

RESEARCH ARTICLE

Reduced thalamic resting-state functional connectivity and impaired cognition in acute abstinent heroin users

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Abstract

As a critical component of cortico-striato-thalamo-cortical loop in addiction, our understanding of the thalamus in impaired cognition of heroin users (HU) has been limited. Due to the complex thalamic connection with cortical and subcortical regions, thalamus was divided into prefrontal (PFC), occipital (OC), premotor, primary motor, sensory, temporal, and posterior parietal association subregions according to white matter tractography. We adopted seven subregions of bilateral thalamus as regions of interest to systematically study the implications of distinct thalamic nuclei in acute abstinent HU. The volume and resting-state functional connectivity (RSFC) differences of the thalamus were investigated between age-, gender-, and alcohol-matched 37 HU and 33 healthy controls (HCs). Trail making test-A (TMT-A) was adopted to assess cognitive function deficits, which were then correlated with neuro-imaging findings. Although no significant different volumes were found, HU group showed decreased RSFC between left PFC_thalamus and middle temporal gyrus as well as between left OC_thalamus and inferior frontal gyrus and supplementary motor area relative to HCs. Meanwhile, the higher TMT-A scores in HU were negatively correlated with PFC_thalamic RSFC with inferior temporal gyrus, fusiform, and precuneus. Craving scores were negatively correlated with OC_thalamic RSFC with accumbens, hippocampus, and insula. Opiate Withdrawal Scale scores were negatively correlated with left PFC/OC_thalamic RSFC with orbitofrontal cortex and medial PFC. We indicated two thalamus subregions separately involvement in cognitive control and craving to reveal the implications of thalamic subnucleus in pathology of acute abstinent HU.

KEYWORDS

craving, heroin use, impaired cognition, resting-state functional connectivity, thalamus

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1 | INTRODUCTION

Heroin is a highly addictive opioid drug, which is agonist of the mu opioid receptors (MORs) (Volkow, Michaelides, & Baler, 2019). Soon after heroin enters the brain it is metabolized to morphine and then combine preferentially to MORs, producing pharmacological effects (Hahn et al., 2016). The stimulation for MORs in the brain reward circuit facilitates to the release of dopamine (DA) in striatum (Volkow, Wang, Fowler, Tomasi, & Telang, 2011; Wise & Bozarth, 1987). Repeated exposure and heroin use then causes reinforcement effects in drug seeking that finally lead to compulsive use of drugs (Volkow et al., 2011; Volkow et al., 2019). The mesocorticolimbic DA system had been proved to be critical for the process mentioned above (Volkow et al., 2011; Volkow et al., 2019), partially through complex interactions between prefrontal cortex (PFC) and striatum (Yager, Garcia, Wunsch, & Ferguson, 2015; Yuan, Jin, et al., 2013; Yuan, Yu, et al., 2017; Yuan, Yu, et al., 2017; Yuan, Zhao, et al., 2018; Yuan, Yu, et al., 2018). Meanwhile, dense MORs exist in thalamus and thus mainly mediate the effects of heroin through the process above (Peckys & Landwehrmeyer, 1999). Thalamus is not only a crucial relay but also coordinates cortical activities and integrates information within the cortico-striato-thalamo-cortical circuit during cognitive control, and may play a critical role in the reinstatement stage and expression of drug-seeking behaviors in addiction (de Bourbon-Teles et al., 2014; Huang, Mitchell, Haber, Alia-Klein, & Goldstein, 2018). Thus, there is a need to better understand the neurophysiological mechanism of thalamus involved in heroin users (HU).

Animal studies have shown the involvement of thalamus in cognition processing. For instance, rodent studies found the reciprocal activity in thalamus and medial PFC that supported maintenance of working memory during the delay (Parnaudeau, Bolkan, & Kellendonk, 2018). In addition, thalamus might critically involve in reinstatement of heroin-seeking behaviors. Rat studies illustrated the activation of thalamus-accumbens shell projection attenuated heroin seeking, which might be a potent target for heroin relapse prevention (Keyes et al., 2020). Thalamus was indispensable to cortico-striato-thalamo-cortical circuit that underlie the response inhibition and reward processes, in which the impaired response inhibition and excessive salience attribution (iRISA) to drug cues were key to clinical symptoms in human addiction (Huang et al., 2018). Addiction study reviewed lower thalamus activation during response inhibition tasks in drug-dependent individuals (Huang et al., 2018). A study reported an increased thalamus activation to heroin-related minus neutral cues in HU group, along with increased craving following exposure to heroin-related cues (Li et al., 2012). Previous studies illustrated acute abstinent HU presented adverse physiological response, severe negative mood (anxiety, depression, and so on) and craving (Nikolaou, Kapoukranidou, Ndungu, Floros, & Kovatsi, 2017; Shi, Zhao, Epstein, Zhang, & Lu, 2007). Furthermore, increased craving during abstinence period was one of the risk factors for relapse, a problem people had been focused on (Erb, 2010). Therefore, it was necessary to investigate the heroin mechanism of action related to thalamus during acute abstinent period. However, the implications of underlying neural

mechanisms between thalamus and distinct brain regions remained unclear in acute abstinent HU.

