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Neurobiological underpinnings of sensation seeking trait in heroin abusers

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Abstract

Neurobiological investigation of heroin revealed that abusers of this highly addictive substance show dysregulation in brain circuits for reward processing and cognitive control. Psychologically, personality traits related to reward processing and cognitive control differed between heroin abusers and non-abusers. Yet, there is no direct evidence on the relationship between these neurobiological and psychological findings on heroin abusers, and whether such relationship is altered in these abusers. The present study filled this research gap by integrating findings obtained via magnetic resonance imaging (structural volume and resting-state functional connectivity) and self-reported personality trait measures (Zuckerman's Sensation Seeking Scale and Barratt Impulsivity Scale) on 33 abstinent heroin users and 30 matched healthy controls. The key finding is a negative relationship between high sensation seeking tendency and midbrain structural volume in the heroin users. Importantly, there was stronger coupling between the midbrain and ventromedial prefrontal cortex and weaker coupling between the midbrain and dorsolateral prefrontal cortex in heroin users. Our findings offer significant insight into the neural underpinning of sensation seeking in heroin users. Importantly, the data shed

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light on a novel relationship between the mesolimbic-prefrontal pathway of the reward system and the high sensation seeking personality trait in heroin abusers.

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1. Introduction

Heroin abuse elicits rapid feelings of euphoria and adverse withdrawal effects. For these reasons, heroin is very addictive and its abuse highly resistive from long-term abstinence. The severe and persistent socio-economic burden caused by heroin addiction (Tang et al., 2006) highlight the significance of understanding the neuropsychological basis of heroin use. At the neurobiological level, heroin abuse is known for disrupting the mesolimbic-prefrontal pathway, which is an integral part of the brain reward system implicated in addiction (Everitt and Robbins, 2005; Goldstein and Volkow, 2011; Schultz, 2011). At the psychological level, sensation seeking and impulsivity traits are two personality constructs commonly associated with heroin addiction (Craig, 1979). One crucial and outstanding issue that needs addressing is the neural underpinning of these personality traits that characterize heroin abuse. Currently, information on such neurobiological basis of heroin use is scarce. This lack of information may be because the accessibility of the heroin-abusing population has been a challenge, even though the abuse of heroin is prevalent among substance abusers (Tang et al., 2006).

Regarding the long-term effect of heroin use on brain structure, a consistent finding is that abstinent heroin users have reduced gray matter volume in the prefrontal cortex (Liu et al., 2009a), among other brain regions (Lyo et al., 2006; Yuan et al., 2009, 2010b). Regarding task-induced changes in blood-oxygenated level dependent (BOLD) signal, regions along the mesolimbic-prefrontal circuit (including the midbrain, striatum, amygdala, hippocampal, and prefrontal regions) have been most commonly found to alter in abstinent heroin users, especially in response to reward stimuli (Zijlstra et al., 2009) or cognitive demand (Lee et al., 2005). Resting-state functional connectivity studies found abnormal coupling in brain regions associated with reward processing and cognitive control (Liu et al., 2009b; Ma et al., 2010, 2011; Yuan et al., 2010a, 2010c), in either abstinent heroin abusers or individuals on methadone maintenance treatment (MMT). Although the vast majority of neuroimaging studies investigated heroin users in a state of abstinence, there are a few recent studies that examined the acute effect of heroin on heroin-dependent individuals enrolled in addiction treatment. These studies revealed that, compared to saline, heroin administration reduced BOLD signal in the prefrontal cortex (in response to cognitive demand) (Schmidt et al., 2013), the amygdala network (in response to emotional stimuli) (Schmidt et al., 2015a), and enhanced BOLD signal in the resting-state functional connectivity of the left putamen (in response to subjective pleasure) (Schmidt et al., 2015b). Furthermore, animal models of addiction demonstrated that the reward system is critically involved in heroin-seeking behavior (e.g., the nucleus accumbens; LaLumiere and Kalivas, 2008).

On a separate line of studies, the personality traits related to reward and cognitive control have been investigated among heroin users. Two personality constructs closely linked with heroin abuse are sensation seeking and impulsivity traits (Craig, 1979). Sensation seeking refers to need to seek intense sensations and the desire to engage in risky behavior associated with such sensations (Zuckerman, 1994). Individuals with heroin addiction scored higher on this trait compared to controls, even after adjusting for group differences in age, education, and intelligence (Platt, 1975). Impulsivity refers to the degree of behavioral control over novel or distracting stimuli and is known to underlie impulsive behavior in various forms of addiction (Patton et al., 1995). Both current and abstinent heroin users were reported to score higher on the impulsivity trait, relative to matched controls (Clair et al., 2009). Neuroimaging studies on healthy adults revealed that these personality traits are associated with the brain reward system. For instance, the novelty/experience seeking trait was found to correlate with the extent of glucose metabolism in the midbrain, parahippocampal region, and right prefrontal cortex (Youn et al., 2002), and with structural volume of the right hippocampus (Martin et al., 2007). A relatively recent study revealed that higher impulsivity trait is associated with lower structural volume of the ventromedial prefrontal cortex (Matsuo et al., 2009). Despite the theoretical postulations that the brain reward system underpins the pathological personality traits in people with addiction, there has not been any study that directly characterized this neuropsychological relationship in heroin abusers. This characterization is important because defining such neuropsychological abnormality would help refine theoretical models of addiction (Dalley et al., 2011; de Wit, 2009; Everitt et al., 2008; Schoenbaum et al., 2006). It would also facilitate the potential to utilize neuroimaging measures as a biological predictor of personality pathology; and vice versa, in which trait measures act as a behavioral predictor of neuropathology.

To these ends, we recruited a group of currently abstinent heroin abusers and matched healthy controls to test for group difference in the relationship between brain and personality trait (sensation seeking and impulsivity traits) measures. A multimodal imaging protocol of structural volume and resting-state functional connectivity was used, as both imaging modalities have strong conceptual grounds for their ability to capture individual differences in cognition and behavior (Harmelech and Malach, 2013; Kanai and Rees, 2011). The Zuckerman Sensation Seeking Scale (SSS) and the Barratt Impulsivity Scale (BIS) were used for measuring sensation seeking trait and impulsivity trait respectively, as both have sound psychometric properties and are widely used self-report measurement scales (Clair et al., 2009; Lai et al., 2011; Patton et al., 1995; Zuckerman, 1994). Abstinent heroin users were

Table 1 Comparison of demographic details between heroin users ($n=33$) and healthy controls ($n=30$). RPM=Raven's Progressive Matrices, HADS=Hospital Anxiety and Depression Scale, \pm =standard deviation, p =associated p -value, ns =non-significant.

