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**Research Article** 

# Comparison of Response Inhibition Behavior Between Methadone Maintenance Patients and Active Opiate Users

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# Abstract

**Background:** Increasing evidence indicates that opiate users and methadone maintenance patients (MMPs) are impaired in executive control tasks and response inhibition behavior compared to healthy individuals; however, the cognitive functional difference between opiate addicts and MMPs has not been clarified.

**Objectives:** This study employed Go/No-Go tasks to evaluate the response inhibition behavior in three groups: active opiate users, stable MMPs and healthy control subjects with negative urine analysis.

**Patients and Methods:** In this study, 45 opiate-dependents (including opium and heroin), 50 successful methadone maintenance patients (MMPs) and 50 normal controls were recruited. These three groups were matched in terms of age, gender and education level. Each subject conducted the six variants of Go/No-Go tasks in a sequential order, after being given the instructions to respond to stimulus displayed on the screen by pressing the space bar as quickly as possible (Go stimuli) and withholding responses to other stimuli (No-Go stimuli). We used Mann-Whitney nonparametric analysis to compare the performances of opiate users, MMPs and healthy controls on Go/No-Go task scores.

**Results:** In Go trials, opiate dependents and MMPs showed better performance than controls with lower omission errors, while in No-Go trials, opiate users and MMPs committed more errors and revealed poorer performance than the controls. No significant difference was found between opiate users and MMPs performance on Go or No-Go trials, and these groups were significantly faster than controls in response to targets on Go trials or non-targets on No-Go trials.

**Conclusions:** Opiate users and MMPs showed significant deficits on measures of response inhibition when compared to the normal participants, while MMPs did not differ from opiate users in their ability to inhibit their response to non-targets.

Keywords: Inhibition (Psychology), Methadone, Opiate, Patients

# 1. Introduction

Chronic substance use produces significant deficits in executive control functions (ECF) and presents with several behavioral problems including apathy, lack of initiative (1), poor judgment, impulsivity (2), goal-neglect and disorganized behavior (3), and likewise leads to cognitive dysfunction by affecting attention, memory (4), intellectual functioning (5), learning, problem solving and perceptual motor speed (6, 7).

In particular, an inability to inhibit response has been identified as a core trait in addicted individuals (3, 4, 8-14) that similarly reflects in compulsive drug seeking and drug self-administration, even when the drug is no longer pleasurable (14-17). Repeated dopaminergic activation of the neural circuits by chronic drug use and subsequent neural dysfunction has been suggested to eventually produce a deficit in control over behavioral impulses (11, 14, 17). The prefrontal cortex (PFC) is the key component that is thought to underlie inhibitory control (18-23) and has recently been implicated in the reward circuit and addiction (3, 16, 24-26).

Methadone maintenance treatment (MMT) is one of the most frequently used opioid substitution treatments for drug addiction. MMT reduces harm associated with drug use and provides the stability necessary for the addict to change their lifestyle (27, 28). Despite the strong evidence on the effectiveness of opioid substitution therapy, there are reports that confirm the adverse effects of chronic methadone treatment on psychomotor and cognitive performance in these patients including processing speed, attention, working memory, short-term memory and decision making (29-34). However, these studies

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compared the cognitive performance between methadone maintenance patients (MMPs) and healthy controls. Comparing MMPs with drug abusers who are not yet enrolled in opioid substitution therapy may yield more accurate findings about the level and extent of methadone treatment's influence on cognitive performance measurements.

# 2. Objectives

This study, therefore, included opiate users, along with MMPs and healthy controls, to detect the possible neuropsychological differences between MMPs and opiate users. We employed the Go/No-Go paradigm to evaluate and compare healthy participants, opiate abusers and MMPs in terms of inhibition response, which is proposed to be one of the core behavioral disruptions in chronic addiction.

# 3. Patients and Methods

# 3.1. Participants

Forty-five opiate-dependent individuals, 50 methadone maintenance patients (MMPs) and 50 healthy participants were recruited into this study through notices posted on an announcement board or by a verbal offer at the Iranian national center for addiction studies (INCAS) over the period of one year. Opiate-abusers were chosen based on the following criteria: 1) meeting the DSM-IV criteria for substance dependence; 2) having no history of any neurological or psychiatric disorders or any current medical illness; 3) self-reporting of opiate abuse (opium, heroin) purely, without abusing other substances such as stimulants or benzodiazepines, confirmed by a five-panel rapid urine test (COC/mAMP/OPI/THC/BZO) at admission. Among the opiate dependents, the number of years of opiate use was 12.2 (1 - 22 years), and the preferred method of abuse was reported as: intranasal (6%), smoking (42%), oral (44%) and intravenous injection (8%).