Thus, it is necessary to divide the thalamus into subregions to systematically investigate the implications of distinct thalamic nuclei in acute abstinent HU. We separately used the seven clusters of bilateral thalamus as regions of interest (ROIs) each with different cortical connection based on probabilistic tractography algorithm (Behrens et al., 2003), to explore the abnormality of thalamic resting-state functional connectivity (RSFC) in acute abstinent HU. On the other hand, previous studies have shown the deficits of information processing in cognitive control within opioid use disorders (Lundqvist, 2010; Welsch, Bailly, Darcq, & Kieffer, 2020). Information processing was considered as the basis of higher-order cognitive process, whose defects affected the transmission speed of brain information (Kelleher, Stough, Sergejew, & Rolfe, 2004). Therefore, identification of neuroimaging biomarkers for HU with developing information processing speed defects was essential that can guide the use of treatment that enhanced individual cognition. Trail making test-A (TMT-A) was widely used as an indicator of brain dysfunction clinically, which can well reflect the defects of information processing speed (Llinas-Regla et al., 2017). Hence, we adopted TMT-A to assess cognitive dysfunctions in acute abstinent HU. However, the relationship between thalamic RSFC changes and the cognitive impairment of HU remained unclear. Correlation analyses were carried out to reveal the clinical implications of the neuroimaging findings. Based on previous studies (Denier et al., 2015; Huang et al., 2018), we hypothesized that thalamo-cortical RSFC will be abnormal, particularly the thalamic subdivision that connected with PFC.

2 | MATERIALS AND METHODS

The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. Each subject signed the informed consent.

2.1 | Subjects

According to the fifth edition of Diagnostic and Statistical Manual on Mental Disorders, 44 HU with opioid use disorder for acute withdrawal (≤ 30 days) were recruited from compulsory Pingtang Mandatory Detoxification in Changsha City, Hunan Province. The, 41 HCs were from local community. With 7 HU and 4 HCs removed for head movement, 37 acute withdrawal HU and 33 HCs were included for the study. During the withdrawal period, subjects received only education and physical exercise without methadone treatment. Inclusion criteria for HU group comprised the range of age from 20 to 50 years old, right-handedness, at least primary school education, no history of neurological and psychiatric disorders except drug addiction. Exclusion criteria for all subjects included a history of head injury, additional substance use except nicotine and alcohol over the past 5 years, and contraindications for magnetic resonance

scanning. BOLD functional magnetic resonance imaging (fMRI) imaging was employed to quantify the RSFC strength between thalamic ROIs and brain regions (Song et al., 2020). The duration, dosage, craving, withdrawal symptoms and the withdrawal period of heroin use were collected in HU group. Fagerstrom Test for Nicotine Dependence and Alcohol Use Disorders Identification Test were used to assess the nicotine dependent severity and alcohol use in participants. Opiate Withdrawal Scale (OWS) that consisted of 32 typical opiate withdrawal signs/symptoms was adopted in our work (Bradley, Gossop, Phillips, & Legarda, 1987), and the scale was used to assess HU withdrawal symptoms in previous study (Smollka & Schmidt, 1999). A 5-point scale of zero (0), mild (1), moderate (2), severe (3), and extremely severe (4) was used to rate the intensity of each signs/ symptoms of heroin withdrawal. Subjective heroin craving was estimated with 0–10 visual analog scale (VAS) when asking “To what extent do you feel the urge to use heroin?” Craving scores (with 0 for the least craving and 10 for the strongest craving) were acquired before MRI scan (Li et al., 2012). TMT-A required participants to link numbers (1–8) in a numerical sequence with pen, and the pen must keep in contact with paper during test (Varjadic, Mantini, Demeyere, & Gillebert, 2018). The TMT-A scores, which were recorded by a stopwatch according to the subjects' connection time, were used to assess the performance of the subjects in the task (Yu et al., 2016).

2.2 | MRI data acquisition

The whole MRI data were acquired on a 3 T Siemens Skyra MRI scanner (Magnetom Skyra, Siemens, Germany) with a 32-channel head coil. The subjects kept lying down and closed their eyes with empty brains during the scanning. For each subject, the three-dimensional T1-weighted image was obtained by a magnetization-prepared rapid gradient echo (176 sagittal slices, slice thickness = 1 mm, gap = 0 mm, field of view (FOV) = 256 mm × 256 mm; repetition time (TR) = 1,450 ms; echo time (TE) = 2.03 ms; inversion time (TI) = 900 ms; flip angle = 30°; and voxel size = 1 × 1 × 1 mm³). Resting-state fMRI parameters were as follows (36 axial slices, thickness = 4 mm; FOV = 220 mm × 220 mm; TR = 2,000 ms; TE = 30 ms; flip angle = 80°; and 225 volumes). In order to minimize head movement, foam was added between the head and the coil of the subjects.

2.3 | MRI data processing

The regional volumes in individual brains were obtained by Freesurfer 6.0 (<https://surfer.nmr.mgh.harvard.edu/>) for structural MRI as described in our previous works (Cai et al., 2016; Yuan, Cheng, et al., 2013). The preprocessing pipeline of subcortical volume was following: (a) skull stripping; (b) automated Talairach transformation; (c) segmentation of the subcortical white matter and deep gray matter volumetric structures; (d) intensity normalization; (e) tessellation of the gray matter/white matter boundary; (f) automated topology

correction; (g) surface deformation; and (h) registration of the subjects' brains to a common spherical atlas.

Analysis of Functional NeuroImages software (<http://afni.nimh.nih.gov/>) and FMRIB's Software Library (FSL 5.0.0, <http://www.fmrib.ox.ac.uk/fsl/>) were used for fMRI resting-state images analysis. The image processing consists of the following steps: (a) slice timing correction; (b) rigid-body head motion correction (head motion exceeded 2 mm or rotation exceeded 2° excluded); (c) removal skull; (d) spatial smoothing; (e) affine coregistration to the skull-stripped structural image; (f) spatially normalized into MNI152 template (with 6 mm half-height full-width Gaussian kernel); and (g) intensity normalization. In addition, wavelet despiking was used in the RSFC analyses to regress out the nuisance signals containing head motions and principle components from white matter and cerebrospinal fluid regions (Patel et al., 2014). The denoising process were as follows: (h) time series despiking (wavelet domain); (i) nuisance signal regression (14-parameters regression); (j) a temporal Fourier filter (0.009–0.10 Hz) (Patel et al., 2014). Thalamus was divided into seven subregions based on the thalamo-cortical connectivity as revealed by DTI-based tractography (Behrens et al., 2003). These seven ROIs were, respectively, connected with PFC, premotor cortex (PMC), primary motor cortex (M1), sensory cortex (SC), temporal cortex (TC), posterior parietal cortex (PPC), and occipital cortex (OC) of brain cortices in anatomical structure (Figure 1). For each participant, Pearson correlation was adopted, respectively, between the bilateral seven ROIs and the rest of the whole brain in a voxel-wise manner, and then Fisher's *r*-to-*z* transformation was used.