	Heroin users ($n=33$)	Controls ($n=30$)	Comparisons
	Mean	Mean	p
Age	35.1 \pm 4.0	33.1 \pm 9.9	ns
Body mass index	22.1 \pm 2.0	23.3 \pm 3.1	ns
Years of education ^a	8.5 \pm 1.8	11.5 \pm 2.9	< .001
Estimated intelligence (RPM) ^b	43.5 \pm 7.6	46.2 \pm 8.8	ns
HADS anxiety	14.4 \pm 3.5	5.5 \pm 3.3	< .001
HADS depression	14.1 \pm 2.5	4.0 \pm 3.0	< .001
Smokers	33/33	8/30	
Cigarette per day ^c	18.5 \pm 4.8	1.6 \pm 3.5	
Drinkers	24/33	3/30	
Drinks per day ^c	2.7 \pm 1.8	2.3 \pm 1.2	
Age of first heroin use	20.8 \pm 4.5		
Duration of previous heroin use (months)	67.0 \pm 65.2		
Duration of abstinence (months)	12.1 \pm 9.8		
Route of administration	26 Injection 4 Smoke 3 Oral		

^aStarting from primary school and excluding the most recent incomplete year.

^bBased on the raw score, with a maximum of 60.

^cCalculated as the mean among individuals who smoke/drink.

recruited to ensure intact gross cognition, which was required for completing self-reported personality scales. Moreover, personality traits are understood as relatively stable attributes, especially in light of evidence that they are possible endophenotypes in the addiction population (Ersche et al., 2010). Given the observation that heroin abuse is associated with reduced structural and functional response within the cognitive/cortical system (e.g., Liu et al., 2009a; Lee et al., 2005; Schmidt et al., 2013; Xie et al., 2014), and heightened response within the emotional/subcortical system (e.g., Schmidt et al., 2015b; Xie et al., 2014; Zijlstra et al., 2009), we hypothesized that any atypical neuropsychological relationship of sensation seeking and impulsivity traits associated with heroin abuse would manifest as cortical-downregulation and subcortical-upregulation along the mesolimbic-prefrontal circuit.

2. Experimental procedures

2.1. Participants

A total of 63 right-handed Han Chinese men consented to participate in this study, which was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority (Hong Kong West Cluster). Among these participants, there were 33 abstinent heroin users and 30 matched healthy controls. The heroin users were recruited from two drug rehabilitation centers, where regular biochemical tests ensured that they were abstinent from any illicit drug of abuse. The abstinent heroin users were selected on the basis that they were not receiving any pharmacological treatments (e.g., methadone maintenance therapy). Based on structured clinical interviews, they were diagnosed with either heroin abuse or dependence when they were admitted to the

rehabilitation centers (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revised; American Psychiatric Association, 2000). Although most of the abstinent heroin abusers used heroin exclusively ($n=27/33$), some abusers reported that they used one or more other substances, which included methamphetamine ($n=4$), diazepam ($n=5$), and other opioids (pethidine and tramadol; $n=2$). Yet, these polydrug users were included in our sample as heroin was their major drug of abuse (i.e., heroin was more than 50% of their overall drug use). The recruitment of healthy controls was conducted via advertisements in the local communities. To qualify for inclusion in this study, both the abstinent heroin users and healthy controls could not have any self-reported history of neurological or psychiatric disorders (other than substance-related disorders) and a contraindication for MRI scanning (i.e. metal implant). They also had to consent to a venipuncture to allow sampling of their peripheral blood, the data for which are presented elsewhere (Cheng et al., 2013). The absence of previous substance abuse was an additional inclusion criterion for the healthy control participants.

To provide estimates of the participants' general intellectual functioning, the Raven's Progressive Matrices (Raven, 2008) was used. The 14-item Hospital Anxiety and Depression Scale (HADS) was used to measure the participants' states of depression and anxiety (Zigmond and Snaith, 1983). For heroin users, we characterized the profile of heroin abuse using the following variables: age of first heroin use, duration of previous heroin use, and duration of abstinence. Comparisons of the demographic details between heroin users and controls, as well as the heroin users' drug abuse records, are shown in Table 1.

2.2. Personality measures: sensation seeking and impulsivity traits

Zuckerman's Sensation Seeking Scale Form V (SSS) is a self-report measure used to determine the participants' need and desire to seek

intense sensations and to engage in risky behaviors (Zuckerman, 1994). The 44-item SSS is widely-used and suitable for use in the Chinese population (Wang et al., 2000).

Impulsivity was measured using the Chinese-translated version of Barratt's Impulsivity Scale Version 11 (BIS). This 30-item self-report questionnaire measures impulsivity as a trait, which is defined as the lack of control over novel or distracting stimulation (Patton et al., 1995). The BIS is the most commonly used measurement tool for impulsivity trait and is suitable for use in the Chinese population (Lai et al., 2011; Lee et al., 2009; Yao et al., 2007).

2.3. Structural brain measure: acquisition, preprocessing, and whole-brain volumetric brain morphometry (VBM) analysis

Brain scanning was performed using a 3T GE Signa Propeller HD MR scanner equipped with a standard whole-head coil. High-resolution whole-brain volume T1-weighted structural images were acquired using the 3D fast spoiled gradient-echo (FSPGR) sequence with the following parameters: TR=9.5 ms; TE=3.9 ms; TI=450 ms; flip angle=20°; partial FOV factor=.9; receiver bandwidth=±31.25 kHz; acquisition matrix=350 × 224; number of excitations (NEX)=1; FOV=240 × 240 mm²; slice thickness=.9 mm; 216 slices in sagittal plane; voxel resolution=1.07 × .90 × .69 mm³. The acquired structural brain images were preprocessed using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) implemented in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Specifically, each image was reoriented to match that of the template by manually locating the anterior commissure as the point of reference. The East Asian template was used for affine registration. The thorough clean up option was used to optimize the removal of non-brain tissues. The images were categorized into three tissue types: gray matter (GM), white matter (WM), and cerebrospinal fluid. High-dimensional DARTEL (Ashburner, 2007) was used for spatial normalization as it was an optimal approach for whole-brain alignment and was particularly sensitive for examining small brain structures, including deep brain nuclei (Yassa and Stark, 2009). The images were modulated with Jacobian determinants to enable testing of the effects at the local level after adjusting for individual differences in global brain size. Normalized, unsegmented images were visually inspected for gross artifacts resulting from normalization. In addition, to identify potential outliers, covariance for both normalized GM and WM segments were confirmed for sample homogeneity. Finally, both the GM and WM segments were smoothed with an 8-mm full-width half-maximum Gaussian kernel. To avoid confusion between the different tissue classes, an absolute threshold masking of <.01 was used for all structural MRI analyses.

