Received: 22 November 2021 | Revised: 11 February 2022 | Accepted: 6 March 2022

DOI: 10.1002/hbm.25841

RESEARCH ARTICLE

WILEY

Recovery of superior frontal gyrus cortical thickness and resting-state functional connectivity in abstinent heroin users after 8 months of follow-up

Wenhan Yang[1] | Min Zhang[2,3] | Fei Tang[1] | Yanyao Du[1] | Li Fan[1] | Jing Luo[1] | Cui Yan[1] | Shicong Wang[2,3] | Jun Zhang[4] | Kai Yuan[2,3,5,6] | Jun Liu[1]

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

[2]School of Life Science and Technology, Xidian University, Xi'an, China

[3]Engineering Research Center of Molecular and Neuroimaging, Ministry of Education, Xi'an, China

[4]Hunan Judicial Police Academy, Changsha, China

[5]Xi'an Key Laboratory of Intelligent Sensing and Regulation of Trans-Scale Life Information, School of Life Science and Technology, Xidian University, Xi'an, China

[6]Inner Mongolia Key Laboratory of Pattern Recognition and Intelligent Image Processing, School of Information Engineering, Inner Mongolia University of Science and Technology, Baotou, China

Correspondence
Kai Yuan, School of Life Science and Technology, Xidian University, Xi'an China.
Email: kyuan@xidian.edu.cn
Jun Liu, Department of Radiology, Second Xiangya Hospital of Central South University, Changsha, China.
Email: junliu123@csu.edu.cn

Funding information
This study was supported by grants from the National Key Research and Development Program of China (grant number 2016YFC0800908), the National Natural Science Foundation of China (grant number 61971451, 81871426 and 81671671), the Key R&D projects in Hunan Province (grant number 2019SK2131), the Fundamental Research Funds for the Central Universities of Central South University (grant number 2021zzts0378), Natural Science Foundation of Hunan Province (grant number 2021JJ40839), the Leading Talents of Scientific and Technological Innovation in Hunan Province in 2021 (grant number 2021RC4016) and the Clinical Research Center For Medical Imaging In Hunan Province (grant number 2020SK4001)

Abstract

Compared with healthy controls, heroin users (HUs) show evidence of structural and functional brain alterations. However, little is known about the possibility of brain recovery after protracted heroin abstinence. The purpose of this study was to investigate whether brain recovery is possible after protracted abstinence in HUs. A total of 108 subjects with heroin addiction completed structural and functional scans, and 61 of those subjects completed 8-month follow-up scans. Resting-state data and 3D-T1 MR images were collected for all participants, first at baseline and again after 8 months. Cognitive function and craving were measured by the Trail Making Test-A (TMT-A) and Visual Analog Scale for Craving, respectively. The cortical thickness and resting-state functional connectivity (RSFC) differences were then analyzed and compared between baseline and follow-up, and correlations were obtained between neuroimaging and behavioral changes. HUs demonstrated improved cognition (shorter TMT-A time) and reduced craving at the follow-up (HU2) relative to baseline (HU1), and the cortical thickness in the bilateral superior frontal gyrus (SFG) was significantly greater at HU2 than at HU1. Additionally, the RSFC of the left SFG with the inferior frontal gyrus (IFG), insula, and nucleus accumbens and that of the right SFG with the IFG, insula and orbitofrontal cortex (OFC) were increased at HU2. The changes in TMT-A time were negatively correlated with the RSFC changes between the left SFG and the bilateral IFG, the bilateral caudate, and the right insula. The changes in

craving were negatively correlated with the RSFC changes between the left OFC and the bilateral SFG. Our results demonstrated that impaired frontal-limbic neurocircuitry can be partially restored, which might enable improved cognition as well as reduced craving in substance-abusing individuals. We provided novel scientific evidence for the partial recovery of brain circuits implicated in cognition and craving after protracted abstinence.

KEYWORDS
abstinence, addiction, brain recovery, cognitive function, craving, heroin

1 | INTRODUCTION

Heroin addiction is a relapsing brain disorder that has been a major public and social concern for many decades. As an opioid receptor agonist (Volkow, Michaelides, & Baler, 2019), heroin binds to the μ-opioid receptors on GABAergic neurons, suppressing the inhibitory effects of GABA and leading to elevated reward effects by increasing the release of dopamine (DA; Darcq & Kieffer, 2018; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Chronic heroin use leads to dysfunction in DA systems, especially those in the prefrontal cortex (PFC) and the striatum (Koob & Volkow, 2010, 2016). In recent decades, neuroscientists have devoted extensive effort to understanding the brain damage caused by addiction (Koob & Volkow, 2010); specifically, structural deficits and dysfunction in the PFC (e.g., orbitofrontal cortex [OFC], inferior frontal gyrus [IFG], dorsolateral prefrontal cortex [DLPFC], ventromedial prefrontal cortex [vmPFC]), striatum, insula, and thalamus related to abnormal reward processing, cognitive control impairments, and craving have been found in substance use disorder (SUD; Jiang et al., 2011; Li et al., 2014; Liu et al., 2011; Qiu et al., 2013; Wang et al., 2021; Yang et al., 2021; Zhang et al., 2021). Complementing previous work, attention to long-term recovery could improve addiction-focused clinical care as well as public policy and open new frontiers in the brain research field Humphreys and Bickel (2018). Along these lines, protracted abstinence has been shown to enhance cognition and reduce craving in SUD (Parvaz et al., 2017; Yang et al., 2008). Brain recovery has also been detected following periods of protracted abstinence; for example, increased levels of DA receptors (Volkow et al., 2001) and an increased density of DA transporters (Witt et al., 2020) have been reported in the striatum in abstinent cocaine and methamphetamine users. Furthermore, longitudinal recovery of PFC gray matter volume (GMV) and brain metabolism has been detected in abstinent cocaine users (He et al., 2018; Volkow et al., 1992). In addition, recovery from alcohol- and withdrawal-related methylation has been observed after several weeks of abstinence following acute alcohol dependence Volkow et al. (1994). Discovering the neuroadaptation processes involved in long-term addiction recovery might therefore illuminate fundamental brain functions relevant to addiction. However, limited evidence has been observed for brain structural and functional recovery caused by long-term abstinence in heroin users (HUs).

Chronic drug use is characterized by persistent seeking and taking of a drug despite its harmful effects; this behavior is driven by disrupted functioning of the PFC Goldstein and Volkow (2011), which mediates the regulation of control circuits (cognition) and craving through strong connections to other cortical and subcortical brain regions (e.g., the striatal circuit, involved in the rewarding effect of heroin; the DLPFC circuit, which plays a vital role in inhibitory control; the insula and medial OFC [mOFC], which are related to craving; and the vmPFC, documented to play major roles in foresight and decision-making; Goldstein & Volkow, 2011; He et al., 2018). During protracted abstinence in cocaine and methamphetamine users, increased PFC GMV and increased resting-state functional connectivity (RSFC) between the PFC and limbic regions have been consistently documented (Balodis et al., 2016; Berlingeri et al., 2017; Gowin et al., 2014; Parvaz et al., 2017). These findings highlight the important roles of PFC circuits in the effects of protracted abstinence on people with addictions. In HUs, task functional magnetic resonance imaging (fMRI) has shown reduced brain activation of prefrontal and limbic regions in response to drug cues after protracted abstinence (Li et al., 2013; Lou, Wang, Shen, & Wang, 2012). However, the possibility of alterations in PFC morphometry and/or PFC-related circuitry after protracted abstinence in HUs remains unclear, and little is known about the association between altered brain functional changes and behavioral changes (reduced craving and enhanced cognition).

Thus, a longitudinal study (8 months) was performed during short-term abstinence in HUs ($n = 61$). Cognition function and craving were measured by the Trail Making Test A (TMT-A) and the Visual Analog Scale for Craving (VASc), respectively (Mottola, 1993). Behavioral data and multimodal neuroimaging data were collected twice: first at baseline and again 8 months later. Cortical thickness changes were evaluated using FreeSurfer, and RSFC alterations were investigated by choosing specific PFC regions that showed significant cortical thickness changes as the seeds. We also examined whether any brain recovery induced by abstinence was associated with behavioral improvement (enhanced cognition and reduced craving). Impaired cognitive function and increased craving have been consistently documented in heroin use disorder in previous studies (Ma et al., 2015; Zhang et al., 2016) and were reported to be associated with dysfunction of the neurocircuitry centered on the PFC Koob and Volkow (2010); Li et al. (2014); Schluter, Daams, van Holst, and

TABLE 1 Characteristics of the participating HUs

$N = 58$	HU1	HU2
Age (years)	43.2 ± 7.1[a]	43.2 ± 7.1[a]
Gender (male/female)	31/27	31/27
Handedness	58 R	58 R
Duration of drug use (years)	15.8 ± 6.8[a]	15.8 ± 6.8[a]
Duration of abstinence (days)	65 (1,381)[b]	318 (244,395)[b]
Interval between MR2 and MR1	254 ± 85	254 ± 85
Drug dosage (g/day)	0.5 (0.01, 1.5)[c]	0.5 (0.01, 1.5)[c]
Trail Making Test-A (s)	11.8 ± 7.8 ($N = 28$)	9.6 ± 4.7 ($N = 28$)

Note: Characteristics of the participating heroin users (HUs). HU1: abstinent heroin users at baseline; HU2: abstinent heroin users at the 8-month follow-up; MR1: time of baseline MR scan; MR2: 8-month follow-up MR scan.
[a]Average ± *SD*.
[b]Average (Q1, Q3).
[c]Median (range).

