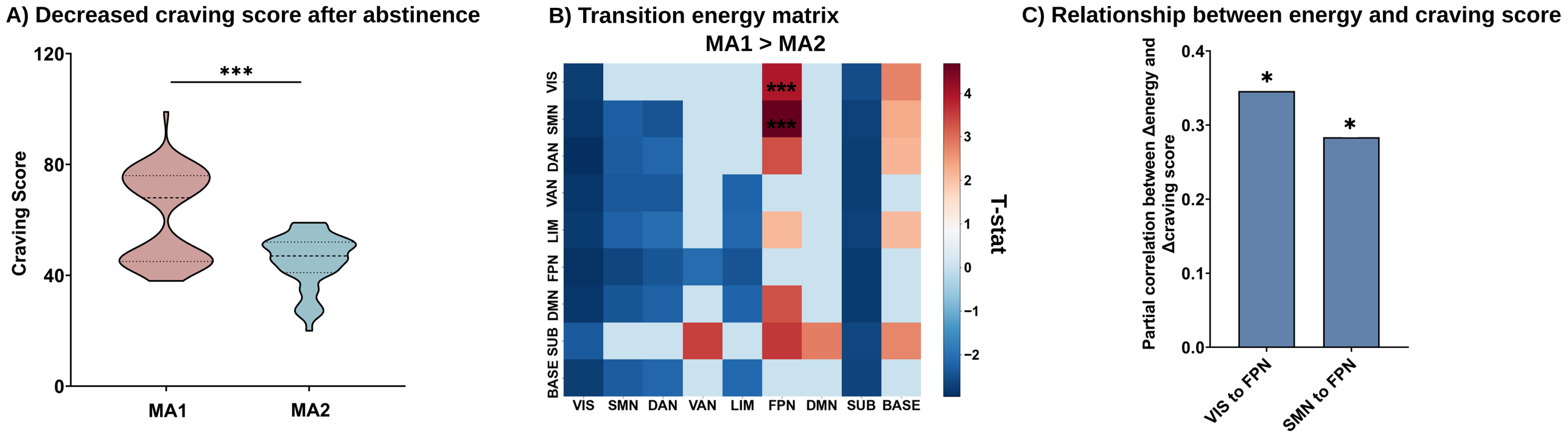
Williams, Mark J, and Bryon Adinoff. 2008. 'The role of acetylcholine in cocaine addiction', Neuropsychopharmacology, 33: 1779-97.

Wilson, Stephen J, Michael A Sayette, and Julie A Fiez. 2004. 'Prefrontal responses to drug cues: a neurocognitive analysis', Nature neuroscience, 7: 211-14.

Yuen, Jason, Abbas Z Kouzani, Michael Berk, Susannah J Tye, Aaron E Rusheen, Charles D Blaha, Kevin E Bennet, Kendall H Lee, Hojin Shin, and Jee Hyun Kim. 2022. 'Deep brain stimulation for addictive disorders—where are we now?', Neurotherapeutics, 19: 1193-215.

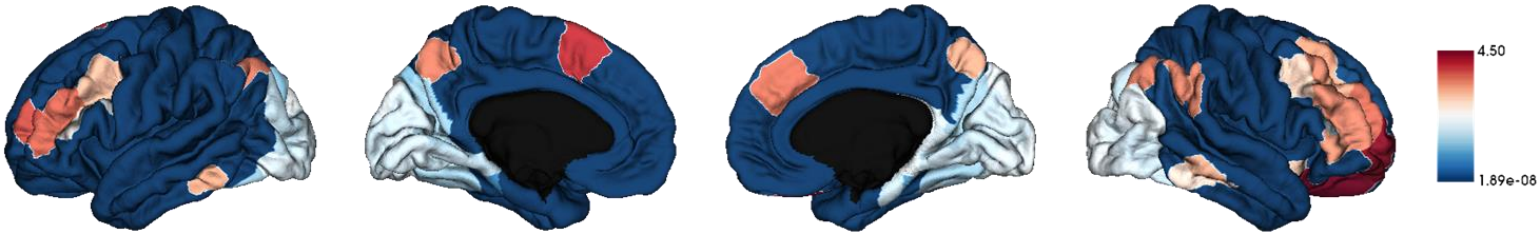
Zhao, Siqi, Xujiang Chen, Jingwen Huang, Xuena Zhang, Jilai Sun, and Li Yang. 2022. 'Point-of-care testing of methylamphetamine with a portable optical fiber immunosensor', Analytica Chimica Acta, 1192: 339345.


