

Exploring Neural Correlates of Different Dimensions in Drug Craving Self-Reports among Heroin Dependents

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Article info:

Received: 15 April 2015

First Revision: 03 July 2015

Accepted: 07 August 2015

ABSTRACT

Introduction: Drug craving could be described as a motivational state which drives drug dependents towards drug seeking and use. Different types of self-reports such as craving feeling, desire and intention, wanting and need, imagery of use, and negative affect have been attributed to this motivational state. By using subjective self-reports for different correlates of drug craving along with functional neuroimaging with cue exposure paradigm, we investigated the brain regions that could correspond to different dimensions of subjective reports for heroin craving.

Methods: A total of 25 crystalline-heroin smokers underwent functional magnetic resonance imaging (fMRI), while viewing heroin-related and neutral cues presented in a block-design task. During trial intervals, subjects verbally reported their subjective feeling of cue induced craving (CIC). After fMRI procedure, participants reported the intensity of their “need for drug use” and “drug use imagination” on a 0-100 visual analog scale (VAS). Afterwards, they completed positive and negative affect scale (PANAS) and desire for drug questionnaire (DDQ) with 3 components of “desire and intention to drug use,” “negative reinforcement,” and “loss of control.”

Results: The study showed significant correlation between “subjective feeling of craving” and activation of the left and right anterior cingulate cortex, as well as right medial frontal gyrus. Furthermore, the “desire and intention to drug use” was correlated with activation of the left precentral gyrus, left superior frontal gyrus, and left middle frontal gyrus. Subjects also exhibited significant correlation between the “need for drug use” and activation of the right inferior temporal gyrus, right middle temporal gyrus, and right parahippocampal gyrus. Correlation between subjective report of “heroin use imagination” and activation of the cerebellar vermis was also observed. Another significant correlation was between the “negative affect” and activation of the left precuneus, right putamen, and right middle temporal gyrus.

Discussion: This preliminary study proposes different neural correlates for various dimensions of subjective craving self-reports. It could reflect multidimensionality of cognitive functions corresponding with drug craving. These cognitive functions could represent their motivational and affective outcomes in a single item “subjective craving feeling” or in self-reports with multiple dissociable items, such as intention, need, imagination, or negative feeling. The new psychological models of drug craving for covering various dimensions of subjective craving self-reports based on their neurocognitive correspondence could potentially modify craving assessments in addiction medicine.

Key Words:

Craving, Self-report,
Heroin, fMRI

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1. Introduction

I Craving is a major concept in addiction, which could be defined as a subjective motivational state, related to the desire for drug use (Tiffany, 1999; Sayette et al., 2000; Tiffany et al., 2012).

The popular definition of craving mainly refers to the meaning of desire, however other concepts such as liking, wanting, intention, compulsion, desire, urge, or need for drug use could also play their role in the multi-dimensional nature of craving self-reports (Sayette et al., 2000; Drummond et al., 2000; Drummond, 2001; Tiffany et al., 2008; Tiffany et al., 2012). Although the aim is to rate the intensity of craving, in some of these instruments, the word “craving” or “desire” are almost ignored (Tiffany et al., 2012). For example, in the “desire for drug questionnaire” (DDQ) tool, a well-known questionnaire for drug craving measurement, the word “craving” is not used at all, and the word “desire” is only used indirectly within one of the 13 questions of this questionnaire (Franken et al., 2002).

There is also no item related to the desire to use a drug in many other craving evaluation questionnaires (Tiffany et al., 2012). Multi-item craving evaluation questionnaires, such as DDQ, usually include items considered equal to desire, or ask questions related to drug use intention, negative reinforcement, and lack of control (Tiffany et al., 2000; Franken et al., 2002; Tiffany et al., 2012). These 3 items are among the more emphasized ones in the field of cue-induced craving neuroimaging studies (Franken et al., 2002; Marissen et al., 2006; Shi et al., 2008; Zijlstra et al., 2009; Tabatabaei-Jafari et al., 2014). However, for evaluation of drug craving in various cue-induced craving neuroimaging studies, besides craving self-report, both multi-dimensional questionnaires and single question self-reports were used (Grant et al., 1996; Garavan et al., 2000; Schneider et al., 2001; Kilts et al., 2001, 2004; Bonson et al., 2002; McClemon et al., 2005; McBride et al., 2006; Franklin et al., 2007; Zijlstra et al., 2009; Goldstein et al., 2009; Mei et al., 2010; Li et al., 2012; Schmidt et al., 2015).

Liking, wanting, urges, intention, compulsion, or need for drug use are some of the concepts in these questionnaires (Sayette et al., 2000; Kozlowski & Wilkinson, 1987; Drummond et al., 2000; Drummond, 2001). Conceptually and functionally, these notions are in some aspects equal and in some other aspects distinct from desire and craving (Kozlowski et al., 1996; Tiffany et al., 2012). In this study, we investigated the multidimensionality of drug craving self-reports and its neural correlates by using functional magnetic resonance imaging technique.