Goudriaan (2018). Based on these findings, we hypothesized that HUs would demonstrate structural and functional plasticity changes in the PFC after protracted abstinence, as well as correlations between brain recovery and behavioral improvement. We expect that our efforts to investigate long-term recovery in heroin could improve addiction-focused clinical care and deepen the understanding of the neuroscience underlying recovery from addiction.

2 | MATERIALS AND METHODS

2.1 | Subjects

A total of 108 subjects with a history of heroin use were recruited from inpatient drug rehabilitation centers in Xinkaipu, Pingtang and Zhuzhou (three cities in Hunan Province, China) isolation drug rehabilitation center were recruited between September 2016 and December 2018. The subjects met the diagnostic criteria for heroin dependence according to the fifth edition of the Diagnostic and Statistical Manual on Mental Disorders (DSM-V) and had a positive urine test for heroin. All subjects ($n = 108$) signed written consent forms prior to participation in the experiment during the first MRI session, and a follow-up interview was conducted approximately 8 months later to invite subjects to participate in the second MRI session (of whom $n = 61$ accepted). During this 8-month period, the patients were admitted to the detoxification centers and treated with education and physical exercise; methadone maintenance treatment was not used. We used the VASc, which ranges from 0 (no craving) to 10 (extreme craving), to assess the craving scores of the HUs just before each of the two MRI scans. The TMT-A was used to assess cognitive dysfunction or recovery in abstinent HUs; this test was carried out after the MRI scan. Three subjects were excluded because of the poor quality of their MRI data. Thus, 31 male and 27 female HUs (age: 43.2 ± 7.1 years) were enrolled in this study. The mean number of days of abstinence was 65 at the time of the baseline MRI scan (HU1) and 318 at the 8-month follow-up scan (HU2; Table 1). Drug use history, that is, the duration of heroin use and abstinence and the dose consumed, was also collected from the HUs (Table 1). Additional inclusion criteria for HUs included negative urine tests for methamphetamine and ketamine. None of the subjects had a history of structural brain disease, epilepsy, head trauma, mental or psychiatric illness, or contraindications for MRI. All subjects were right-handed individuals of Han ancestry.

The Institutional Review Board at the Second Xiangya Hospital/Central South University approved the protocol (number: 8167071216). Written informed consent was obtained after the experimental procedure was explained and after the participants had read the consent form.

2.2 | MRI data acquisition

All MRI data were acquired on a 3 T MRI scanner (MAGNETOM Skyra, Siemens) equipped with a 32-channel head receiving coil at the Second Xiangya Hospital of Central South University, Changsha, China. To obtain high-quality MRI data, participants were instructed to remain still with their eyes open, and their heads were restricted by a pad and head restraint belt during the MRI scan. Conventional T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) scans were acquired to rule out visible brain structural lesions. High-resolution T1-weighted MRI was acquired using a 3D fast gradient echo sequence, repetition time (TR) = 1,450 ms, echo time (TE) = 2.0 ms, inversion time (TI) = 900 ms, field of view (FOV) = 256 × 256 mm, slices = 176, slice thickness = 1 mm, flip angle = 12°, and voxel size = 1 × 1 × 1 mm^3. The 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°.

2.3 | MRI data analysis

FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu) was used to examine the structural changes in the brain as described in our previous studies Wang et al. (2021); Zhang et al. (2021). The main processes included (a) removal of nonbrain tissue, (b) automatic Talairach transformation, (c) segmentation of subcortical white matter and deep GMV structures, (d) intensity normalization, (e) gray/white matter mosaic boundary delineation, (f) automatic topology correction, (g) surface deformation, and (h) registration of the subject's brain to a common spherical atlas.

Then, we used 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/) to analyze fMRI resting-state imaging data. The main steps were as follows: (1) slice-timing correction; (2) rigid-

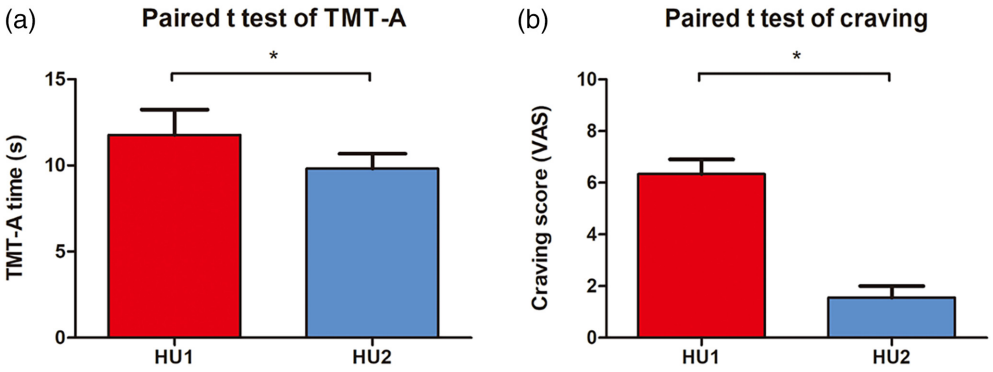

FIGURE 1 (a) The TMT-A time for HU2 was significantly higher than that for HU1 ($p = .027$). (b) The craving score for HU2 was significantly lower than that for HU1 ($p < .001$). * indicates significant differences (TMT-A time) in HU1 and HU2. HU, heroin user; TMT-A, Trail Making Test-A

