Title: Temporal Dynamics of the Neural Response to Drug Cues: An fMRI Study among Methamphetamine Users

Authors: Mohamad B. Soleymani[1,2], Arshiya Sangchooli[3,4], Mitra Ebrahimpoor[5], Mohamad A. Najafi[1,2], Bijan Vosoughi Vahdat[1], Alireza Shahbabaie[3,4], Mohammad Ali Oghabian[5], and Hamed Ekhtiari[3,5*]

1. *Sharif University of Technology, Tehran, Iran.*
2. *Material and Biomaterial Research Center, Tehran, Iran*
3. *Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran.*
4. *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.*
5. *Neuroimaging and Analysis Group, Imam Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.*

# Contributed equally as first authors

*__Corresponding author__: Hamed Ekhtiari, MD, PhD, Neurocognitive Laboratory, Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran. H_ekhtiari@razi.tums.ac.ir

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Abstract

Objective: Cue-induced craving is central to addictive disorders. Most cue-reactivity fMRI studies are analysed statically and report averaged signals, disregarding the dynamic nature of craving and task fatigue.

Methods: Thirty-two early abstinent methamphetamine users underwent fMRI-scanning while viewing visual methamphetamine cues. A Craving>Neutral contrast was obtained in regions of interest. To explore changes over time, the pre-processed signal was divided into three intervals. Contrast estimates were calculated within each interval, and were compared using ANOVA followed by post hoc t-tests. The results were compared with those from a static analysis across all blocks.

Results: A priori expected activations in the prefrontal cortex, insula and striatum not detected by static analysis were discovered by the dynamic analysis. Post hoc tests revealed distinct temporal activation patterns in several regions. Most showed rapid activation (including both ventral/dorsal striata and most regions in the prefrontal, insular and cingulate cortices) whereas some had delayed activation (the right anterior insula, left middle frontal gyrus, and left dorsal anterior cingulate cortex).

Conclusions: This study provides preliminary insights into the temporal dynamicity of cue-reactivity, and the potential of a conventional blocked-design task to consider it using a simple dynamic analysis. We highlight regional activations that were only uncovered by a dynamic analysis, and discuss the interesting and theoretically expected early versus late regional activation patterns. Rapidly activated regions are mostly those involved in the earlier stages of cue-reactivity, while regions with later activation participate in cognitive functions relevant later, such as reappraisal, interoception and executive control.

Keywords: Cue reactivity, Addiction, Methamphetamine, fMRI, Craving

1. Introduction

Addictive disorders are increasingly significant causes of mortality and morbidity worldwide (Merikangas & McClair, 2012; NIDA, 2015; Robbins & Clark, 2015; Whiteford et al. 2015). Recently, there have been attempts to better conceptualize these disorders neuro-cognitively (Volkow et al. 2011) and to develop clinically useful biomarkers on this basis (Moeller & Paulus, 2018). Long recognized as a central process in addiction (Robinson & Berridge, 1993; Wise, 1988), craving appears as a key symptom of substance use disorders (SUDs) in DSM-V (American Psychiatric Association, 2013).

Substance cue presentation is the conventional method for controlled craving induction (Reynolds & Monti, 2013) and it has been widely incorporated in functional neuroimaging studies of craving (Garrison & Potenza, 2014; Ekhtiari et al. 2016). fMRI literature on cue-reactivity and craving has matured sufficiently to allow for qualitative (Yalachkov et al. 2012) and quantitative (Chase et al. 2011; Kühn & Gallinat, 2011) reviews that analyse brain activation across cue-reactivity studies, even for specific SUDs (Engelmann et al., 2012; Schacht et al. 2013).

Multiple brain regions underlie cue-induced craving, including the anterior cingulate cortex (Kühn & Gallinat, 2011), ventral striatum and amygdala (Kühn & Gallinat, 2011; Chase et al., 2011), the orbitofrontal cortex (Chase et al., 2011) and other regions of the prefrontal cortex (Wilson et al. 2004), the insula (Noori et al. 2016) and the cerebellum (Moreno-Rius & Miquel, 2017). However, while these findings have risen hopes of clinical translation, no activation pattern has been consistent enough for clinical utility (Tiffany & Wray, 2012). Many potential causes of inconsistency in psychiatric neuroimaging have been outlined (Lui et al. 2016; Milham et al. 2017; Whelan & Garavan, 2014), and in the cue-reactivity literature, heterogeneity might be due to study design, drug use patterns, craving regulation (Jasinska et al. 2014) and urge intensity (Wilson & Sayette, 2015).

One problem is that event-related and conventional blocked design studies of cue-reactivity usually consider the average overall neural reaction to drug cue exposures alternating with neutral cue presentation, assuming a stable response across blocks that becomes easier to detect by analyzing the entirety of the signal at once (Hartwell et al., 2011; Hedger et al. 2018; Limbrick-Oldfield et al., 2017; Schacht et al., 2011). This approach fails to account for the fact

that cue-induced craving is comprised of interacting stages unfolding over seconds and minutes. These include exposure to drug cues, top-down or bottom-up attention, implicit and explicit salience processing, subjective craving and an appetitive/compulsive state, executive control mechanisms employed to regulate the craving state, and ultimately either abstinence or drug consumption. This process has been referred to as the cue-induced craving pipeline (see Ekhtiari, Nasseri, et al., 2016). Also. drug cue-reactivity likely causes fatigue and habituation during the task due to the affective/appetitive salience of drug cues. The habituation of brain activation to various emotionally salient cues has been reported previously in other contexts (Phan et al., 2003; Wright et al., 2001).

