# Pattern Change of Inhibitory Drug Craving Control in Brain: A Study of Effective Connectivity

Zare-Sadeghi A.[1,2], Jafari A. H.[3]*, Oghabian M. A.[3], Salighe-Rad H.[3], Batouli S. A. H.[2,4]

[1]Faculty, Skull Base Research Center, Iran University of Medical Sciences, Tehran, Iran
[2]Research Assistant at Neuroimaging and Analysis Group (NIAG), Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran Iran
[3]Faculty, Biomedical Engineering and Medical Physics Department, Tehran University of Medical Sciences, Tehran, Iran
[4]School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

## ABSTRACT

**Background:** The inhibitory behavioral control of brain in treated drug abusers encountering drug cues, as well as the constructing regions of its network, has been widely studied previously. The causal relation of relevant brain regions has also been noticed in the literature, but the time/task condition variability of this causal network has not been studied yet.

**Method:** Thirteen drug abusers successfully treated with Methadone maintenance therapy, were scanned during a drug cue fMRI task. Two regions of interest (VMPFC and amygdala) were chosen based on the literature. Using Dynamic Causal Modelling (DCM), an effective connectivity network was estimated between these two brain regions and a craving-inducing input. Later, implementing a sliding window method on the extracted time-series, five further DCM networks were estimated to evaluate the time variability of the DCM network.

**Results:** The result of ordinary DCM showed that there were reciprocal connections between regions, and the craving input only affects the amygdala region. Sliding window showed that the input link strength changes during the task. This change was an exponential growth which moved from near zero to a positive value.

**Discussion:** The pattern of our DCM network demonstrated that the craving input passes from bottom brain regions to the top, and therefore, it indirectly affects top regions. However, the causal relations of this network varies during the task, and the craving link strength also grows exponentially. Our findings are in agreement with the hypothesis of craving inducement during stimulation, and therefore it may be considered as a proxy craving measurement.

## Keywords

DCM, Sliding Window, Drug Craving, Craving Measurement

## Introduction

There are distinguished studies on drug craving and inhibitory behavioral control mechanisms of the brain [1, 2]. These studies have highlighted the pivotal roles of ventromedial prefrontal cortex (VMPFC) and the amygdala in dissuasive decisions about drug taking [3, 4]. These regions function as correlated parts of the top-down and bottom-up regulatory systems [1, 5, 6].

There are a few studies monitoring the causal relations between these regions [7]. These studies have reported a causal effective connectivity network in different conditions [8-10]. There are some methods for quantifying the causal network but Dynamic Causal Modeling (DCM)

*Corresponding author:
A. H. Jafari
Faculty, Biomedical Engineering and Medical Physics Department, Tehran University of Medical Sciences, Tehran, Iran
E-mail: h_jafari@sina.tums.ac.ir

Received: 18 June 2016
Accepted: 12 July 2016

has shown prominent results in networks with external input [11]. In addition to this, neuronal activations have shown to be time-variable, and the resulted effective connectivity networks also have been proved to behave in a similar manner [12, 13]. These changes may depend on different conditions of the task [14, 15].

We have applied a sliding window to regional fMRI time-series, acquired during a cue inducing craving task, and implementing DCM in each window; 5 different effective connectivity networks were quantified. We hypothesized that the network would change during the whole duration of the task which will not be the same in 5 time-points.

## Material and Methods

### Participants

Thirteen formal drug abusers, treated with MMT method, were scanned during a cue inducing craving task. The procedure was fully described for each subject before scanning, and the written informed consent was obtained. The study protocol and consent form were approved by the Ethics Committee of Tehran University of Medical Sciences. Demographic data can be found in Table 1.

### fMRI Acquisition

Functional images were acquired on Avento 1.5 T scanner (Siemens, Germany) using echo-planar imaging with a T2*-weighted gradient-echo multi-slice sequence (TR = 3000 ms, TE = 50 ms, flip angle = 90 degrees, voxel size 3 × 3 × 3 mm3, matrix 64 × 64). T1 3-dimensional–weighted images were obtained (MPRAGE, TE = 3.55 ms, TR = 1910 ms, voxel size 1 × 1 × 1 mm3, flip angle = 30 degrees).