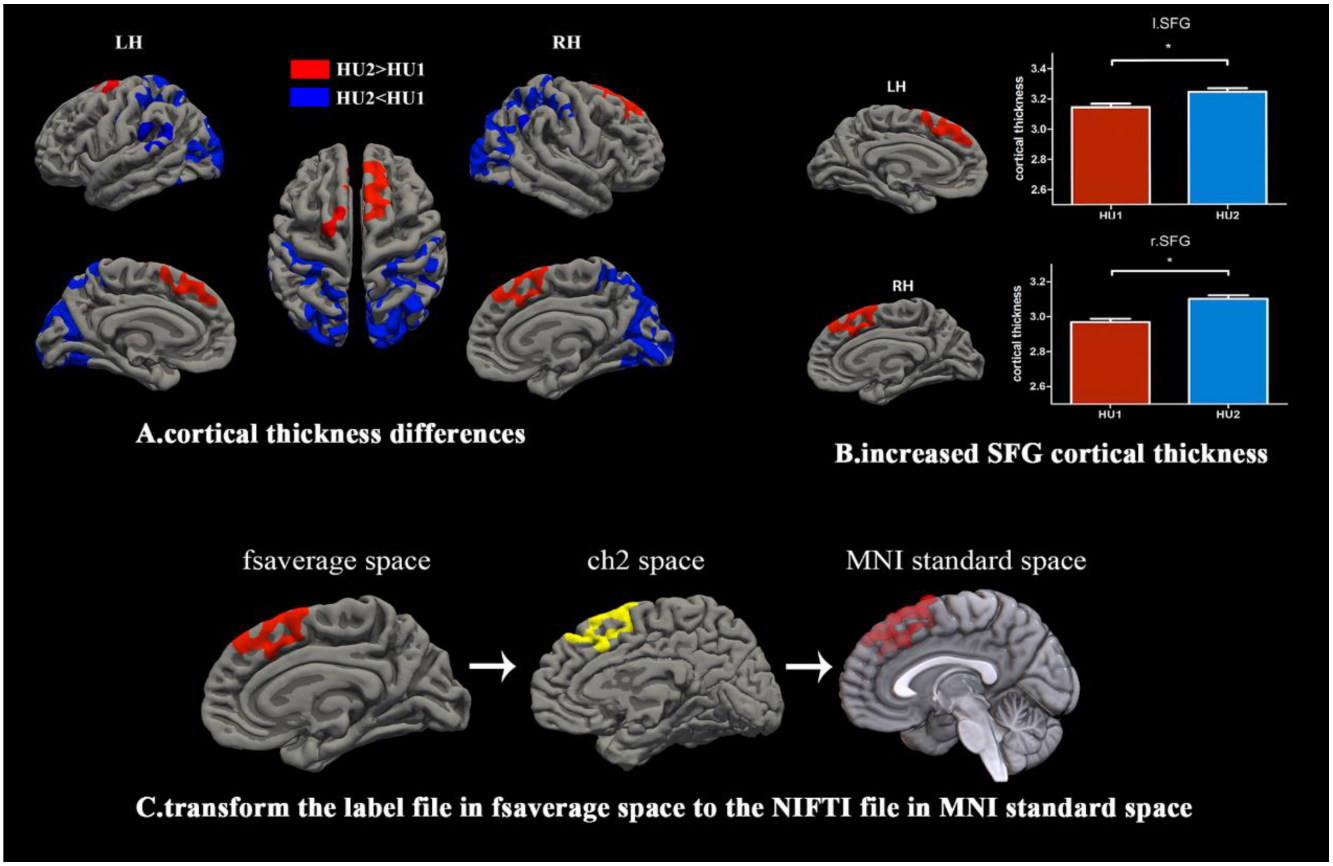

FIGURE 2 (a) Structural differences between HU1 and HU2. HU1: abstinent heroin users at baseline. HU2: abstinent heroin users at the 8-month follow-up. Compared with HU1, HU2 demonstrated significantly increased cortical thickness in the bilateral SFG and significantly decreased cortical thickness in the left pericalcarine, left postcentral, left fusiform, left paracentral, bilateral superior temporal, bilateral supramarginal, and right precentral regions. Monte Carlo simulation cluster analysis with 5,000 iterations and a cluster threshold of $p < .05$ was performed to correct for multiple comparisons. (b) SFG cortical thickness difference between HU1 and HU2; the mean bilateral SFG cortical thickness for HU2 was greater than that for HU1. (c) Transformation of the label file in fsaverage space to the NIFTI file in MNI standard space. * indicates significant cortical thickness differences between HU1 and HU2. HU, heroin user; MNI, Montreal Neurological Institute; SFG, superior frontal gyrus

body head motion correction (head motion exceeding 2 mm or rotation exceeding 2° was excluded); (3) removal of the skull; (4) spatial smoothing; (5) affine coregistration to the skull-stripped structural image; (6) spatial normalization to the Montreal Neurological Institute 52 (MNI152) template (with a 6 mm full width at half maximum Gaussian kernel); and (7) intensity normalization. In addition, wavelet despiking was used in the RSFC analyses to regress out the nuisance signals containing head motions and the principal components from white matter and cerebrospinal fluid regions Patel et al. (2014). The denoising process consisted of time-series despiking (wavelet domain), nuisance signal regression (14-parameter regression), and temporal Fourier filtering (0.009–0.10 Hz) Patel et al. (2014).

TABLE 2 Differences in cortical thickness between HU1 and HU2

Region	Hemisphere	Talairach coordinates			Number of vertices	Max. vertex	Clusterwise *p* value	Cohen's *d*
		x	*y*	*z*				
Cortical thickness: HU1 < HU2								
Superior frontal	Left	−7.4	11.4	58.2	856	152,796	.0002	1.2221
		−10.9	8.9	63.4	534	140,568	.0006	
Superior frontal	Right	21.6	28.8	42.9	2,803	66,607	.0002	1.3721
		7.9	56.1	30.1	406	98,477	.0052	
Cortical thickness: HU1 > HU2								
Pericalcarine	Left	−18.7	−73.3	8.6	11,500	87,350	.0002	1.3182
Postcentral	Left	−22.5	−31.8	61.0	5,496	6,149	.0002	1.3049
Fusiform	Left	−29.7	−72.0	−10.1	2,636	57,862	.0002	1.3079
Paracentral	Left	−11.3	−39.4	58.4	1,437	109,325	.0002	1.5302
Superior temporal	Left	−46.5	−38.3	10.4	776	33,558	.0006	1.5178
Supramarginal	Left	−57.0	−34.0	27.7	545	156,123	.0016	1.1571
Superior parietal	Right	19.2	−78.8	40.6	22,680	54,165	.0002	1.3092
Superior temporal	Right	62.1	−24.2	5.7	1,516	43,795	.0002	1.6020
Supramarginal	Right	52.5	−31.8	42.9	1,047	57,507	.0002	1.3049
Precentral	Right	34.6	−15.7	37.5	444	82,053	.0386	1.2984

Note: HU1: abstinent heroin users at baseline; HU2: abstinent heroin users at the 8-month follow-up.

To investigate the potential functional changes in the brain regions that showed structural changes, the clusters that changed in the paired *t* test during the structural analysis were selected as regions of interest. These changed clusters were transformed from the label file in fsaverage space to the NIFTI file in Montreal Neurological Institute (MNI) standard space using the following steps (Figure 2c). First, mri_label2label was used to transfer the label file from fsaverage space to ch2 space. Next, tkregister2 was used to obtain the parameters used to map from fsaverage space to MNI standard space. Then, mri_label2vol was used to convert the label file in ch2 space to the NIFTI file in MNI standard space. Finally, we resliced the NIFTI file to align the data to the 2 mm standard template in MNI standard space.

2.4 | Statistical analysis

Statistical analyses of the behavioral data were conducted using SPSS 21.0. We adopted the paired *t* test to evaluate the differences in TMT-A and craving scores at a significance level of $p < .05$. Additionally, the paired *t* test was performed to assess the significance of alterations in cortical thickness, subcortical volume and RSFC. For the structural results, a Monte Carlo simulation cluster analysis with 5,000 iterations and a cluster threshold of $p < .05$ (false discovery rate corrected) was performed to correct for multiple comparisons. The volumes of the striatum subsets, including the putamen, NAc, caudate and pallidum, were extracted, divided by the intracranial volume and then compared ($p < .05/8$, Bonferroni corrected). Subsequently, RSFC differences between HU1 and HU2 were assessed at a cluster threshold of $p < .05$ (familywise error [FWE] corrected). Whole brain regression analysis was used to study the relationship between the changes in RSFC and the changes in TMT-A and craving scores.

3 | RESULTS

3.1 | Behavioral results

The TMT-A time for HU2 was significantly shorter than that for HU1 ($p = .027$; Figure 1a). The craving score for HU2 was significantly lower than that for HU1 ($p < .001$; Figure 1b).

3.2 | Structural results

Compared with HU1, HU2 showed significantly increased cortical thickness in the bilateral superior frontal gyrus (SFG) and significantly decreased cortical thickness in the left pericalcarine, left postcentral, left fusiform, left paracentral, bilateral superior temporal, bilateral supramarginal, and right precentral regions (Figure 2a; Table 2). No significant differences were observed in the volumes of the striatum subsets between HU1 and HU2.

3.3 | Functional connectivity results

Compared with HU1, HU2 was associated with increased RSFC between the left SFG and the bilateral IFG (FWE correction, $p < .05$; Figure 3; Table 3). No significantly increased RSFC of the right SFG

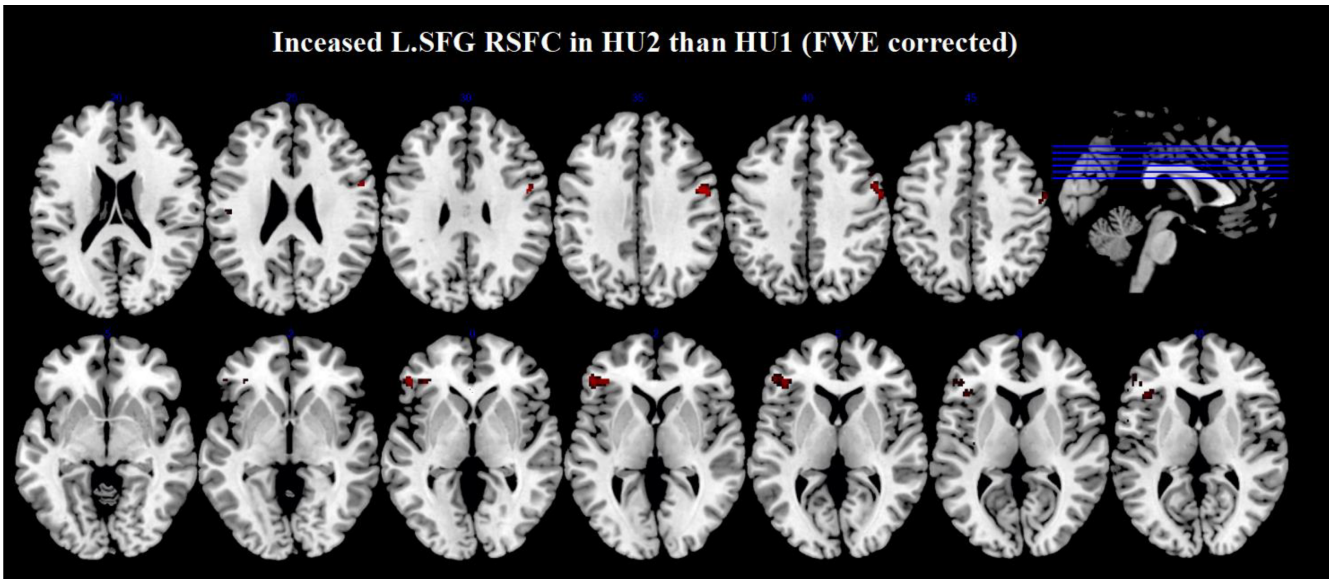

FIGURE 3 Increased RSFC was observed between the L.SFG and the bilateral inferior frontal gyrus (FWE corrected) for HU2 relative to HU1. FWE, familywise error; HU, heroin user; L.SFG: left superior frontal gyrus; RSFC, resting-state functional connectivity