During past two decades, neuroimaging techniques have helped scientists to identify the association between brain regions and cue-reactivity. The most commonly reported regions activated during heroin cue-presentation are different prefrontal cortical regions (i.e. anterior cingulate cortex, posterior cingulate cortex, midcingulate cortex, dorsolateral prefrontal cortex, superior frontal gyrus, orbitofrontal cortex, and medial frontal gyrus), various sub-cortical areas (i.e. amygdala, nucleus accumbens, caudate nucleus, putamen and thalamus), insula, hippocampus/parahippocampal region, and cerebellum (Sell et al., 1999, 2000; Daghli et al., 2001; Xiao et al., 2006; Langleben et al., 2008; Zijlstra et al., 2009; Yang et al., 2009; Liu et al., 2011; Wang et al., 2011; Li et al., 2012, 2013b, 2014; Langleben et al., 2014; Walter et al., 2015). Moreover, some studies have shown a correlation between one of the self-reports of heroin-craving and certain brain regional activities such as the orbitofrontal cortex, insula, amygdala, anterior cingulate cortex, posterior cingulate cortex, inferior frontal gyrus, superior temporal gyrus, nucleus accumbens, subcallosal cortex, caudate nucleus, putamen, precuneus, thalamus, hippocampus, temporal and occipital cortices, lingual gyrus, and cerebellum (Sell et al., 2000; Daghli et al., 2001; Wang et al., 2011; Li et al., 2012, 2013a, 2014; Lou et al., 2012; Wang et al., 2014; Liu et al., 2014; Tabatabaei-Jafari et al., 2014; Schmidt et al., 2014, 2015).

The aim of this study was to investigate the possibility of a correlation between regional brain activities and different dimensions of self-reported heroin craving. We used fMRI with cue exposure paradigm as the neuroimaging technique to detect activation of brain regions elicited by craving. Then, we measured the intensities of self-reported heroin cue-induced “craving,” “desire and intention for drug use,” “negative reinforcement,” “loss of control,” “drug use imagination,” and “negative affect” induced by cue exposure. We hypothesized that different dimensions of subjective craving correlate with activities in specific brain regions related to their underlying neurocognitive processes.

2. Methods

2.1. Subjects

Twenty-five male, cue-responding active crystalline-heroin smokers (at least past six months; ages: 25–45 years) who met DSM-IV criteria for heroin dependence participated in this study. Demographics and drug abuse characteristics of participants are presented in Table 1.

All participants were right-handed (based on Edinburgh Handedness Inventory (Oldfield, 1971)). Subjects at least had 5 years of education, and were able to read, understand, and answer the requested questions. They were recruited from volunteers admitted for treatment in 10 residential abstinence-based treatment centers of Rebirth Society in Tehran. All volunteers underwent full medical and psychiatric interviews and examinations. Subjects with any medical and psychiatric co-morbidity, visual and MRI limitations, history of head trauma, as well as, abuse of other opiate drugs, stimulants, hallucinogenic drugs, and sedatives (based on urine analysis and self-reports) were excluded. Non-cue-responding subjects were also excluded. The last time of heroin use was between 4 to 6 hours prior to scanning in all participants. The study procedure was comprehensively explained to participants who signed consent forms. Participants were rewarded with 1-month treatment costs. The Medical Ethics Committee of Tehran University of Medical Sciences approved the study protocol.

2.2. The study assessments

2.2.1. Cue-response evaluation task

Cue-responding evaluation task (CRET) consists of 10 crystalline heroin-related pictures and two neutral ones. The subjects reported their intensities of craving induced by each picture on a 0-100 visual analog scale (VAS) (Ekhtiari et al., 2008). Responding cut off point was set at 40 out of 100.

2.2.2. Opiate withdrawal and intoxication scales

Opiate withdrawal scale (OWS) consists of 26 questions about opiate withdrawal symptoms and is rated as follow: (0) not at all, (1) a little, (2) moderately, (3) quite a bit, and (4) extremely. Opiate intoxication scale (OIS) consists of two distinctive parts. The first part includes 12 questions about opiate drug use related symptoms, and is called the subjective part of the OIS. The second part consists of 9 questions related to drug use signs, and is called the objective part of the OIS. This checklist is also rated as follows: (0) not at all, (1) a little, (2) moderately, (3) quite a bit and (4) extremely. Participants who were experiencing moderate or more severe states of withdrawal or intoxication were excluded.

2.2.3. Verbal self-report of "drug craving due to being exposed to heroin cues"

It consists of verbally reporting the craving intensity on a scale from 0 to 100.

2.2.4. The 0-100 visual analog scale for evaluating the intensities of "need for drug use" and "drug use imagination"

It was done by answering these questions consecutively: "How much did you feel in need of heroin use by watching drug-related pictures within the MRI machine?", and "How much did you imagine heroin use by watching drug-related pictures within the MRI machine?" Subjects answered these questions on a 0-100 VAS.

2.2.5. Desire for Drug Questionnaire

DDQ includes 3 different sub-scales; "desire and intention," "negative reinforcement," and "loss of control" (Franken et al., 2002). "This questionnaire has been validated for Persian-speaking crystalline-heroin smokers in the Iranian National Center for Addiction Studies. We asked the participants to answer it on a 7-scale Likert-type answer sheet."