Thus, the inconsistent results of cue-reactivity studies might partly be due to this framework of task design and analysis. A recent fMRI cue-reactivity study in 65 individuals with MUD demonstrated that while many brain regions display relatively static activation, regions such as the VMPFC, amygdala and ventral striatum show a dynamic and generally decreasing habituation response across time. These results were replicated in two separate samples as well (Ekhtiari et al., 2020). Another study with prolonged drug-cue exposure reported an initially increasing and later decreasing left amygdala activation, associated with changes in induced subjective craving. Furthermore, the dorsal anterior cingulate cortex showed increasing activity only as craving began to decrease, consistent with assumptions about its prominent role in the top-down inhibition of craving (Murphy et al., 2017). These preliminary findings suggest that considering the changes that occur during the neural cue-response across time can provide us with important information on the stages of cue-induced craving as they unfold, and help recognize and account for the effects of habituation and fatigue. We hope to show the importance of further investigations into the temporal character of cue-induced craving as it might help in the wider effort in developing a clearer picture of the temporal character of the brain craving response and its stages, and could ultimately improve our understanding of the neural underpinnings of cue-induced craving and developing valid fMRI biomarkers in addiction medicine.

Here, we recruited abstinent individuals with methamphetamine use disorder (MUD) who underwent a drug cue-reactivity task. We used a conventional blocked design, but compared brain activations across temporally distinct intervals (the dynamic analysis) in addition to a

conventional analysis of activation across all blocks (the static analysis). Our goal was to examine the differences between dynamic and static analysis results, and explore the temporal dynamics of brain activations (i.e. early responding or delayed responding) that are lost during static analysis.

2. Methods

2.1 Participants

Thirty-two abstinent (mean abstinence duration =17.63±15.78 days), male methamphetamine (meth) smokers (mean age=30.47±5.46; age range=22-43) were recruited. The participants had no moderate to severe traumatic brain injury, past or current major neurologic disorder or history of any DSM-IV-TR Axis I disorder except SUD.

All participants met DSM-IV-TR criteria for methamphetamine dependence and were recruited from Omid-e-Javid, an abstinence-based residential center affiliated with Tehran Welfare Organization. The subjects were treated only by abstinence under observation, and no medications were used. All subjects reported methamphetamine use at least six days a week in the last month before entering the treatment program and were screened to ensure negative urine toxicology for any drug (except nicotine) for at least a week prior to study enrolment. All participants provided written informed consent before enrollment. An independent ethics committee in Tehran University of Medical Sciences reviewed and approved the study protocol and the consent form.

2.2 Stimuli and Procedure

We utilised a cue-induced craving task (CICT) based on a previous study (Ekhtiari, Alam-Mehrjerdi, Nouri, George, & Mokri, 2010). The task consisted of six meth-cue blocks and six neutral-cue blocks, each followed by a rest block. Blocks contained four visual stimuli, and each stimulus was presented for six seconds. The complete run (consisting of rest, neutral, rest, drug cue blocks) was repeated six times (96 seconds), so the CICT took 576 seconds to complete. Overall, participants viewed 24 meth-related images and 24 neutral images. The meth stimuli included pictures of meth, paraphernalia, and individuals smoking or preparing

meth. The neutral stimuli included nature scenes selected from non-copyrighted images on the internet, and were psycho-physically matched to drug-cue images (Ekhtiari et al., 2010). F

2.3 Image acquisition

Imaging was performed with a 3T MRI system (Siemens Tim Trio whole-body MRI system, Siemens Medical Solutions, Erlangen, Germany). MRI scanner with an eight-channel head coil was used to acquire T1-weighted 3D anatomical images using a magnetization prepared rapid gradient-echo (MP-RAGE) sequence, with the following parameters: TR = 1800 ms, TE = 3.4 ms, Field of view (FOV) = 256 × 256 mm, flip angle = 7°, and 1mm3 voxels parameters. Functional imaging using a standard T2* weighted echo-planar imaging (EPI) sequence was performed with the following parameters: TR = 3000 ms, TE = 30 ms, matrix = 64 × 64, Flip Angle=90°, FOV= 192 mm, in-plane resolution of $3mm^2$ and slice thickness 3 mm. 196 continuous EPI volumes were acquired in each session of the fMRI.

2.4 Data Pre-processing

Image preprocessing was conducted in FEAT (Woolrich et al., 2001), part of the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). The following preprocessing steps were applied for each subject: the first four volumes were discarded due to the T1 none-equilibrium effect, motion correction with MCFLIRT, B0 unwarping with field map images, brain extraction using BET, spatial smoothing with a Gaussian kernel of full-width half-maximum 6mm and high-pass temporal filter with Gaussian-weighted least-squares straight-line fitting with σ = 100s. Subject-specific data were registered to the MNI152 2 mm3 standard space template (Montreal Neurological Institute, Montreal, QC, Canada) and the fMRI data was transformed into standard space using the registration transformation matrices.

2.5 Statistical Analysis

To address the study question, we divided the functional data (576 seconds) into three separate intervals, each comprised of two consecutive runs (Figure-1).