TABLE 3 Significantly increased RSFC with L.SFG from HU2 to HU1

Region	Brodmann area	Peak voxel			Volume (mm^3)	Peak
		X	*Y*	*Z*		*p* value
Left inferior frontal gyrus	45/46	24	−50	36	1,200	.02079
Right inferior frontal gyrus	9	174	56	4	160	.01419

Note: All the coordinates refer to Montreal Neurological Institute space.
Abbreviations: HU, heroin user; L.SFG: left superior frontal gyrus; RSFC, resting-state functional connectivity.

was found at HU2 relative to HU1 ($p < .05$, FWE corrected). No significantly decreased RSFCs of the bilateral SFG were found for HU2 relative to HU1 ($p < .05$, FWE corrected).

Compared with HU1, HU2 was associated with increased RSFC between the left SFG and several regions ($p < .005$, no correction), such as the bilateral IFG, bilateral insula, and bilateral NAc (Figure 4). At HU2, subjects also demonstrated comparatively increased RSFC of the right SFG with the left IFG, insula and OFC and right IFG and insula ($p < .005$, no correction; Figure 5). No significantly decreased RSFC of the bilateral SFG were found at HU2 relative to HU1 ($p < .005$, no correction).

3.4 | Correlation between RSFC changes and behavior improvements

Resting-state functional connectivity changes between the left SFG and the bilateral IFG (left: $r = -.752$, $p < .0001$; right: $r = -.692$, $p < .0001$), the bilateral caudate (left: $r = -.544$, $p = .0028$; right: $r = -.720$, $p < .0001$), the left pallidum ($r = -.703$, $p < .0001$), and the right insula ($r = -.778$, $p < .0001$) were negatively correlated with changes in the TMT-A duration (Figure 6). The changes in craving were negatively correlated with RSFC changes between the left OFC and the SFG in both hemispheres (left: $r = -.810$, $p < .0001$; right: $r = -.860$, $p < .0001$; Figure 7).

4 | DISCUSSION

The purpose of this study was to examine possible behavioral, structural and functional recovery in heroin addiction using behavioral and neuroimaging data as well as associations between changed behavioral and neuroimaging measures observed in HUs after periods of abstinence. The present longitudinal study revealed improved cognition, reduced craving, and increased SFG cortical thickness and RSFC after abstinence in HUs, which indicated potential structural and functional recovery in the SFG from baseline to 8 months. In addition, negative correlations were found between changes in the left SFG RSFC and both the TMT-A time and craving scores. Our findings are consistent with previous SUD studies showing recovered PFC GMV in cocaine (Parvaz et al., 2017), methamphetamine and nicotine (Morales, Lee, Hellemann, O'Neill, & London, 2012), and alcohol (Demirakca et al., 2011) users after periods of abstinence. Here, we extended the study of brain recovery after protracted abstinence from

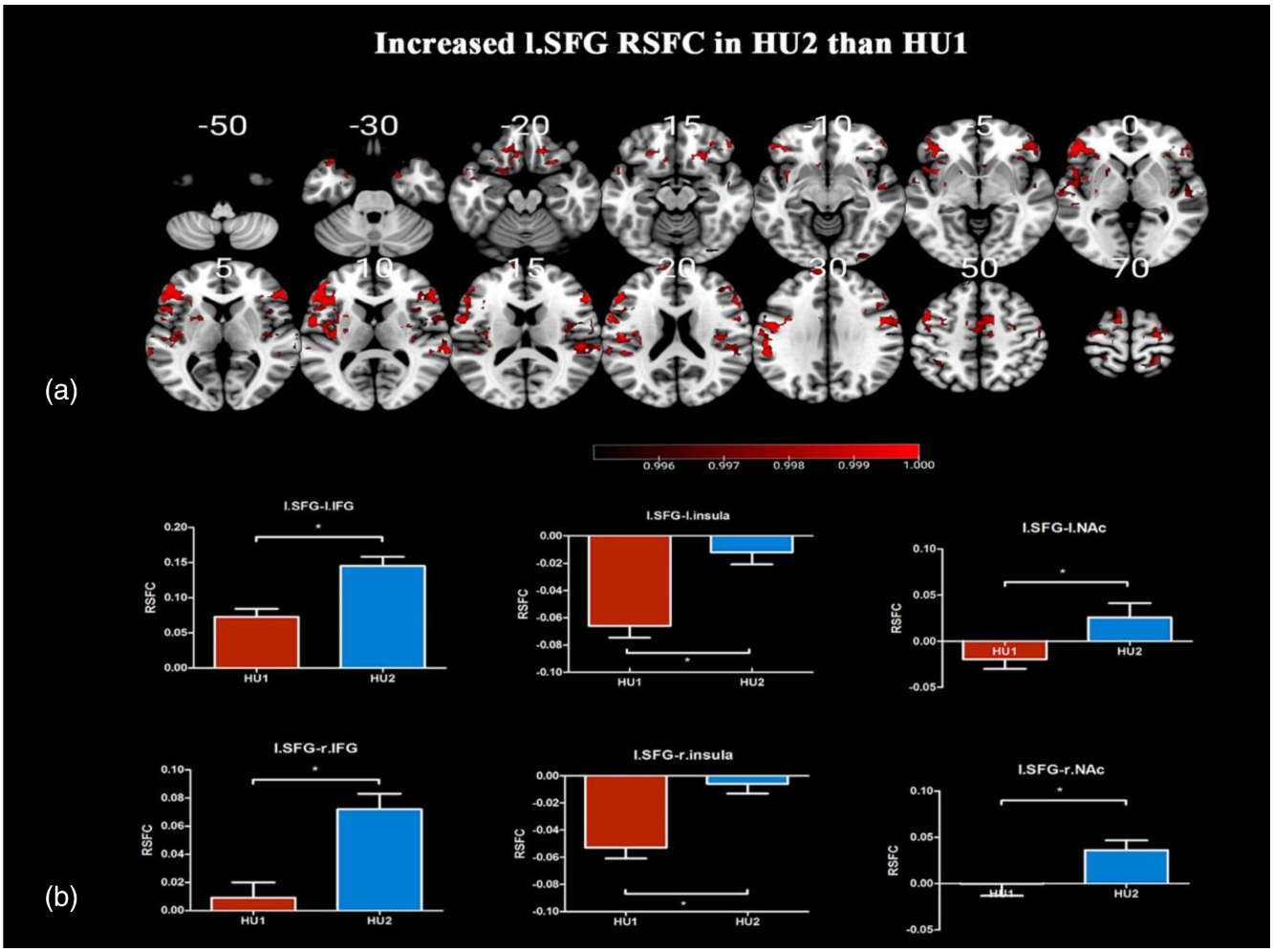

FIGURE 4 (a, b) Increased RSFC was observed between the L.SFG and the left inferior frontal gyrus (IFG), left insula, left NAc, right IFG, right insula, and right NAc (uncorrected) for HU2 relative to HU1. * indicates significant RSFC differences between HU1 and HU. HU, heroin user; L. SFG: left superior frontal gyrus; NAc, nucleus accumbens; RSFC, resting-state functional connectivity

cocaine, methamphetamine and alcohol users to HUs. Furthermore, we provided novel evidence of this recovery at both the regional and circuit levels of the PFC. These findings implicate the role of neuroadaptation after protracted abstinence and advance brain plasticity research in the neuroscience field.