2.4 | Statistical analysis

We adopted the two independent-sample *t* test to evaluate the differences in age, years of education, nicotine, alcohol, and subcortical volume of the bilateral thalamus, and chi-square test to assess the differences in gender between HU and HCs group with SPSS24 (IBM, Armonk, NY) (Preacher & Hayes, 2004). Cognitive impairment of HU was also evaluated by TMT-A performances. The significant level was $p < .05$. For the neuroimaging results, two independent-sample *t* test was performed to test the thalamic RSFC differences based on bilateral seven ROIs between two groups. The significant level was $p < .05$ with family-wise error (FWE) corrected. A series of Pearson correlation analyses were used to study the relationship between the thalamic RSFC of bilateral seven ROIs and TMT-A, craving, duration, dosage, withdrawal days, and withdrawal symptoms.

3 | RESULTS

3.1 | Sociodemographic and diagnostic characteristics

Sociodemographic and diagnostic characteristics of 37 HU and 33 HCs were listed (Table 1). Education and nicotine use were significantly different in age-, gender-, and alcohol-matched groups.

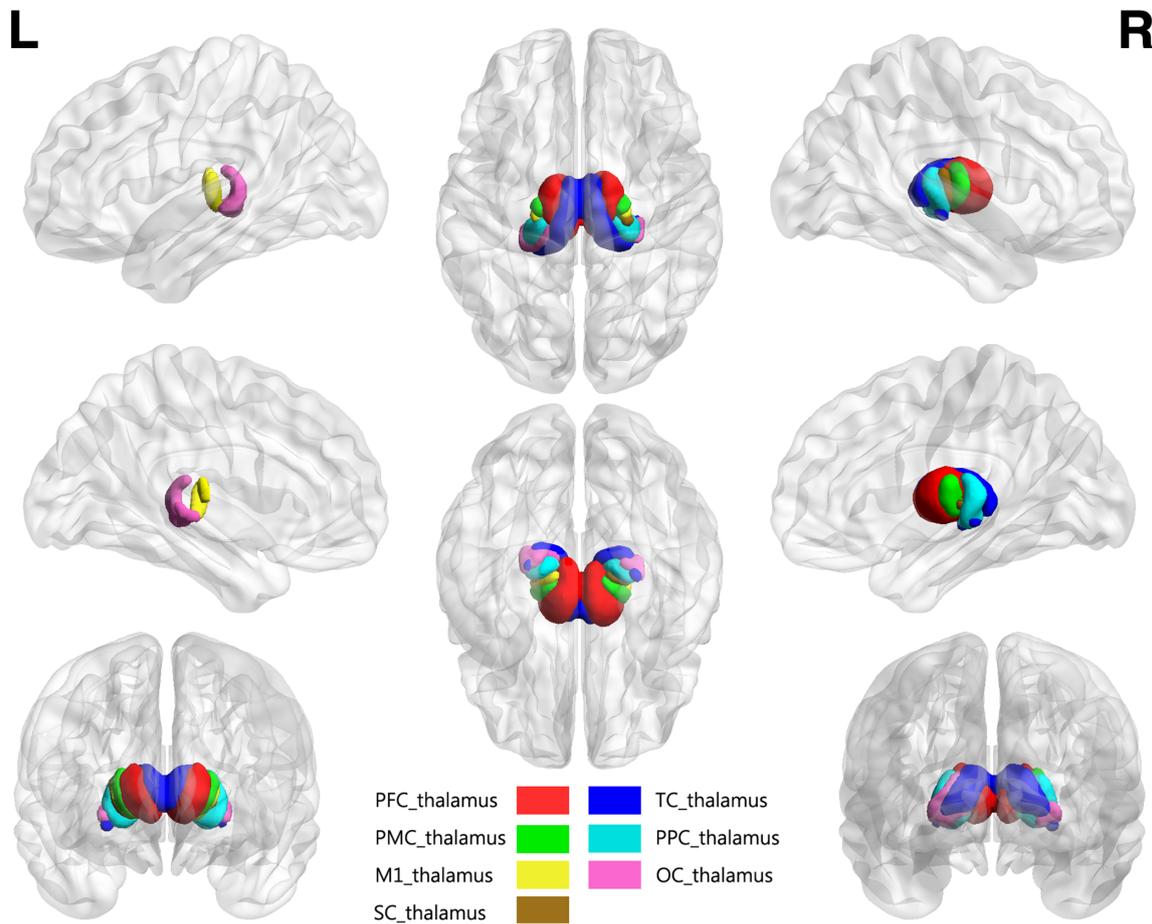


FIGURE 1 The seven regions of interest (ROIs) of the left and right thalamus connected with PFC, PMC, M1, SC, TC, PPC, and OC separately. M1, primary motor cortex; OC, occipital cortex; PFC, prefrontal cortex; PMC, premotor cortex; PPC, posterior parietal cortex; SC, sensory cortex; TC, temporal cortex

Measurements	HU (n = 37)	HCs (n = 33)	p-Values
Age (years)	41.08 ± 5.12	41.52 ± 4.65	.713
Gender (male/female)	28/9	23/10	.581
Education (years)	9.41 ± 2.10	10.58 ± 2.42	.034*
Nicotine (FTND)	5.95 ± 2.46	3.36 ± 2.69	.001*
Alcohol (AUDIT)	2.97 ± 4.76	3.18 ± 4.84	.856
Withdrawal (days)	13.24 ± 8.96	—	—
Craving (scores)	5.71 ± 2.92 (n = 35)	—	—
Duration (years)	14.86 ± 7.54	—	—
Dosage (g/day)	0.59 ± 0.50	—	—
OWS (scores)	80.00 ± 25.58 (n = 26)	—	—
TMT-A (s)	9.19 ± 4.52 (n = 18)	6.21 ± 2.30 (n = 32)	.016*

Note: Data are given as mean ± SD. *p < .05.

