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Meysam Siyah Mansoory, Vahid Farnia

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Resting-state effective connectivity in the motive circuit of methamphetamine users: a case controlled fMRI study

Meysam Siyah Mansoory, Vahid Farnia* vahidfarnia@yahoo.com

Substance Abuse Prevention Research Center, Health institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

***Corresponding author.**

ABSTRACT

Methamphetamine (MA) and other psychostimulants target the motive circuit of the brain, which is involved in reward, behavioral sensitization, and relapse to drug-seeking/taking behavior. In spite of this fact, the data regarding the effective connectivity (EC) in this circuit among MA users is scarce. The present study aimed to assess resting-state EC in the motive circuit of MA users during abstinence using the fMRI technique. Seventeen MA users after abstinence and 18 normal controls were examined using a 3T Siemens fMRI scanner. After extracting time series of the motive circuit, EC differences in the motive circuit were analyzed using dynamic causal modeling (DCM). The findings revealed that abstinent MA users had an enhanced EC from the prefrontal cortex (PFC) to the ventral palladium (VP) (PFC→VP) and on the mediodorsal thalamus (MD) self-loop (MD→MD), but they showed a decreased connectivity on the VP self-loop (VP→VP) compared to healthy controls. The findings suggest that abstinent MA users may suffer from a limited pathology in connectivity within the motive circuit involved in reward, behavioral sensitization, and relapse. The enhanced PFC→VP seems to be a compensatory mechanism to control or regulate the subcortical regions involved in reward and behavioral sensitization. Furthermore, the enhanced connectivity on the MD self-loop and the decreased connectivity on the VP self-loop in abstinent MA users may, at least partially, affect the output of the limbic system, which can be seen in the behavioral sensitization and relapse processes. Nonetheless, further investigation in this area is strongly recommended to elucidate the exact mechanisms involved.

Keywords: Effective connectivity; methamphetamine; motive circuit; behavioral sensitization

1. Introduction

Using methamphetamine (MA), a potent psychostimulant drug, is increasingly recognized as a worldwide public health concern [1]. MA is known as the most popular psychostimulant in the world with an estimated 24 million users worldwide [1]. MA affects synaptic transmission in the mesocorticolimbic system of the brain, which may, in part, be responsible for producing its hedonic and rewarding effects [2]. Indeed, MA and other drugs of abuse "hijack" the neurobiological mechanisms involved in memory, reward, and behavioral sensitization, thereby leading drug abusers to relapse to drug-seeking/taking behavior, even after a long drug-free period [3-6]. Acute use or low doses of MA may enhance alertness, concentration, and energy, while MA induces neurotoxicity, cognitive impairment, and pathological effects on mood upon chronic use or at its higher doses [2, 7, 8].

Repeated, intermittent exposure to MA and other psychostimulants can lead to reverse tolerance, known as behavioral sensitization, which is defined as a progressive and persistent enhancement of the locomotor-activating effects of the drug [9, 10]. Such kind of behavioral plasticity in a collection of interconnected limbic nuclei, known as the motive circuit of the brain, may result in relapse to drug-seeking/taking behavior [11]. The most known neural circuitry involved in behavioral sensitization includes the dopaminergic (DA) pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and the glutamatergic pathway from the prefrontal cortex (PFC) to the NAc, which play an important role in relapse to drug use [6]. Nonetheless, behavioral sensitization may involve more complicated neural mechanisms which should be considered for further investigations.

Previous neuroimaging studies using functional magnetic resonance imaging (fMRI) have reported that MA affects the neural circuits involved in reward and behavioral sensitization [12, 13]; however, far too little attention has been paid to assessing effective connectivity (EC) in the motive circuit of MA users. Evaluating EC can provide a better understanding of the causal

influence one brain area exerts over another [14], and, therefore, provide valuable information regarding the neural circuits involved in drug addiction and relapse. This study, therefore, set out to assess resting-state EC in the motive circuit of MA users during abstinence, including the VTA, NAc, mediodorsal thalamus (MD), ventral pallidum (VP), and PFC, using the fMRI technique and compare the results with healthy controls. It is hypothesized that EC changes within the motive circuit of abstinent MA users compared with healthy controls might participate in the psychopathology of addictive behaviors including relapse to drug-seeking/taking.

