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# Acute opioid withdrawal is associated with increased neural activity in reward-processing centers in healthy men: A functional magnetic resonance imaging study

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ABSTRACT

*Background:* Opioid analgesics are frequently prescribed for chronic pain. One expected consequence of long-term opioid use is the development of physical dependence. Although previous resting state functional magnetic resonance imaging (fMRI) studies have demonstrated signal changes in reward-associated areas following morphine administration, the effects of acute withdrawal on the human brain have been less well-investigated. In an earlier study by our laboratory, ondansetron was shown to be effective in preventing symptoms associated with opioid withdrawal. The purpose of this current study was to characterize neural activity associated with acute opioid withdrawal and examine whether these changes are modified by ondansetron.

*Methods:* Ten participants were enrolled in this placebo-controlled, randomized, double-blind, crossover study and attended three acute opioid withdrawal sessions. Participants received either placebo or ondansetron (8ɣmg IV) before morphine administration (10ɣmg/70ɣkg IV). Participants then underwent acute naloxone-precipitated withdrawal during a resting state fMRI scan. Objective and subjective opioid withdrawal symptoms were assessed.

*Results:* Imaging results showed that naloxone-precipitated opioid withdrawal was associated with increased neural activity in several reward processing regions, including the right pregenual cingulate, putamen, and bilateral caudate, and decreased neural activity in networks involved in sensorimotor integration. Ondansetron pretreatment did not have a significant effect on the imaging correlates of opioid withdrawal.

*Conclusions:* This study presents a preliminary investigation of the regional changes in neural activity during acute opioid withdrawal. The fMRI acute opioid withdrawal model may serve as a tool for studying opioid dependence and withdrawal in human participants.



## 1. Introduction

Opioid medications are frequently prescribed for pain relief, including as a long-term treatment for chronic pain. When given over time, physical dependence can occur. If opioid medications are abruptly stopped, unpleasant withdrawal effects, such as agitation and nausea, are often experienced. Changes in mood, such as increased anxiety, are also an expected part of opioid withdrawal. The objective and subjective signs and symptoms of opioid withdrawal are well-documented, and validated scales have been developed for their assessment (Handelsman et al., 1987). While objective changes during opioid withdrawal (e.g., mydriasis and piloerection) are simple to observe, relatively little is known about the neural changes associated with subjective experience of withdrawal. A better understanding of withdrawal-related changes in brain functioning may allow us to more effectively combat withdrawal effects, and perhaps even prevent some forms of dependence.

Resting state functional magnetic resonance imaging (fMRI) is a method for evaluating changes in brain activity that occur when a participant is not performing an explicit task. The approach can provide a non-invasive method of characterizing the acute neuropharmacological effects of drugs. Resting state fMRI relies on low-frequency fluctuations in blood oxygen that are presumed to

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represent changes in neural activity. The resulting blood oxygen level-dependent (BOLD) signal provides an endogenous image contrast that allows active brain regions to be distinguished from less active ones.

In pharmacologic fMRI studies of drugs that do not have ultrafast half-lives, it is often impossible to use a task-related design. Instead, long, taskless, timeseries data must be analyzed. Taskless designs (often referred to as "resting-state" designs) preclude traditional fMRI analytic techniques in which a canonized hemodynamic response pattern is convolved with the task timeline. Interpretation of the BOLD signal can be difficult in such cases. Seed- or network-based analyses can be conducted, but there is insufficient information on networks involved in opioid processes in the human brain. For those reasons, it may be more informative to examine low frequency oscillations (LFO), which can be considered a potential index of spontaneous fluctuations at rest. Previous fMRI studies investigating LFO amplitudes have reported meaningful differences among brain regions and clinical populations (Hoptman et al., 2010; Zang et al., 2007). An approach called amplitude of low frequency fluctuations (ALFF) provides a measure of regional changes in neural activity in a resting state scan (Zang et al., 2007). ALFF analyzes signal fluctuations in a range associated with neural activity (0.01–0.08 Hz), only considering frequencies lower than those attributed to cardiac motion and respiration (approximately 1 Hz and 0.2–0.3 Hz, respectively) (Wang et al., 2008). Previous research has shown that ALFF results correlate reliably with cerebral blood flow (Li et al., 2012). ALFF provides clusters of BOLD-signal change that can be interpreted in the same way as traditional task-related BOLD analyses.