A) Recruit MA users (N=62)
MA1
28.11±18.88 days
Follow-up Abstinence
MA2
347.52±99.25 days
Questionnaires
MEDICAL RECORDS
Characteristics
Craving scores
MR Imaging
T1, DTI, fMRI
B) Quantify state transition energy
B.1 Define brain states
Brainnetome atlas
Yeo7 networks
VIS
SMN
DAN
VAN
LIM
FPN
DMN
SUB
B.2 Network control theory
X1
X(T)
X(0)
Xn
Optimal Energy u(t)
X2
Control Sets B
C) Explore underlying biological factors
Regional difference
Receptor densities
Spearman correlation
(spin test)
Associated biological factors
DAT
5HTT
...
NET

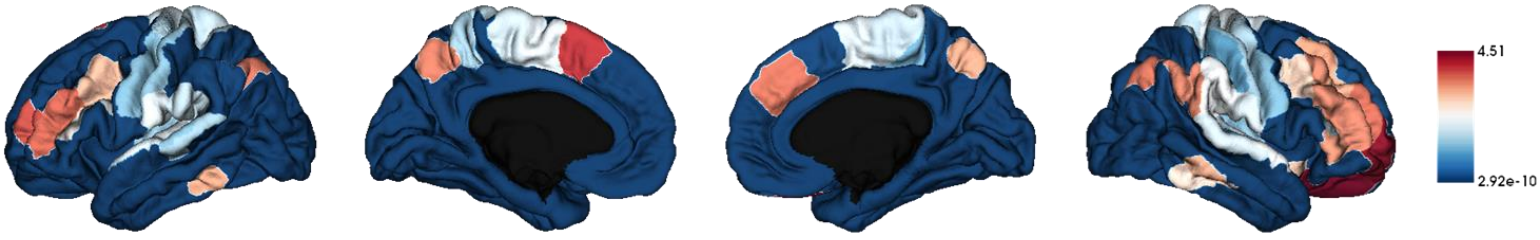

A) Decreased craving score after abstinence
Craving Score
120
80
40
0
***
MA1
MA2
B) Transition energy matrix
MA1 > MA2
VIS
SMN
DAN
VAN
LIM
FPN
DMN
SUB
BASE
***
***
T-stat
4
3
2
1
0
−1
−2
C) Relationship between energy and craving score
Partial correlation between Δenergy and Δcraving score
0.4
0.3
0.2
0.1
0.0
*
*
VIS to FPN
SMN to FPN