2. Materials and methods

2.1. Subjects

In this study, 18 right-handed male subjects ranging in age from 23 to 46 years were selected as the control group from a local community. In addition, 17 right-handed male subjects with a history of MA abuse ranging from 22 to 39 years of age were selected as the case group during their first four weeks of drug abstinence. The subjects were selected from an addiction treatment center in Verdij, a rural area near Tehran, Iran, owned by the Rebirth Society Organization (RSO) and a nonprofit charity. The mean and standard deviation of age in the MA and control groups was 30.52 ± 4.57 and 31.67 ± 7.98, respectively (Table 1). Table 1 shows the demographic data and history of drug abuse of the abstinent MA users examined in this study. MA dependence was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (fifth edition). The dominant use of MA was at least 6 months. The subjects with a history of serious psychiatric or neurological disorders, surgery, or brain damage, based on their medical records and examinations, were excluded from the study. The control group included normal healthy subjects.

This research was approved by the Medical Ethics Committee of Kermanshah University of Medical Sciences (code no. IR.KUMS.REC.1397.994). Before imaging, a general description of the imaging process was given to the participants. All subjects were able to understand and follow the imaging steps. In accordance with the Helsinki Declaration, written consent was received from the participants before the MRI scan was begun.

2.2. Data acquisition

The data was collected at the Medical Imaging Center of Imam Khomeini Hospital in Tehran using a Siemens Tim Trio 3-Tesla scanner. For rest fMRI data, echo-planar imaging (EPI) with the

following parameters was performed to obtain T2-weighted images: TR = 3000 ms, TE = 30 ms, flip angle = 90, matrix = 64×64, FOV = 192 mm2, thickness/gap = 4.5 mm, 22 whole-brain-covering axial slices, and 240 volumes obtained in about 12 min. In addition, T1-weighted images (TR = 1800 ms, TE = 30 ms, flip angle = 90, matrix = 256×256, FOV = 230×230 mm2, thickness = 1.0 mm, and 190 sagittal slices) were taken to capture 3D high resolution images. The whole brain was covered with 240 volumes in 12 minutes. Participants were asked to close their eyes, keep calm, not to think about anything systematically, and not to sleep. None of the lights in the scanning room were illuminated during rest fMRI imaging.

2.3. Data preprocessing

The SPM12 toolbox was used to complete all of the preprocessing steps, including slice timing, head motion correction, normalization, co-registration, and filtering. Initially, for all data, the skull was eliminated and the brain cortex was extracted. In the next step, ten original frames were set aside in functional images for signal balancing in order to stabilize the magnetic field of the imaging machine and allow the participants to adapt to the scanning noise. Consequently, the time correction of the scans (correcting the difference between the times of receiving the slideshows) and the correction of the head motion (realignment) was performed by matching different scans. (The data was excluded for studying if the patient's head motion was greater than 3 mm.) Subsequently, anatomical image adaptation with functional images (co-registration) as well as normalization of images (data transfer to a standard Montreal Neurological Institute (MNI) space) were done. Finally, since blood changes in the brain are gradual and slow, a low pass filter was used to remove noise with high variations on functional images using a 6 mm wide Gaussian filter (smoothing).

2.4. Effective connectivity analysis

Dynamic causal modeling (DCM) is aimed to determine the effective relationship between brain regions by analyzing fMRI data. As a biophysical and neurobiological model, DCM uses basic data to select a model [15], and then models the effect of nodes by nonlinear mechanisms using blood-related changes at nodes. In this study, a DCM model was used to investigate an effective motive circuit. The steps of the DCM analysis are shown in Figure 1.

2.5. ROIs selection

After data preprocessing, to calculate DCM, the anatomical regions of interest (ROI) in the brain should be determined to clarify the relationships of these areas. Given the heavy computational constraints in DCM analysis, many ROIs cannot be determined practically. In the current study, some components of the motive circuit which are involved in reward, motivation, and sensitization, including VTA, NAc, MD, VP, and PFC, were assessed as shown in Figure 2 and Table 2.

2.6. Extraction of time series

The time series represents the changes in blood hemodynamics (variation of blood-oxygen-level dependence (BOLD) during imaging. According to Biswal et al., the frequency range containing useful information for BOLD signal lies within the low frequency range of 0.08 to 0.01 Hz [16]. Thus, using Fourier transform and low frequency analysis, a low frequency mapping was extracted for the brain [16]. After specifying the areas (ROIs), the time series (BOLD changes in time) of each area were extracted using low frequency oscillation analysis, and these time series were used as inputs for model estimation.

2.7. Estimating DCM model

The DCM nonlinear method was used to understand the relationship between the selected brain regions associated with behavioral sensitization utilizing the DCM model in the SPM12b toolbox of MATLAB software. The model depicted in Figure 2 was used to determine the cerebral effect graph associated with the motive circuit. Among the existing models, the DCM model has been proven to be optimum based on the Bayesian method. This method of selecting the optimum model proposed by Friston et al. is widely used for neuroscience research [17].