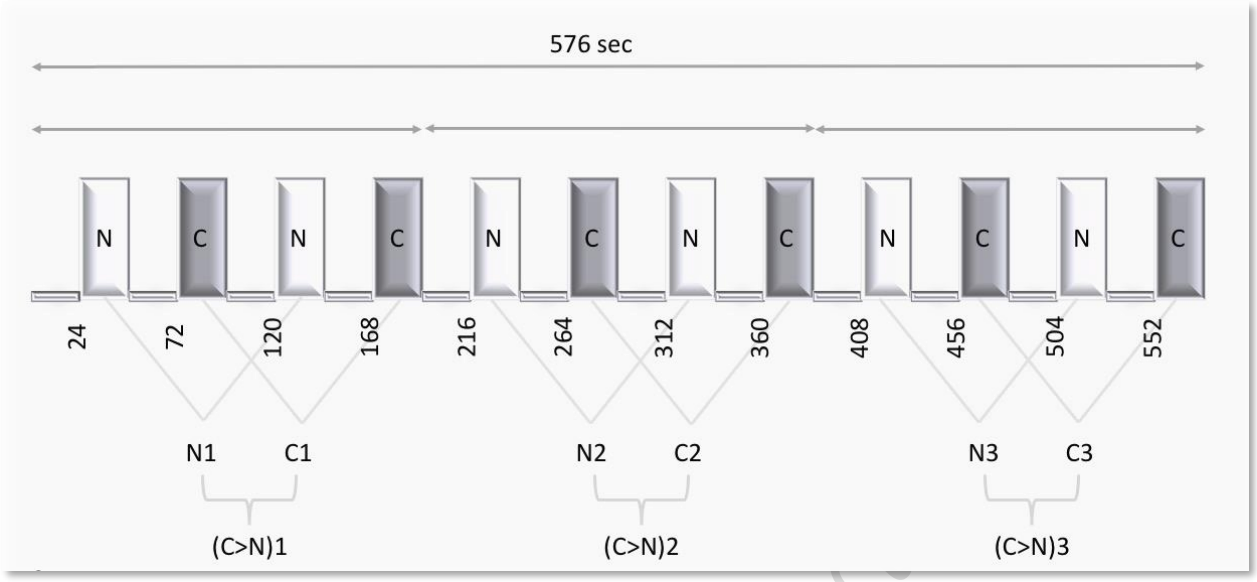

Figure-1 Block design scheme. The cue-induced craving task was divided into three equal intervals. C: drug cue block; N: neutral stimulus block.

A craving>neutral contrast was defined as the contrast of interest within each interval and parameter estimates for the contrasts were estimated with a General Linear Model using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/).

The results were then entered into a second-level analysis based on a repeated measures ANOVA design. The main contrast was compared across intervals with an F-test. Regions with a positive ANOVA test were termed "dynamically active". To compare the three intervals in dynamically active regions, a series of post-hoc t-tests were performed, using F test results as a binary mask to exclude dynamically inactive regions. The statistical maps from group-level F-test were thresholded based on a cluster significance threshold of $p = 0.05$ after masking. A set of areas were considered as a priori regions of interest (ROIs) based on Harvard–Oxford cortical and subcortical structural atlases in FSL, including the left (l-) and right (r-) caudate, ventral striatum (Vent-Striatum), amygdala, posterior insula (Post-Insula) and anterior insula (Ant-Insula), middle frontal gyrus (MFG), superior frontal gyrus (SFG), inferior frontal gyrus (IFG), dorsal anterior cingulate (Dorsal-ACC), rostral anterior cingulate (Rostral-ACC), and ventromedial prefrontal cortex (vmPFC). (Figure-2).

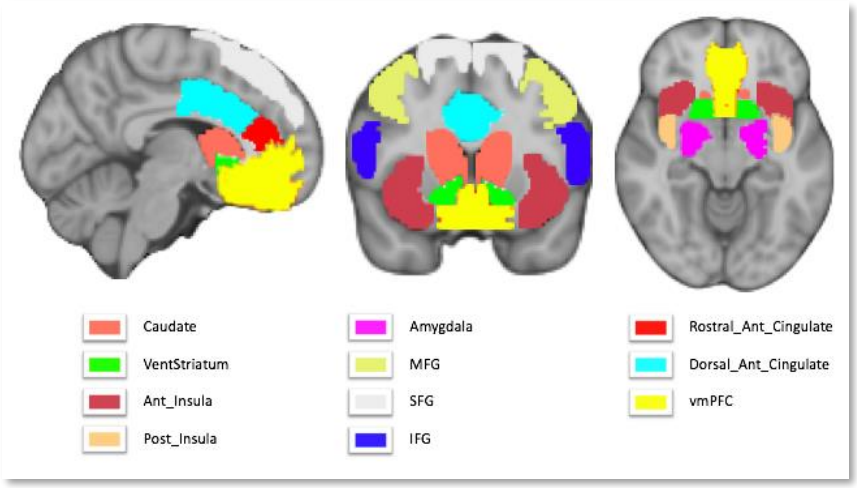

Figure-2 Masks used as a prior region of interest overlaid on structural template from MNI.

Conventional (static) analysis, where complete fMRI time series were analysed at once, was also performed so the results could be compared with those from the main analysis. Contrast images (Craving>Neutral) obtained from each subject entered a group analysis. Activated brain areas were determined using one sample t-tests within each ROI, and were termed "statically active".

3. RESULTS

Regarding imaging analysis results, group-level F-test results (Table-1, Figure-3) showed dynamic activity in several brain regions: l-Caudate, r-Caudate, l-Vent Striatum, l-Ant-Insula, r-Ant-Insula, l-Post-Insula, l-MFG, r-SFG, vmPFC, l-Dorsal-ACC, r-Dorsal-ACC, l-Rostral-ACC, r-Rostral-ACC. Figure-4 illustrates the changes in the activation pattern of intervals based on cluster mean values for each significant cluster.

Table-1 Significant clusters of the repeated measures ANOVA. Showing regions with significantly dynamic activity. Respective activation maps are displayed in Figure-3

Anatomic Region	Cluster	F-value	Z-value	X	Y	Z	Cluster size (#Voxels)
l-Caudate	1	4.69	2.24	-12	20	-2	55
r-Caudate	1	4.00	1.99	18	12	6	10
l-Vent Striatum	1	4.54	2.19	-12	20	-4	17
l-Ant-Insula	1	6.51	2.78	-44	16	-14	132
	2	3.96	1.98	-28	30	2	38
r-Ant-Insula	1	4.05	2.01	44	12	-14	10
l-Post-Insula	1	5.25	2.42	-46	-10	-4	27
	2	4.32	2.11	-38	2	-14	24
	3	4.30	2.10	-44	-16	10	29
l-MFG	1	4.58	2.20	-40	8	32	47
	2	3.99	1.99	-42	38	24	19
	3	3.90	1.96	-48	28	26	44
r-SFG	1	4.33	2.11	24	32	54	17
vmPFC	1	4.84	2.29	10	36	-8	303
l-Dorsal-ACC	1	4.95	2.32	-10	26	18	29
	2	3.94	1.98	-6	-14	38	133
r-Dorsal-ACC	1	4.08	2.03	14	30	22	11
	2	3.87	1.95	2	-2	42	11
l-Rostral-ACC	1	5.45	2.48	-10	30	12	149
	2	3.95	1.98	-10	40	-6	14
r-Rostral-ACC	1	4.97	2.33	6	30	12	65
	2	3.74	1.90	10	36	-6	15
	3	3.50	1.80	8	42	16	11