2.2.6. Positive and negative affect scale

Positive and negative affect scale (PANAS) consists of a number of single-word adjectives (10 positive and 10 negative agents), which describe different feelings and emotions (Watson et al., 1988). In this study, participants were asked to answer the Persian-validated version of PANAS (Bakhshi-Pour and Dejjkaam, 2006) on a 5-scale Likert-type answer sheet.

It was administered to measure the intensity of each of the above mentioned emotions after watching the heroin-related pictures while in MRI machine. The original PANAS measures emotions during the daily life in a general term. However, we asked the participants to report the intensity of the elicited emotions by heroin-related pictures at the moment they are shown the pictures in the MRI machine.

It is worth mentioning that even when someone is reporting his feelings intensity during a specific period, the reported intensity is mostly related to the episode with peak intensity, as well as, the most recent episode in the requested period of time (Davidson, 2001). PANAS items were rated as follows: (1) very slightly or not at all, (2) a little, (3) moderately, (4) quite a bit and (5) extremely (Watson et al., 1988).

2.3. Procedure

Before administering craving-related self-reports, we evaluated participants using opiate withdrawal and intoxication checklists. It was done to make sure the proposed 4-6 hours abstinence was appropriate and the participants were in a stable situation.

In the present study, we used 3 types of instruments to assess drug craving and its dimensions. The first one was verbal self-report of “drug craving due to being exposed to heroin cues” intensity, inside the scanner. The second instrument was 0-100 VAS for evaluating the intensities of “need for drug use” and “drug use imagination” after being exposed to heroin-cues inside the scanner, immediately after scanning. Afterwards DDQ, as well as PANAS questionnaire were administered for evaluating the intensities of “desire and intention to drug use”, “negative reinforcement”, “loss of control”, “negative affect”, and “positive affect.” All these instruments were also used before the task presentation, to make sure that the acquired data are due to heroin-related cues.

Inside the scanner, during five 17-second gaps between 6 cue presentation trials and after the last trial that we had no image recording, participants verbally reported their craving intensity on a scale from 0 to 100. We fixed subjects’ head inside the scanner and instructed them carefully on how to report verbally without any head tilt in order to avoid head movement artifacts due to verbal self-reports between imaging trials.

Immediately after scanning, the participants were asked to report their intensities of the “need for drug use” and “drug use imagination” due to exposure to heroin-cues inside the scanner. Afterwards we asked the participants to answer the PANAS and DDQ.

At the completion of the study, each participant underwent a brief counseling session with an expert clinical psychologist in order to mitigate the intensity of their potentially induced-craving. Finally, they were transferred to a residential center to start their residential abstinence-based treatment program.

2.4. Image acquisition:

MRI scanning was performed by a 1.5T American GE® Signa scanner. fMRI data were obtained using an Echo Planar Imaging (EPI) protocol (TE=60 ms, TR=3000 ms, slice thickness=5 mm, band width=62.5 KHZ, and flip angle=90°). T1-weighted 3D images were obtained for registration of fMRI data to the brain’s structural map

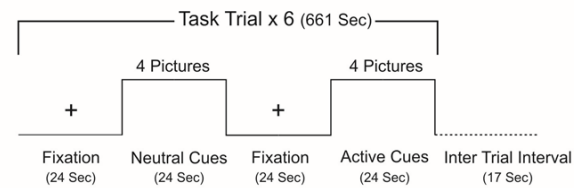


Figure 1. Study task design.

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(TE=4200 ms, TR=9850 ms, slice thickness=1 mm, band width=61 KHZ, and flip angle=30°). The fMRI task was a pictorial block design that consisted of 24 crystallized-heroin stimuli (crystallized-heroin, paraphernalia, preparation, smoking, and co-smoking related cues) and 24 neutral stimuli selected from the International Affective Picture System (IAPS) (Lang et al., 2008). Figure 1 shows the task design. It was developed in E-Prime platform (Psychology Software Tools, Inc.) and projected on a white screen sheet in front of the scanner. In-plane resolution of the task pictures were tested by all participants before running the task to be ensured of their ability to observe the pictures clearly.

2.5. Data analysis:

2.5.1. Psychological data analysis:

The mean and standard deviation of demographics, heroin craving and other constructs of drug dependence variables were computed by SPSS-16 software.

We correlated the neural activities with self-report of heroin craving and other measured heroin-dependence variables for all participants. Voxel-wise correlation between the neural effect of the cue-induced task (brain activation in heroin-related>neutral contrast) and the corresponding heroin dependence self-report variables was conducted for all subjects.