To reveal the main effects of group (i.e., heroin users and controls) on brain structure, whole-brain independent *t*-tests were performed on both gray matter (GM) and white matter (WM) volumes. Critically, to investigate whether the neuropsychological relationship differed between heroin users and healthy controls, whole-brain interaction analyses were performed. In keeping with our previous procedures (Cheng et al., 2013), an interaction model was used because it is the statistically appropriate procedure for testing the difference between two sets of correlation (Nieuwenhuis et al., 2011). The interaction model consisted of the categorical variable of group (i.e., heroin users versus healthy controls) and the continuous variable of trait score (i.e., SSS or BIS, in separate models). The resulting contrasts would show brain regions where the relationship between the GM/WM volume and the sensation seeking/impulsivity trait score was significantly different between groups. For each significant brain cluster, the average GM/WM volumes were derived and included in the correlation analyses to examine their relationship with the trait score separately for each group. These simple main effect analyses aimed to characterize each significant interaction effect.

The structural analysis was thresholded at $p < .001$ and corrected for multiple comparisons using AlphaSim from the REST toolbox. The AlphaSim correction involved running a Monte Carlo simulation that determined the minimum size of clusters (given a specific threshold) that was required to maintain the corrected experiment-wise error rate at the canonical level ($p = .05$). Based on the imaging parameters, the Monte Carlo simulation revealed that the minimum number of voxels required in a cluster to be considered significant at a threshold level of $p < .001$ were 156 (GM structural analysis) and 147 (WM structural analysis). Years of education and HADS anxiety and depression scores (Table 1) were included as covariates not of interest. Thus, the resulting analyses revealed effects between groups matched on sex, age, BMI, and estimated IQ, with adjustments for education and affective status.

2.4. Functional resting-state brain measure: acquisition, preprocessing, and seed-based correlation analysis

Resting-state functional connectivity magnetic resonance imaging (MRI) data were acquired using the same scanner and in the same scanning session as the structural MRI. During the acquisition, subjects were awake with their eyes closed and not engaged in any task-driven cognitive processes for 6 min. The T2*-weighted echo-planar imaging sequence with the following acquisition parameters were used: TR=2000 ms; TE=30 ms; flip angle=90°; acquisition matrix=64 × 64; NEX=1; FOV=22 cm; phase FOV=1; 180 volumes acquired; slice thickness=3 mm; 36 slices in axial plane; slice gap=.6 mm; and voxel size=3.44 × 3.44 × 3.60 mm³. The acquired resting-state functional brain images were preprocessed and analyzed using the DPARSF (Yan and Zang, 2010), REST (Song et al., 2011), and SPM8 toolboxes. For each participant, the first 10 volumes were discarded to avoid interference stemming from unstable signals. The preserved images were corrected for acquisition time difference among multiple slices within an image and spatially realigned to the first volume to correct for head motion. Functional images were co-registered to each individual's high-resolution T1 image and normalized to the Montreal Neurological Institute template at a resolution of 3 × 3 × 3 mm³ via unified segmentation. Normalized images were spatially smoothed with a 6 mm FWHM Gaussian kernel. Next, using the REST toolkit, the images were band-pass filtered (at .01-.08 Hz), and their linear trends were removed and the nuisance variables regressed. The nuisance variables included 6 head motion parameters and mean signals of the whole brain (i.e., global trend), white matter and cerebrospinal fluid. The seed-based correlation analysis method was used. For each subject, the BOLD level of the seed was computed as the mean time series of all voxels within the region-of-interest (ROI) mask. The functional connectivity between the mean time series in the seed and all other voxels in the brain was then calculated using Pearson's correlations. The correlation *R*-values were transformed into Fisher's *Z*-scores for each voxel of the brain.

The seed regions were chosen based on the conjunction between our a priori prediction that the mesolimbic-prefrontal circuit would be associated with altered neuropsychological relationships in heroin abuse and the significant GM clusters identified through structural interaction analysis. In other words, the significant mesolimbic-prefrontal clusters identified from the structural analysis were used to create masks, which act as the seeds in the subsequent functional connectivity analysis. The *Z*-images representing the standardized functional connectivity between the seeds and every other voxel in the brain were used in second-level whole-brain interaction analyses to reveal any group difference in the relationship between functional connectivity with the seeds and the personality trait that yielded the significant structural brain result. The average *Z*-values of each significant brain cluster were derived

Table 2 Whole-brain *t*-test analyses of the gray matter (GM) and white matter (WM) volumes with group (i.e., heroin abusers and matched controls) as the main factor. The statistical threshold was established at $p < .001$, with a minimum of 156 (GM) or 147 (WM) voxels within a cluster to be classified as significant (AlphaSim corrected $p = .05$). Montreal Neurological Institute (MNI) space coordinates are reported. GM=gray matter, WM=white matter, L=left, R=right.

Anatomical region	Laterality	x	y	z	Number of voxels	Peak <i>t</i> -value
Controls > heroin users, GM						
Fusiform gyrus	L	-36	-76	-15	448	5.25
Thalamus	R	20	-28	9	240	5.23
Middle cingulate gyrus	R	3	-4	43	415	4.97
Precentral gyrus	L	-41	-1	45	815	4.78
		-29	0	63		4.73
		-24	21	52		4.07
		-44	0	-3		1037
Insula/superior temporal gyrus	L	-57	-6	4	1037	4.13
		-33	3	4		4.12
		65	-15	37		255
Postcentral gyrus	R	62	-3	34	255	3.86
		11	50	9		435
Superior medial frontal gyrus/superior rostral gyrus	R	14	54	16	435	4.01
		11	51	0		3.84
		50	-67	28		229
Middle occipital gyrus	R	50	-67	28	229	4.13
Controls > heroin users, WM						
No suprathreshold cluster						
Heroin users > controls, GM						
No suprathreshold cluster						
Heroin users > controls, WM						
Medial orbitofrontal region	L	-18	39	-14	360	4.30
Supramarginal region	R	59	-30	37	235	4.28

and used in correlation analyses as the simple main effect analyses for characterizing the significant interactions. The average *Z*-values were also used in the heroin group to explore their relationships with the profiles of heroin use.