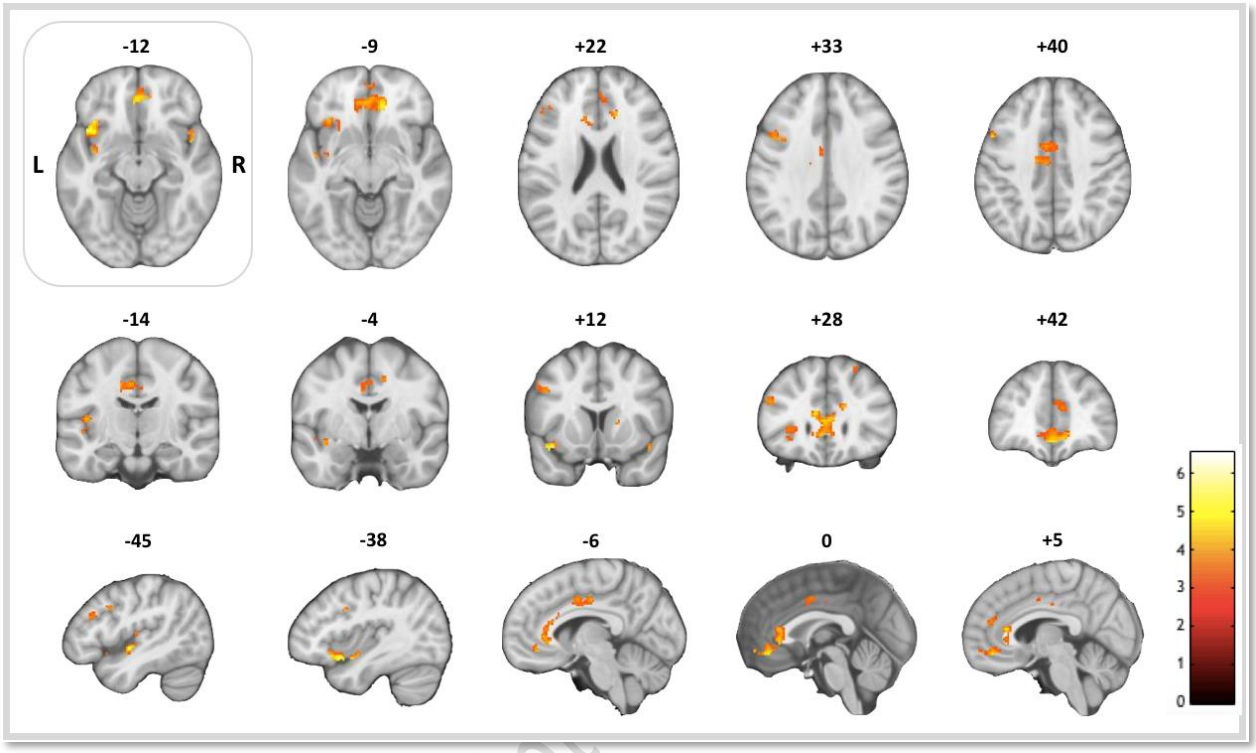

Figure-3 Brain areas showing a significantly different activation through time, based on F-test; Cluster labels and F-values are presented in Table-1

The results of the three post-hoc tests on dynamically active regions for pairwise comparisons of activity between intervals are shown in Table-2. All of these regions showed significantly higher activity in the first and second intervals than the third interval. This suggests an initial activation and later deactivation of these regions during the task (Figure-4, based on Table-2).