Fifty opioid-dependent MMPs were recruited from outpatient methadone maintenance programs in the addiction treatment clinic at the Iranian national center for addiction studies (INCAS) who fulfilled the following criteria: 1) being involved in a formal methadone maintenance treatment program; (b) being stabilized in their current methadone dose for at least one month; and (c) a minimum abstinence period of 48 hours from any drug except methadone, verified by urine screening. At the time of testing, none of the participants were experiencing withdrawal symptoms. The mean time of methadone maintenance therapy (MMT) was  $12.2 \pm 2.8$  months and the mean dose was  $77.6 \pm 44.6$  mg/day.

Fifty healthy participants were subsequently selected to be matched with the study groups in terms of age, gender and education level and who met the conditions that: 1) they had not taken any substances (excluding alcohol (at low level) or cigarette smoking) in the past; 2) they had no history of psychiatric or neurological disorders or were not on any medication for medical diseases.

The demographic data of the three groups are presented in Table 1. All the subjects provided written informed consent approved by the institutional review board (IRB) of Tehran University of Medical Sciences (TUMS), and thereafter, they were tested with six versions of Go/No-Go tasks.

# 3.2. Procedure

This study was conducted in a condition-controlled room at the neurocognitive laboratory of the Iranian national center for addiction studies (INCAS). Each subject came separately to the room and was seated in a comfortable chair in front of the computer screen. After filling out the demographic information form, the subject received instructions to respond by pressing the space bar as quickly as possible to certain stimuli (Go stimuli) that were briefly displayed, one by one, in the center of the dark screen. In addition, they were instructed to withhold responses to other stimuli (No-Go stimuli). Each subject conducted the six variants of the Go/No-Go (GNG) tasks in a sequential order, and before each run, they were given a short break to receive instructions on the new target and distractor stimuli.

#### 3.3. Measurements

In the neuro-cognitive laboratory of the Iranian national center for addiction studies (INCAS), six versions of Go/No-Go tasks (V1-V6) were provided based on a classic Go/No-Go paradigm in which subjects have to respond as quickly as possible to target stimuli and withhold responses to distractor stimuli. All seven versions of Go/No-Go tasks were developed using E-Prime V.2 software.

In V1 to V4, the Go stimuli were blue circles and the No-Go stimuli were yellow circles, while in V5 the target stimulus was the "O" sign and the No-Go stimulus was the 'X' sign. In V6, the target stimulus was the appearance of colored circle/s at the upper left and lower right, and the No-Go stimulus was the appearance of colored circle/s at the lower left and upper right. Each version consisted of an 80-stimulus presentation (trials) displayed one by one in a predefined fixed order. The ratio of Go to No-Go stimuli was 20% in all versions except V4, which had a target probability of 50%. Stimulus presentation time (SPT) is defined as the duration of stimuli appearance on the screen, which

	Controls, n = 57	MMPs, n = 50	Addicts, n = 45	P Value
Age, y	$33.7 \pm 1.1$	$34.0\pm1.1$	$36.3\pm1.3$	0.233
Male gender (%)	38 (66.7%)	40 (80%)	35 (77.8%)	0.237
Education, y	$9.6\pm0.5$	$10.5\pm0.5$	$9.0\pm0.4$	0.101
a	()			

Table 1. Demographic Characteristics of Samples<sup>a</sup>

<sup>a</sup>Data are presented as Mean  $\pm$  SD or No. (%).

varied from 1,200 ms in V1 to 300 ms in the other five versions, while the inter-stimulus intervals (ISI) varied from 900 ms to 1,200 ms in different versions. Detailed characteristics of these six different versions are presented in Table 2.

The number of responses to targets (hits) and the number of "no" responses to non-targets (stops) are the two main measurements that the GNG task yields. "Hits" are the number of targets that are correctly detected through Go-trials, and "stops" are the number of non-targets that are accurately rejected. There are three other scores derived from these "hit" and "stop" scores: "omission errors (misses)" defined as the number of Go stimuli that were mistakenly missed; "commission errors" indicate the number of No-Go stimuli that are falsely responded to and could be regarded as the marker of disinhibition; "total true score" is the sum of "hits" and "stops" and shows the total number of true responses to both Go and No-Go stimuli. The number of "hits" can be regarded as a measure of behavioral initiation, whereas "commission errors" can be considered as a measure of inhibitory response.