2.5.2. Single brain analysis:

Imaging data were analyzed with FEAT (fMRI Expert Analysis Tool) version 5.98 part of FSL (FMRIB software library, version 4.1, www.FMRIB.ox.ac.uk/fsl). Motion correction was done using FMRIB’s Linear Registration Tool (MCFLIRT) (Jenkinson and Smith, 2001). Exclusion of non-brain areas was calculated by FMRIB’s Brain Extraction Tool (BET) (Smith, 2002). Slice timing was corrected with the mean-based intensity normalization to remove linear trends. Spatially smoothed was calculated with the 5-mm full width at half maximum (FWHM) Gaussian kernel. And the nonlinear high-pass temporal filtering to exclude low frequency confounds such as breath-

Table 1. Demographics and drug abuse characteristics of Participants (25 male, cue-responding active crystalline-heroin smokers)

Age (y)		31.9±4.8
Education (y)		8.57±2.6
Marital status	Married	15 (%60)
	Single	5 (%20)
	Separated	3 (%12)
	Divorced	2 (%8)
History of drug injection		8 (%32)
Imprisonment	Life time	5 (%20)
	Last year	3 (%12)
Drug dealing	Life time	8 (%32)
	Last month	3 (%12)
Age of onset (y)		28.28±4.79
Heroin dependence duration (y)		3.02±1.91

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ing was calculated by the Gaussian-weighted least squares straight line fit ($\sigma=96.0$ s).

A 3-step registration procedure was used. EPI images were registered to the structural image, and then into the standard (MNI) space, using affine transformations by FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Statistical analysis was performed in the native image space with the statistical maps normalized to the standard space prior to higher-level analysis. Time series statistical analysis was carried out by using FMRIB's Improved Linear Model (FILM) with local auto-correlation correction.

Regressors were modeled for conditions of interest (heroin-related stimuli and neutral stimuli), using a canonical hemodynamic response function with a temporal derivative. Contrasts at this level were examined whether the parameter estimate (PE) of the hemodynamic response to heroin-related pictures was greater than the PE for the hemodynamic response to neutral pictures. For further analysis (group comparison), this contrast (heroin-related>neutral contrast) was used as the main contrast.

2.5.3. Higher level analysis:

All higher level analyses were carried out by using FMRIB's Local Analysis of Mixed Effects (FLAME). All self-reports' scores were used as covariates to investigate involved brain activation areas. Z (Gaussianized T/F) statistic images were thresholded using cluster detection

statistics, with a height threshold of $z \geq 2$, and a cluster probability of $P=0.05$, corrected for whole-brain multiple comparisons based on the Gaussian random field theory (GRFT).

3. Results

3.1. Participants

We excluded 5 participants due to head movement or data defects. Demographics and drug abuse characteristics of participants are presented in Table 1.

3.2. Craving and other self-report assessments:

Average verbally reported intensity of craving slightly increased during scanning (62%, $SD=32$ after the first series of presentation to 74%, $SD=28$ after the last series). The mean percentage for the different dimensions of craving self-reports are shown in Table 2.

It is obvious that participants, after watching drug-related pictures inside MRI machine, experienced moderate to high levels of "negative affect" and mild to moderate levels of "positive affect". They were also in an approximately moderate state of "desire and intention to drug use," mild to moderate state of "negative reinforcement," and mild state of "control deficit."

Correlation analysis among different self-reported variables exhibited no significant relationship between them, except between the intensity of "drug use imagination" and "need for heroin use" ($P=0.003$), as well as between the intensity of "drug use imagination" and "verbal self-report of cue-induced craving" ($P=0.003$). Apart from "drug use imaginations", other craving self-reports are statistically noncorrelated.

3.3. Neuroimaging results:

3.3.1. Whole brain analysis:

Viewing crystallized-heroin cues resulted in significant activations (heroin-related blocks>neutral blocks) in varying brain regions as shown in Table 3.

3.3.2. Correlation with self-reported factors:

Whole brain analysis revealed the following significant positive correlations between different self-reported factors: (1) between the series of "verbal self-reports of craving" inside the scanner and activations in the left anterior cingulate cortex, right anterior cingulate cortex, and right medial frontal gyrus (Table 3, Figure 2), (2) between the

Table 2. Different dimensions of craving intensities for 20 heroin dependents.

Craving Dimensions		Mean of intensity	Standard Deviation
CIC (Inside the scanner)		67 of 100	26
Need for drug use due to cue exposure		77 of 100	25
Drug use imagination due to cue exposure		68 of 100	32
Negative affect due to cue exposure		3.15 of 5	0.9
Positive affect due to cue exposure		2.23 of 5	0.6
DDQ	Desire & intention component	2.8 of 7	1.46
	Negative reinforcement component	2.15 of 7	1.23
	Control component	1.7 of 7	1.4

Abbreviation: CIC, Cue-induced craving; DDQ, Desire for Drug Questionnaire.

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“desire and intention to drug use” and activation in the left superior frontal gyrus, left middle frontal gyrus, and left precentral gyrus (Table 3, Figure 3), (3) between the “need for drug use” and activation in the right inferior temporal gyrus, right middle temporal gyrus and right parahippocampal gyrus (Table 3, Figure 3), (4) between “imagination of drug use” and activations in the right cerebellum (culmen and declive) and left cerebellum (lingual gray matter) (Table 3, Figure 3); it should be mentioned that these 3 regions are parts of the cerebellar vermis, (5) between the “negative affect” and activation in the left precuneus, right putamen, and right middle temporal gyrus (Table 3, Figure 3).