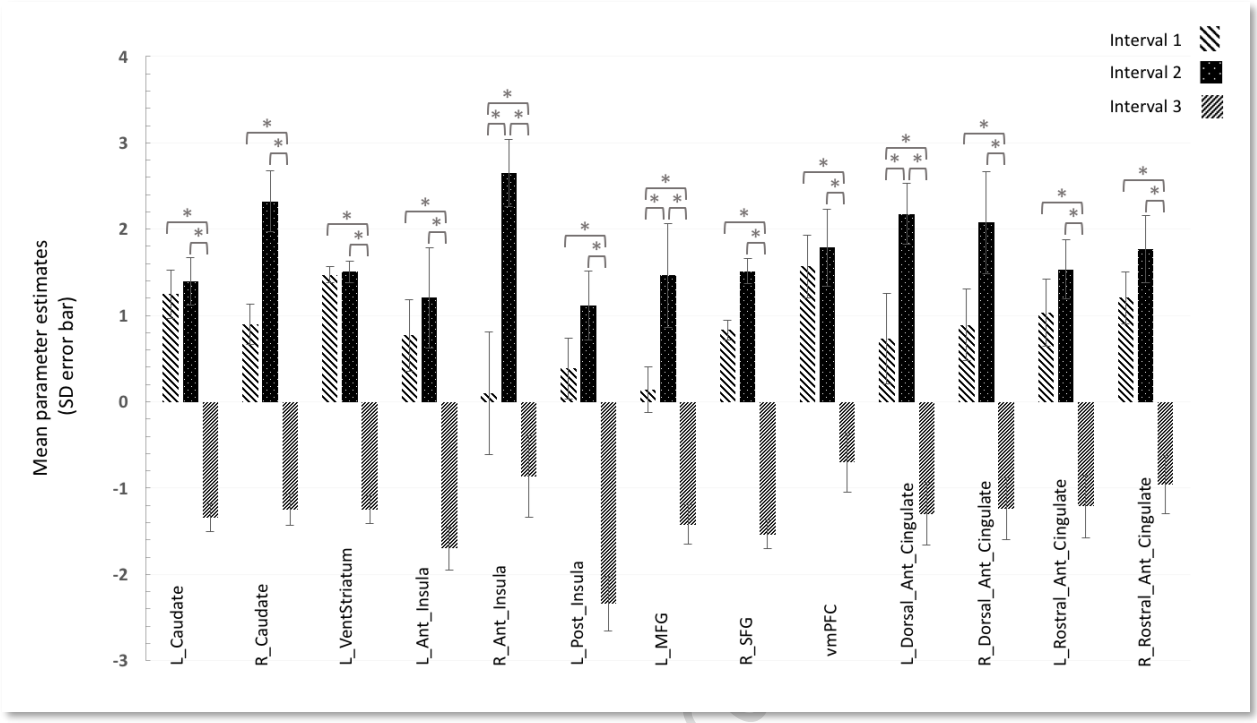

Figure-4 Mean parameter estimates each region with a positive F test result for at least one cluster. Significance of post-hoc comparisons based on paired t-test results are indicated by a * for P-value<0.05; detailed results of the tests are presented in table-2. The tests were performed on clusters within each region, but the mean parameter estimates (height of each bar) and their dispersions are reported for all voxels within each region.

Table-2 Post-hoc pairwise comparisons of the 3 intervals based on paired t-test

Test	Z-value	P-value	x	y	z	*Anatomic Label*
T1 & T2	2.42	0.008	42	24	-4	*r-Ant-Insula*
	2.02	0.022	-52	8	44	*l-MFG*
	1.78	0.038	-12	24	18	*l-Dorsal-ACC*
T2 & T3	2.58	0.005	-12	20	-2	*l-Caudate*
	2.72	0.003	18	12	6	*r-Caudate*
	2.49	0.006	-10	20	-2	*l-Vent Striatum*
	3.33	0.000	-44	16	-14	*l-Ant-Insula*
	2.62	0.004	44	12	-16	*r-Ant-Insula*
	3.07	0.001	-46	-10	-4	*l-Post-Insula*
	2.88	0.002	-40	8	32	*l-MFG*
	2.72	0.003	24	34	54	*r-SFG*
	2.74	0.003	0	44	-12	*vmPFC*
	2.99	0.001	-10	26	18	*l-Dorsal-ACC*
	2.64	0.004	2	-2	42	*r-Dorsal-ACC*
	2.97	0.001	-10	26	16	*l-Rostral-ACC*
	2.84	0.002	6	30	12	*r-Rostral-ACC*
T1 & T3	2.63	0.004	-12	20	-4	*l-Caudate*
	2.13	0.017	8	4	-2	*r-Caudate*
	2.63	0.004	-12	20	-4	*l-Vent Striatum*
	2.80	0.003	-40	14	-14	*l-Ant-Insula*
	2.21	0.014	42	24	-4	*r-Ant-Insula*
	2.43	0.008	-36	-6	-10	*l-Post-Insula*
	2.29	0.011	-42	36	24	*l-MFG*
	2.41	0.008	2	52	24	*r-SFG*
	2.84	0.002	10	38	-8	*vmPFC*
	2.07	0.019	0	0	38	*l-Dorsal-ACC*
	2.44	0.007	14	30	22	*r-Dorsal-ACC*
	2.80	0.003	-10	30	12	*l-Rostral-ACC*
	2.51	0.006	10	36	-6	*r-Rostral-ACC*

Concerning the comparison of the first two intervals, two groups of dynamically activated regions were separated. The r-Ant-Insula, l-MFG, and l-Dorsal-ACC had significantly higher activations in the second compared to the first interval (Figure-5), while for other regions the first and second intervals had no significant difference.

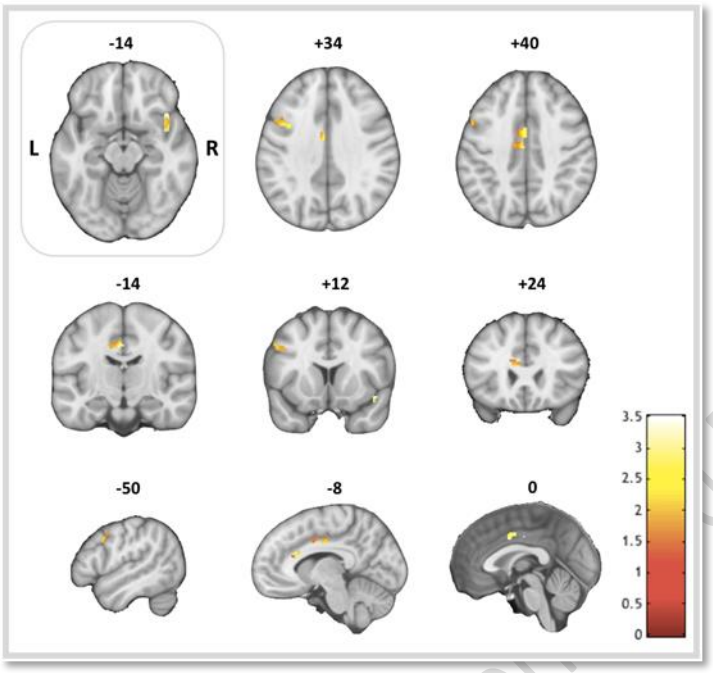

Figure-5 activation pattern in post-hoc test between interval 1 and interval 2 including: r-Ant-Insula, l-MFG, and l-Dorsal-ACC; Table-2 provides the relative cluster information.

It was assumed that the former group responded to the presented cues with a relative delay, while the regions in the latter group had no further increase in activity moving from the first to the second interval, and therefore were early responders. This second group included l-Caudate**,** r-Caudate**,** l-Vent-Striatum**,** l-Ant-Insula**,** l-Post-Insula**,** r-SFG**,** vmPFC**,** r-Dorsal-ACC**,** l-Rostral-ACC**,** r-Rostral-ACC.

As for the conventional analysis, one sample t-test results showed several activated regions including the l-Caudate, r-Caudate, r-Ant-Insula, r-MFG, r-IFG, vmPFC, l-Dorsal-ACC, and r-Dorsal-ACC. Table-3 portrays the BOLD-response to Craving>Neutral contrast, and Figure-6 presents the corresponding activation maps.