Abbreviation: AUDIT, Alcohol Use Disorders Identification Test; FTND, Fagerstrom Test for Nicotine Dependence; HC, healthy control; HU, heroin users; OWS, Opiate Withdrawal Scale; TMT-A, Trial Making Test-A.

TABLE 1 Sociodemographic and diagnostic characteristics of the subjects

3.2 | Structural and RSFC differences

Thalamic volume for acute abstinent HU was 8,446.75 ± 632.14 mm³ in left and 8,035.97 ± 765.00 mm³ in right. Thalamic volume for HCs

was 8,280.44 ± 963.74 mm³ in left and 7,854.81 ± 887.00 mm³ in right. No significant subcortical volume differences in left thalamus ($t = 0.843$, $p = .403$) and right thalamus ($t = 0.917$, $p = .362$) between groups. HU group showed reduced left PFC_thalamic RSFC with left

middle temporal gyrus (MTG) as well as left OC_thalamic RSFC with opercular part of the left inferior frontal gyrus (IFG) and bilateral supplementary motor area (SMA) compared with HCs group (Table 2 and Figure 2).

3.3 | Correlation analysis

Because some subjects failed to participate in the follow-up experiment, the number of TMT-A subjects were 18 for HU and 32 for HCs. The TMT-A score of HU group was significantly higher than that of HCs group ($t = 2.615$, $p = .016$; Figure 3a). Duration was significantly negative with the RSFC between left OC_thalamus and right medial superior frontal gyrus (SFG) within HU ($r = -.5115$, $p = .0012$; Figure 3b). TMT-A score was negatively correlated with the RSFC

between left PFC_thalamus and left inferior temporal gyrus (ITG) ($r = -.7459$, $p < .001$), right fusiform ($r = -.6164$, $p = .0064$) and right precuneus ($r = -.6788$, $p = .0020$) in HU group (Table 3 and Figure 3c). Craving scores was negatively correlated with left OC_thalamic RSFC with the left nucleus accumbens (NAc) ($r = -.4294$, $p = .0101$), left hippocampus ($r = -.5299$, $p = .0011$), right insula ($r = -.5560$, $p < .001$) (Table 3 and Figure 3d). OWS score was negatively correlated with left PFC_thalamic RSFC with left medial orbitofrontal cortex ($r = -.5903$, $p = .0015$) and left medial SFG ($r = -.7282$, $p < .001$) in HU group (Figure 4a). Similarly, OWS score was negatively correlated with left OC_thalamic RSFC with left ($r = -.6524$, $p < .001$) and right orbital part of the SFG ($r = -.5002$, $p = .0093$) in acute abstinent HU (Figure 4b). No significant correlations were found between neuroimaging findings and withdrawal days. The thalamic RSFC was negatively correlated with dosage

TABLE 2 Brain regions exhibiting decreased thalamic RSFC in HU relative to HCs

Region	Hemisphere	Peak voxel			Cluster size (mm ³)	Peak p value
		X	Y	Z		
Left PFC_thalamus as ROI						
Medial temporal gyrus	Left	-62	-38	-4	248	.038
Left OC_thalamus as ROI						
Opercular part of the inferior frontal gyrus	Left	-38	8	24	336	.029
Supplementary motor area	Left	0	-12	48	2,800	.019
Supplementary motor area	Right	2	-12	50	1,624	.019

Note: All the coordinates are located in the MNI space.

Abbreviation: HC, healthy control; HU, heroin users; OC, occipital cortex; PFC, prefrontal cortex; RSFC, resting-state functional connectivity.