Previous studies have revealed the presence of cognitive impairments among SUD (Fitzpatrick, Rubenis, Lubman, & Verdejo-Garcia, 2020; Ramey & Regier, 2018; Sampedro-Piquero et al., 2019), including deficits in decision-making, inhibition and flexibility cognitive function. In this study, improved cognition was found in HUs after long-term abstinence (8 months), which was reflected by shorter TMT-A time at HU2 than at HU1. The TMT-A is a measure that assesses cognitive function, evaluating cognitive function while performing tasks associated with psychomotor performance, mental flexibility, working memory, and executive function (Bowie & Harvey, 2006; Yu et al., 2016). Our results suggest the possibility of enhanced cognitive function to a certain extent in HUs after protracted abstinence. Notably, impaired cognitive function has been consistently found to be accompanied by disruption of the PFC in HUs (Zhang et al., 2016). Li et al. (2014) found decreased bilateral SFG cortical thickness in HUs with respect to HCs, and we further verified the involvement of the SFG in heroin addiction by showing the longitudinal recovery of the SFG structure after protracted abstinence (Figure 2b). In addition, we found increased RSFC between the SFG and the IFG, insula and NAc in this study (Figure 3), which was correlated with cognitive improvement (reduced TMT-A response time) in HUs after protracted abstinence (Figure 5). These neuroimaging findings are consistent with previous findings on SUD (Jager, Kahn, Van Den Brink, Van Ree, & Ramsey, 2006; Verdejo-Garcia & Perez-Garcia, 2007; Steele et al., 2018). The IFG is involved in cognition (attention and flexibility); its dysfunction in SUD is reflected by an attention bias toward drug-related stimuli while overlooking other stimuli as well as by an inflexibility in goals to procure the drug (Dong et al., 2021; Goldstein & Volkow, 2011). The NAc and insula are vital parts of the limbic system that are closely related to addiction (Naqvi, Rudrauf, Damasio, & Bechara, 2007; Seifert et al., 2015; Tanabe et al., 2013). Decreased RSFC or regional resting-state measures between frontal, limbic, and other regions have been consistently

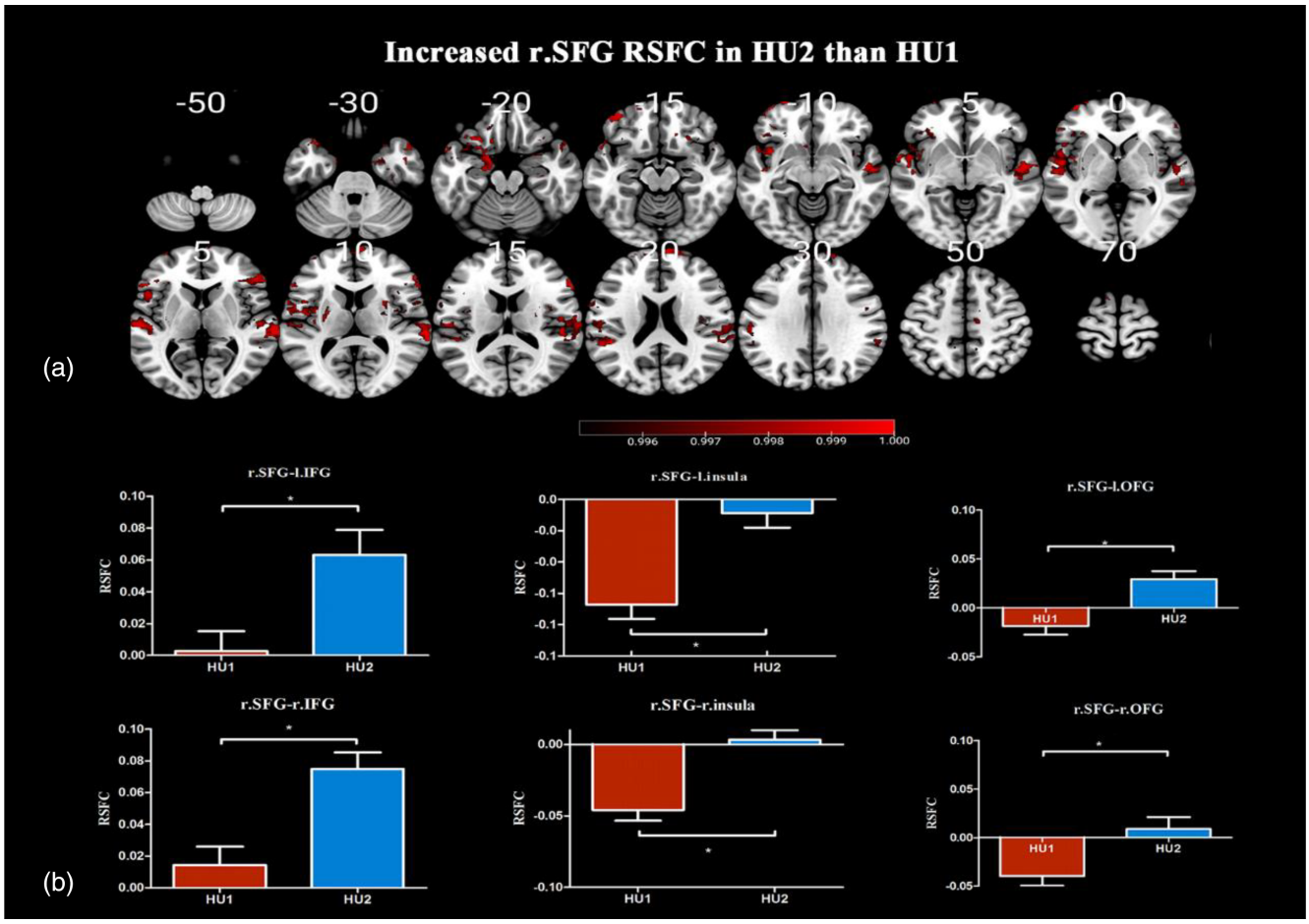

FIGURE 5 (a, b) Increased RSFC of the right SFG was observed with the bilateral IFG, insula and OFC (uncorrected) for HU2 relative to HU1. HU, heroin user; IFG, inferior frontal gyrus; OFC, orbitofrontal cortex; RSFC, resting-state functional connectivity; SFG: superior frontal gyrus

demonstrated in short-term abstinent HUs or opioid users relative to HCs in previous cross-sectional studies (Jiang et al., 2011, 2013; Wang et al., 2013; Xie et al., 2011). Moreover, a longitudinal study demonstrated increased structural connectivity in frontal and striatal regions in HUs after 1 month of treatment and abstinence (Fahmy et al., 2018). Taken together, these and our results suggest that these SFG circuit RSFC changes can be potential neuroimaging biomarkers for cognition improvement after protracted abstinence in HUs.

Reduced craving was also observed in HUs after protracted abstinence. Craving is the key to maintaining chronic drug-seeking and drug-taking behaviors (Koob & Volkow, 2016) and is regulated via interactions between the PFC (e.g., SFG and DLPFC) and several regions, including the striatum, OFC and insula (Li et al., 2014, 2016; Wilson, Sayette, & Fiez, 2004). Recently, our study on heroin use demonstrated the presence of significant functional couplings between the PFC and the OFC and striatum during a drug cue exposure task (Liu et al., 2021). Consistently, we found that after protracted abstinence, reduced craving was correlated with improved RSFC between the bilateral SFG and the left OFC (Figure 6). Our results highlight the possible roles of SFG-OFC circuits in craving Joffe, Winder, and Conn (2021). The OFC is a crucial region for controlling goal-oriented behavior in SUD and is thought to be related to the incubation of heroin craving (Altshuler et al., 2021) induced by salient stimuli, which then leads to drug-seeking and drug-taking behaviors. Additionally, the OFC is densely connected with the striatum and limbic regions, which are associated with motivational behavior and reward processing (Wilson et al., 2004). The current study advances this field by illustrating the relationship between increased SFG RSFC and reduced craving after protracted abstinence.

Finally, we also found that the cortical thickness in the bilateral superior temporal and supramarginal regions, the left pericalcarine and postcentral, fusiform, paracentral regions, and the right precentral region was decreased after protracted abstinence compared with the baseline. The alterations in these brain regions were consistent with previous longitudinal structural studies in cocaine users (Li et al., 2018; Lou et al., 2012; Xu et al., 2010; Zhang et al., 2015). These regions are hypothesized to be associated with impulsivity and drug-seeking behaviors in HUs (Ma et al., 2015; Sun et al., 2017; Xie et al., 2011). In the current study, the decreased cortical thickness of these regions might reflect the impulsivity changes seen in HUs. Evidently, the lack of impulsivity scales in the current study makes it difficult to test these hypotheses, which therefore needs to be confirmed in future studies.