2.8. Estimation of DCM model and group analysis

To determine the EC graph with DCM, the neural state equations model was used. The brain connection network was estimated for all people in both control and abstinent MA groups using the DCM model, and brain EC were extracted for all individuals. The false discovery rate (FDR) method with $p = 0.05$ was used for group analysis. To compare the brain network associated with behavioral sensitization between the two groups, the DCM connection power between the two groups was compared using the Bayesian parameter averaging (BPA) method [18]. All analyses of EC in MATLAB software were calculated using SPM12.

2.9. Statistical analysis

Statistical tests were used to examine the significance of the difference between the power of EC through brain regions among control subjects and abstinent MA users. The normal EC distribution of each area in healthy controls and abstinent MA individuals was determined using the Kolmogorov-Smirnov test at a significant level of $\alpha = 0.05$. If the distribution was normal, the Student's t-test was used; if it was not normal, the Mann-Whitney test was used at a significant level of $\alpha = 0.05$. To visualize the difference in EC between different areas of the brains of subjects in the two groups, a box diagram of the results was used.

3. Results

The U Mann-Whitney test revealed no significant differences between the normal and addict groups regarding demographic characteristics ($p > 0.05$). Data obtained from the two groups was extracted using the DCM model after preprocessing and extracting the time series from the studied areas in the motive circuit, and the effect values between these brain regions were calculated. Optimized DCMs for the healthy and abstinent MA groups are graphically displayed in Figure 3. As illustrated, the brain connections between the regions obtained by the model differ between the two groups in terms of amount, declining effect, and increase in number of connections, which indicates the effect of the material on the brain connections related to the motive circuit.

After estimating DCM model parameters and determining the relationships between the components of the motive circuit, statistical analysis was performed to compare EC between the brain regions of healthy and abstinent MA individuals. As shown in Figure 4, the results demonstrated that the levels of EC in some areas were different between the healthy and MA groups.

The Kolmogorov-Smirnov test revealed normal distribution of EC across all areas except for PFC→VP, PFC→PFC, and PFC→VTA-N which were normal. The *p*-value of the normality test for EC in these three connections was 0, 0.049, and 0, respectively, but in the remaining connections, it was more than 0.05. Therefore, to compare dynamic relationships in these three areas, the Mann-Whitney test was used, and in other areas the Student's t-test was used. All *p*-values of the normality test (for all connections) are shown in Figure 5. The results indicated that the mean EC in healthy individuals and abstinent MA users were significantly different in the

VP→VP, MD→MD, and PFC→VP connections ($p = 0.009$, $p = 0.001$, and $p = 0.008$, respectively), but no other connection differed significantly between the two groups ($p > 0.05$). Thus, the results indicated that connectivity on the VP self-loop (VP→VP) was higher in the healthy group than in MA users, while connectivity from PFC to VP (PFC→VP) and on the MD self-loop (MD→MD) was higher in the MA group than in the healthy group.

4. Discussion

It has been well established that MA and other drugs of abuse target the reward and motive circuits of the brain, thereby producing hedonic effects and sensitization which may increase the risk for relapse to drug abuse. Nevertheless, investigations into the effects of MA on EC in neural circuits involved in reward and motivation are limited. To the best of our knowledge, the current study is the first to assess resting-state EC in the motive circuit of abstinent MA users. The findings revealed that abstinent MA users had enhanced EC from PFC to VP (PFC→VP) and on the MD self-loop (MD→MD), but they showed a decreased connectivity on the VP self-loop (VP→VP) compared with healthy controls. These results provide a novel insight into the effects of amphetamine-like psychostimulants on EC in the motive circuit which is involved in behavioral sensitization and relapse.

Drug addiction affects neurotransmission in the brain circuits involved in reward and motivation and promotes neural sensitization [19]. It has been reported that even low doses of amphetamines can promote sensitization in the mesolimbic system of individuals with no history of drug abuse [20]. The motive circuit plays a key role in translating environmental or pharmacological stimuli into behavioral responses [5]. Lesions of the motive circuit components, including NAc, amygdala, MD, or VP, may attenuate conditioned responses for food or psychostimulants [12-18]. The results of the current study also showed some changes in connectivity strengths within the motive circuit between abstinent MA users and healthy controls. In contrast to FC, EC in the motive circuit of MA users has not been previously examined. Using resting-state FC in abstinent MA users, connectivity has been shown to be heightened within the mesocorticolimbic system and between midbrain and other parts of the brain, including the hippocampus, amygdala, striatum, insula, and PFC [21]. Such strengthened connectivity has been reported to produce psychostimulant sensitization [22]. It should, however, be noted that the current results indicated that the connectivity from VTA and

NAc to PFC and vice versa was not significantly different between MA users and normal controls; nonetheless, the MA users showed a more enhanced EC from PFC to VP than the controls.