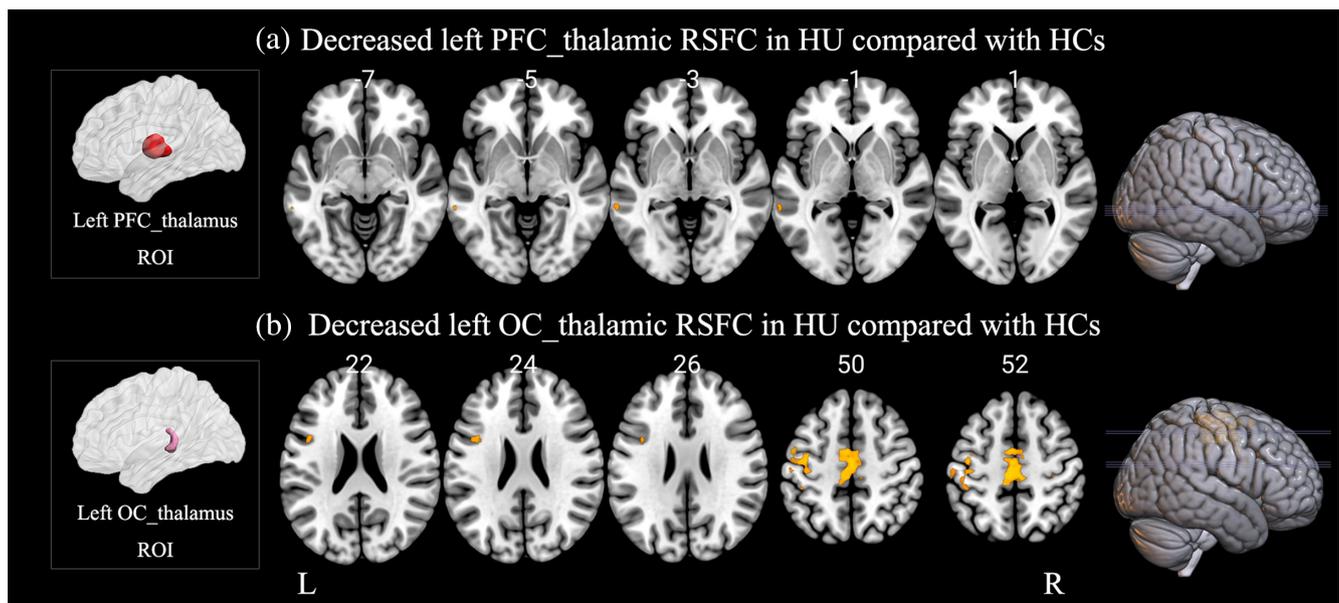


FIGURE 2 The differences of thalamic RSFC between acute abstinent heroin users (HU) and healthy controls (HCs). (a) Significantly decreased left PFC_thalamic RSFC with left MTG in HU group compared with HCs group. FWE corrected, $*p < .05$. (b) Significantly decreased left OC_thalamic RSFC with opercular part of the left IFG and bilateral SMA in HU group compared with HCs group. Family-wise error (FWE) corrected, $*p < .05$. RSFC, resting-state functional connectivity. IFG, inferior frontal gyrus; MTG, middle temporal gyrus; OC, occipital cortex; PFC, prefrontal cortex; SMA, supplementary motor area

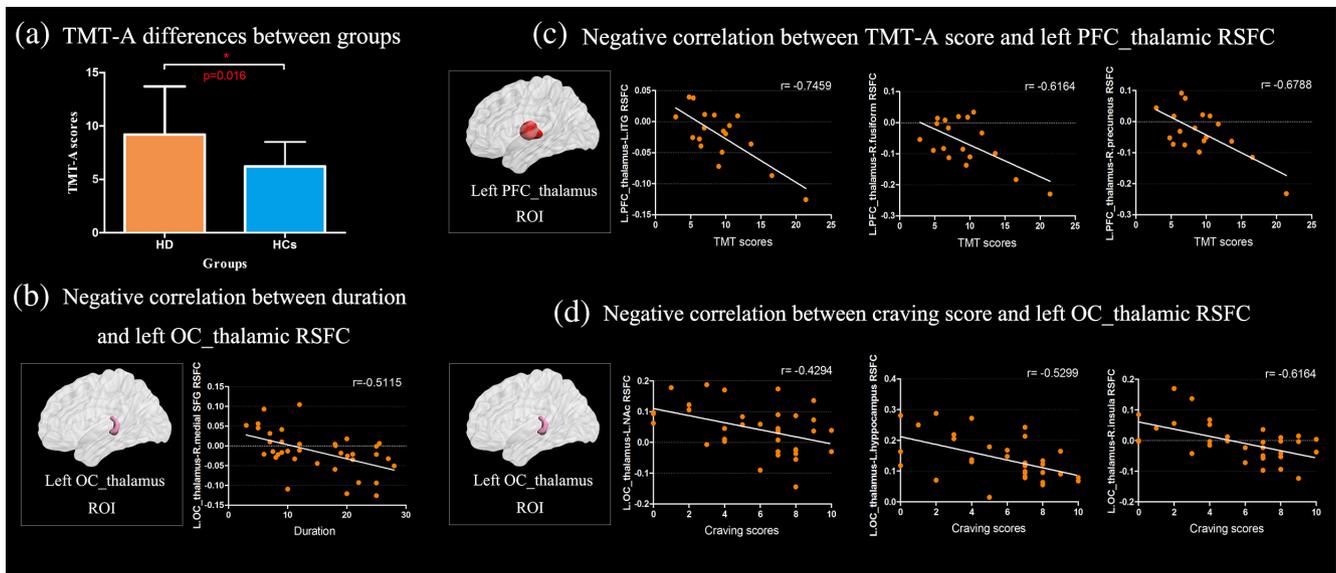


FIGURE 3 (a) Heroin users (HU) group showed significantly higher TMT-A scores relative to healthy controls (HCs) group. $*p < .05$. (b) Negative correlation between duration of heroin and left OC_thalamic RSFC with right medial SFG in acute abstinent HU. (c) Negative correlation between TMT-A score and left PFC_thalamic RSFC with cortical and subcortical regions in acute abstinent HU. (d) Negative correlation between craving score and left OC_thalamic RSFC with cortical regions and subcortical regions in acute abstinent HU. ITG, inferior temporal gyrus; OC, occipital cortex; PFC, prefrontal cortex; RSFC, resting-state functional connectivity; SFG, superior frontal gyrus; TMT-A, trial making test

TABLE 3 Brain regions exhibiting thalamic RSFC in negative correlation with TMT-A/craving within HU

Region	Hemisphere	Peak voxel			Cluster size (mm ³)	Peak <i>p</i> value
		X	Y	Z		
TMT-A in correlation with left PFC_thalamic RSFC						
Inferior temporal gyrus	Left	-58	-24	-20	200	<.001
Fusiform	Right	28	-44	-12	24	<.001
Precuneus	Right	24	-62	38	56	<.001
Craving in correlation with left OC_thalamic RSFC						
Nucleus accumbens	Left	-10	14	-10	168	.013
Hippocampus	Left	-26	-38	0	872	.001
Insula	Right	42	-2	0	1,024	.005

Note: All the coordinates are located in the MNI space.