"Reaction time of hits" and "reaction time of commission errors" show the time interval in milliseconds (ms) between the appearances of a Go or No-Go stimulus and pressing the space bar. The GNG task measurements and their range of variability are summarized in Table 3.

## 3.4. Statistics

The results are presented as mean  $\pm$  SD (standard deviation) for the quantitative variables and are summarized by frequency (percentage) for the categorical variables. One-way analysis of variance (ANOVA) was used to explore group differences in age and education level, while group differences regarding gender were examined using a  $\chi^2$ analysis. Go/No-Go scores were not normally distributed (as assessed by Kolmogorov-Smirnoff tests) and were analyzed using the Kruskal-Wallis test. Pairwise comparisons were conducted via the Mann-Whitney nonparametric test. The differences with P < 0.05 were considered statistically significant between groups. For statistical analysis, the statistical software SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL) was used.

#### 4. Results

To simplify, all the Go/No-Go scores are presented as percentages in tables and figures. According to Table 1, all three groups, opiate dependents, MMPs and controls, were well matched on age, education and gender. As can be seen in Table 2, there is a significant difference between groups in terms of reaction time (RT) and errors in both Go and No-Go trials, with longer reaction time (RT) for both Go trials and No-Go trials in controls than opiate users and MMPs in all six versions.

Figures 1 and 2 reveal that controls omitted much more targets in Go trials than opiate abusers and MMPs, while they committed much fewer errors in No-Go trials in comparison to the other two groups in all six versions, indicating better response inhibition in normal controls.

Post-hoc analyses on No-Go trial scores as a measure of inhibition response did not show any significant difference on commission errors between opiate users and MMPs, suggesting that these two groups did not differ in terms of response inhibition. Regarding Go trials, there was no significant difference between opiate users and MMPs in terms of omission errors on VI to V3, while opiate users performed significantly worse than MMPs on V4 to V6.

# 5. Discussion

Compared to controls, opiate users and MMPs showed poorer performance on the No-Go trials of a GNG task, attributable to the higher number of commission errors. No significant difference was found between opiate users and MMPs in terms of No-Go scores. The results revealed the subtle deficits in the ability of opiate users and MMPs to inhibit response against normal controls but did not show significant differences between opiate users and MMPs.

Consistent with current results, previous studies, also have demonstrated that substance dependent individuals, particularly cocaine users, present a higher number of commission errors in tests of response inhibition, such as a Go/No-Go task (9, 10, 35) or choice reaction time (RT) task (11) when compared against healthy controls. On the

Variants	Go Stimulus	No-Go Stimulus	SPT, ms	ISI, ms	No-Go/Go Ratio	Number of Trials	Stimulus Position
V1	•	•	1200	-	1/4	80	Center
V2	•	•	300	900	1/4	80	Center
V3	•	•	300	1200	1/4	80	Center
V4	•	•	300	900	1/1	80	Center
V5	0	х	300	900	1/4	80	Center
V6	•	•	300	900	1/4	80	Center

Table 2. Context Characteristics of Six Versions (V1 to V6) of the GNG Task

Abbreviations: ISI, inter-stimulus interval; SOI, stimulus onset interval.

Table 3. Go/No-Go Task Scores Definition and Range of Variability

Variable	Definition	Range
Overall Score (OS)	True hits on Go and No-Go trials	0 - 80
Hit	True hits on Go trials	0 - 64 (All), 0 - 40 (V4)
Stop	True inhibitions on No-Go trials	0 - 16 (All), 0 - 40 (V4)
Omission error (Miss)	Missed Go trials	Similar to TGS
Commission error (Error)	False hits on No-Go trials (Disinhibition)	Similar to TNGS
Reaction time of Hits	Reaction time of true Go trials (ms)	100 - 1000
Reaction time of omission error	Reaction time of false No-Go trials (ms)	100 - 1000

Table 4. Comparison of GNG Task Performance Between Normal Controls, Methadone Maintenance Patients (MMPs) and Opiate Users

