

Assessment of brain activity changes in patients with former heroin dependency under methadone maintenance treatment, by using functional magnetic resonance imaging

Abstract

Introduction: Functional magnetic resonance imaging (fMRI) has been successful in illustrating the brain function of patients addicted to different drugs. Methadone maintenance is proposed as the standard agonist substitution treatment for opiate dependent patients. In this study we aimed to systematically review all the MRI findings related to former heroin addicts under long term methadone maintenance therapy.

Method: PubMed was performed by the following search strategy: (methadone OR Dolophine) AND (MRI OR magnetic resonance imaging), with no language and date restrictions.

Results: Out of 56 articles found at the initial search, 5 articles were eligible to be included in the systematic review, which were published from 2008 – 2014. In all the included studies the effect of long term MMT in confronting with drug related cues was compared with healthy control individuals or neutral stimuli. One article studied the acute efficacy of methadone use and one article compared the effect of different durations of MMT on brain responses to drug related cues.

Conclusion: Different brain parts from prefrontal to deep limbic structures have been activated by drug related cues observation in patients under long term MMT. However methadone has shown the ability to inhibit the heroin craving and decreasing withdrawal symptoms, the learned brain response to drug stimuli persists despite long-term MMT.

Keywords: methadone maintenance treatment (MMT); heroin; functional magnetic resonance imaging

Introduction

Substance abuse is one of the major health and social problems which seriously threaten the mental and physical health. In South East Asia and China heroin is the most prominent drug of use. In this regard there is an increasing need for a standard treatment approach that can preserve stable drug abuse abstinence with the minimum side effect (1).

Treatment strategies for drug dependency mostly focus on controlling and restraining the craving behavior as the main part. Despite various methods used for preventing the craving during recovery of former drug-dependent individuals, there isn't certain agreement on one ideal treatment (2)

Functional magnetic resonance imaging (fMRI) is a type of neuroimaging tool with high spatial and temporal resolution which has been successful in illustrating the brain function of patients addicted to different drugs including nicotine(3), alcohol(4), cocaine(5), and heroin(6).

Various fMRI investigations have provided evidence that shows that prefrontal cortex, mesolimbic dopamine system, visuospatial cortex, and subcortical structures are the main parts of brain involved in addicts following stimulation by drug related cues (7, 8). Based on these fMRI findings functional organization are not normal in heroin addicted individuals.

Methadone is among opiates which leads to stimulation of μ -opioid receptors, hyperpolarisation of GABAergic neurons, and eventually reduce the release of dopamine. Methadone is used for decreasing the pain and also as a treatment and detoxification strategy for those with opioids dependence.

Methadone maintenance is proposed as the standard agonist substitution treatment for opiate dependent patients; it is used as the agonist substitution which can effectively decrease withdrawal and euphoria symptoms, however illicit opiate consumption remains the most important problem during the treatment period with methadone. Drug-related cues are important stimulants that encourage relapse to seeking and consuming heroin in patients under MMT (9). Although methadone is a μ -opioid receptor agonist with some effects similar to heroin consumption, it might inhibit the disruption of molecular, cellular, and physiologic events caused by the chronic use of heroin and normalize those functions(1). There are limited number of studies on the efficacy of long term MMT on brain function of the former heroin addicted individuals.

In this study we aimed to systematically review all the MRI findings related to brain responses to drug related cues in patients under long term methadone maintenance therapy.

Methods

Search strategy

PubMed was searched by the following search strategy: (methadone OR Dolophine) AND (MRI OR magnetic resonance imaging). The last search was done on December 25, 2015. The search strategy was performed with no date and language restrictions.

Study selection

In total, 56 articles were obtained following the initial search, then the title and abstract of all articles were screened at the first step of article selection, all the review articles, case reports, experimental studies, and articles about the maternal effect of methadone use were excluded. The full texts of the potentially eligible articles were reviewed and relevant articles were included in this study. Eventually, the reference list of the included articles were hand-searched not to miss the relevant articles.

Inclusion criteria were all the articles that employed FMRI tool to study the brain activity alternations following drug related cues presentation, in former heroin addicts who are under MMT.