Abbreviation: HC, healthy control; HU, heroin users; OC, occipital cortex; PFC, prefrontal cortex; RSFC, resting-state functional connectivity; TMT-A, trial making test-A.

(Supplementary Figure 1). In order to exclude the effects of significant between-group differences in nicotine, we selected nicotine-matched subjects for 24 HUs and 23 HCs from the age-, gender-, and alcohol-matched subjects above. The reduced left PFC_thalamic RSFC with left MTG was still significant in HU compared with HCs. TMT-A scores were still negatively correlated with left PFC_thalamic RSFC with left ITG (Supplementary Figure 2).

4 | DISCUSSION

The thalamus has a complex connection that received dopaminergic projections from the striatum through the globus pallidus, and then

projects back to the frontal cortex in the cortico-striato-thalamo-cortical loop (Huang et al., 2018). Addiction studies had demonstrated that this loop played crucial roles in reward and cognitive control (Huang et al., 2018). However, related literatures about the critical implications of thalamus in heroin have been very limited. In order to systematically investigate the RSFC differences of thalamic nuclei between HU and HCs, we used bilateral thalamic seven ROIs separately for the first time within acute withdrawal patients in heroin study. We found reduced RSFC of left PFC_thalamus-MTG and left OC_thalamus-IFG/SMA in HU compared with HCs. HU exhibited significant higher TMT-A scores relative to HCs indicating the impaired cognition in acute abstinent HU. In order to study the relationship between thalamic RSFC and the impaired cognition, correlation

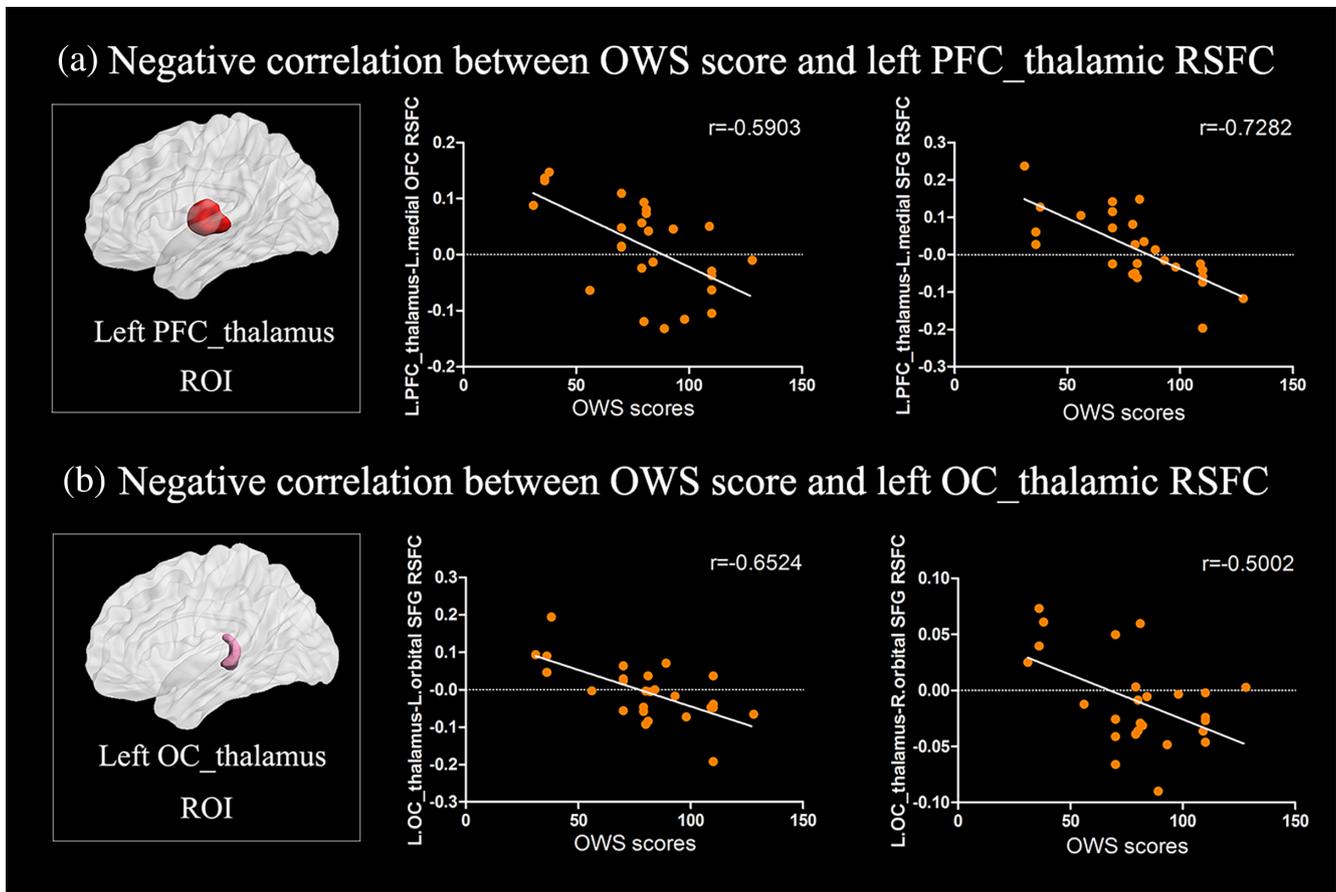


FIGURE 4 (a) Negative correlation between OWS score and left PFC_thalamic RSFC with left medial OFC and medial SFG in acute abstinent HU. (b) Negative correlation between OWS score and left OC_thalamic RSFC with orbital part of the bilateral SFG in acute abstinent HU. HU, heroin users; OFC, orbitofrontal cortex; OWS, Opiate Withdrawal Scale; RSFC, resting-state functional connectivity; SFG, superior frontal gyrus

analysis was adopted. The RSFC of PFC_thalamus and OC_thalamus was separately negative correlated with TMT-A and craving scores in acute abstinent HU. OWS scores were negatively correlated with left PFC/OC_thalamic RSFC with orbitofrontal cortex and medial PFC. A negative association between duration of heroin use and left OC_thalamus with right medial SFG demonstrated that heroin use is a chronic brain disease. Our results might shed novel insights into the neural mechanisms of the impaired cognition and drug-seeking, and has implications for treatment in acute abstinent HU.