Table-3 One-sample t-test, showing significant activation in Craving>Neutral contrast under static analysis. Respective maps are presented in Figure-6.

Anatomic Region	Z-value (max)	P value	X	Y	Z	Cluster size (#Voxels)
l-Caudate	2.01	0.022	-8	-4	18	20
r-Caudate	2.43	0.008	10	-4	18	117
r-Ant-Insula	2.25	0.012	38	14	-	67
r-MFG	2.05	0.020	50	14	10	42
r-IFG	2.47	0.007	40	14	34	77
vmPFC	1.87	0.031	-8	48	24	109
l-Dorsal-ACC	2.43	0.008	0	-14	-8	160
r-Dorsal-ACC	2.34	0.010	2	-14	36	15
					36	

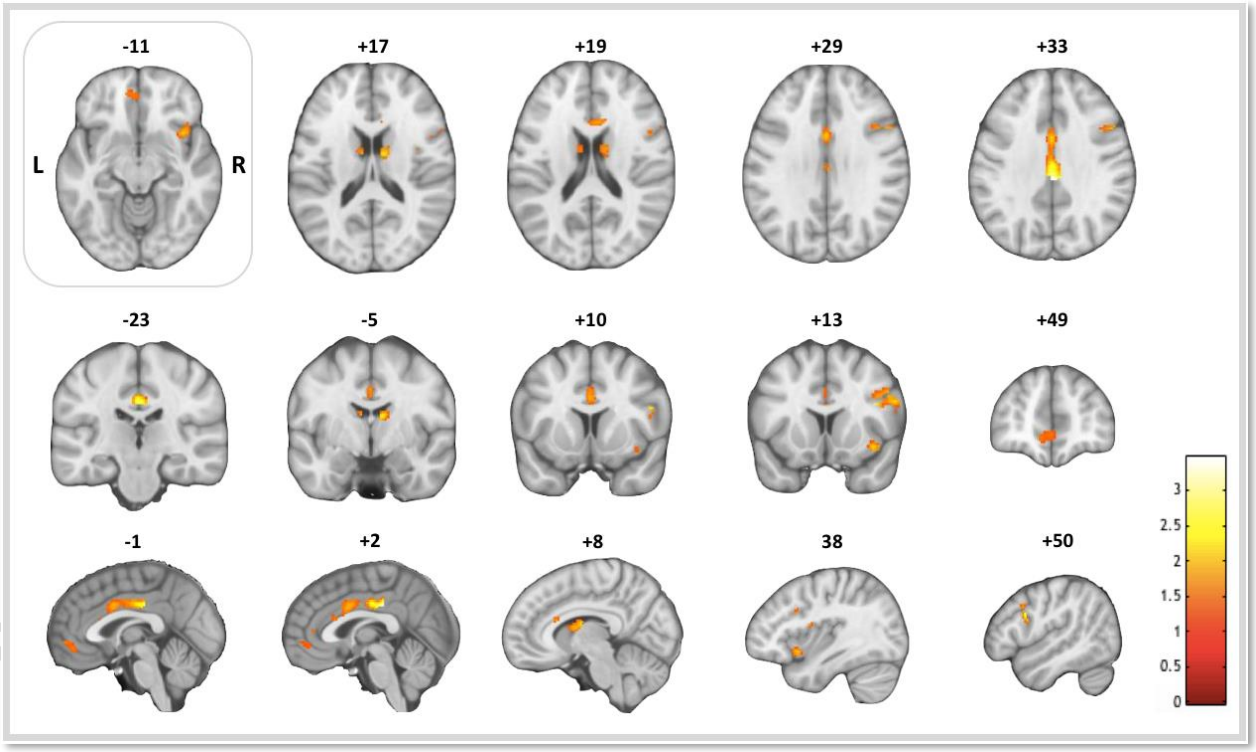

Figure-6 Activation maps of one-sample t-test results regarding Craving>Neutral contrast entire time including: l-Caudate, r-Caudate, r-Ant-Insula, r-MFG, r-IFG, vmPFC, l-Dorsal-ACC, and r-Dorsal-ACC. Cluster information are presented in table-3

4. Discussion

This preliminary study explores a novel and simple method of analysis in a classic blocked design visual cue-reactivity task in methamphetamine users. We sought to assess whether a static analysis (by the conventional averaging of the signal for such blocked design studies) might miss meaningful regional activations and temporal patterns discovered by a simple dynamic analysis, using a comparison of signal across distinct intervals. While newer cue-reactivity paradigms such as continous cue exposure (long presentation blocks) may have better validity than classical blocked designs (Murphy et al., 2017), we aimed to investigate if dynamic changes in fMRI signal will occur with the brief pictorial cue presentations of a typical blocked design paradigm, as these comprise the majority of cue-reactivity fMRI studies. This is similar to a recent, more sophisticated fMRI study of drug cue-reactivity in individuals with MUD (Ekhtiari et al., 2020).

4.1 Dynamic versus Static analysis

Only six regions, l-Caudate and r-Caudate nuclei, l-Dorsal-ACC and r-Dorsal-ACC, vmPFC and r-Ant-Insula showed both static and dynamic activity. As most regions showed an increase in signal from the first to the second interval and a relative drop in the last interval, the discrepancy seems to suggest that in static t-tests BOLD signal changes may have cancelled each other out in the regions with static, but not dynamic, activity. These seven regions include the l-Vent-striatum, l-Ant-Insula and l-Post-Insula, l-MFG, r-SFG, l-Rostral-ACC and r-Rostral-ACC. All these regions have been implicated in drug cue-reactivity research. The ventral striatum is activated with perceptions of appetitive value (Haber & Knutson, 2010), and recent meta-analyses have confirmed its activation during cue-induced craving (Chase et al., 2011; Kühn & Gallinat, 2011). Some other studies of methamphetamine cue-reactivity may have failed to detect ventral striatal activation because of their static analyses (Huang et al., 2018; Yin et al., 2012). The insula has a central role in interoception (Naqvi & Bechara, 2009) and salience processing (Liu et al. 2011). Compared to the ventral striatum, however, the data regarding insular activation in cue-reactivity studies seems to have been less consistent. One meta-analysis of cue-reactivity studies failed to detect insular activation (Chase et al., 2011), and others noted activity only within the right insula (Kühn & Gallinat, 2011) or anterior insula (Tang et al., 2012). We also observed static activation within the right anterior Insula, and all

other regions of the insular cortices had only dynamic activation. Those activations would have been missed without the dynamic analysis, which might have been the case in previous studies.