Previous studies have reported that MA users generally show lower cortical but higher striatal gray-matter volumes compared with normal controls. However, along with an increase in the abstinence period (by 3-4 months), they exhibit increases in the volumes of some cortical and subcortical regions [23-25]. In other words, along with increases in the period of abstinence, cortical gray-matter deficits and reduced cortical connectivity are reversed in MA users [26]. Such findings indicate that MA abuse may result in abnormal connectivity between cortical and subcortical regions of the brain, thereby leading to deficits in executive function and control over drug seeking/taking, which can be reversed as the period of abstinence increases [26]. It may, therefore, be reasonable to assume that the strengthened connectivity of PFC in abstinent users, as observed in the current study (form PFC to VP), may be a compensatory mechanism to control/regulate the subcortical regions involved in reward and behavioral sensitization [27]. Another possible mechanism for the enhanced PFC-VP connectivity seen in the current study might be the reduced inhibitory modulation of dopaminergic neurotransmission in the PFC, which may result in an increased glutamate transmission from the PFC to subcortical regions. This is seen in sensitized animals [28-30].

The motive circuit projects information from the limbic system to motor (pyramidal and extrapyramidal) pathways, and therefore, VP plays an important role in producing behavioral sensitization induced by the drugs of abuse [5]. It is stated that behavioral sensitization to psychostimulants increases GABA release in the VP, which may attenuate the GABAergic efferents to the VTA and MD thalamus [5]. VP also projects the corticolimbic projections back to PFC by way of the MD nucleus of the thalamus [5]. Because of such connectivity, the VP is referred to as the final common limbic pathway for reward signals in the brain [31]. In the current study, an enhanced connectivity was observed on the MD self-loop (MD-MD), but reduced connectivity was observed on the VP self-loop (VP-VP) in MA users compared with the healthy controls. Such findings are interesting but rather difficult to explain as no changes were observed in the connectivity between the nuclei. It seems, however, that the decreased VP-VP connectivity may, at least partially, be responsible for the anhedonia and lack of motivation which are seen in withdrawn/abstinent drug users. Because the motivational and hedonic signals converge in the VP and the VP projects the limbic outputs to both the PFC and the motor system [5, 31, 32], the

decreased VP-VP connectivity seen in the current study may be a possible mechanism for reduced mood in abstinent MA users. It may, therefore, be hypothesized that such anhedonia in abstinent MA users can drive them to relapse to drug seeking/taking (to avoid the lack of motivation).

Some other important issues should be addressed here. It is important to point out that the abstinent MA users examined in this study were not pure MA users, as previously described. Such condition may have affected EC in the current study as factors other than MA use *per se* may change the abnormality in the structure of the brain [26]. It has, for example, been reported that smoking potentiates MA-induced gray-matter loss in cortical and subcortical regions of the brain [33]. Thus, the current findings cannot interpret the exact mechanisms involved as most of the MA users examined in this study also exhibited a history of other drug use, including cigarette, cocaine, opium, alcohol, and hashish. Furthermore, it should be mentioned that this study is the first to assess EC in the motive circuit of MA users, while FC in abstinent MA users has been examined in previous studies, as previously mentioned. Because this was a resting-state fMRI study, the results observed herein should only be interpreted for the resting, but not active, state of MA users. This means that further EC studies on MA users, for example, may perform cognitive tasks, which can be valuable. It should also be noted that the initiation of behavioral sensitization to drugs of abuse occurs due to the action of drugs on the VTA, while the expression of sensitization happens because of the action on NAc [6]. In contrast, no significant differences in EC were observed either within or between the VTA and NAc of abstinent MA users compared with the controls. It is also noteworthy that the durations of abstinence in the MA users of this study were not similar to each other. The mean abstinence period was 54.12 days with a maximum of 233 days and a minimum of 3 days. As mentioned before, deficits in volume and connectivity within and between various cortical regions of the brains of drug users will be reversed along with increases in the period of abstinence [26]. Finally, and importantly, several limitations may have affected the findings, including a small sample size and intrinsic limitations from matching the behavioral and demographic characteristics of the participants because of the unavailability of backgrounds for the subjects. Another important limitation of this study was that more than 5 nodes could not be used in EC analysis. However, a recent study has reported on a method with which it is possible to use more (up to 8) nodes to assess EC [34], albeit with challenges, including determining the optimal window selection. Nonetheless, it is worthy to point out that selecting 5 nodes is a standard way to examine EC. In other words, it is not necessary to examine more nodes in studies on the addiction-