4.1 | Reduced thalamus RSFC in HU

Reduced cortico-cortical/subcortical functional connectivity had been illustrated in heroin studies (Li et al., 2018; Lin et al., 2018; Ma et al., 2010; Zou et al., 2015). In contrast, researches on thalamo-cortical/subcortical RSFC has been very limited in HU, although it has been reported in alcohol-, cocaine-, nicotine-, and ketamine-related studies (Liao et al., 2016; Liu et al., 2019; Tomasi et al., 2010; Wang et al., 2017; Yuan, Yu, et al., 2016; Zhornitsky et al., 2018). Consistent with previous heroin study (Denier et al., 2015), we detected decreased thalamo-MTG RSFC in acute abstinent HU

relative to HCs (Figure 2a). It is worthy to note that our results were confirmed in further thalamic subdivision (left PFC_thalamus) while the previous study employed the bilateral thalamus as ROI. Compared with HCs, HU group exhibited decreased left OC_thalamic RSFC with right IFG (Figure 2b), which was critically associated with cognitive control and reward processing (Aron & Poldrack, 2006; Ross et al., 2020).

4.2 | Thalamic RSFC and TMT-A in HU

To investigate the clinical implications of the abnormal thalamic RSFC, TMT-A was adopted to measure the cognition impairments in HU. Compared with HCs, HU showed higher scores (indicating slower information processing speed) in TMT-A (Figure 3a) (Varjadic et al., 2018). TMT-A was a visual motor sequence-tracking task, which required the converging of psychomotor speed, visuospatial search and motor tracking (Bowie & Harvey, 2006; Varjadic et al., 2018). The PFC_thalamus provided communication with the cognitive cortex via projections of thalamus and PFC (Behrens et al., 2003), a brain region frequently implicated in inhibitory control (Bari & Robbins, 2013; Yuan, Qin, et al., 2016). An addiction study reviewed the distribution

of peaks of activation in the thalamus comparing addicted and healthy control using response inhibition, drug cue exposure, nondrug reward paradigms in human imaging studies (Huang et al., 2018). The thalamic peak coordinates of the response inhibition paradigm seemed to overlap with our PFC_thalamus that further support our study. Our investigation complemented the findings of thalamus in heroin-related cognitive literature by showing negative correlation between TMT-A scores and thalamic RSFC with several regions, including ITG (involved in visual comprehensions), fusiform (involved in the processing of visual information) and precuneus (involved in environmental monitoring and awareness) (Cavanna & Trimble, 2006; Lin et al., 2020; Palejwala et al., 2020). We found the involvement in information processing of PFC_thalamus-centered circuits, a potential neuroimaging biomarker of cognitive impairment in acute abstinent HU.

4.3 | Thalamic RSFC and craving in HU

Previous literature on craving in drug addiction has been focused on dorsolateral PFC, orbitofrontal cortex and NAc, presenting a potential efficacious approach to reducing craving in drug users (Liu et al., 2020; Shen et al., 2016; Yuan et al., 2020; Zhao et al., 2019). However, several studies had shown the involvement of thalamus in the reinstatement of drug-seeking behavior (roughly correspond to craving stage in human drug addiction), while insistent drug craving and relapse was the core clinical problem of addiction in human (Huang et al., 2018; Tanabe, Regner, Sakai, Martinez, & Gowin, 2019). Our study found negative correlation between self-reported craving scores and OC_thalamic RSFC with NAc (involved in reward and craving), hippocampus (involved in reward) and insula (involved craving) (Cai et al., 2016; Garavan, 2010; LeGates et al., 2018). A alcohol-related investigation showed negative correlation between alcohol expectancy scores and OC_thalamic RSFC with insula and striatum (Zhornitsky et al., 2018), in which positive alcohol expectancy was related to craving (Zhornitsky et al., 2019). A cocaine study reported significant greater activation in thalamus to heroin-related minus neutral cues (He et al., 2018), and a similar study in heroin reported greater activation of thalamus and NAc (Li et al., 2012). These findings and our results related to thalamus were consistent with the iRISA model, which suggested an imbalance between drug reward and inhibition control that related to relapse in humans (Huang et al., 2018).

4.4 | The implications of thalamus subnuclei in connection to distinct cortical and subcortical structures

The different RSFC between HU and HC were mainly observed in the left PFC_thalamus (partially overlapped with MD nucleus) and left OC_thalamus (partially overlapped with pulvinar nucleus and intralaminar nuclei). Other RSFC differences of thalamic subregions between HU and HCs did not survive the FWE corrected multiple comparisons. As we know, thalamus is mainly composed of several distinct nuclei