Similarly to the structural VBM analysis, the AlphaSim correction was used. It was found that the minimum number of voxels required in a cluster to be considered significant at a threshold level of $p < .001$ was 13. Covariates not of interest (years of education and HADS anxiety and depression scores) were also included.

2.5. Relationship of main findings with the amount of alcohol and cigarette consumption

To understand whether the observed group differences could be attributed to group differences in cigarette use or alcohol consumption, for the heroin group, we performed correlation analyses between the number of cigarettes and amount of alcohol consumed each day with the volume or connectivity value of the clusters found to be significant in the interaction analyses.

3. Results

3.1. Group differences in sensation seeking/impulsivity traits

For the SSS, there was a significantly higher score for the heroin users (mean=25.4, SD=4.2), relative to controls

[mean=15.6, SD=3.9; $t(62) = -9.64$, $p < .001$]. For the BIS, there was also a significantly higher score for the heroin users (mean=74.3, SD=5.8), relative to controls [mean=64.3, SD=7.5; $t(62) = -5.94$, $p < .001$]. These results were consistent with previous studies that also reported higher sensation seeking and impulsive tendencies in heroin abusers, relative to matched controls.

3.2. Group differences in neuropsychological relationships: structural volume investigated using whole-brain voxel-based morphometry

Total brain volumes (defined by combination of GM and WM) analysis revealed no significant difference between the two groups in terms of overall brain volume [1196.31 cm³ and 1221.33 cm³ for heroin group and control group, respectively; $t(61) = 1.07$, $p > .05$]. Independent *t*-test voxel-wise analyses of group difference in GM revealed a widely distributed pattern of cortical and thalamic atrophy in heroin users, which was consistent with previous reports (Liu et al., 2009a; Lyoo et al., 2006; Reid et al., 2008; Yuan et al., 2009, 2010b). Specifically, heroin users had lower amounts of GM in the prefrontal, temporal, parietal, occipital, and thalamic regions (Table 2, Figure 1). There was no brain cluster that showed lower amounts of WM in heroin users, but there were greater amounts of WM in heroin users in the medial orbitofrontal and

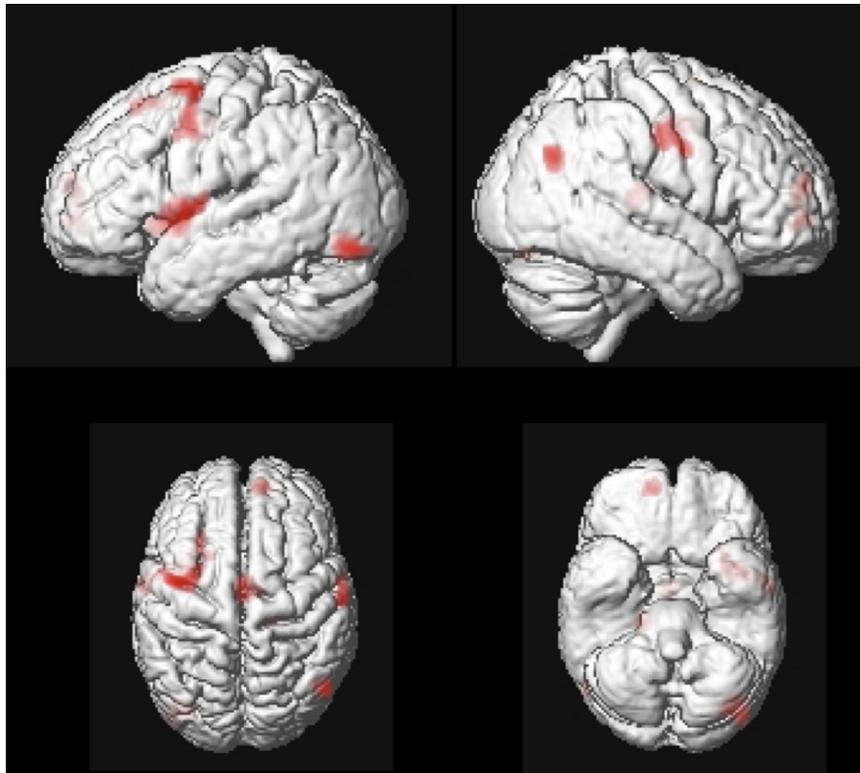


Figure 1 Brain regions with higher gray matter (GM) volume in healthy controls compared to heroin users. The results were overlaid onto a randomly selected participant's 3D rendered brain surface. Significant clusters spanned across the entire cortex, including the prefrontal, temporal, parietal, and occipital regions. The control group also showed a significantly higher GM volume in the thalamus, which may not be easily identified in this figure.

supramarginal regions. Since it was not our objective to investigate absolute group difference in brain measures in isolation from the personality trait measures, the subsequent results and discussions focused on the interaction analyses.

The brain structural interaction analyses revealed clusters where the relationship between the GM/WM volume and SSS/BIS scores significantly differed between the heroin users and matched controls (Table 3). It was found that for the GM-SSS relationship, a cluster within the midbrain was more positively correlated with SSS for the controls compared to the heroin users. Further analyses revealed that, for the control group, higher SSS scores were correlated with greater amounts of midbrain GM ($r = .61, p < .001$). However, the opposite correlation was observed in the heroin group, such that higher SSS scores were correlated with lower GM amounts in this region ($r = -.39, p < .05$) (Figure 2A). A cluster in the cerebellum also revealed a significant interaction. In this case, for the controls, there was a negative correlation between the amount of GM and SSS ($r = -.38, p = .038$). However, for the heroin controls, there was a positive correlation between the GM in the same cluster and SSS ($r = .54, p = .001$) (Figure 2B).