	Go Trial			P Value	No-Go Trial			P Value
	Controls	MMPs	<b>Opiate Users</b>	-	Controls	MMPs	<b>Opiate Users</b>	-
Version 1								
Error	$17.7\pm2.7$	$5.7\pm1.2^{\ast}$	$6.4\pm1.3$	0.057	$14.7\pm1.4$	$21.4\pm2.6$	$27.2 \pm 2.8^{***}$	0.002
<b>Reaction time</b>	$479\pm13$	$399\pm16^{***}$	$401 \pm 15^{***}$	0.000	$284\pm19$	$44\pm5^{***}$	$68\pm7^{***}$	0.000
Version 2								
Error	$24.5\pm2.6$	$11.4\pm1.7^{**}$	$15.5\pm2.2$	0.003	$14.8\pm1.9$	$22\pm2^*$	$23.1\pm2.6^{**}$	0.016
<b>Reaction time</b>	$378\pm8$	$313\pm10^{***}$	$327\pm14^{**}$	0.000	$322\pm20$	$65\pm11^{***}$	$76 \pm 14^{***}$	0.000
Version 3								
Error	$18.5\pm2.7$	$2.1\pm0.7^{***}$	$4.8 \pm 1.5^{**}$	0.000	$9.4\pm1.8$	$21.2\pm3.0^{***}$	$22.9\pm3.7^{**}$	0.000
<b>Reaction time</b>	$400\pm11$	$358\pm11^{**}$	$379\pm12$	0.008	$314\pm32$	$93\pm26^{***}$	$109\pm29^{***}$	0.000
Version 4								
Error	$23.1\pm1.9$	$11.1 \pm 1.4^{***}$	$19.6\pm1.8{\text{+++}}$	0.000	$4.1\pm0.8$	$9.5\pm2.0^{**}$	$9.9\pm1.6^{***}$	0.000
<b>Reaction time</b>	$366\pm7$	$315\pm10^{***}$	$307\pm9^{***}$	0.000	$324\pm27$	$31\pm10^{***}$	$33\pm7^{***}$	0.000
Version 5								
Error	$32.9\pm2.5$	$16.3 \pm 2.4^{***}$	$29.6\pm2.9{\text{+++}}$	0.000	$12.5\pm1.5$	$20.1\pm2.7^*$	$21.4\pm2.8^{**}$	0.015
<b>Reaction time</b>	$360\pm7$	$276 \pm 13^{***}$	$235 \pm 12^{***} +$	0.000	$274\pm10$	$49\pm10^{***}$	$46\pm4^{***}$	0.000
Version 6								
Error	$30.5\pm2.6$	$15.9 \pm 2.5^{***}$	$27.3\pm2.6\text{++}$	0.000	$10.7\pm1.5$	$22.1\pm3.2^{**}$	$20.0\pm3.7^{\ast}$	0.012
Reaction time	$345\pm7$	$255\pm11^{***}$	$257 \pm 12^{***}$	0000	$313\pm15$	$46\pm7^{***}$	$45\pm8^{***}$	0.000

other hand, MMPs are shown to be significantly more impaired on measures of psychomotor performance, processing speed, working memory and short term memory (32, 34), and attention and visual orientation (33) than controls or abstinent heroin abusers (29). Inhibition behaviors have not been studied in MMPs as much as other aspects of executive function; however, Minitzer et al. suggested possible impairment in inhibitory mechanisms measured via



Figure 1. Go trials Performance in Normal Controls, Opiate Users and Methadone

Maintenance Patients (MMPs) in Terms of A, Omission Errors and B, Reaction Time

(RT) to Go Stimulus

Data are presented as Mean  $\pm$  SD. \*, P value < 0.5; \*\*, P value < 0.01; \*\*\*, P value < 0.001 compared to controls; +, P value < 0.5; ++, P value < 0.01; +++, P value < 0.001 compared to MMPs.

**Figure 2.** No-Go trials Performance in Normal Controls, Opiate Users and Methadone Maintenance Patients (MMPs) in Terms of (a) Commission Errors and (b) Reaction Time (RT) to Go Stimulus



Data are presented as Mean  $\pm$  SD. \*,P value < 0.5; \*\*, P value < 0.01; \*\*\*, P value < 0.001 compared to controls; +, P value < 0.5; ++, P value < 0.01; +++, P value < 0.001 compared to MMPs.

the Stroop color-word paradigm compared to control participants (34).