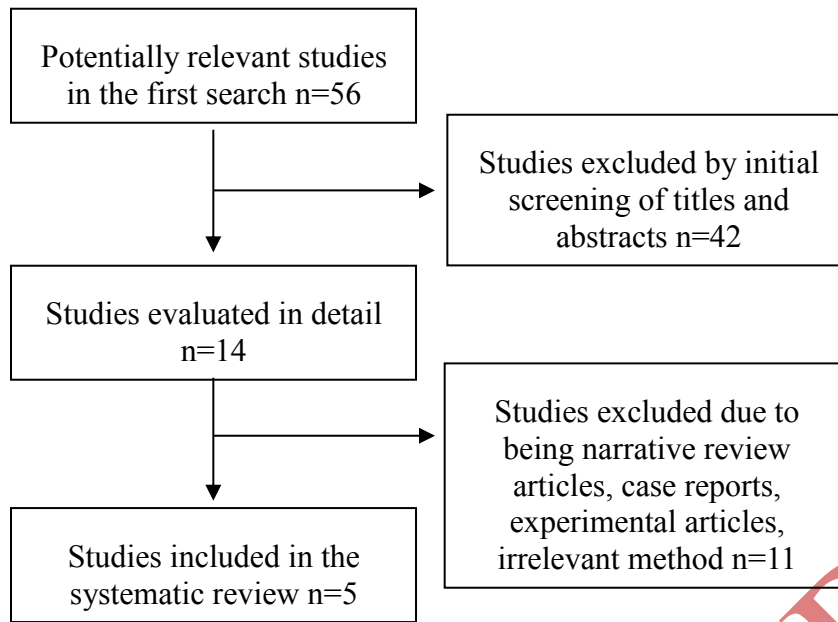
Exclusion criteria were articles that included patients under other substitution therapies in addition to methadone and those with less than 3 months of methadone application..

Results

Study selection

The initial search step provided a total of 56 articles with content of f MRI and methadone. 42 of them were excluded due to irrelevant title and abstract, and the full text of the remaining 14 articles were retrieved to find the relevant articles with the purpose of this study. Eventually 9 articles were eliminated due to irrelevancy with the purpose of this systematic review and 5 articles were eligible to be included in the systematic review. The flowchart describing the process of the selecting articles is provided below (Figure 1).

Figure 1: Articles inclusion process



Study characteristics

Data regarding the study characteristics (authors, year), patients features (sample size), dose and duration of MMT, and imaging characteristics are presented in Table 1. Data about the fMRI findings and reported correlations in each study are provided in Table 2.

In all the included (published from 2008 – 2014) studied brain activation in response to heroin related cues was studied by fMRI following of long-term MMT durations (10-14).

The image acquisition was performed at least 4 hours after the administration of daily methadone to prevent the withdrawal signs (11) and prevent the acute effect of methadone (12). The blood oxygen-level dependence (BOLD) data was obtained in two studies. The event-related fMRI design in all the included studies contained 48 trials (24 heroin-related cues and 24 neutral cues) presented for at least 2 seconds.

According to the selected articles, all the included patients were former addicts to heroin, receiving MMT for at least 3 months or longer. Abstinence from illicit drug use and compliance with methadone maintenance was confirmed by urine toxicology testing at enrollment. In all the included studies the effect of long term MMT in confronting with drug related cues was compared with healthy control individuals or neutral stimuli. Only in one of the included articles the acute efficacy of MMT by comparing the brain responses before and after methadone daily

dose was screened by FMRI (14). One out of 5 included studies has compared the effect of different durations of MTT on brain responses to drug related cues (11).

Table 1. Characteristics of each of the included studies

Study	Sample	Study designs
Wang, Y 2014,(11)	MMTGrA:30 male, age (24-43 yr) MMTGrB:15 male, age (25-46 yr) ControlGrC:17 healthy male, age (19-49) Duration of heroin use (months) GrA: 48.6±49.9 (8.2–194.9) GrB: 49.64±42.5 (20.0–180.0) MMT duration (months) GrA: 7.92±2.89 (5–11) GrB: 29.62±3.53 (24–34) Methadone dosage (mg/day) GrA: 40.0 ± 15.4 (20–71) GrB: 45.0 ± 13.6 (26–69)	A: Imaging was performed 4 hours after the daily methadone dosage (methadone peak plasma level). B. imaging consisted of C. BOLD functional imaging data was acquired
Li Q, 2014,(10)	MMT:21 male, mean age (39.1 ± 7.6 yr) Duration of heroin use (months): 92.3 ± 70.5 Average methadone dose (mg/day): 41.0 ± 18.5 Duration of MMT (months): 25.5 ± 17.3 Control:20 male, mean age (35.2 ± 7.0 yr)	A: mock scanning session, 1 minute prior to formal experimental scanning
Tabatabaei-Jafari H, 2014,(12)	MMT: 20 male, mean age (33.6 ± 4.7 yr)	A:Imaging performed at least 6 hours after the last dose of methadone