With regard to group difference in the WM-SSS relationship, there was a large cluster that spanned across the pons, midbrain, and thalamus. Correlation analyses revealed that this interaction was driven by a negative correlation between WM volume in this cluster and SSS for the control group ($r = -.70, p < .001$), as well as a positive correlation between WM in the same cluster and SSS for the heroin group ($r = .37, p = .033$)

(Figure 2C). There were no other brain areas that showed a significant group difference in the WM-SSS relationship.

Finally, there was only one brain region where the relationship between brain structure and BIS significantly differed between groups. This was a cluster within the lingual gyrus where the GM-BIS relationship was more positively correlated in the heroin users compared to the controls. This interaction was driven by a negative lingual gyrus GM-BIS correlation in the control group ($r = -.51, p = .004$) and a positive GM-BIS correlation in the same cluster in the heroin group ($r = .40, p = .023$) (Figure 2D).

Taken together, heroin abuse was associated with an atypical relationship between sensation seeking and the midbrain (manifested in both GM and WM). A similar observation was made in the cerebellum. The impulsivity of heroin users was also atypically related to the lingual gyrus. In the subsequent resting-state functional connectivity analysis, we used the midbrain as the seed region because this region was consistent with our a priori prediction of being implicated in heroin abuse and related personality traits.

3.3. Group differences in neuropsychological relationships: functional connectivity with the midbrain

Using the midbrain region identified from the previous structural analysis as the seed region, an interaction analysis was performed on the functional connectivity data to reveal brain

Table 3 Whole-brain interaction analyses of the gray matter (GM) and white matter (WM) volumes with group and total scores on the Sensation Seeking Scale (SSS) and the Barratt Impulsivity Scale (BIS) as factors. The statistical threshold was established at $p < .001$, with a minimum of 156 (GM) or 147 (WM) voxels within a cluster to be classified as significant (AlphaSim corrected $p = .05$). Montreal Neurological Institute (MNI) space coordinates are reported. GM=gray matter, WM=white matter, L=left, R=right, B=bilateral.

Anatomical region	Laterality	x	y	z	Number of voxels	Peak t-value
Association between SSS and GM						
Controls > heroin users						
Midbrain	R	5	-36	-23	289	3.84
		6	-30	-9		3.54
Heroin users > controls						
Cerebellum	L	-41	-57	-57	737	4.45
Association between SSS and WM						
Controls > heroin users						
No suprathreshold cluster						
Heroin users > controls						
Pons-Midbrain-Thalamus	B	0	-3	3	1752	4.43
	B	0	-31	-23		4.26
		0	-7	-9		4.14
Association between BIS and GM						
Controls > heroin users						
No suprathreshold cluster						
Heroin users > controls						
Lingual gyrus	R	18	-72	-2	316	4.53
Association between BIS and WM						
Controls > heroin users						
No suprathreshold cluster						
Heroin users > controls						
No suprathreshold cluster						

regions where the relationship between the midbrain and sensation-seeking trait significantly differed between the heroin users and matched controls. Consistent with our prediction, several prefrontal brain regions revealed a significant interaction, among other cortical and cerebellar regions (Table 4). A close examination of the locations of the significant prefrontal regions revealed an interesting pattern (Figure 3). Namely, the relationship between the sensation seeking trait and the midbrain's coupling with the dorsolateral prefrontal cortex (DLPFC) was significantly more positive and with the ventromedial prefrontal cortex (VMPFC) was significantly more negative in healthy controls. The opposite pattern of results was observed for the heroin users.

Similar to the structural analysis, the functional connectivity values of the significant clusters were derived and entered into the correlation analyses with the sensation seeking trait, independently for each group. None of the correlations were significant ($p > .05$ for all correlations). However, this did not deter us from interpreting the interaction effect, because the lack of simple main effect does not preclude the significance of an interaction effect (Keppel and Wicken, 2004).

3.4. Correlation with the profile of heroin use and alcohol/cigarette consumption

Exploratory correlation analyses were performed to investigate possible associations between the profile of heroin use and each of the significant brain clusters. We found that the coupling between the midbrain and a cluster within the VMPFC (Montreal Neurological Institute co-ordinate of cluster peak: 18, 66, -9) was positively correlated with the age of first heroin use ($r = .37$, $p = .035$).

Furthermore, the cerebellum GM cluster identified from the structural interaction analysis was significantly correlated with cigarette consumption ($r = .42$, $p = .016$), suggesting that the group difference in the relationship between the cerebellum GM and SSS may partly stem from the group difference in cigarette use. There was no other correlation between the identified brain regions (with respect to both structural and functional connectivity) and number of cigarettes smoked or amount of alcohol consumed (all $p > .05$). This suggests that the identified group differences in the neuropsychological relationship (apart from the cerebellum) were unlikely to be influenced by the group difference in tobacco and alcohol use.