In summary, we identified improved cognitive function and reduced craving in HUs after protracted abstinence, as well as

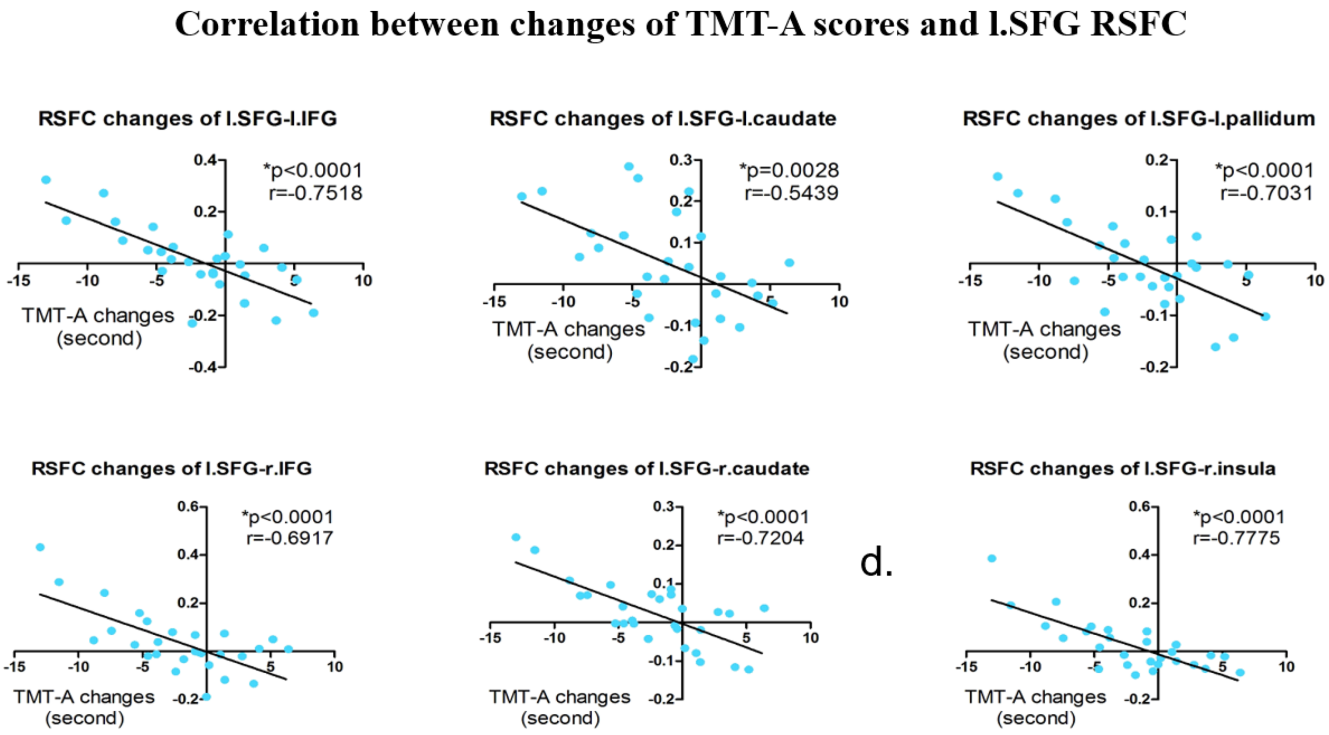

FIGURE 6 RSFC changes between the left SFG and the bilateral inferior frontal gyrus (left: $r = -.752$, $p < .0001$; right: $r = -.692$, $p < .0001$), the bilateral caudate (left: $r = -.544$, $p = .0028$; right: $r = -.720$, $p < .0001$), the left pallidum ($r = -.703$, $p < .0001$), and the right insula ($r = -.778$, $p < .0001$) were negatively correlated with changes in TMT-A scores. RSFC, resting-state functional connectivity; SFG: superior frontal gyrus; TMT-A, Trail Making Test-A

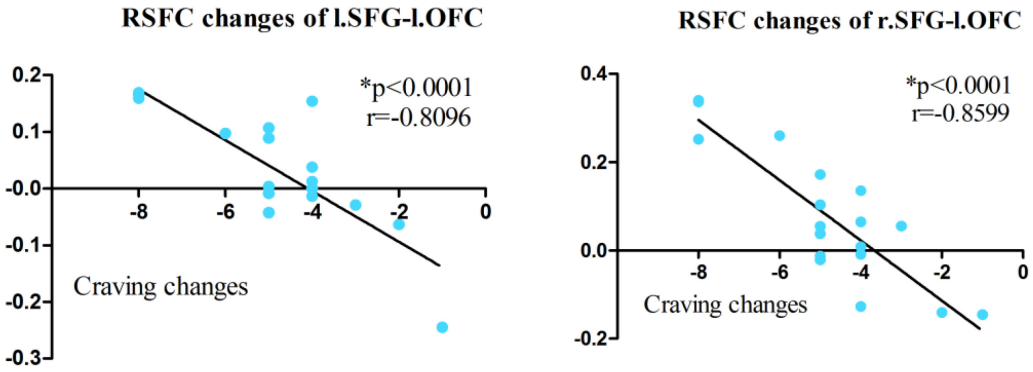

FIGURE 7 Changes in craving scores in HUs were negatively correlated with RSFC changes between the left OFC in both hemispheres and the left OFC in both hemispheres (left: $r = -.810$, $p < .0001$; right: $r = -.860$, $p < .0001$). HU, heroin user; OFC, orbitofrontal cortex; RSFC, resting-state functional connectivity; SFG: superior frontal gyrus

increased SFG cortical thickness and enhanced SFG RSFC. The association between changes in behavior and neuroimaging further implies the potential for brain recovery in HUs after protracted abstinence. Our results demonstrate that impaired frontal-limbic neurocircuits can be partially recovered, which would support both cognitive improvement and reduced craving. No correlation between the right SFG RSFC and improved cognitive function or reduced craving was found, which might be due to asymmetry of the brain. Since structural asymmetry is one of the organizing characteristic of the cerebral cortex (Roe et al., 2021), it is unknown whether chronic drug use alters cortical structural or functional asymmetry and/or the asymmetric interhemispheric recovery of structure or function.

4.1 | Limitations

This study had several limitations. First, a comparison with HCs was lacking in this study. Second, only approximately 56% (61/108) of subjects were included in the 8-month follow-up; that is, some HUs in this study were lost to follow-up. Further work in larger follow-up

samples is warranted. Third, some subjects refused to complete both the baseline and follow-up TMT and/or craving assessment, and only a portion of subjects completed the TMT (28/58) and craving (18/58 assessment) at both time points, which limits the interpretability of the results due to the very small sample size. Another limitation is that we did not assess cognition or craving levels during acute abstinence. Given the relatively especial nature of the population in this study, this limited sample size is difficult to increase; thus, this is a preliminary study. In addition, treatment consisting of education and physical exercise might be an effective way to maintain abstinence and cognitive recovery. Finally, age- and gender-matched control groups are needed to exclude the possible effect of time. Further work will be needed to investigate the possible relationship between SFG RSFC and craving in HUs after protracted abstinence to understand the implications of the structural and functional recovery of the brain after protracted abstinence.

ACKNOWLEDGMENTS

The authors express their appreciation for the patients and other volunteers who participated in this study.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

Wenhan Yang, Jun Liu, and Kai Yuan conceived and designed the study. Wenhan Yang, Min Zhang, Fei Tang, and Yanyao Du conducted the behavioral and imaging analyses. Jing Luo, Li Fan, Cui Yan, Shicong Wang, Jun Zhang, and Jun Liu conducted the assessments. Jun Liu and Kai Yuan revised the manuscript and supervised the study. Wenhan Yang wrote the first draft, and all the authors provided input on the final version of the manuscript.