A) Control impact of brain regions in MA1

VIS to FPN

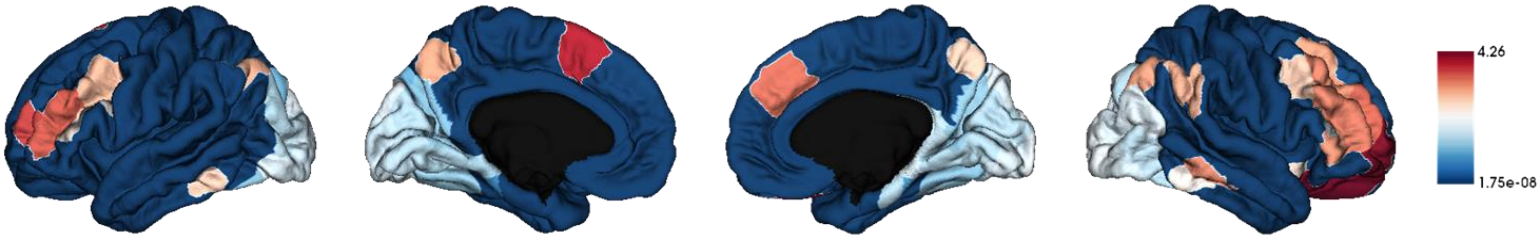


SMN to FPN

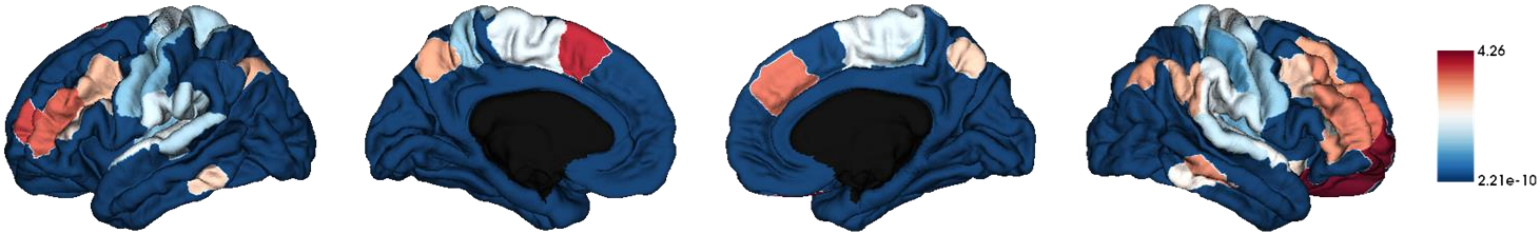


B) Control impact of brain regions in MA2