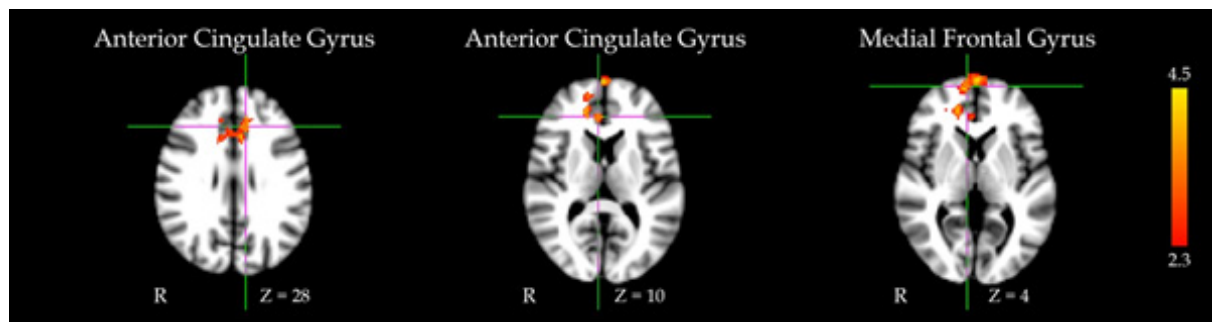
No significant correlation existed between “negative reinforcement,” “loss of control,” and “positive affect” and activated brain areas.

4. Discussion

This study explored potential neural substrates for different dimensions of subjective craving self-reports. We found significant correlations between reports of “craving severity” after being exposed to cues (Cue Induced Crav-

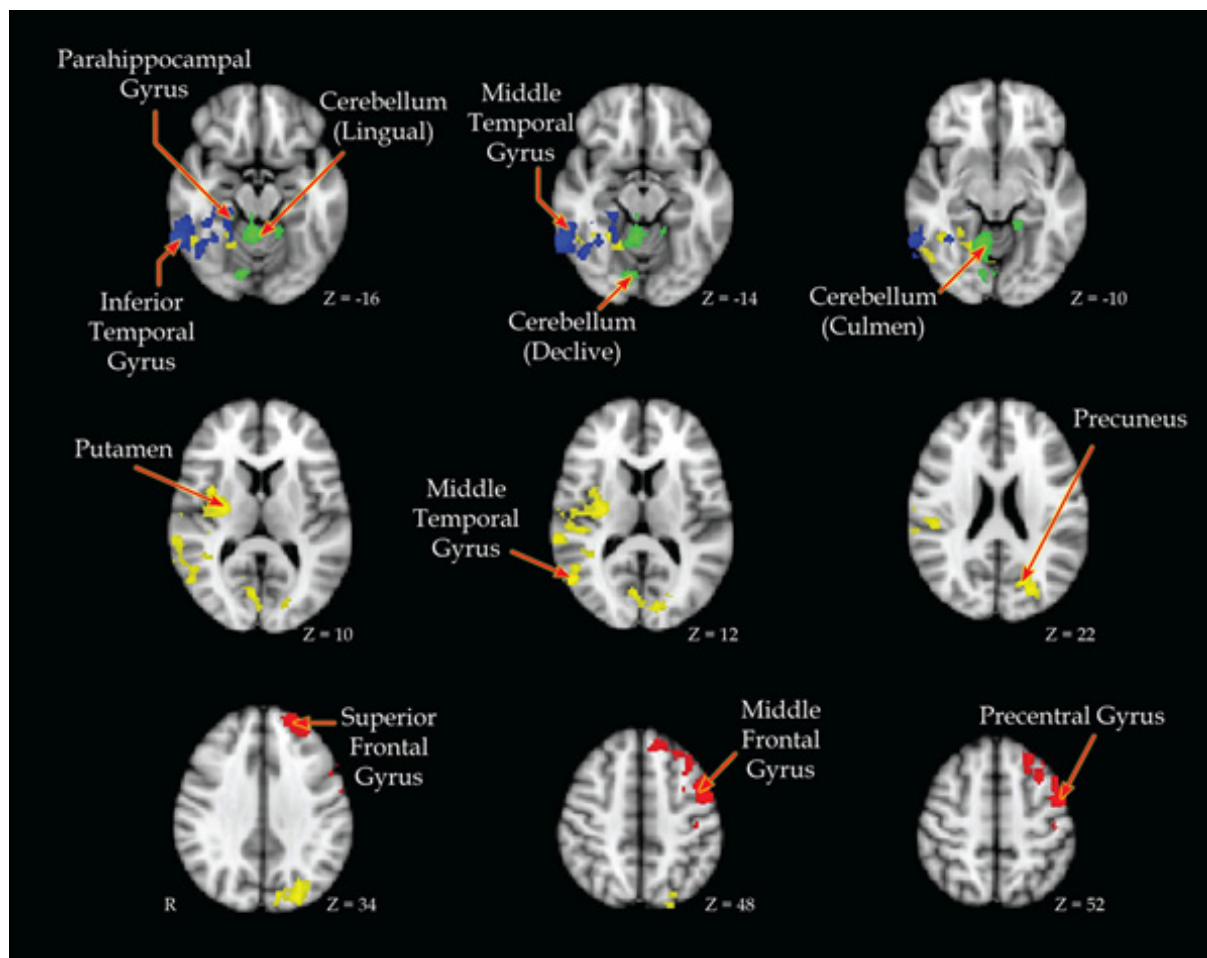
ing or CIC), bilateral anterior cingulate cortex, and right medial frontal gyrus activations. The correlation between “desire and intention to drug use” and activation of the left superior and middle frontal gyri and left precentral gyrus; and correlations between subjective report of “need for heroin use” and activation of right inferior temporal, middle temporal and parahippocampal gyri and between subjective report of “heroin use imagination” and activation of the cerebellar vermis were also shown. Moreover subjective report of “negative affect” was significantly related to activation of the left precuneus, right putamen, and right middle temporal gyrus.