related motive circuit. However, it is recommended that more than 5 nodes be assessed in future related studies. Such limitations mean that the current findings need to be interpreted cautiously. Furthermore, this research has thrown up many questions in need of further investigation.

5. Conclusion

Taken together, these findings indicate that abstinent MA users showed an enhanced EC from PFC to VP (PFC→VP) and on the MD self-loop (MD→MD), but they showed a decreased connectivity on the VP self-loop (VP→VP) compared with the healthy controls. The results seem to suggest that abstinent MA users suffer from a limited pathology in the connectivity within the motive circuit involved in reward, behavioral sensitization, and relapse. Now, it seems to be reasonable to hypothesize that EC changes within the motive circuit of abstinent MA users compared with healthy controls might play a role in the psychopathology of addictive behaviors, including relapse to drug-seeking/taking. The findings may also indicate that EC in abstinent MA users may depend on various factors, and the exact interpretations of behavior need to be studied. It seems that the enhanced PFC→VP connectivity observed in the current study may be a compensatory mechanism to control or regulate the subcortical regions involved in reward and behavioral sensitization. The results may also suggest that the enhanced connectivity on the MD self-loop (MD→MD) and the decreased connectivity on the VP self-loop (VP→VP) in abstinent MA users may, at least partially, affect the output of the limbic system, which can be seen in behavioral sensitization and relapse processes. In other words, since VP projects back the corticolimbic projections to PFC and also projects to motor pathways, the changes in the VP observed in this study seem to suggest that VP may affect motivational and behavioral responses in abstinent MA users. Furthermore, the decreased connectivity on the VP self-loop may also be interpreted as a possible mechanism for the lack of motivation in abstinent MA users. Considering the paucity of studies regarding EC in MA users, we believe that our findings could help achieve a better understanding of the pathophysiology of behavioral sensitization in this population. Finally, it is recommended that further research be undertaken in assessing EC in other brain circuits involved in drug addiction, assessing EC in the motive circuit and other networks while participants do cognitive tasks, etc.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Author Contributions

Meysam Siyah Mansoory and Vahid Farnia designed and performed the study. Bijan Pirnia, Meysam Siyah Mansoory, Maryam Behboudi, and Hamid Sharini assisted with preprocessing, data collection, and data analysis. Meysam Siyah Mansoory, Vahid Farnia, Mehdi Khodamoradi, and Mostafa Alikhani drafted the manuscript and revised it. All authors read and approved the final manuscript.

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Table 1

Demographic characteristics and history of drug abuse of the abstinent MA users examined in this study

Subject code	*Duration of abstinence*	*Duration of add.*	*Age*	*Education years*		**Opium abuse**	**Heroin abuse**	**Crystalline heroin abuse**	**Alcohol abuse**	**Hashish abuse**	**Cocaine abuse**	***Cigar and tobacco abuse***
1	233.00	4.5	34	16		1	0	1	1	1	1	1
2	50.00	6	36	12		0	0	0	0	0	0	0
3	210.00	4	31	16		0	0	0	0	0	0	0
4	3.00	0.5	28	16		0	0	0	0	0	0	0
5	69.00	2.5	28	14		0	0	0	0	0	0	0
6	7.00	5	32	9		1	1	1	1	1	1	1
7	11.00	2	36	9		0	0	0	0	0	0	0
8	210.00	3	26	12		1	1	1	1	1	0	1
9	20.00	1	33	16		1	1	1	1	1	0	1
10	12.00	3	35	7		1	0	0	1	1	0	1
11	13.00	4	30	8		1	1	0	1	1	0	1
12	19.00	2	39	12		1	1	1	1	1	0	1
13	10.00	2	27	12		1	0	1	1	1	0	1
14	18.00	5	27	12		1	1	1	1	1	0	1
15	8.00	7	30	12		1	1	1	1	1	0	1
16	10.00	4	22	9		0	0	0	1	1	1	1
17	17.00	4	25	12		1	1	1	1	1	1	1
Mean	54.12	3.5	30.52941	12	Sum	11	8	9	12	12	4	12
SD	79.8795	1.741049	4.570526	2.915476								

For the right columns, 0 represents no and 1 represents yes regarding history of drug abuse.