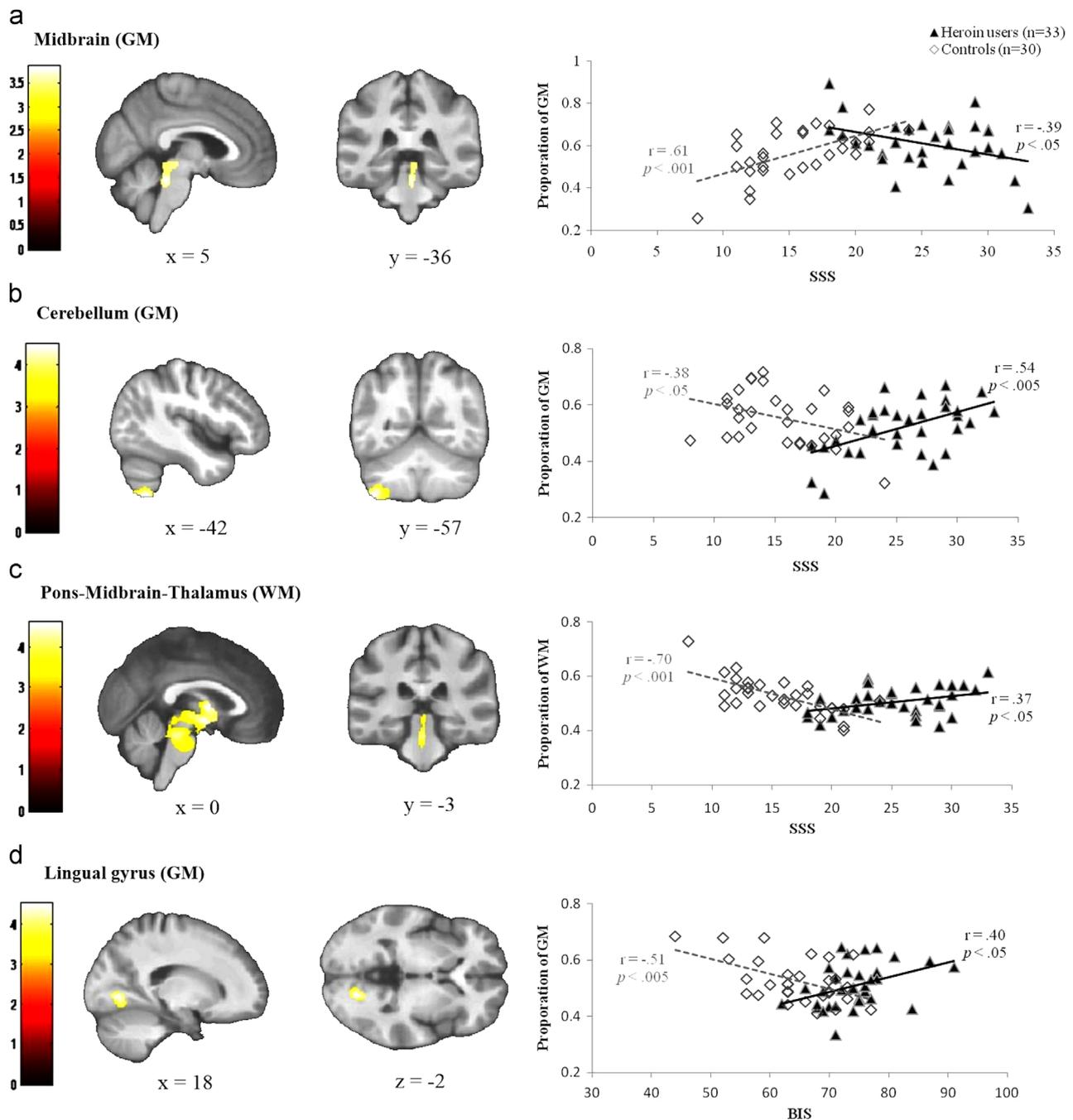


Figure 2 Structural brain regions with significant interactions between group and trait scores and the corresponding scatterplots that depict the correlations within each group. (A) The midbrain gray matter (GM) volume was positively correlated with the Sensation Seeking Scale (SSS) total score for the controls but was negatively correlated for the heroin users. (B) The cerebellum GM volume was negatively correlated with the SSS total score for the controls but was positively correlated for the heroin users. (C) The white matter (WM) volume through the Pons-Midbrain-Thalamus was negatively correlated with the SSS total score for the controls but was positively correlated for the heroin users. (D) The lingual gyrus GM volume was negatively correlated with the Barratt Impulsivity Scale (BIS) total score for the controls but was positively correlated for the heroin users. The brain image template used was the bias-corrected average image of all of the participants. The left side of the brain is shown on the left. Montreal Neurological Institute (MNI) space coordinates are used. r =Pearson's correlation coefficient. p =the associated p -value.

4. Discussion

This study investigated whether past abusers of heroin exhibited atypical neuropsychological relationships between the reward processing/cognitive control network and personality

traits by characterizing the extent to which this relationship represents an abnormal interaction with heroin abuse. Three main results emerged: (1) heroin abuse was associated with an atypical relationship between the midbrain's structural volume and high sensation seeking trait; (2) heroin users' with high

Table 4 Whole-brain interaction analyses of resting-state functional connectivity with group and Sensation Seeking Scale (SSS) scores as factors. The seed region was chosen from the midbrain cluster found to be significant in the previous brain structural interaction analysis. The statistical threshold was established at $p < .001$, with a minimum of 13 voxels within a cluster to be classified as significant (AlphaSim corrected $p = .05$). MNI space coordinates are reported. L=left, R=right, B=bilateral.

Anatomical region	Laterality	x	y	z	Number of voxels	Peak t-value
Controls > heroin users						
Supramarginal gyrus	R	63	-36	36	105	5.64
Middle temporal gyrus	R	63	-51	-3	49	4.53
Middle cingulate gyrus	R	15	15	30	14	4.47
Inferior frontal operculum	R	54	15	27	69	4.31
		42	0	36		3.71
		48	6	21		3.56
Middle frontal gyrus	R	42	39	36	46	4.17
		39	45	30		4.13
Fusiform gyrus	R	33	-18	-33	20	4.04
Middle temporal gyrus/inferior occipital gyrus	L	-57	-66	0	20	4.03
		-54	-75	0		3.74
Cerebellum	L	-18	-84	-45	22	3.94
		-15	-75	-45		3.46
		-21	-69	-51		3.34
Middle frontal gyrus	L	-33	33	21	13	3.91
Supramarginal gyrus	L	-54	-39	27	21	3.73
Heroin users > controls						
Cerebellum/precuneus/vermis	B	-6	-45	-3	104	4.76
		21	-54	15		4.68
		6	-48	6		4.59
Superior medial frontal gyrus/anterior cingulate gyrus	L	-15	60	12	98	4.72
		-6	45	9		4.24
Medial orbitofrontal cortex	L	0	48	-6	36	4.62
Calcarine	L	-9	-57	12	44	4.54
Superior orbitofrontal gyrus	R	18	66	-9	15	4.25
Cerebellum	R	24	-39	-18	13	3.78

levels of sensation seeking trait were also atypically related to the midbrain's coupling with the prefrontal cortex; and (3) the midbrain's atypical coupling with the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC) were differentially associated with heroin abuse. Altogether, this study revealed a novel understanding of the abnormal neurobiological and psychological functioning associated with heroin abuse.