	<p>Average methadone dose (mg/day): 84.75 ± 37.95</p> <p>Duration of MMT (months): at least 3</p> <p>Duration of drug use (yr): 11.05±8.2</p> <p>Control:20 male, mean age (30.8 ± 5.0 yr)</p>	<p>B: T2-weighted gradient-echo multislice sequence and T1 3-dimensional-weighted images were obtained</p>
<p>Langleben D, 2008,(14)</p>	<p>MMT: 25, male:13, mean age (yr): 36</p> <p>Daily methadone dose: 115 mg</p> <p>Duration of MMT (months):54</p>	<p>A: Imaging was performed on two separate session, 3 to 4 weeks apart</p> <p>B: the predose session was 90 min before the scheduled dosing, and the postdose session was 90 minutes after the dosing</p> <p>C: Blood samples to determine plasma concentrations of methadone 30–60 minutes before each imaging session</p>
<p>Wang W, 2011,(13)</p>	<p>MMT: 14 male, mean age (yr): 36.1</p> <p>Average methadone dose (mg/day): 39.0 ± 22.5</p> <p>Duration of MMT (months): 5-24, mean: 6.5 ±5.2</p> <p>Duration of heroin use (yr): 7.9 ±5.2</p>	<p>A: “mock scans” on a 3-T whole-body MRI system</p> <p>B: BOLD data were obtained</p>

Gr= group. BOLD= blood oxygen-level dependence; MMT= methadone maintenance therapy;
BOLD= blood oxygen-level dependence

Table 2. FMRI findings regarding the brain activation in response to drug-related cues in patients under long term MMT

Study	Finding	Correlations
<p>Wang, Y 2014,(11)</p>	<p>Brain activated regions in</p>	<p>Between heroin cue induced BOLD signal intensity in</p>

	<p>Total MMT groups>control: mesolimbic system, prefrontal regions and visuospatial-attention regions</p> <p>GrB<GrA: bilateral caudate</p> <p>GrA: left dlPFC, bilateral parahippocampal gyrus, left MFG, left IPL, SPL, left precuneus, right fusiform gyrus, MOG and temporal gyrus</p> <p>GrB: right dlPFC, anterior prefrontal gyrus, bilateral inferior occipital gyrus, left MOG, right occipital lobe, left IPL, right fusiform, right inferior temporal gyrus, right frontal eye fields and bilateral MTG</p>	<p>bilateral caudate and accumulated methadone consumption:</p> <p>Right: $r = -0.702, p = 0.000$</p> <p>Left: $r = -0.687, p = 0.000$</p> <p>Between heroin-related brain activity in bilateral caudate with MMT duration:</p> <p>Right: $r = -0.697, p = 0.000$</p> <p>Left: $r = -0.618, p = 0.002$</p>
Li Q, 2014,(10)	<p>Brain activated regions :MMT>control</p> <p>The mesolimbic system (caudate, pallidum), prefrontal regions (left ACC and dlPFC), visuospatial-attention regions (precuneus, inferior parietal lobule and superior parietal lobule), midbrain and cerebellum, putamen, parahippocampal gyrus, hippocampus, right middle cingulate gyrus, precentral gyrus.</p>	-
Tabatabaei H,2014(12)	<p>Brain activated regions in MMT>control</p> <p>bilateral declive (cerebellum) and right and left lingual gyrus</p>	-
Langleben D, 2008(14)	<p>Brain activation regions</p> <p>Predose session (cues>nutral stimuli)</p> <p>orbitofrontal cortex, ACC, hippocampal complex, insulae and the right amygdala</p> <p>postdose session (cues>nutral stimuli)</p> <p>orbitofrontal cortex, the insulae, and the left hippocampal complex, but not ACC or amygdala</p> <p>postdose > predose session: left and right orbitofrontal cortex, insulae, and hippocampal complex, and the left amygdala</p> <p>Mean plasma M concentration (ng/ml) predose/postdose:388/545</p>	-
Wang W, 2011, (13)	<p>Brain activation regions to cues > neutral stimuli</p> <p>bilateral ACC, dlPFC, fusiform, postcentral gyrus, PCC, precuneus,</p>	<p>A:No significant correlation between heroin/methadone use and brain activation</p>