**Table 1:** Demographic Data of Participants.

| | |
|---|---|
| Age | 34.7 ± 2.52 |
| Gender (male) | 13 |
| Education (Year) | 11.2 ± 1.7 |
| Abstinence Duration (month) | 16.4 ± 3.82 |
| Opium abusers | 13 |
| Heroin abusers | 13 |
| Alcohol abusers | 10 |
| Tabaco Users | 13 |

### fMRI Task

The fMRI cognitive task had a block design with 6 runs; each run consisted 4 blocks with the length of 24 seconds for each block. The first and third blocks were a rest block in which a cross was shown to the subject, in the second block 4 neutral images similar to drug abusing situations were shown to the subject each for 6 seconds, and in the fourth block 4 images directly related to drug abusing were shown. The task structure is depicted in Figure 1.

### Analysis

FSL5 FLIRT [16] was used to correct EPI images for the head motion. Slice timing correction was done using interleaved order, high-pass temporal filtering was done with the size of 96s to remove the signal trend, a Gaussian kernel with the size of 5 mm FWHM was used to smooth functional images, and for group comparison the intensity normalization was done as the last part of the preprocessing step.

The FEAT tool [17] from FMRIB's package was used to model the data and find the activations in the brain. Canonical hemodynamic response with its derivative was used to model the regressors for the condition of interest; craving> neutral. Next, an ROI-based analysis was carried out using FLAME2 [18] tool of the FSL5 package, as the group level analysis for the contrast "craving > neutral".

### Dynamic Causal Modelling

A model space with 9 models were defined which included models with different connections. After estimating models for single subjects, we divided model space into two fami-