4.1. Heroin use, sensation seeking trait, and the midbrain

The finding that heroin use was associated with an atypical relationship between the midbrain and high sensation seeking trait suggests a possible connection between the neuronal reward-signaling system and an excessive need to seek sensory experiences. The atypical midbrain-sensation seeking relationship this study revealed was such that there was an upward slope between midbrain volume and sensation seeking in healthy controls, but the reverse for the high sensation seeking heroin abusers. These findings suggest that the inverted-U-shape hypothesis of dopamine functioning that explain cognitive impairment in some

neuropsychiatric disorders, such as schizophrenia (Cools and Robbins, 2004), might be extended to explain the neuropathology of heroin abuse. An inverted-U relationship has been reported for sensation seeking trait (measured using the SSS) and dopamine receptor availability in the striatum in the healthy population (Gjedde et al., 2010). The present finding suggest that heroin users' pathologically high sensation seeking trait is more closely related to dopamine properties within the midbrain, although the involvement of other neurotransmitters (especially catecholamines along the ascending pathway) cannot be excluded because some are also known to follow an inverted-U distribution (Arnsten, 1998). This requires clarification through the use of radio-tracer positron emission tomography that can directly measure neurochemical functioning in the brain in-vivo. Interestingly, a previous study demonstrated that dopamine synthesis within the midbrain is related to reward processing and this relationship is age-dependent (Dreher et al., 2008). This finding runs parallel to our recent observation that heroin abuse is associated with acceleration in biological aging (Cheng et al., 2013). These findings combine to suggest that heroin abuse might be associated with a particular vulnerability in midbrain dopaminergic synthesis.

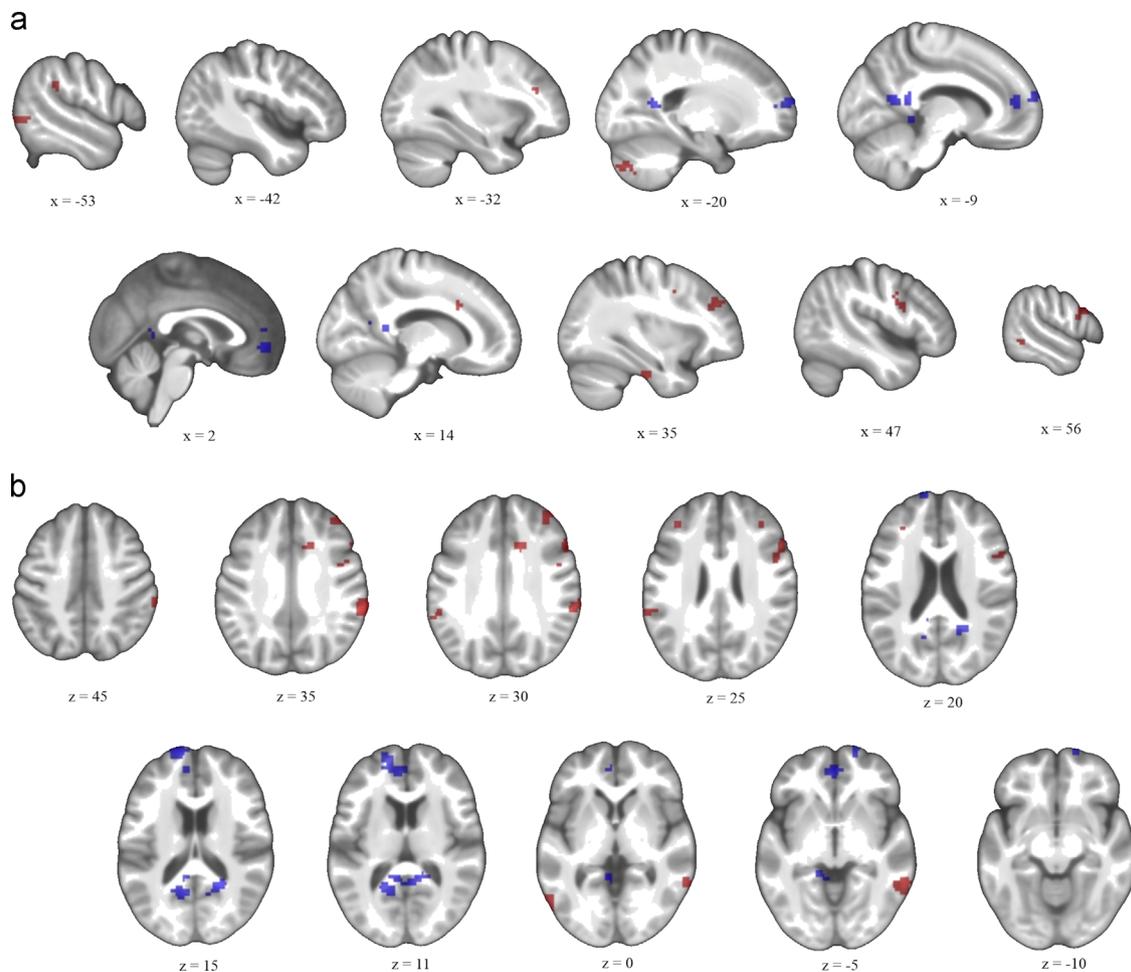


Figure 3 Brain regions where the functional connectivity with the midbrain showed a significant interaction between group and Sensation Seeking Scale (SSS) scores. Sagittal slices are shown in (A), and axial slices are shown in (B). The color red indicates clusters where the correlation between functional connectivity and SSS was significantly more positive for the control group. The color blue indicates clusters where the correlation between functional connectivity and SSS was significantly more positive for the heroin group. Among the significant brain clusters, the dorsolateral prefrontal cortex (DLPFC) was more positively correlated with the SSS in the controls, whereas the opposite pattern of results was observed for the ventromedial prefrontal cortex (VMPFC). The template brain image used was the bias-corrected average image of all of the participants. The left side of the brain is shown on the left. Montreal Neurological Institute (MNI) space coordinates are reported.