COMPLIANCE WITH ETHICAL STANDARDS

All human studies were approved by the local Institutional Review Board (IRB) of the Second Xiang-Ya Hospital of Central South University. All subjects provided signed written consent forms before participating in any experiments.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ORCID

Wenhan Yang https://orcid.org/0000-0001-8690-6847
Kai Yuan https://orcid.org/0000-0002-3098-1124

REFERENCES

Altshuler, R. D., Yang, E. S., Garcia, K. T., Davis, I. R., Olaniran, A., Haile, M., … Li, X. (2021). Role of orbitofrontal cortex in incubation of oxycodone craving in male rats. *Addiction Biology*, *26*(2), e12927. https://doi.org/10.1111/adb.12927

Balodis, I. M., Kober, H., Worhunsky, P. D., Stevens, M. C., Pearlson, G. D., Carroll, K. M., … Potenza, M. N. (2016). Neurofunctional reward processing changes in cocaine dependence during recovery. *Neuropsychopharmacology*, *41*(8), 2112–2121. https://doi.org/10.1038/npp.2016.11

Berlingeri, M., Losasso, D., Girolo, A., Cozzolino, E., Masullo, T., Scotto, M., … Paulesu, E. (2017). Resting state brain connectivity patterns before eventual relapse into cocaine abuse. *Behavioural Brain Research*, *327*, 121–132. https://doi.org/10.1016/j.bbr.2017.01.002

Bowie, C. R., & Harvey, P. D. (2006). Administration and interpretation of the trail making test. *Nature Protocols*, *1*(5), 2277–2281. https://doi.org/10.1038/nprot.2006.390

Darcq, E., & Kieffer, B. L. (2018). Opioid receptors: Drivers to addiction? *Nature Reviews. Neuroscience*, *19*(8), 499–514. https://doi.org/10.1038/s41583-018-0028-x

Demirakca, T., Ende, G., Kammerer, N., Welzel-Marquez, H., Hermann, D., Heinz, A., … Mann, K. (2011). Effects of alcoholism and continued abstinence on brain volumes in both genders. *Alcoholism, Clinical and Experimental Research*, *35*(9), 1678–1685. https://doi.org/10.1111/j.1530-0277.2011.01514.x

Dong, H., Wang, M., Zhang, J., Hu, Y., Potenza, M. N., & Dong, G. H. (2021). Reduced frontostriatal functional connectivity and associations with severity of internet gaming disorder. *Addiction Biology*, *26*(4), e12985. https://doi.org/10.1111/adb.12985

Fahmy, R., Wasfi, M., Mamdouh, R., Moussa, K., Wahba, A., Wittemann, M., … Wolf, R. C. (2018). Mindfulness-based interventions modulate structural network strength in patients with opioid dependence. *Addictive Behaviors*, *82*, 50–56. https://doi.org/10.1016/j.addbeh.2018.02.013

Fitzpatrick, R. E., Rubenis, A. J., Lubman, D. I., & Verdejo-Garcia, A. (2020). Cognitive deficits in methamphetamine addiction: Independent contributions of dependence and intelligence. *Drug and Alcohol Dependence*, *209*, 107891. https://doi.org/10.1016/j.drugalcdep.2020.107891

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews. Neuroscience*, *12*(11), 652–669. https://doi.org/10.1038/nrn3119

Gowin, J. L., Harle, K. M., Stewart, J. L., Wittmann, M., Tapert, S. F., & Paulus, M. P. (2014). Attenuated insular processing during risk predicts relapse in early abstinent methamphetamine-dependent individuals. *Neuropsychopharmacology*, *39*(6), 1379–1387. https://doi.org/10.1038/npp.2013.333

He, Q., Huang, X., Turel, O., Schulte, M., Huang, D., Thames, A., … Hser, Y. I. (2018). Presumed structural and functional neural recovery after long-term abstinence from cocaine in male military veterans. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *84*(Pt. A), 18–29. https://doi.org/10.1016/j.pnpbp.2018.01.024

Humphreys, K., & Bickel, W. K. (2018). Toward a neuroscience of long-term recovery from addiction. *JAMA Psychiatry*, *75*(9), 875–876. https://doi.org/10.1001/jamapsychiatry.2018.0956

Jager, G., Kahn, R. S., Van Den Brink, W., Van Ree, J. M., & Ramsey, N. F. (2006). Long-term effects of frequent cannabis use on working memory and attention: An fMRI study. *Psychopharmacology*, *185*(3), 358–368. https://doi.org/10.1007/s00213-005-0298-7

Jiang, G., Wen, X., Qiu, Y., Zhang, R., Wang, J., Li, M., … Huang, R. (2013). Disrupted topological organization in whole-brain functional networks of heroin-dependent individuals: A resting-state FMRI study. *PLoS One*, *8*(12), e82715. https://doi.org/10.1371/journal.pone.0082715

Jiang, G. H., Qiu, Y. W., Zhang, X. L., Han, L. J., Lv, X. F., Li, L. M., … Tian, J. Z. (2011). Amplitude low-frequency oscillation abnormalities in the heroin users: A resting state fMRI study. *NeuroImage*, *57*(1), 149–154. https://doi.org/10.1016/j.neuroimage.2011.04.004

Joffe, M. E., Winder, D. G., & Conn, P. J. (2021). Increased synaptic strength and mGlu2/3 receptor plasticity on mouse prefrontal cortex Intratelencephalic pyramidal cells following intermittent access to ethanol. *Alcoholism, Clinical and Experimental Research*, *45*(3), 518–529. https://doi.org/10.1111/acer.14546

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, *35*(1), 217–238. https://doi.org/10.1038/npp.2009.110

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

Li, M., Tian, J., Zhang, R., Qiu, Y., Wen, X., Ma, X., … Huang, R. (2014). Abnormal cortical thickness in heroin-dependent individuals. *NeuroImage*, *88*, 295–307. https://doi.org/10.1016/j.neuroimage.2013.10.021

Li, Q., Li, Z., Li, W., Zhang, Y., Wang, Y., Zhu, J., … Liu, Y. (2016). Disrupted default mode network and basal craving in male heroin-dependent individuals: A resting-state fMRI study. *The Journal of Clinical Psychiatry*, *77*(10), e1211–e1217. https://doi.org/10.4088/JCP.15m09965

Li, Q., Liu, J., Wang, W., Wang, Y., Li, W., Chen, J., … Wang, W. (2018). Disrupted coupling of large-scale networks is associated with relapse behaviour in heroin-dependent men. *Journal of Psychiatry & Neuroscience*, *43*(1), 48–57.

Li, Q., Wang, Y., Zhang, Y., Li, W., Zhu, J., Zheng, Y., … Tian, J. (2013). Assessing cue-induced brain response as a function of abstinence duration in heroin-dependent individuals: An event-related fMRI study. *PLoS One*, *8*(5), e62911. https://doi.org/10.1371/journal.pone.0062911

Liu, J., Qin, W., Yuan, K., Li, J., Wang, W., Li, Q., … Tian, J. (2011). Interaction between dysfunctional connectivity at rest and heroin cues-induced brain responses in male abstinent heroin-dependent individuals. *PLoS One*, *6*(10), e23098. https://doi.org/10.1371/journal.pone.0023098

Liu, S., Wang, S., Zhang, M., Xu, Y., Shao, Z., Chen, L., … Yuan, K. (2021). Brain responses to drug cues predict craving changes in abstinent heroin users: A preliminary study. *NeuroImage*, *237*, 118169. https://doi.org/10.1016/j.neuroimage.2021.118169

Lou, M., Wang, E., Shen, Y., & Wang, J. (2012). Cue-elicited craving in heroin addicts at different abstinent time: An fMRI pilot study. *Substance Use & Misuse*, *47*(6), 631–639. https://doi.org/10.3109/10826084.2011.646381

Ma, X., Qiu, Y., Tian, J., Wang, J., Li, S., Zhan, W., … Xu, Y. (2015). Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. *PLoS One*, *10*(4), e120861. https://doi.org/10.1371/journal.pone.0120861

Morales, A. M., Lee, B., Hellemann, G., O'Neill, J., & London, E. D. (2012). Gray-matter volume in methamphetamine dependence: Cigarette smoking and changes with abstinence from methamphetamine. *Drug and Alcohol Dependence*, *125*(3), 230–238. https://doi.org/10.1016/j.drugalcdep.2012.02.017

Mottola, C. A. (1993). Measurement strategies: The visual analogue scale. *Decubitus*, *6*(5), 56–58.