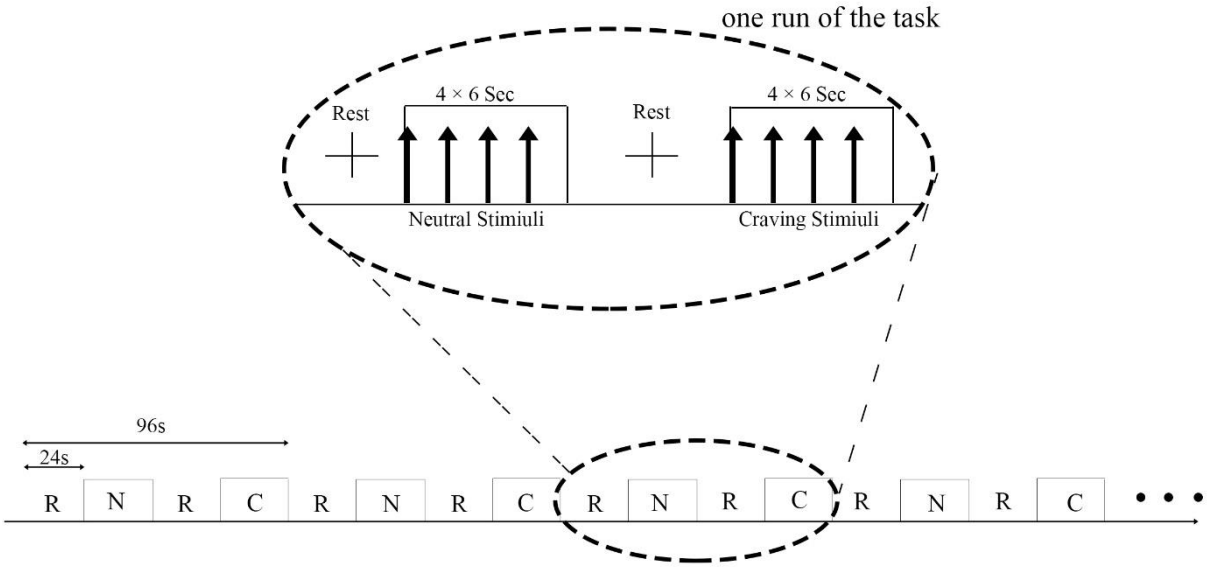


**Figure 1:** fMRI Task Structure. R stands for rest, N stands for neutral, and C stands for craving.

lies regarding the link from craving input to the amygdala region; one family included models in which craving was not directly linked to the amygdala and the other models in the second family all have link from input to amygdala. Using Bayesian Model Selection (BMS) and Bayesian Model Averaging (BMA), the final DCM model for the group was quantified. This single model was used in the time-variability check. For time-variability, a sliding window method was used. The length of window was selected to be in the length of 2 runs (for the sake of convergence) and the step size was selected as one run. Having 6 runs in total, 5 time-points were drawn from each time-series. The single DCM network which was resulted from the last step was estimated again for each part of the time-series of all subjects. Using BMA on these DCM networks, the final 5 DCM networks were concluded.

## Results

### Activations

The results of GLM analysis for the whole group can be seen in Table 2.

### Effective Connectivity

The families of models with craving input to the amygdala were the winning family from BMS results and implementing BMA, concluded in the network depicted in Figure 2 (Left). The sliding window method resulted in an exponential change in craving input strength. Figure 2 (Right) depicts these changes schematically.

We have to mention that the changes in other links were not statistically significant. The maximum variance of the input link strength was 0.03.

## Discussion

Implementing DCM, we reached an effective connectivity network between two regions of interest, VMPFC and the amygdala and the task based external input. Further considering sliding window, 5 different DCMs with the same structure, were estimated among these three nodes.

The result of classic DCM showed that there were reciprocal links between selected ROIs and the input has a direct effect on the amygdala, only. These are in compliance with previous studies on brain inhibitory behavioral con-

**Table 2:** Group Results for Contrast Craving > Neutral

| Anatomical Regions | Cluster Size | Z-values | Local Maximums Co-ordinates | | |
|---|---|---|---|---|---|
| Visual Cortex | 1426 | 3.8 | 20 | -64 | 14 |
| Lingual Gyrus | | 3.6 | 0 | -80 | 22 |
| Lingual Gyrus | | 3.56 | 2 | -80 | 26 |
| Cuneus | | 3.45 | 22 | -64 | 2 |
| retrosplenial cortex | | 3.42 | -10 | -78 | 14 |
| Cuneus | | 3.42 | -16 | -70 | 0 |
| Insula | 718 | 3.65 | -48 | -20 | 2 |
| Inferior parietal lobule | | 3.57 | -60 | -38 | 20 |
| Inferior parietal lobule | | 3.53 | -50 | -36 | 14 |
| Inferior parietal lobule | | 3.43 | -54 | -34 | 12 |
| Inferior parietal lobule | | 3.23 | -60 | -36 | 10 |
| Insula | | 3.17 | -38 | -30 | 8 |
| Primay somatosensory cortex | 454 | 3.43 | 16 | -46 | 56 |
| Primay somatosensory cortex | | 3.4 | 18 | -46 | 60 |
| Superior parietal lobule | | 3.23 | 16 | -46 | 52 |
| Superior parietal lobule | | 3.23 | 24 | -46 | 68 |
| Superior parietal lobule | | 3.13 | 12 | -50 | 68 |
| Postcentral Gyrus | | 3.06 | 12 | -46 | 68 |
| Secondary somatosensory cortex | 263 | 3.44 | 50 | -10 | 24 |
| Secondary somatosensory cortex | | 3.25 | 58 | -2 | 12 |
| Primay somatosensory cortex | | 3.21 | 56 | -6 | 22 |
| Secondary somatosensory cortex | | 3.08 | 60 | 0 | 4 |
| Secondary somatosensory cortex | | 2.87 | 58 | -12 | 12 |
| Secondary somatosensory cortex | | 2.85 | 64 | -14 | 10 |
| Heschl's Gyrus | 262 | 3.3 | 56 | -28 | 14 |
| Inferior parietal lobule | | 3.19 | 56 | -38 | 12 |
| Inferior parietal lobule | | 3.18 | 58 | -48 | 10 |
| Heschl's Gyrus | | 3.12 | 60 | -28 | 16 |
| Superior temporal Gyrus | | 2.96 | 60 | -36 | 6 |
| Inferior parietal lobule | | 2.91 | 46 | -42 | 12 |

trol mechanism [1] and studies considering the roles of the regions in this inhibitory system [2, 19, 20].