Table 2

MNI coordinates of ROIs

ROIs	**X**	**y**	**Z**
Ventral tegmental area (VTA)	0	-16	-7
Ventral pallidum (VP)	-22	-8	-2
Prefrontal cortex (PFC)	-1	49	-5
Nucleus accumbens (NAc)	-8	12	1
Mediodorsal thalamus (MD)	-4	-3	4

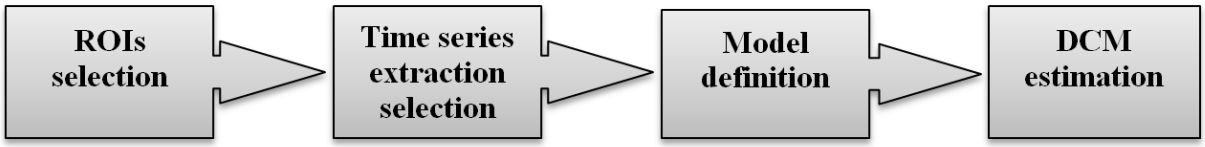

Figure 1: Stages of dynamic causal modeling model estimation. ROI, anatomical region of interest; DCM, dynamic causal modeling

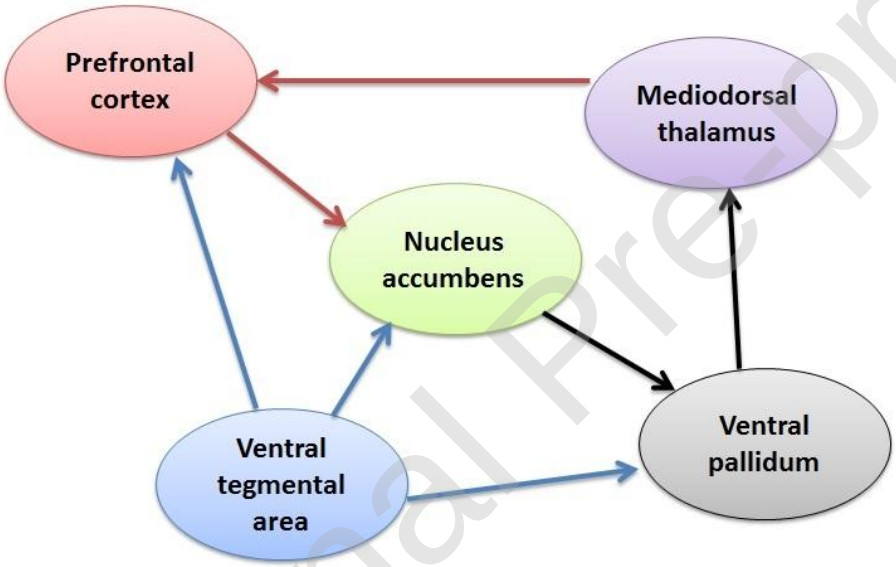

Figure 2: A schematic for selection of ROIs regarding the components of the motive circuit evaluated in this study. The red arrows represent glutamatergic pathways; blue arrows represent dopaminergic pathways; and black arrows represent GABAergic pathways. Other components of the motive circuit are not shown in the figure.