	thalamus, inferior temporal gyrus, middle occipital gyrus, middle temporal gyrus, inferior occipital gyrus, superior parietal lobule, left caudate, putamen, inferior parietal gyrus, and pons	B: BOLD intensity was significantly greater during exposure to heroin-related cues, compared to neutral cues in brain areas studied
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Gr= group; M= male; MMT= methadone maintenance therapy; Yr= year; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; L = left; MPFC = medial prefrontal cortex; NAc/SCC = nucleus accumbens/subcallosal cortex; OFC = orbitofrontal cortex; PCC=posterior cingulate cortex; MFG=bilateral middle frontal gyrus; BOLD= blood oxygen-level dependence

There were some limitation regarding the included studies, first; the low number of the individuals in each study, second; the low number of female than men enrolled in each study.

Discussion

Methadone as a potent, long lasting, and specific opioid agonist, has chemical effect on opioid receptors in reward circuits and positively is involved in weakening drug desire and their euphoric effect. Methadone is reported to be beneficial in decreasing the craving behavior and related feelings during the recovery time. Subjective self-reporting of craving is different from the definite craving influence on brain (the subconscious part of craving). According to the study of Wang w et al, FMRI showed the significant higher cure induced activation of the brain regions compared to neutral stimuli, however the difference obtained between heroin cue related craving was not statistical different compared to neutral stimuli, which might be due to the pharmacological long lasting characteristics of methadone used at stable daily dose that is able to prevent heroin abstinence syndrome (13)

So the method of MMT as the standard substitution therapy might have beneficial effect not only on reducing the craving, but also improve health and reduce overdose rate and the associated infectious diseases transmission because of the power of methadone in blocking euphoric effect of drugs. Different changes of the brain in opioid dependent patients under MMT have been reported through FMRI including: changes in the functional connectivity of the default mode network (DMN) and the risk of relapse(15), verbal working memory(16), cognitive and psychomotor functioning, functional connectivity(17), and regional hemogeneity (18).

Brain activated regions in MMT patients to healthy controls

Results obtained from the articles on brain activation following heroine related cues presentation showed that mesolimbic dopamine reward system including caudate, prefrontal cortical regions (anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC)), occipital regions (right and left lingual gyrus-visual cortex), cerebellar vermis (declive) and cerebellum, visuospatial attention system (precuneus, inferior parietal lobule and superior parietal lobule), in MMT patients are the brain regions activated by heroin-related cues stimulations compared to healthy control or neutral stimuli; no brain region was more activated in response to neutral stimuli than to heroin-related stimuli (11-13). It is suggested that mesolimbic reward circuitry and visuospatial attention circuitry show enhanced responses to drug related cues despite long term MMT.

Drug related cues can stimulate emotional reactions in the caudal part of ACC (evaluation of emotions) and rostral portion (regulation of emotions). ACC as a paralimbic region is involved in drug-seeking behavior (13). Inputs from limbic system and prefrontal regions to ACC can affect the evaluation of emotional and correctness of decision makings (19). DLPFC is also influential in decision making and regulatory processes (20).

It might be suggested that functional abnormality in the ACC and DLPFC of former heroin addicts under MMT might could be due to decreased gray matter, so functional alternations might have structural basis which is needed to be studied through structural MRI in addition to FMRI (12, 13, 21).

Inferior frontal gyrus (IFG) is a brain portion involved in response inhibition in patients to control their undesirable craving behaviors; this portion was not activated in MTT patients compared with healthy controls, however methadone neurochemical effect as opioid agonist might compensate that effect in MTT method.