In this study, self-reported CIC correlated with activation of the left and right anterior cingulate cortex (ACC), and right medial frontal gyrus (MeFG). Activation of ACC due to heroin craving was previously reported (Liu et al., 2011; Lou et al., 2012; Li et al., 2012, 2013a; Tabatabaei-Jafari et al., 2014). Activation of ACC due to other types of drugs cue-reactivity or craving was also demonstrated (Goldstein et al., 2007; Luijten et al., 2011; Moeller et al., 2014). Other studies have reported activation of the MeFG in relation to heroin craving (Liu et al., 2011) and cue-reactivity (Daglish et al., 2001; Li et al., 2012, 2013b;



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Figure 2. Significant fMRI activations in brain areas due to heroin-cue contrast (Heroin-related blocks>neutral blocks) that correlated with “verbal self-report of craving”, inside the scanner, for 20 heroin dependents.



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Figure 3. Significant fMRI activations in brain areas due to heroin-cue contrast (heroin-related blocks > neutral blocks) that is correlated with: (1) “desire and intention to drug use” (red color), (2) “need for drug use” (blue color), (3) “drug use imagination” (green color), and (4) “negative affect” (yellow color); for 20 heroin dependents.

Langleben et al., 2014). Overall, these studies supported our study findings that suggested a correlation between ACC and MeFG activation as well as heroin cue-induced craving. There are various explanations for correlation of craving severity and brain activity in ACC and MeFG. A number of other published studies have revealed that these areas are members of a neural network concerned with self-referential processing (Johnson et al., 2006). For example, Ochsner et al., 2005 and Vogt and Laureys, 2005 noted the involvement of the anterior medial cortex (medial frontal gyrus and/or ACC), and posterior medial cortex (precuneus and/or PCC) in self-referential processing (Johnson et al., 2006; Moeller et al., 2014). The impairment of self-referential processing in drug-users might lead them to drug-taking behaviors in confrontation of drug-related cues, without considering its negative consequences (Moeller et al., 2014). ACC and MeFG are also involved in emotion regulation (Goldstein et al., 2007; Liu et al., 2011) and executive functions such as “error monitoring,” “shifting attention,” “inhibitory control,” and “de-

cision making” (Talati & Hirsch, 2005; Goldstein et al., 2007; Luijten et al., 2011; Liu et al., 2011). Drug addicts try to control their emotions, which are elicited by drug-related cue exposure and internal or external stressors (Goldstein et al., 2007). In drug users, drug-related cues activate and trigger attentional biases. These biases might be able to induce decision making and motor responses, which may increase the chance of drug-seeking behaviors (Luijten et al., 2011). Moreover, disruption of error monitoring might result in impulsive behaviors that could lead to drug-taking behaviors (Goldstein et al., 2007). The intensity of brain functional connectivity of default mode networks of chronic heroin users compared to healthy subjects was previously investigated. It was demonstrated that the severity of MeFG functional connectivity in heroin users was significantly higher than the control group, and it was in a positive relationship with the same area’s brain activity in drug-related task. It was also exhibited that the severity of ACC functional connectivity at rest was significantly reduced in heroin users, and it was in a

Table 3. Significant fMRI activations in brain areas due to heroin-cue contrast (heroin-related blocks>neutral blocks) that is correlated with “cue-induced reactivity” and different independent self-reported factors (“subjective craving” inside scanner, “desire and intention to drug use,” “need for drug use,” and “negative affect,” excluding “drug use imagination) for 20 heroin dependents.