for MD nucleus (partially overlapped with PFC/TC_thalamus), intralaminar nuclei (partially overlapped with OC_thalamus), pulvinar nucleus (partially overlapped with OC/PPC/TC_thalamus), ventral lateral nuclei (partially overlapped with M1/PMC_thalamus), ventral anterior nucleus (partially overlapped with PMC_thalamus), and ventral posterior nuclei (partially overlapped with SC_thalamus) (Behrens et al., 2003; Grodd, Kumar, Schuz, Lindig, & Scheffler, 2020). MD nucleus, pulvinar nucleus and intralaminar nuclei and were part of the higher-order thalamic nuclei, which were associated with a variety of cognitive control, including attention, learning, orienting and reward-based behavior (Cortes, de Souza, & Casanova, 2020; Fredericksen, McQueen, & Samuelsen, 2018; Saalman, 2014). As the largest thalamic nucleus in mammals, pulvinar was associated with several visual processes, including attention and visual salience (Cortes et al., 2020). The intralaminar nuclei projected to dorsal and limbic areas of the striatum (Saalman, 2014), which was associated with the striatal response to reward-related stimuli and were allowed to mediate the motivational behavior (Huang et al., 2018; Saalman, 2014). Animal studies had been focused on paraventricular (PVT) of thalamus, a part of the midline and intralaminar thalamus of rats (Parsons, Li, & Kirouac, 2007), in mediating associations between drug and drug-related cues (Huang et al., 2018). PVT neuron was activated after the reinstatement of drug-seeking behavior, while the activation abolished heroin-seeking in chronically food-restricted rats (Chisholm et al., 2020). PVT orchestrated the maintenance of opiate-associated memories via projections to the NAc (Keyes et al., 2020). PVT-NAc pathway inhibition induced disruption of morphine CPP, which might be a potent target for heroin relapse prevention (Keyes et al., 2020). MD nucleus is a MORs-dense thalamic nucleus and is the subcortical components of the cortico-striato-thalamo-cortical loop before dopaminergic projection from thalamus back to frontal cortex (Denier et al., 2015; Huang et al., 2018). Human being studies showed that the MD nucleus of thalamus was critical in the cognition and emotion, comprising higher-order valuation/motivation and cognitive function due to its extensively connection to PFC and thus mediates the activity within PFC (Huang et al., 2018). Rationally, our RSFC results were partially consistent with these findings.

4.5 | Probable effects of nicotine and alcohol on thalamus as well as lateralization of results

Nicotine use is common among HU, with the motivation of maintaining heroin pleasure (Li, Liu, Zhang, Beveridge, & Zhou, 2010). Previous nicotine-dependent study had reported abnormal volume and reduced RSFC of thalamus (Wang et al., 2017; Yu, Yuan, Cheng, Guan, & Li, 2018), indicating the vulnerability of thalamus to the addictive effects of nicotine. Moreover, the abnormal thalamic RSFC was associated with smoking relapse, which might be used to predict treatment efficacy of nicotine addiction (Wang et al., 2020). In addition to the above effects of nicotine, alcohol use might affect the structure and function of thalamus. Abstinent male alcohol users showed reduced thalamic RSFC compared with controls

(Liu et al., 2019). Another study reported abnormal brain structure, with higher fractional anisotropy of thalamus reported in alcohol use disorder (Pandey et al., 2018). Therefore, it was necessary to exclude the influence of nicotine and alcohol by selecting nicotine matched people.

Our findings revealed a lateralization that the reduced thalamic RSFC in acute abstinent HU relative to HCs were found on the left. The hemispheric laterality difference might be associated with the lateralization of dopaminergic system (Wang et al., 2020), with an increased vulnerability for left dopaminergic substantia nigro-striatal projection found in other dopaminergic dysfunction disorders (Scherfler et al., 2012). This might be supported by the fact that activation of D2 DA receptors mediated reinstatement of heroin seeking (De Vries, Schoffelmeer, Binnekade, Raasø, & Vanderschuren, 2002). Previous addiction literature suggested that thalamic abnormalities seem to be more left-sided. In a heroin cue-induced task, left thalamus showed more broad activation than the other side in HU group versus healthy group (Li et al., 2013). A nicotine-dependent study reported increased thalamic volume in smokers versus controls as well as reduced thalamic volume and RSFC in relapsers versus nonrelapsers, especially on the left side (Wang et al., 2020). In addition, the distribution of activation peaks in thalamus seems to be more left-sided in addicts versus healthy individuals using drug cue exposure, nondrug reward and response inhibition paradigms (Huang et al., 2018). The issue of thalamic laterality in addiction needed further study.

4.6 | Limitations

The limitation of this study should be clarified. First, we did not find thalamic volume difference in HU relative to HCs, which was consistent with previous heroin study. Next, the differences of thalamic RSFC and the correlation between RSFC and TMT-A existed after excluding the effects of nicotine, but the sample size of the experiment was reduced. In addition, the subjects' number of TMT-A and OWS were inconsistent with the total number of the experiment because some individuals failed to participate in follow-up test. Another limitation is that the craving rating was assessed with VAS and lacked a baseline level. Finally, there are often obvious withdrawal symptoms during the acute abstinence, while the extent of withdrawal symptoms may be related to brain dysfunction in acute abstinence HU. Further studies should be conducted to make sense of the implications of thalamic nuclei and the more detailed neurophysiology mechanism in human HU.

5 | CONCLUSIONS

We used bilateral thalamic seven ROIs separately to systematically study the thalamic RSFC differences in acute abstinent HU and found the reduced RSFC showed in left PFC_thalamus and left OC_thalamus. Furthermore, the thalamic RSFC with other regions were related to the impaired cognitive control and increased craving in acute abstinent

HU. The findings might provide evidences for the involvements of thalamus in cortico-striato-thalamo-cortical loop within cognitive impairment of HU. The RSFC of left OC_thalamus-NAc and left PFC_thalamus-ITG might separately be the neuroimaging biomarker of relapse and cognitive impairment in acute abstinent HU. Our study may provide novel information for the implications of thalamus in the impaired cognition and in the neural mechanism of drug seeking behavior within acute abstinent HU.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Second Xiangya Hospital, Central South University.

PATIENT CONSENT STATEMENT

The patients/participants provided their written informed consent to participate in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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