The result of sliding window revealed that the reciprocal connections between regions and also the self-inhibitory connections of each region, do not change during the task (the change was not statistically significant), and the brain intrinsic network is constant. However, the strength of the task based craving input link changed exponentially and increased in value from near zero to some considerable amount. This proved our hypothesis about the network change during the task.

Our study may be considered as a proxy craving measurement method, as it is quantifying the craving input during the task, and that it is not based on subjective reports [21]. Of

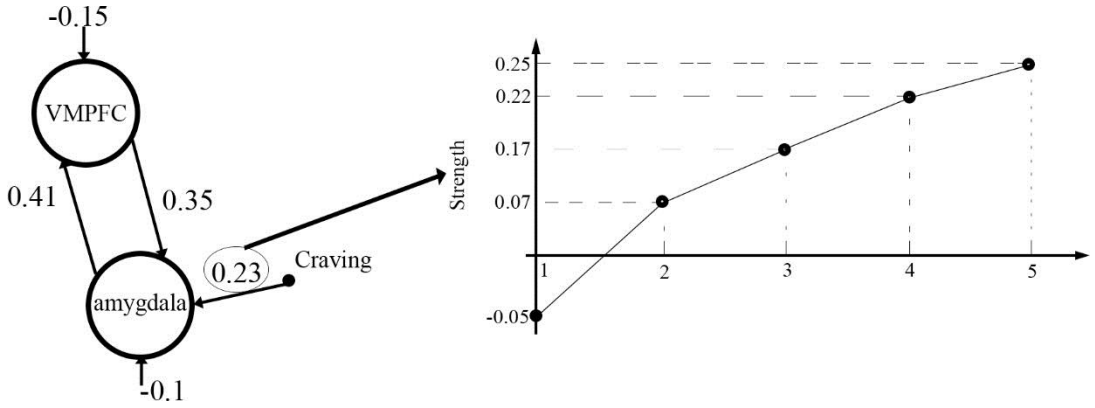


**Figure 2:** Result of DCM Network (left) and the Change of Craving Link Strength with Time (right)

course, the advantage of the method is not being subjective and so not be biased under different conditions [22], but the validity of using it as a craving measurement can be questioned and studied further. However, our results demonstrated an exponential growth of craving input during the task; this is in compliance with the idea of the fMRI task design which was targeted to do this biologically [23].