Prefrontal cortical regions have been widely implicated in drug cue-reactivity (Wilson et al., 2004). The SFG might have a role in drug-related attentional processes (Hopfinger et al. 2000). Several meta-analyses (Chase et al., 2011; Noori et al., 2016; Schacht et al., 2011) have identified SFG activation in drug>control cue contrasts before. The lack of dynamic analysis may have contributed to the failure to detect a SFG activation in one cue-reactivity study in MUD subjects (Yin et al., 2012). The MFG has more evidence supporting its role in cue-reactivity and overlaps with the dorsolateral prefrontal cortex (DLPFC) area. The DLPFC has been implicated in the inhibitory control of drug-related behavioural responses (Koob & Volkow, 2010). We expected to observe a dynamic MFG activation as subjects begin to inhibit their craving later during the task, and an activation was identified only in the dynamic analysis. While many meta-analyses have reported a DLPFC or MFG activation in cue-reactivity and craving (Chase et al., 2011; Kühn & Gallinat, 2011; Noori et al., 2016; Schacht et al., 2013; Tang et al., 2012), the three studies of individuals with MUD (Huang et al., 2018; Malcolm et al., 2016; Yin et al., 2012) failed to do so, potentially due to static analyses.

Perhaps most intriguingly, the static analysis revealed expected activity in only two of the four ACC-related regions, the dorsal left and right ACCs. The ACC is involved in several central processes related to drug craving, including attentional bias (Luijten et al., 2011), goal setting and error processing (Goldstein et al., 2007), conflict monitoring (Lütcke & Frahm, 2008), self-referential processing (Moeller et al., 2014), emotion regulation (Goldstein et al., 2007) and salience (Seeley et al., 2007). Most meta-analyses (Engelmann et al., 2012; Kühn & Gallinat, 2011; Noori et al., 2016; Schacht et al., 2011; Tang et al., 2012) and all of the three methamphetamine cue-reactivity study previously mentioned (Huang et al., 2018; Malcolm et al., 2016; Yin et al., 2012) reported ACC activation in cue-reactivity and craving reactions. As these studies and others have mostly not made a rostral/dorsal ACC division, it remains unclear why only the dorsal ACC had a dynamic activation. Generally, it is significant that dynamic analysis seems to have captured a wider ACC activity than was seen with the static analysis.

Conversely, the r-IFG and r-MFG (unlike l-MFG) showed a significant overall activation but no dynamic activity over time according to ANOVA. These regions had a significant but

sustained activation across the three intervals. In the case of r-MFG, static activity without dynamic activity was unexpected, as the MFG (and DLPFC) would hypothetically activate only in the final stages of the cue-induced craving process for craving inhibition and perhaps top-down attention. However, lateral asymmetry in MFG activation has been noted in several cue-reactivity studies before (Diggs et al. 2013; Nestor, McCabe, Jones, Clancy, & Garavan, 2011; Sun et al., 2012) and a functional difference between the two MFGs is possible. The IFG is another region which we expected to activate dynamically, considering its role in response inhibition (Prisciandaro et al., 2014) and emotion regulation (Goldstein et al., 2007). The main reason for the unexpected lack of dynamic activity in the r-MFG and r-IFG was the flat and stable activation trends of these regions, perhaps because they are involved in providing an executive control "tone", rather than acute inhibition. Even though the stable activation of these regions meant that their activation could be reliably found by a static analysis, a more powerful dynamic analysis of activation trends, with a longer task and higher temporal resolution, would probably have found these regional activations as well.

We demonstrate that discrepancies in regional activation patterns across studies of cue-reactivity can also to be observed between our two analytic methods, and some unexpected results could be explained using a simple dynamic method. These suggest that in addition to differences in study design, static analyses in original studies might have distorted regional activation patterns in each study differently and led to discrepancies. This differential distortion is reasonable, considering the differences in temporal activation pattern that a dynamic model of craving would suggest is the case. Other causes further complicating the picture provided by a static analysis might be the differences in hemodynamic responses of various brain regions, and the length and number of blocks and cue presentations. This alteration of detected activations, as an artifact of static signal analysis, has been mostly overlooked as a potential cause of heterogeneity (Jasinska et al., 2014).

4.2 Temporal activation patterns

Another group of noteworthy observations are the patterns of signal change across the three intervals. These patterns were obviously disregarded in the static analytical approach.

Most regions with dynamic activity showed no difference in activation between the first two intervals, suggesting a relatively sudden increase which declines by the third interval. The

caudate nuclei are involved in habitual motor responses observed in SUDs (McClernon et al., 2009) and the relevant procedural memory (Volkow et al., 2006). The ventral striatum has been shown to be involved in different aspects of reward-related processing (Haber & Knutson, 2010), like salience attribution (Koob & Volkow, 2016), motivation (David et al., 2007) and reward prediction (O'Doherty et al., 2004). The vmPFC is also involved in reward processing. It is activated by exposure to primary rewards (Haber & Knutson, 2010) and reward cues (Bray & O'Doherty, 2007; Gottfried et al. 2003). The SFG is involved in attentional processes (Hopfinger et al., 2000).

Three dynamically active regions, the l-MFG, r-Ant-Insula, and l-Dorsal-ACC were observed to have a significantly greater BOLD signal contrast in the second interval compared to the first interval. This suggests a relatively delayed activation in the course of cue-response. The l-MFG's late activation pattern is well in line with its role in inhibitory control (Koob & Volkow, 2010) as abstinent patients inhibit their cue-induced craving response after it is initiated, and l-MFG activation has been more commonly reported in meta-analyses of cue-reactivity studies (Chase et al., 2011; Kühn & Gallinat, 2011; Schacht et al., 2013).