Naqvi, N. H., Rudrauf, D., Damasio, H., & Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. *Science*, *315*(5811), 531–534. https://doi.org/10.1126/science.1135926

Parvaz, M. A., Moeller, S. J., D'Oleire, U. F., Pflumm, A., Maloney, T., Alia-Klein, N., … Goldstein, R. Z. (2017). Prefrontal gray matter volume recovery in treatment-seeking cocaine-addicted individuals: A longitudinal study. *Addiction Biology*, *22*(5), 1391–1401. https://doi.org/10.1111/adb.12403

Patel, A. X., Kundu, P., Rubinov, M., Jones, P. S., Vertes, P. E., Ersche, K. D., … Bullmore, E. T. (2014). A wavelet method for modeling and despiking motion artifacts from resting-state fMRI time series. *NeuroImage*, *95*, 287–304. https://doi.org/10.1016/j.neuroimage.2014.03.012

Qiu, Y. W., Jiang, G. H., Su, H. H., Lv, X. F., Tian, J. Z., Li, L. M., … Zhuo, F. Z. (2013). The impulsivity behavior is correlated with prefrontal cortex gray matter volume reduction in heroin-dependent individuals. *Neuroscience Letters*, *538*, 43–48. https://doi.org/10.1016/j.neulet.2013.01.019

Ramey, T., & Regier, P. S. (2018). Cognitive impairment in substance use disorders. *CNS Spectrums*, *4*(1), 102–113. https://doi.org/10.1017/S1092852918001426

Roe, J. M., Vidal-Pineiro, D., Sorensen, O., Brandmaier, A. M., Duzel, S., Gonzalez, H. A., … Westerhausen, R. (2021). Asymmetric thinning of the cerebral cortex across the adult lifespan is accelerated in Alzheimer's disease. *Nature Communications*, *12*(1), 721. https://doi.org/10.1038/s41467-021-21057-y

Sampedro-Piquero, P., Ladron, D. G. D., Pavon, F. J., Serrano, A., Suarez, J., Rodriguez, D. F. F., … Castilla-Ortega, E. (2019). Neuroplastic and cognitive impairment in substance use disorders: A therapeutic potential of cognitive stimulation. *Neuroscience and Biobehavioral Reviews*, *106*, 23–48. https://doi.org/10.1016/j.neubiorev.2018.11.015

Schluter, R. S., Daams, J. G., van Holst, R. J., & Goudriaan, A. E. (2018). Effects of non-invasive Neuromodulation on executive and other cognitive functions in addictive disorders: A systematic review. *Frontiers in Neuroscience*, *12*, 642. https://doi.org/10.3389/fnins.2018.00642

Seifert, C. L., Magon, S., Sprenger, T., Lang, U. E., Huber, C. G., Denier, N., … Walter, M. (2015). Reduced volume of the nucleus accumbens in heroin addiction. *European Archives of Psychiatry and Clinical Neuroscience*, *265*(8), 637–645. https://doi.org/10.1007/s00406-014-0564-y

Steele, V. R., Maurer, J. M., Arbabshirani, M. R., Claus, E. D., Fink, B. C., Rao, V., … Kiehl, K. A. (2018). Machine learning of functional magnetic resonance imaging network connectivity predicts substance abuse treatment completion. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(2), 141–149. https://doi.org/10.1016/j.bpsc.2017.07.003

Sun, Y., Wang, G. B., Lin, Q. X., Lu, L., Shu, N., Meng, S. Q., … Shi, J. (2017). Disrupted white matter structural connectivity in heroin abusers. *Addiction Biology*, *22*(1), 184–195. https://doi.org/10.1111/adb.12285

Tanabe, J., York, P., Krmpotich, T., Miller, D., Dalwani, M., Sakai, J. T., … Rojas, D. C. (2013). Insula and orbitofrontal cortical morphology in substance dependence is modulated by sex. *American Journal of Neuroradiology*, *34*(6), 1150–1156. https://doi.org/10.3174/ajnr.A3347

Verdejo-Garcia, A., & Perez-Garcia, M. (2007). Profile of executive deficits in cocaine and heroin polysubstance users: Common and differential effects on separate executive components. *Psychopharmacology*, *190*(4), 517–530. https://doi.org/10.1007/s00213-006-0632-8

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Franceschi, D., Sedler, M., … Logan, J. (2001). Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *The Journal of Neuroscience*, *21*(23), 9414–9418.

Volkow, N. D., Hitzemann, R., Wang, G. J., Fowler, J. S., Wolf, A. P., Dewey, S. L., … Handlesman, L. (1992). Long-term frontal brain metabolic changes in cocaine abusers. *Synapse*, *11*(3), 184–190. https://doi.org/10.1002/syn.890110303

Volkow, N. D., Michaelides, M., & Baler, R. (2019). The neuroscience of drug reward and addiction. *Physiological Reviews*, *99*(4), 2115–2140. https://doi.org/10.1152/physrev.00014.2018

Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D., & Telang, F. (2011). Addiction: Beyond dopamine reward circuitry. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(37), 15037–15042. https://doi.org/10.1073/pnas.1010654108

Volkow, N. D., Wang, G. J., Hitzemann, R., Fowler, J. S., Overall, J. E., Burr, G., … Wolf, A. P. (1994). Recovery of brain glucose metabolism in detoxified alcoholics. *The American Journal of Psychiatry*, *151*(2), 178–183. https://doi.org/10.1176/ajp.151.2.178

Wang, S., Zhang, M., Liu, S., Xu, Y., Shao, Z., Chen, L., … Yuan, K. (2021). Impulsivity in heroin-dependent individuals: Structural and functional

abnormalities within frontostriatal circuits. *Brain Imaging and Behavior*. *15*(5), 2454–2463. https://doi.org/10.1007/s11682-020-00445-w

Wang, Y., Zhu, J., Li, Q., Li, W., Wu, N., Zheng, Y., … Wang, W. (2013). Altered fronto-striatal and fronto-cerebellar circuits in heroin-dependent individuals: A resting-state FMRI study. *PLoS One*, *8*(3), e58098. https://doi.org/10.1371/journal.pone.0058098

Wilson, S. J., Sayette, M. A., & Fiez, J. A. (2004). Prefrontal responses to drug cues: A neurocognitive analysis. *Nature Neuroscience*, *7*(3), 211–214. https://doi.org/10.1038/nn1200

Witt, S. H., Frank, J., Frischknecht, U., Treutlein, J., Streit, F., Foo, J. C., … Rietschel, M. (2020). Acute alcohol withdrawal and recovery in men lead to profound changes in DNA methylation profiles: A longitudinal clinical study. *Addiction*, *115*(11), 2034–2044. https://doi.org/10.1111/add.15020

Xie, C., Shao, Y., Fu, L., Goveas, J., Ye, E., Li, W., … Yang, Z. (2011). Identification of hyperactive intrinsic amygdala network connectivity associated with impulsivity in abstinent heroin addicts. *Behavioural Brain Research*, *216*(2), 639–646. https://doi.org/10.1016/j.bbr.2010.09.004

Xu, J., DeVito, E. E., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., … Potenza, M. N. (2010). White matter integrity is associated with treatment outcome measures in cocaine dependence. *Neuropsychopharmacology*, *35*(7), 1541–1549. https://doi.org/10.1038/npp.2010.25

Yang, W., Wang, S., Shao, Z., Yang, R., Tang, F., Luo, J., … Yuan, K. (2021). Novel circuit biomarker of impulsivity and craving in male heroin-dependent individuals. *Drug and Alcohol Dependence*, *219*, 108485. https://doi.org/10.1016/j.drugalcdep.2020.108485

Yang, Z., Shao, Y. C., Li, S. J., Qi, J. L., Zhang, M. J., Hao, W., … Jin, G. Z. (2008). Medication of l-tetrahydropalmatine significantly ameliorates opiate craving and increases the abstinence rate in heroin users: A pilot study. *Acta Pharmacologica Sinica*, *29*(7), 781–788. https://doi.org/10.1111/j.1745-7254.2008.00817.x

Yu, Y., Zhao, Y., Si, Y., Ren, Q., Ren, W., Jing, C., … Zhang, H. (2016). Estimation of the cool executive function using frontal electroencephalogram signals in first-episode schizophrenia patients. *Biomedical Engineering Online*, *15*(1), 131. https://doi.org/10.1186/s12938-016-0282-y

Zhang, M., Liu, S., Wang, S., Xu, Y., Chen, L., Shao, Z., … Yuan, K. (2021). Reduced thalamic resting-state functional connectivity and impaired cognition in acute abstinent heroin users. *Human Brain Mapping*. *42*(7), 2077–2088. https://doi.org/10.1002/hbm.25346

Zhang, R., Jiang, G., Tian, J., Qiu, Y., Wen, X., Zalesky, A., … Huang, R. (2016). Abnormal white matter structural networks characterize heroin-dependent individuals: A network analysis. *Addiction Biology*, *21*(3), 667–678. https://doi.org/10.1111/adb.12234

Zhang, Y., Gong, J., Xie, C., Ye, E. M., Jin, X., Song, H., … Shao, Y. (2015). Alterations in brain connectivity in three sub-regions of the anterior cingulate cortex in heroin-dependent individuals: Evidence from resting state fMRI. *Neuroscience*, *284*, 998–1010. https://doi.org/10.1016/j.neuroscience.2014.11.007

How to cite this article: Yang, W., Zhang, M., Tang, F., Du, Y., Fan, L., Luo, J., Yan, C., Wang, S., Zhang, J., Yuan, K., & Liu, J. (2022). Recovery of superior frontal gyrus cortical thickness and resting-state functional connectivity in abstinent heroin users after 8 months of follow-up. *Human Brain Mapping*, *43*(10), 3164–3175. https://doi.org/10.1002/hbm.25841