Regarding Go-trials, our results surprisingly indicate that opiate users, and particularly MMPs, performed better and missed less target stimuli (less omission errors) than controls. This difference between drug users and controls might be attributable to differences in the reaction time (RT). As we see from the results, the RT of both Go and No-Go trials was significantly lower in opiate users and MMPs compared to controls, indicating that these individuals are faster to respond to a stimulus against healthy participants. Thus, it could be deduced that the probability of missing a target stimulus diminishes as RT decreases, because of the limited time available to respond to the stimulus. Consistently. Specka et al. reported that MMPs were faster but produced more errors compared to controls on a choice RT task (33). Here, it should be noted that the Go trials scores could not be interpreted by themselves as independent measures, since Go stimuli were intended to create a prepotent tendency to respond, which then necessitates inhibition with the appearance of a No-Go stimulus, and thus, the No-Go score is regarded as an exclusive score for the inhibitory process.

In conclusion, opiate users and MMPs seem to have a lower ability to control their responses than healthy controls; however, no significant difference was found between opiate users and MMPs on this measure of inhibition. The duration of methadone maintenance therapy (MMT) and the prescribed daily dose may affect the level of response inhibition behavior. Likewise, evaluation of individuals before and after starting opioid substitution therapy may aid in future investigations to better elucidate the possible and dose dependent effect of MMT on inhibition behavior.

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### Footnotes

Authors' Contribution: Study concept and design: Hamed Ekhtiari; acquisition of data: Mehrshad Gole Sorkhi, Aiden Nasiri Eghbali, and Ensieh Ghassemian; analysis and interpretation of data: Mehrnaz Rezvanfard; drafting of the manuscript: Mehrnaz Rezvanfard; critical revision of the manuscript for important intellectual content:Azarakhsh Mokri; statistical analysis: Mehrshad Gole Sorkhi, and Mehrnaz Rezvanfard; administrative, technical, and material support: Alireza Noroozi; Study supervision: Hamed Ekhtiari.

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## References

- Kalechstein AD, Newton TF, Leavengood AH. Apathy syndrome in cocaine dependence. *Psychiatry Res.* 2002;**109**(1):97–100. [PubMed: 11850056].
- Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*. 2001;**39**(4):376–89. [PubMed: 11164876].
- 3. Verdejo-Garcia A, Lopez-Torrecillas F, Gimenez CO, Perez-Garcia M. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. *Neuropsychol Rev.* 2004;**14**(1):1–41. [PubMed: 15260137].
- Ardila A, Rosselli M, Strumwasser S. Neuropsychological deficits in chronic cocaine abusers. *Int J Neurosci.* 1991;57(1-2):73–9. [PubMed: 1938157].
- O'Malley S, Adamse M, Heaton RK, Gawin FH. Neuropsychological impairment in chronic cocaine abusers. *Am J Drug Alcohol Abuse*. 1992;18(2):131-44. [PubMed: 1562011].
- Beatty WW, Katzung VM, Moreland VJ, Nixon SJ. Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend*. 1995;37(3):247–53. [PubMed: 7796719].
- Strickland TL, Stein R. Cocaine-induced cerebrovascular impairment: challenges to neuropsychological assessment. *Neuropsychol Rev.* 1995;5(1):69–79. [PubMed: 8589732].
- Rogers RD, Robbins TW. Investigating the neurocognitive deficits associated with chronic drug misuse. *Curr Opin Neurobiol.* 2001;11(2):250-7. [PubMed: 11301247].
- Verdejo-Garcia AJ, Perales JC, Perez-Garcia M. Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addict Behav.* 2007;**32**(5):950–66. doi: 10.1016/j.addbeh.2006.06.032. [PubMed: 16876962].
- Verdejo-Garcia A, Bechara A, Recknor EC, Perez-Garcia M. Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *J Int Neuropsychol Soc.* 2006;**12**(3):405– 15. [PubMed: 16903133].

- Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend.* 2002;66(3):265-73. [PubMed: 12062461].
- Biggins CA, MacKay S, Clark W, Fein G. Event-related potential evidence for frontal cortex effects of chronic cocaine dependence. *Biol Psychiatry.* 1997;**42**(6):472–85. doi: 10.1016/S0006-3223(96)00425-8. [PubMed: 9285083].
- Horner B, Scheibe K, Stine S. Cocaine abuse and attention-deficit hyperactivity disorder: Implications of adult symptomatology. *Psychol Addictive Behav.* 1996;10(1):55–60. doi: 10.1037/0893-164x.10.1.55.
- Volkow ND, Ding YS, Fowler JS, Wang GJ. Cocaine addiction: hypothesis derived from imaging studies with PET. J Addict Dis. 1996;15(4):55–71. doi: 10.1300/J069v15n04\_04. [PubMed: 8943582].
- Fillmore MT. Drug abuse as a problem of impaired control: current approaches and findings. *Behav Cogn Neurosci Rev.* 2003;2(3):179–97. doi: 10.1177/1534582303257007. [PubMed: 15006292].
- Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)*. 1999;**146**(4):373– 90. [PubMed: 10550488].
- Lyvers M. "Loss of control" in alcoholism and drug addiction: a neuroscientific interpretation. *Exp Clin Psychopharmacol.* 2000;8(2):225–49. [PubMed: 10843306].
- Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage*. 2002;17(4):1820–9. [PubMed: 12498755].
- Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res.* 2002;**53**(2):647-54. [PubMed: 12169339].
- Kawashima R, Satoh K, Itoh H, Ono S, Furumoto S, Gotoh R, et al. Functional anatomy of GO/NO-GO discrimination and response selectiona PET study in man. *Brain Res.* 1996;**728**(1):79–89. [PubMed: 8864300].
- Tsujimoto T, Ogawa M, Nishikawa S, Tsukada H, Kakiuchi T, Sasaki K. Activation of the prefrontal, occipital and parietal cortices during go/no-go discrimination tasks in the monkey as revealed by positron emission tomography. *Neurosci Lett.* 1997;**224**(2):111–4. [PubMed: 9086469].
- Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y. No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *Eur J Neurosci.* 1998;10(3):1209–13. [PubMed: 9753190].
- Watanabe J, Sugiura M, Sato K, Sato Y, Maeda Y, Matsue Y, et al. The human prefrontal and parietal association cortices are involved in NO-GO performances: an event-related fMRI study. *Neuroimage*. 2002;**17**(3):1207-16. [PubMed: 12414261].
- Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci.* 2011;12(11):652–69. doi: 10.1038/nrn3119. [PubMed: 22011681].
- 25. Garavan H, Stout JC. Neurocognitive insights into substance abuse. *Trends Cogn Sci.* 2005;9(4):195–201. doi: 10.1016/j.tics.2005.02.008. [PubMed: 15808502].
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002;**159**(10):1642–52. doi: 10.1176/appi.ajp.159.10.1642. [PubMed: 12359667].
- Goldstein RZ, Volkow ND, Wang GJ, Fowler JS, Rajaram S. Addiction changes orbitofrontal gyrus function: involvement in response inhibition. *Neuroreport*. 2001;12(11):2595–9. [PubMed: 11496155].
- Darke S, Ross J, Teesson M, Ali R, Cooke R, Ritter A, et al. Factors associated with 12 months continuous heroin abstinence: findings from the Australian Treatment Outcome Study (ATOS). J Subst Abuse Treat. 2005;28(3):255–63. doi: 10.1016/j.jsat.2005.01.006. [PubMed: 15857726].

- 29. Verdejo A, Toribio I, Orozco C, Puente KL, Perez-Garcia M. Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug Alcohol Depend*. 2005;**78**(3):283–8. doi: 10.1016/j.drugalcdep.2004.11.006. [PubMed: 15893159].
- Appel PW, Gordon NB. Digit-symbol performance in methadonetreated ex-heroin addicts. *Am J Psychiatry*. 1976;133(11):1337–40. doi: 10.1176/ajp.133.11.1337. [PubMed: 984229].
- Gritz ER, Shiffman SM, Jarvik ME, Haber J, Dymond AM, Coger R, et al. Physiological and psychological effects of methadone in man. *Arch Gen Psychiatry*. 1975;**32**(2):237-42. [PubMed: 1115571].
- 32. Darke S, Sims J, McDonald S, Wickes W. Cognitive impairment among methadone maintenance patients. *Addiction*. 2000;**95**(5):687-95.

[PubMed: 10885043].

- 33. Specka M, Finkbeiner T, Lodemann E, Leifert K, Kluwig J, Gastpar M. Cognitive-motor performance of methadone-maintained patients. *Eur Addict Res.* 2000;**6**(1):8–19. [PubMed: 10729738].
- Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend. 2002;67(1):41-51. [PubMed: 12062778].
- Lane SD, Moeller FG, Steinberg JL, Buzby M, Kosten TR. Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. *Am J Drug Alcohol Abuse*. 2007;**33**(5):717–26. doi: 10.1080/00952990701522724. [PubMed: 17891664].