Region Of Interest	Cue-induced reactivity					Correlation with subjective self-reported craving (Inside the scanner)					Correlation with other self-reported factors (except craving)					constructs of drug dependence
	BA	Z sc	X	Y	Z	BA	Z sc	X	Y	Z	BA	Z sc	X	Y	Z	
Right superior frontal gyrus	9	3.58	22	54	26											
Left superior frontal gyrus	9 8	3.15 3.98	-20 4	54 50	28 42							3.01	-12	42	46	Desire and intention to drug use
Right middle frontal gyrus	10 8	3.84 3.68	28 40	54 34	14 40											
Left middle frontal gyrus	8	3.33	-36	24	44						6	3.04	-44	6	48	Desire and intention to drug use
Right medial frontal gyrus						10	2.85	8	64	4						
Right inferior temporal gyrus											20	4.05	64	-50	-16	Need for drug use
Right middle temporal gyrus											20	3.16	58	-42	-14	Need for drug use
Right middle temporal gyrus											39	3.17	54	-66	12	Negative affect
Right precentral gyrus	9	3.97	44	30	34											
Left precentral gyrus		3.15	-46	24	36						6	3.27	-48	0	52	Desire and intention to drug use
Right post central gyrus	40	4.07	54	-28	56											
Left post central gyrus	5	3.40	-40	-40	64											
Right superior parietal lobe	7	3.62	30	-50	48											
Left superior parietal lobe	7	3.55	-34	-52	64											
Right inferior parietal lobe		3.96	44	-52	54											
Left inferior parietal lobe	40	3.68	-54	-28	48											
Left precuneus											31	3.12	-18	-70	22	Negative affect
Left anterior cingulate cortex	24	3.89	-2	20	24	9	2.89	-10	30	28						
Right anterior cingulate cortex	32	4.22	6	40	14	32	2.89	6	38	10						
Right parahippocampal gyrus											36	3.07	24	-32	-16	Need for drug use
Right cerebellum		4.45 4.24	30 34	-72 66	-30 -32							3.33 3.14	12 12	-56 78	-10 14	Imagination of drug use
Left cerebellum		3.46 3.14	-26 -34	-72 62	-32 -38							2.83	0	-46	-16	Imagination of drug use

positive relationship with drug-related cue-elicited craving activities. The achieved results might claim that two different neural circuits are involved in drug-related cue-reactivity tasks in the brain of heroin users. These findings all together might clarify the relationship between self-reported craving and its dimensions, with the function of CIC measurement tasks.

Self-reporting of “desire and intention to drug use” was observed in correlation with activation of the left precentral gyrus, and the left superior and middle frontal gyri. Activation of the left precentral gyrus due to heroin cues was previously reported (Mei et al., 2010; Langleben et al., 2014) which suggests a possible role for the precentral gyrus in heroin cue-reactivity. Some researchers have suggested a logical relationship between the precentral gyrus and “intention to drug use” (planning to use drugs and/or prevention of this action is conceptually associated with the precentral gyrus function) (Stinear et al., 2009). Activation of the superior frontal gyrus due to heroin cues was also reported (Yang et al., 2009). Researchers have also reported activation of both superior and middle frontal gyri due to cocaine, nicotine, and alcohol craving and cue-reactivity (Grant et al., 1996; Bonson et al., 2002; McClemon et al., 2005; Kilts et al., 2001; Garavan et al., 2000; Lee et al., 2005; Brody et al., 2007; Park et al., 2007). These reports suggest that the superior and middle frontal gyri might be related to drug cue-reactivity. On the other hand, activation of the left middle frontal and superior frontal gyri was observed in heroin abusers while performing Go/No-Go response inhibition tasks (Fu et al., 2008) which means, observed activation might be related to this executive control and motor inhibition while facing heroin related cues.

Moreover, both the left superior and middle frontal gyri are involved in working memory (Du Boisgueheneuc et al., 2006, Lue et al., 2006). Working memory is a cognitive function, which is related to the brain system for short time collecting and manipulating required information; for complex cognitive tasks such as reasoning (Baddeley, 1992), desire could be considered as a material for reasoning, which is in a relation with working memory. Moreover, it is reported that working memory guides human subjects to goal-directed behaviors (Goldman-Rakic, 1987), suggesting that the left superior and middle frontal gyri might be associated with the concept of “desire for drug use.”

The self-report of “need for drug use” is correlated with activation of the right middle and inferior temporal and parahippocampal gyri. Reports exist about activation of the parahippocampal and inferior temporal gyri and their

relationship with heroin cue-reactivity (Zijlstra et al., 2009 and Mei et al., 2010). Activation of temporal cortex and parahippocampal gyrus due to heroin cue-induced craving is also reported (Lou et al., 2012). Moreover, activation of the middle temporal gyrus due to nicotine, alcohol, and cocaine (but not heroin) cues was previously reported (Wexler et al., 2001; Smolka et al., 2005; Park et al., 2007, Yalachkov et al., 2009). These findings support the idea that these 3 brain regions are related to drug cue-reactivity. The middle temporal gyrus is involved in semantic memory processing (Onitsuka et al., 2004), multimodal sensory integration (Mesulam, 1998), and motor planning (Yalachkov et al., 2009). The inferior temporal gyrus is implicated in visual perception (Onitsuka et al., 2004), cue recognition and classification (Park et al., 2007), multimodal sensory integration (Mesulam, 1998), and motor planning (Yalachkov et al., 2009); whereas the parahippocampal gyrus is involved in visual memory and navigation (Epstein and Kanwisher, 1998). Apparently, there is no logical relation between need and these activated areas; but “need for drug use” may show itself as an integration of semantic memories related to the need to use drugs and visual memories related to this concept, as well as visual memories of the presented drug-related pictorial cues.