Cerebellar vermis (declive), occipital area (lingual gyrus), and the midbrain and pallidum (involved in reward processing) have been reported to be activated significantly in MMT groups compared to healthy controls in some of the included studies (10-13); Cerebellum is involved in generating, maintaining and/or retrieving drug memories (22), and its activation MMT patients is shown to be associated with risk of heroin relapse in these patients abnormal memory retrieval

function of cerebellum (10). So cue-induced cerebellar activity might also be a potential biomarker of relapse, however further study are needed to determine its predictive value.

The significantly higher activation of the visual cortex (lingual gyrus) in response to drug related cues compared to neutral stimuli (13) or healthy controls(12) was in line with the reported activation of visuospatial-attention regions (cuneus, precuneus, and superior parietal lobule) in MTT patients compared to health controls which might be associated to the increased visual attention to drug related cues (13).

In this regard, although stable methadone levels during daily dosing have benefits in preventing the individuals craving, could not positively reduce the neural substrate involved in brain activation of former heroin addicted cases. In this regard, despite long-term methadone treatment, brain activation can be observed by FMRI following drug related cues presentation.

Based on evidence, Caudate (dorsal striatum) the principal constituent of cortical-basal ganglia network is known as the major brain region involved in substance dependence, decision making and drug seeking. In this regard dopamine is an influential on drug craving and addictive drugs increases dopamine in limbic system which lead to neuroadaptive long-term changes in dopaminergic system following chronic substance use. An impaired dorsal striatum function has been reported in chronic heroin addicted individuals, which be revealed following higher activation intensity of the right caudate in heroin addicted patients and the generation of drug related craving. MMT has shown advantages on recovering the impaired neural function of the dorsal striatum and normalizing the abnormal stimuli-response caused by chronic heroin use (11)(14).

Acute efficacy of daily methadone dose

Methadone has shown a half-life of 42 hours in opioid addict under MT treatment; one daily dose of methadone can lead to steady state (23). According to clinical experiments the effectiveness of daily methadone dose on craving might be tempered toward the end of the 24 hours interval. Patients were screened before and after the daily methadone use, so decreased response to drug related cues was observed after the methadone application compared with before the application of the daily methadone dose in the amygdala, the hippocampal complex, and the insulae. This consequence might be related to attenuated drug expectancy and higher

methadone plasma level. Heroin related cues can activate the brain insula which is involved in interoception behavior in addicted individuals. Reduced insula activation shown through FMRI after the administration of daily methadone confirms the efficacy of methadone in reducing the brain response to drug related cues and craving. Although, low orbitofrontal cortex effect, no ACC effect, and a noticeable amygdala, insula, and hippocampal complex effects following methadone administration confirm the persistence of the stimulation effect of drug related cues, despite the administration of the acute dose of methadone, interoceptive effect is not a noticeable effect of methadone. It can be suggested that long term heroin administration and the following methadone maintenance strategy could modify the acute effect of methadone administration. The maintained brain responses in patients under MMT to drug related cues is acutely reduced following daily methadone administration; however this acute effect will be continued for lower than a 24-hour period and patients will have the highest vulnerability at the end of the 24-hour after the last administration. There is a critical need to determine the stable dose of methadone with the best effect on brain response to drug related cues.

Despite several reports about the brain activation part during the observation of drug related cues in patients under MMT (10-14), the exact neural substrates that mediate brain activation is not revealed.

Duration of MMT

Former heroin addicted patients with at least 2 years of MT treatment showed reduced responses to heroin-related stimuli in the bilateral caudate (dorsal striatum) as the major region associated with human substance addiction and reward processing (11). A negative correlation has been reported between the MMT duration with drug-related blood oxygen level dependent (BOLD) signal intensity in caudate and also the drug-related cue induced craving (DCIC). In this regard longer MMT might be able to decrease the risk of relapse during recovering of heroin dependent individuals due to its ability for controlling and reducing the brain activation in bilateral caudate as reward and memory processing, decision making and drug seeking portion of the brain and also reducing the BOLD signal intensity following heroin related stimuli presentation (11).

In conclusion

Different brain parts from prefrontal to deep limbic structures have been activated by drug related cues observation in patients under long term MMT. However methadone has shown the ability to inhibit the heroin craving and decreasing withdrawal symptoms, the learned brain response to drug stimuli persists despite long-term MMT. Methadone can reduce drug related responses in some parts of the brain, however its efficacy will last for lower than a 24-hour period.

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