4.2. Pathological midbrain-PFC coupling in heroin abusers

Partially consistent with our prediction that heroin abuse would be associated with atypical neuropsychological relationships in the mesolimbic-prefrontal network, several PFC regions were found to couple with the midbrain abnormally. Specifically, there was a difference in the profile of abnormality in the DLPFC and VMPFC. Compared to healthy controls, higher sensation seeking in heroin users was correlated with decreased coupling between the midbrain and DLPFC, but increased coupling between the midbrain and VMPFC. In the context of addiction, it has been suggested that the DLPFC underlies effortful, top-down executive control that guides behavior in the presence of salient stimulation (e. g., drug-related reward signals) (Goldstein and Volkow, 2011). Our previous study indicated that long-term heroin abuse may

indeed impair such top-down control processing (Lee and Pau, 2002; Pau et al., 2002), which is related to DLPFC malfunctioning (Lee et al., 2005). Consistently, the acute effect of heroin was found to reduce response at a lateral prefrontal area in relation to stimulus-driven attention (Schmidt et al., 2013). Although also involved in the guidance of behavior, the VMPFC appears to be deeply implicated in impaired utilization of information on expected outcomes, resulting in the intense “drive” for and compulsion towards drug-taking behavior (Dalley et al., 2011; Schoenbaum et al., 2006). In line with these differing roles of the DLPFC and VMPFC, a recent resting-state functional connectivity study revealed that heroin users had reduced temporal synchronization within the dorsal executive network (including the DLPFC and parietal cortex) and increased synchronization within the ventral valuation network (including the VMPFC and limbic regions) (Xie et al., 2014). Given such an understanding, the present findings may be interpreted in one of the following two ways. First, it could

be that in a healthy model, intact top-down control suppresses the learned associations in relation to drug cues, but in heroin users, this suppression diminishes due to the failure of the midbrain-DLPFC coupling. Alternatively, it was also possible that for heroin users, hyperconnectivity between the brain systems that subserve reward signals disturbs the healthy top-down control that guides healthy behavior. These alternative interpretations notwithstanding, the present findings highlight an important difference in how the midbrain is functionally connected with the DLPFC and VMPFC in the context of the heroin abusers' excessive sensation seeking tendency. The present findings also accentuate the need for future neurobiological studies in drug addiction to take into account the abusers' baseline personality traits because these traits may reflect neurobiological alteration of varying degrees. Similarly, clinical assessment of personality traits may potentially help to tailor individualized intervention strategies aimed at targeting specific neurobiological deficit in people with addictive behaviors.

No limbic region was found to correlate abnormally with the high sensation seeking or impulsivity traits that were characteristic of heroin users. This null finding was unexpected because the limbic circuit has been reported to be implicated in altered neural response of reward and emotional processing after acute heroin administration (Schmidt et al., 2015a, 2015b), as well as being critically involved in an animal model of heroin-seeking behavior (LaLumiere and Kalivas, 2008). Our finding, however, suggest that this brain area (in connection with the midbrain) is either more protected from damage relative to the prefrontal cortex or that the induced damage is more reversible through the spontaneous recovery of abstinence. Given the well-characterized limbic role in drug-seeking "habit" behavior (Everitt et al., 2008), the latter interpretation seems the more likely explanation for the present finding. Functionally, the restoration of limbic regions might serve as a driving force for enhancing insight in the importance of drug cessation (Goldstein et al., 2009).

4.3. Cerebellum and addiction: an incidental finding

The high sensation seeking trait of heroin users was found to correlate with structural deficit in a region of the left cerebellum. Whether the cerebellum contributes to psychiatric conditions or cognitive functioning remains a largely unresolved issue (Tedesco et al., 2011; Beaton and Marien, 2010; Schmahmann et al., 2007). In the context of addiction, cerebellar abnormality has been associated with abuse severity (Cousijn et al., 2012; Solowij et al., 2011; Sim et al., 2007), cognitive functioning (Medina et al., 2010; Sim et al., 2007) and motor functioning (Sim et al., 2007). However, with only one exception (Sim et al., 2007), previously reported cerebellar findings were incidental and did not result from a priori effort to study the role of this brain region in the neuropathology of addiction. The present finding is also incidental and suggests that cerebellar abnormality may be related to the high sensation seeking trait of heroin users. It is important to note that the cerebellum cluster identified in this study correlated with the heroin users' cigarette consumption. Thus, it is possible that this cerebellum finding was at least

partly driven by the effects that are non-specific to heroin, such as nicotine-induced changes in vascular metabolism (Domino et al., 2004). Taken together, there has been increasing suggestion that the cerebellum may be involved in drug addiction; however, the nature of this involvement is not fully understood and requires further investigation for a more complete understanding to be achieved.

4.4. Study limitations and future directions

The limitations of this study warranted discussion. Firstly, the directionality of cause and effect could not be determined. It was possible that the abuse of heroin led to decreased midbrain volume, which contributed to increased sensation seeking tendencies; alternatively, high sensation seeking trait may have predisposed an individual to engage in heroin abuse, which affected midbrain functioning. This is an inherent limitation of any cross-sectional neuroimaging study but one that is vital to overcome in the future. Important progress on this issue has been made for stimulant addiction (e.g. Ersche et al., 2013), but not yet for heroin. Secondly, only male participants were investigated because male abusers are over-represented in the heroin addiction population. Thirdly, measures of structural brain connectivity (e.g., diffusion tensor imaging), which could provide an additional dimension of understanding in the neurobiology of heroin addiction, were not included in this study. Fourthly, the amount of alcohol and cigarette consumption was higher in the heroin group compared to the control group. This was the case in our study and some other studies (Clair et al., 2009) that also recruited an ecological sample of heroin abusers, who showed high rates of comorbidity in the abuse of other substances (Darke and Ross, 1997). Although all of our primary findings did not correlate with the amount of alcohol and cigarette consumption, such correlation analyses could not wholly exclude the possibility that alcohol or cigarette interacted with heroin use to contribute to the results. The existence of such an interaction is an interesting and important research question that will need to be systematically studied. Finally, even though procedures were taken to prevent false positive results, it remains a statistical possibility that the findings were a reflection of Type I errors. Future replicative studies were needed to determine the robustness of the present findings.

4.5. Conclusion

This study revealed that past abusers of heroin are associated with atypical relationships between high sensation seeking trait and midbrain structural volume, together with the midbrain's functional coupling with the PFC. Furthermore, the direction of midbrain's couplings with the DLPFC and VMPFC are differentially related to the sensation seeking trait, such that there is a weaker midbrain-DLPFC coupling and stronger midbrain-VMPFC coupling in the heroin abusers. To our knowledge, this study is the first to identify abnormality in midbrain structure and connectivity in relation to heroin abuse. The findings are important and have direct implications for future studies that seek to unravel the mechanistic processes that characterize similar neuropsychological relationships in people with addiction.

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Contributors

TMCL and ZH were responsible for the study concept and design. ZH, TMCL, YPL and KFS contributed to data acquisition. GLFC performed the data analysis. CCH and TMCL assisted with data analysis and interpretation of findings. GLFC drafted the manuscript. TMCL provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

Conflict of interest

None.

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