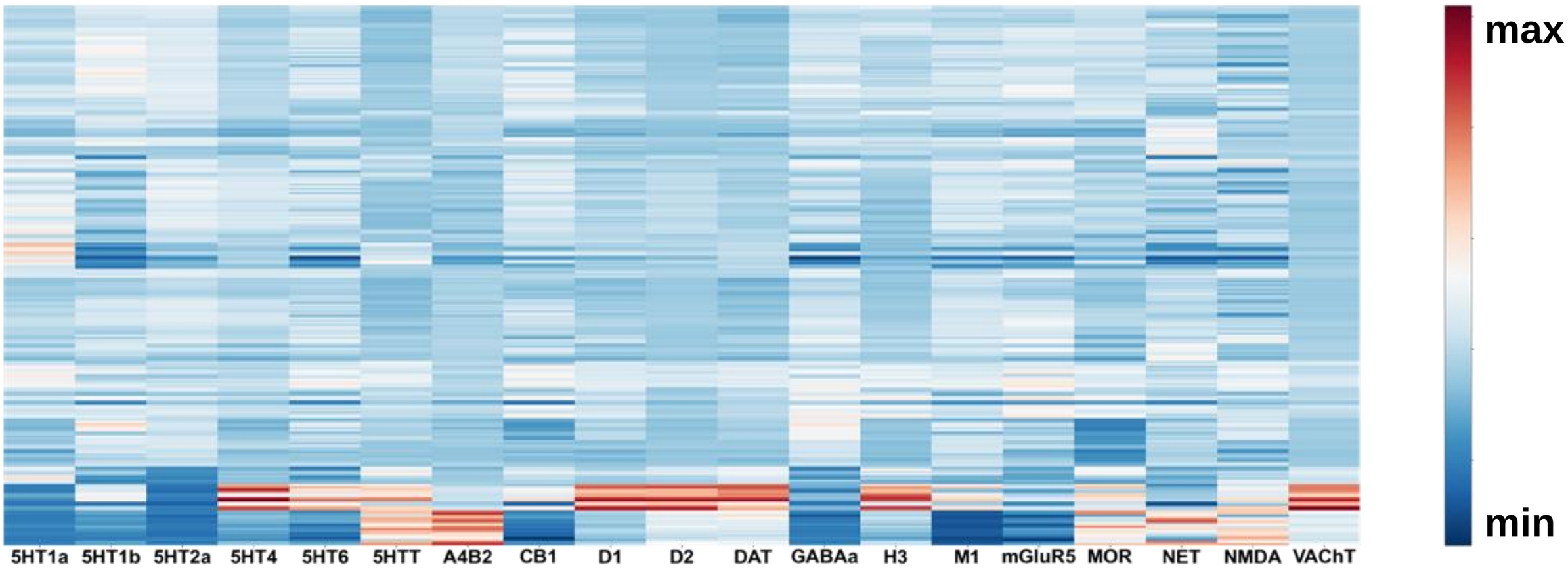
VIS to FPN



SMN to FPN



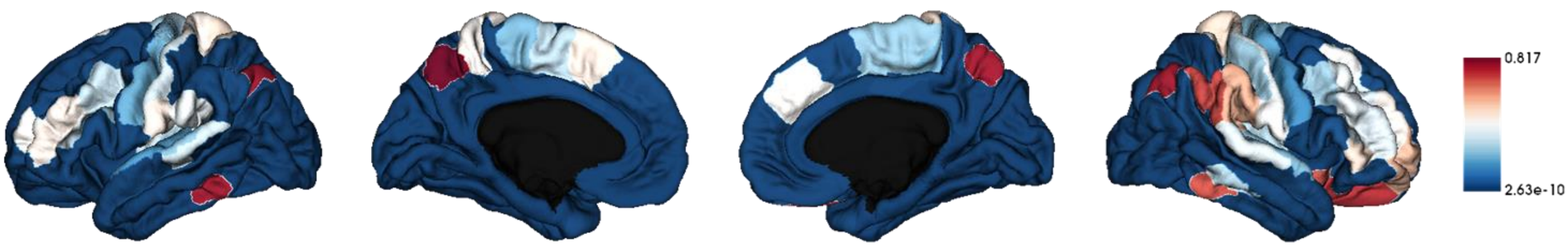
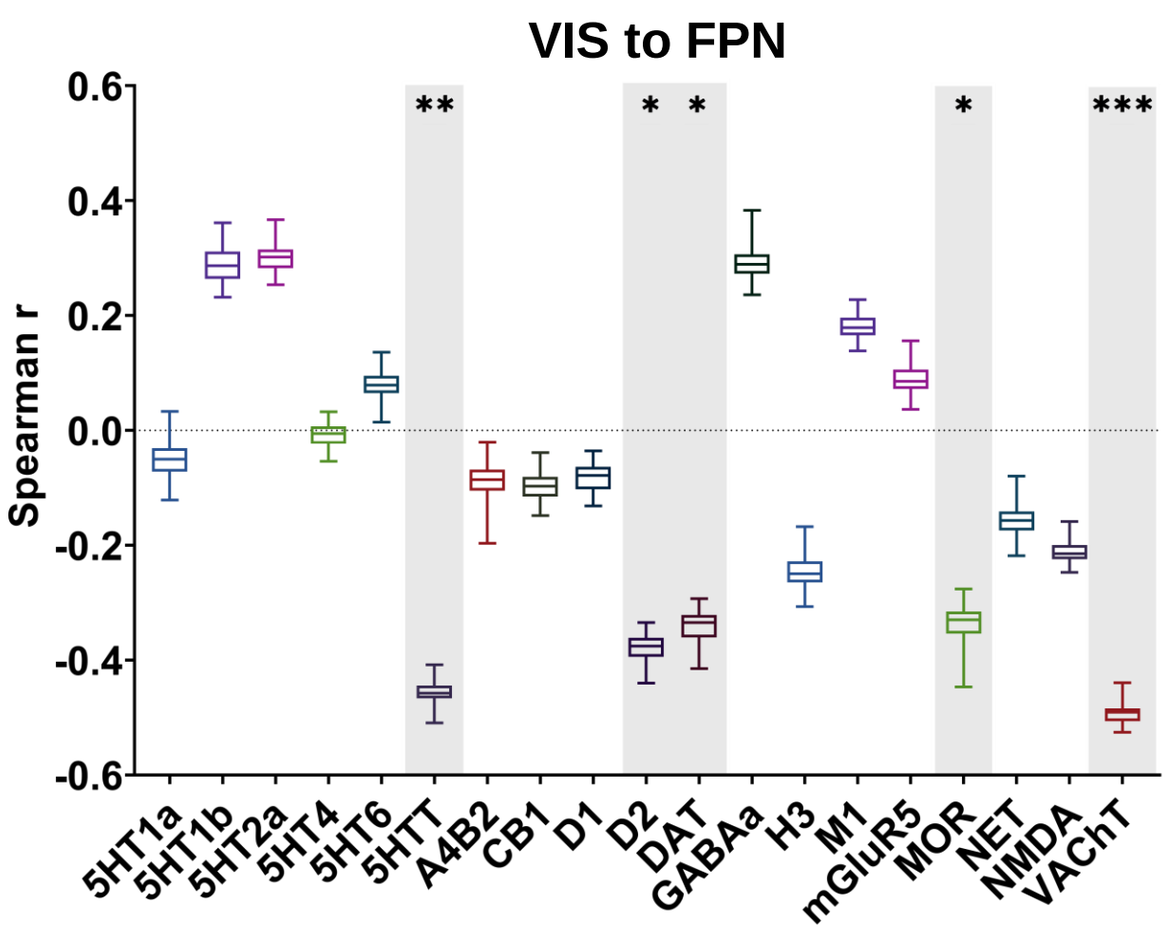