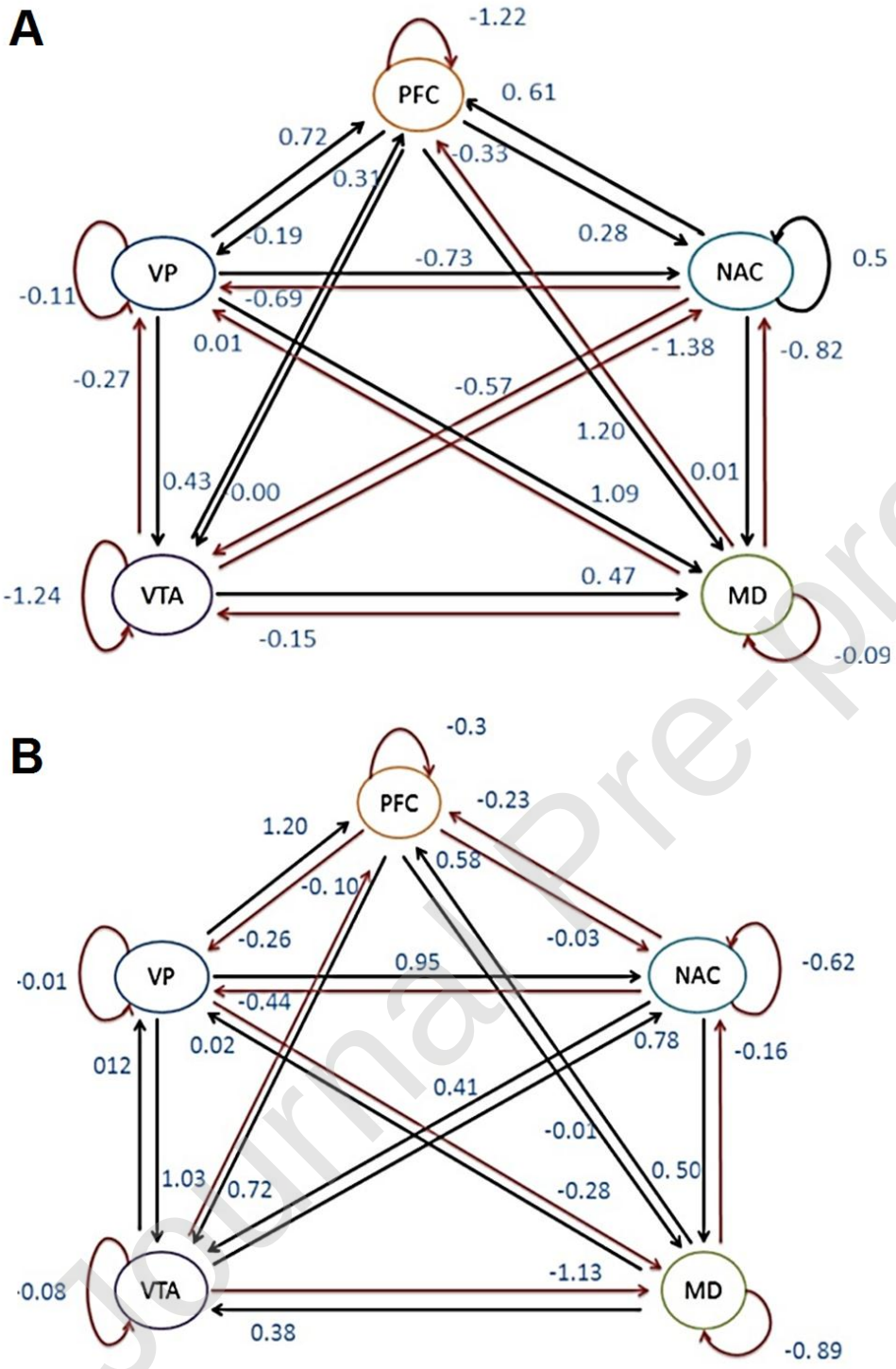

Figure 3: Graphical representation of the optimal DCM model for normal group (A) and abstinent MA users (B), which includes connections between brain regions and self-loop (the connections of a region on itself). Negative values indicate the decremental connection of BOLD variations of a region to another region, meaning that the source region neurons have decreased the activity of neurons in the target region. Positive values, on the other hand, indicate the incremental connection of BOLD changes of one region to another, meaning that the neurons of the source region have increased the activity of the neurons of the target region [35].