## Conflict of Interest

None

## References


1. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci*. 2005;**8**:1458-63. doi.org/10.1038/nn1584. PubMed PMID: 16251988.
2. Bechara A. The Neural Basis of Decision Making in Addiction. *Biological Research on Addiction: Comprehensive Addictive Behaviors and Disorders.* 2013;**2**:341. doi.org/10.1016/B978-0-12-398335-0.00035-2.
3. Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci*. 1999;**19**:5473-81. PubMed PMID: 10377356.
4. Bechara A, Damasio H, Damasio AR. Role of the amygdala in decision-making. *Annals of the New York Academy of Sciences*. 2003;**985**:356-69. doi.org/10.1111/j.1749-6632.2003.tb07094.x.
5. Heatherton TF, Wagner DD. Cognitive neuroscience of self-regulation failure. *Trends Cogn Sci*. 2011;**15**:132-9. doi.org/10.1016/j.tics.2010.12.005. PubMed PMID: 21273114. PubMed PMCID: 3062191.
6. Noel X, Brevers D, Bechara A. A neurocognitive approach to understanding the neurobiology of addiction. *Curr Opin Neurobiol*. 2013;**23**:632-8. doi.org/10.1016/j.conb.2013.01.018. PubMed PMID: 23395462. PubMed PMCID: 3670974.
7. Ma L, Steinberg JL, Cunningham KA, Lane SD, Bjork JM, Neelakantan H, et al. Inhibitory behavioral control: A stochastic dynamic causal modeling study comparing cocaine dependent subjects and controls. *Neuroimage Clin*. 2015;**7**:837-47. doi.org/10.1016/j.nicl.2015.03.015. PubMed PMID: 26082893. PubMed PMCID: 4459041.
8. Hayashi T, Ko JH, Strafella AP, Dagher A. Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proc Natl Acad Sci U S A*. 2013;**110**:4422-7. doi.org/10.1073/pnas.1212185110. PubMed PMID: 23359677. PubMed PMCID: 3600476.
9. Yang W, Wang F, Zhang Z, Ren X, Li Y, Sun T. Altered effective connectivity of insula in nicotine addiction. *Zhonghua Yi Xue Za Zhi*. 2014;**94**:1667-70. PubMed PMID: 25152295.
10. Ray S, Haney M, Hanson C, Biswal B, Hanson SJ. Modeling Causal Relationship Between Brain Regions Within the Drug-Cue Processing Network in Chronic Cocaine Smokers. *Neuropsychopharmacology*. 2015;**40**:2960-8. doi.org/10.1038/npp.2015.150. PubMed PMID: 26038158. PubMed PMCID: 4864631.
11. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage*. 2003;**19**:1273-302. doi.org/10.1016/S1053-8119(03)00202-7. PubMed PMID: 12948688.
12. Friston K, Frith C, Frackowiak R. Time-dependent

changes in effective connectivity measured with PET. *Human Brain Mapping*. 1993;**1**:69-79. doi.org/10.1002/hbm.460010108.

13. Cooray GK, Sengupta B, Douglas PK, Friston K. Dynamic causal modelling of electrographic seizure activity using Bayesian belief updating. *Neuroimage*. 2016;**125**:1142-54. doi.org/10.1016/j.neuroimage.2015.07.063. PubMed PMID: 26220742. PubMed PMCID: 4692455.
14. Sun Y, Taya F, Chen Y, Delgado Martinez I, Thakor N, Bezerianos A. Topological changes of the effective connectivity during the working memory training. *Conf Proc IEEE Eng Med Biol Soc*. 2014;**2014**:6242-5. PubMed PMID: 25571423.
15. Poch C, Garrido MI, Igoa JM, Belinchon M, Garcia-Morales I, Campo P. Time-varying effective connectivity during visual object naming as a function of semantic demands. *J Neurosci*. 2015;**35**:8768-76. doi.org/10.1523/JNEUROSCI.4888-14.2015. PubMed PMID: 26063911.
16. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;**5**:143-56. doi.org/10.1016/S1361-8415(01)00036-6. PubMed PMID: 11516708.
17. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage*. 2001;**14**:1370-86. doi.org/10.1006/nimg.2001.0931. PubMed PMID: 11707093.
18. Woolrich M. Robust group analysis using outlier inference. *Neuroimage*. 2008;**41**:286-301. doi.org/10.1016/j.neuroimage.2008.02.042. PubMed PMID: 18407525.
19. Noel X, Van Der Linden M, Bechara A. The Neurocognitive Mechanisms of Decision-making, Impulse Control, and Loss of Willpower to Resist Drugs. *Psychiatry* (*Edgmont*). 2006;**3**:30-41. PubMed PMID: 21103176. PubMed PMCID: 2990622.
20. Martinez Selva JM, Sanchez Navarro JP, Bechara A. A distributed brain system for decision-making. *SALUD I CIENCIA*. 2010;**17**:409-13.
21. Rosenberg H. Clinical and laboratory assessment of the subjective experience of drug craving. *Clin Psychol Rev*. 2009;**29**:519-34. doi.org/10.1016/j.cpr.2009.06.002. PubMed PMID: 19577831.
22. Schwarz, N., Self-reports: How the questions shape the answers. American Psychologist, 1999. 54(2): p. 93.
23. Tabatabaei-Jafari, H., et al., Patterns of brain activation during craving in heroin dependents successfully treated by Methadone maintenance and abstinence-based treatments. *J Addict Med*. 2014;**8**(2):123-9.