The insula and ACC had both regions with early activation and regions with late activation. This could be due to the complexities of the role these regions play in the cue-reactivity pipeline. In the Insula's case, all activated regions except for the r-Ant-Insula followed the same early activation pattern. The insula's involvement in salience attribution (Ekhtiari, Nasseri, et al., 2016), interoception (Naqvi & Bechara, 2009) and subjective craving (Garavan, 2010) place it in the middle of the cue-induced craving pipeline. The two insulae might have somewhat differentiated functions, as there is some evidence for the lateral asymmetry of Insulae's role in addictive processes (Craig, 2010; Naqvi et al. 2007; Paulus et al. 2005). Regarding the ACC, every part except the l-Dorsal-ACC displayed an early activation. The ACC is involved in processes associated with both the earlier (attention (Luijten et al., 2011), goal setting (Goldstein et al., 2007) and salience (Seeley et al., 2007)) and later (self-referential processing (Moeller et al., 2014) and emotion regulation (Goldstein et al., 2007)) stages of the cue-reactivity process. Considering ACC's many functions, it is more difficult to find specific temporal correspondences between ACC activation and any stage of the pipeline as we did for other regions, especially considering the methodological limitations of our exploratory study.

Overall, temporal activation patterns for most ROIs fit expectations based on the cue-induced craving pipeline and previous research. While there were unexpected activation patterns, some of the irregularities could be explained by the fact that the cue-induced craving pipeline is not completely linear. For example, the top-down attentional role of executive control regions such as the prefrontal cortex and ACC might only become significant after the induction of craving and as a result of the patient's attempt at suppressing the induced craving response.

4.3 Regions of interest with no activation

Finally, the l-IFG, r-Vent-Striatum, r-Post-Insula, l-SFG, and both amygdalae did not show an activation in any of the analyses. Considering the observed activations in their opposite-hemisphere pair, the lack of activation in the first four regions could be due to hemispherically asymmetric activity; but in amygdala's case not even a one-sided static or dynamic activation was observed. This was arguably the most unexpected result, as many clinical and preclinical studies confirm the amygdala's roles in cue-induced craving, Integration of cue-related information, and influencing relapse and drug-taking behaviour (Buffalari & See, 2010; Li et al., 2008). Amygdalar activation has been found to be affected by pharmacological (Fox et al., 2012; Xu et al., 2014; Young et al., 2014) and psycho-social (McClernon et al., 2007; Wiers et al., 2015) interventions as well, and this modulation of amygdalar activity has been suggested to be crucial to treatment.

Amygdalar activation has been reported in several meta-analyses of reactivity to drug cues (Chase et al., 2011; Kühn & Gallinat, 2011; Noori et al., 2016). Some one-drug meta-analyses (Engelmann et al., 2012; Schacht et al., 2013) and methamphetamine cue-reactivity studies (Huang et al., 2018; Malcolm et al., 2016; Yin et al., 2012) have failed to detect amygdalar activation, we expected to do so with either of our two analytical approaches. In a study with sustained stimulus presentation and dynamic analysis, subjective craving across was correlated with left amygdala activation better than any other regional activation, and authors suggest that signal averaging might be one reason that many opioid cue-reactivity studies do not report amygdalar activation (Murphy et al., 2017). Future research might include various factors that affect amygdalar activation, and consider the cue-reactivities of various amygdalar sub-compartments. It has been noted, for example, that the basolateral amygdala is specifically involved in addictive processes (Wassum & Izquierdo, 2015).

4.4 Limitations and future studies

Our exploratory study lacked a control group, and only male patients with MUD were included. Studies with controls, other SUDs or behavioral addictions, and female participants are necessary to test the limits of our approach and its generalizability.

Further, attempts could be made at separating the hypothesized steps of the cue-induced craving pipeline and studying activation patterns corresponding to each. Design features could be altered for increased ecological validity, and approaches such as the continuous cue presentation utilized by Murphy et al. (2017) may better elicit the desired craving response.

We used only three intervals and our total task duration might not have been long enough to be divided as it was. Future research could involve longer-duration tasks to capture more of the induced craving, more temporal intervals, and overlapping intervals to attain a finer view of signal change. It could also be argued that our approach is in fact measuring fatigue, since it is not clear whether a cohesive craving response is induced across the three entirety of the task. Blocked-design studies with sufficient power are required to disentangle the effects of fatigue and habituation in blocked-design tasks from the temporal stages of the craving response. Lastly, our participants were treatment seeking abstinent individuals with MUD. These specifications limit the generalizability of our findings, as even treatment seeking status has been shown to influence cue-reactivity (Wilson et al., 2004).

4.5 Conclusion

Overall, the results suggest that a temporally dynamic analysis might reveal theoretically plausible activations that a static analysis would have failed to detect, possibly due to certain activations not surviving signal averaging across time. This demonstrates that static analysis might be deficient in answering simple questions about region activation. Also, several interesting spatial patterns of dynamic activity emerged that seem to have been mostly overlooked in the extant literature and provide new avenues for investigation, such as the laterality of dynamic and static activation and the different dynamic activations in the rostral and dorsal anterior cingulate cortices. Our analysis uncovered temporal patterns of activity across regions of interest that mostly conformed to our a priori predictions based on their roles

in a dynamic model of cue-induced craving. These patterns cannot be uncovered by conventional analysis.

We believe that the results justify more extensive investigations based on a conception of cue-induced craving as a multi-staged and temporally dynamic process, potentially yielding replicable results and promoting a dynamic view of cue-induced craving, or better elucidating the effects of habituation in these studies. Hopefully, studies with more robust methodologies adopting sophisticated techniques used recently in other fields such as resting state fMRI analysis will help investigate the under-studied temporality of craving and cue-reactivity.

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