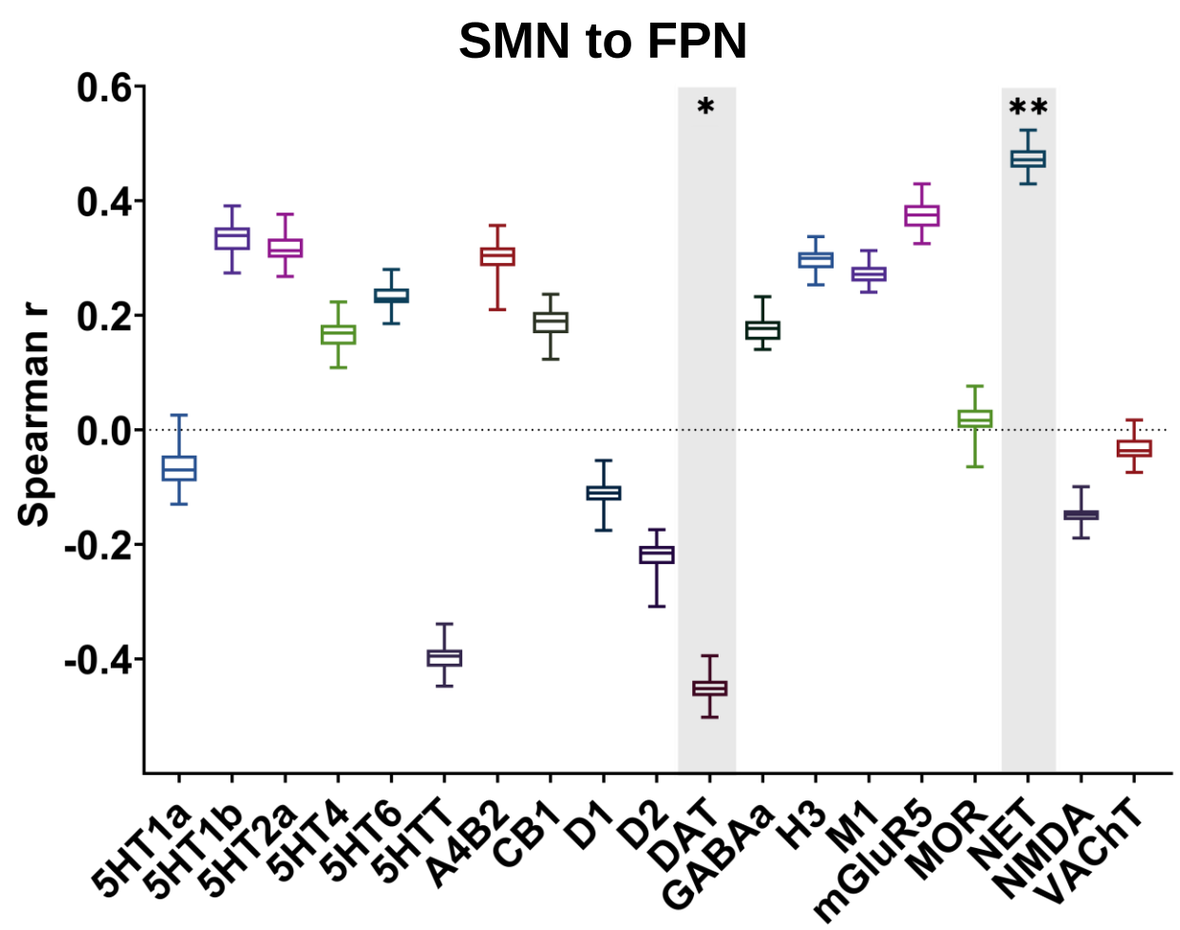
A) PET receptor densities



B) Alterations in control impact

VIS to FPN

SMN to FPN



C) Relationship between receptor density and alterations in control impact