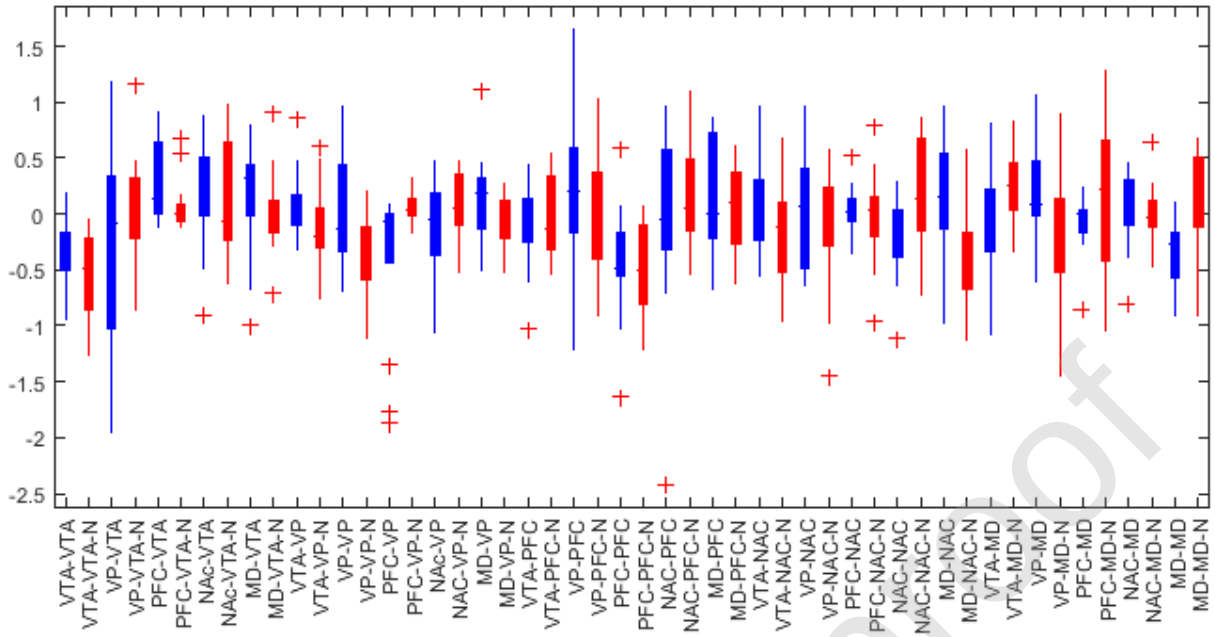

Figure 4: Box plot for effective connectivity of all ROIs in healthy individuals and abstinent MA users. The blue boxes represent effective connectivity of the MA group and the red boxes represent effective connectivity of the healthy group.

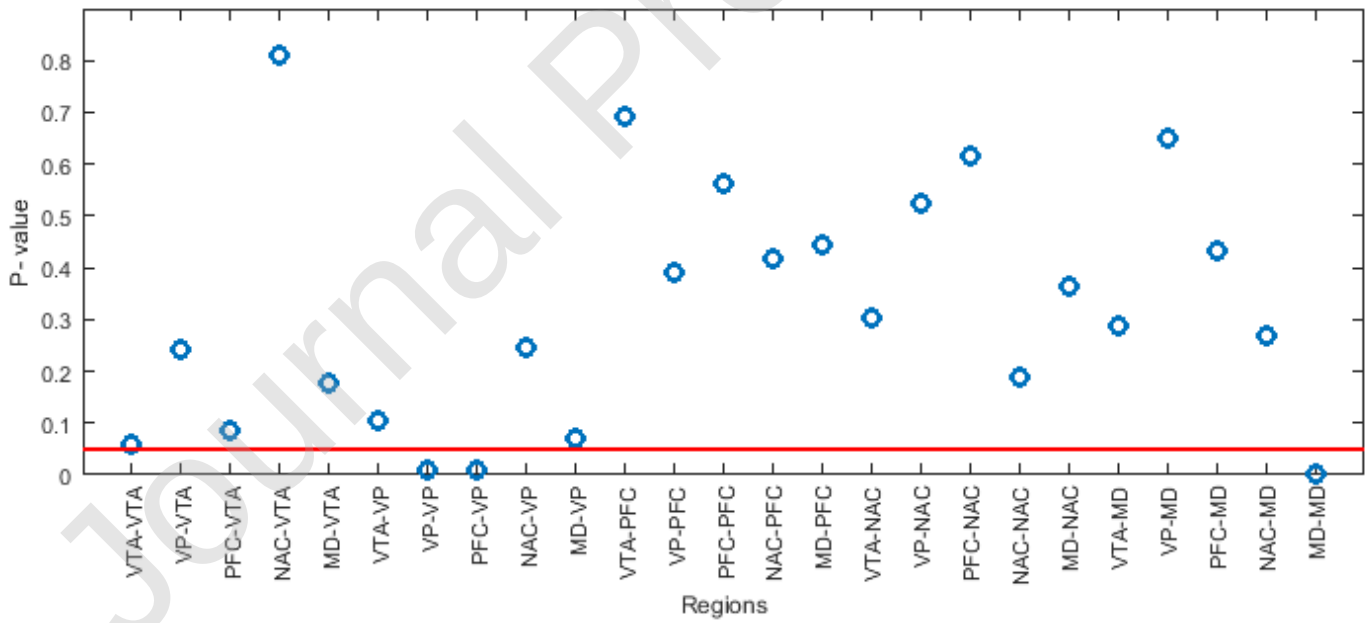

Figure 5: P-values of all comparisons for effective connectivity between the healthy individuals and abstinent MA users and their comparison with the significant level of 0.05 (red line). The *p*-values below the red line represent significant differences between the two groups (for the mean of effective connectivity).