In this study, self-report of “drug use imagination” was correlated with bilateral activation of the cerebellar vermis. Some evidence has indicated a correlation between activation of the cerebellum and heroin craving elicited by cue-reactivity (Sell et al., 1999 & 2000; Xiao et al., 2006) and baseline craving (Lou et al., 2012; Li et al., 2014; Tabatabaei-Jafari et al., 2014). Activation of the cerebellar vermis due to cocaine, nicotine, and alcohol cue-reactivity or craving has also been reported (Grant et al., 1996; Schneider et al., 2001; and Olbrich et al., 2006). Overall, these reports support our finding about the correlation between activation of this area with heroin cue-reactivity and craving. Cerebellum is involved in habitual responses, accordingly this may lead to compulsive drug-seeking and drug taking (Wang et al., 2013).

Furthermore, it is demonstrated that cerebellum has a central role in working memory, especially the verbal working memory (Marvel et al., 2012). The importance of this region in verbal working memory of heroin addicts was previously reported. It was shown that the difficulty of working memory tasks was associated with the hyperactivity of the superior and inferior cerebellum (Marvel et al., 2012). Moreover, it has been reported that activation of the cerebellar vermis along with cocaine cue-induced craving (CIC) is due to cerebellar cognitive functions, especially explicit episodic memory (Grant et al., 1996). Studies also showed that activation of the cerebellar ver-

mis in correlation with alcohol CIC is due to cerebellar learning and memory functions, especially explicit episodic memory, as well as motor or multisensory coordination functions (Grant et al., 1996; Schneider et al., 2001; Olbrich et al., 2006). Worth mentioning that cerebellum has also a main role in retrieval of procedural memory, which would be triggered by internal or external cues (Wang et al., 1999). This consensus supports the idea of this study that a logical and statistical relationship exists between activation of the cerebellar vermis and “drug use imagination”. In this scope, “drug use imagination” could be considered as the retrieval of explicit episodic memories due to previous experiences of drug abuse.

Self-reporting of “negative affect” was reported in correlation with the activation of the left precuneus, right putamen, and right middle temporal gyrus due to heroin cues. Activation of precuneus and putamen due to heroin craving (Li et al., 2012, 2013a) and heroin cues (Sell et al., 2000; Zijlstra et al., 2009; Li et al., 2013b; Langleben et al., 2014) were previously reported. Activation of the middle temporal gyrus due to nicotine, alcohol, and cocaine (but not heroin) cues was also reported (Smolka et al., 2005; Park et al., 2007; Wexler et al., 2001). Moreover, activation of precuneus due to emotional states (Cavanna and Trimble, 2006), putamen due to emotional pictures (Canli et al., 2002), and the middle temporal gyrus due to affective words were also demonstrated (Kuchinke, et al., 2005). These findings suggest a relationship between these brain regions and drug cue-reactivity, as well as the affective situation of the participants. Furthermore, these brain regions are involved in memory processing, besides the emotional processing. Precuneus is implicated in episodic memory retrieval (Cavanna and Trimble, 2006); putamen is involved in reinforcement learning (Packard and Knowlton, 2002) and emotional memory (Canli et al., 2002), and the middle temporal gyrus is involved in semantic memory processing (Onitsuka et al., 2004). These functional involvements suggest that the relationship between negative affect and activation of the precuneus, putamen, and middle temporal gyrus (due to heroin cues) might be related to emotional memory processing that occurs during heroin cue-presentation.

Some limitations of this study should be mentioned. First, all participants in this study were “shortly abstinent” treatment-seeking subjects, thus the results might not extend to other groups of heroin abusers. Second, testing a single race, gender, and handedness in this study limited generalization of the study results to a larger community. Third, using just single self-report questions for “need for drug use” and “drug use imagination” is not enough for certain evaluation of the neural substrates of these craving-

ing-related factors. We recommend some other studies that use the valid questionnaire for these craving-related factors. Fourth, covering all correlates of drug craving is impossible in one study because of methodological subject limitations. In this regard, we suggest another study to evaluate the neural basis of some other important craving correlates such as liking, wanting, urge, positive reinforcement, reward expectation, compulsion, and thinking about drug use.

In conclusion, different dimensions of elicited craving (due to exposure to crystallized-heroin cues) correlate with activities in various brain regions, which may correspond with the neurocognitive processes and underlie these dimensions. This preliminary evidence support multiple dimensions for craving self-reports, which indirectly include different neurocognitive dimensions during the measurement of this complex concept in addiction science, “Drug Craving.”

Funding /support:

This study was funded by a grant from Tehran University of Medical Sciences to H E and A M in Neurocognitive Laboratory of Iranian National Center for Addiction Studies (INCAS) and Research Center for Cellular and Molecular Imaging (RCMCI).

Authors’ Contributors:

HE, P H-A, A M designed the study and participated in writing the protocol. P H-A and H E were involved in participant recruitment. P H-A, H T-J and H G performed the study, and authors H E, A M and M O supervised it. Author H G and H E performed data analysis. P H-A and H T-J wrote the first draft of the manuscript, and H E, M O supervised writing the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest:

None.

Acknowledgements:

The authors wish to thank the Rebirth Society members, in particular Mr Deilamizade. We also express our appreciation to Nader Molavi, Mehdi Ghafaari, Mehri Noori, Pedram Rezaei, Reza Daneshmand, Amir-Hossein Batooli, and Behrooz Rafie with special thanks to Professor Mohammad-Reza Zarrindast for his useful suggestions.

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