The selective serotonin $(5\text{-HT})_3$ receptor antagonist ondansetron has been shown to decrease nausea and vomiting following exposure to opioid, anesthetic, and chemotherapeutic medications (Kaasa et al., 1990; Leeser and Lip, 1991; Rung et al., 1997). Animal evidence provides additional support for the notion that ondansetron can prevent signs of opioid withdrawal. Roychoudhury and Kulkarni (1996) found that 0.1 mg/kg ondansetron prevented naloxone-induced opioid withdrawal in mice, and similar findings have been observed in rats (Hui et al., 1996; Pinelli et al., 1997). Previous work from our laboratory exploring genetic data on inbred strains of mice revealed that the gene most strongly associated with withdrawal severity was that for the $5\text{-HT}_3$ receptor that is targeted by ondansetron. Furthermore, the animal data also show that blockade of this receptor leads to a reduction in withdrawal-related behavior (Chu et al., 2009). Ondansetron has likewise been shown to ease or prevent objective opioid-withdrawal symptoms in healthy humans given morphine experimentally (Chu et al., 2009). This model for assessing acute opioid-withdrawal effects has be shown to be safe and effective in producing acute opioid withdrawal in healthy men, and has been utilized in previous publications (Compton et al., 2003, 2004).

The primary purpose of the current study was to characterize changes in brain activity associated with acute opioid withdrawal using fMRI. Based on evidence from animal and human studies, it was hypothesized that changes in neural activity, manifested as changes in ALFF, would be observed in the reward-related regions. A secondary aim was to examine whether withdrawal-related changes in brain activity could be modified by pretreatment with ondansetron.

## 2. Materials and methods

### 2.1. Participants

Fifteen healthy male volunteers were enrolled in this randomized, double-blinded, placebo-controlled crossover study. Participants were excluded on the basis of (1) regular medication use; (2) a history of substance use, including cannabis and nicotine, as well as opioid use within the last 12 months; (3) Raynaud's Disease or Coronary Artery Disease; and (4) MRI contraindications. Female participants were not recruited for this study because menstrual cycles can alter the opioid response (Hoehe, 1988).

The Institutional Review Board (Stanford University) authorized the human experimental protocol on April 15th, 2009, and the study was part of a larger study that was registered in the clinicaltrials.gov database (identifier NCT01006707). Written informed consent was obtained from all participants before this research was undertaken.

### 2.2. Overall study protocol

The protocol used for opioid-induced withdrawal has been previously described (Compton et al., 2003). During this study, each participant attended three separate laboratory-based acute opioid withdrawal sessions. The first session was undertaken in a mock MRI scanner and was designed to determine if participants could tolerate withdrawal in the scanning environment. Participants who were able to successfully and safely tolerate opioid withdrawal while in the scanner were approved to continue with the following study sessions.

Participants were pretreated intravenously (IV) with either 0.9% normal saline placebo or 8 mg ondansetron prior to IV morphine (10 mg/70 kg). Later, participants in all sessions received IV naloxone (10 mg/70 kg) to precipitate opioid withdrawal. In the mock MRI session, all participants received placebo pretreatment. In the two subsequent sessions, participants were assigned to ondansetron or placebo pretreatment conditions in a randomized (double-blinded) and counter-balanced order. All study sessions were conducted by a blinded research assistant (AC, JS, DH, HA) and supervised by an unblinded physician (LC) who administered the study medication and monitored participants throughout the study. The three separate study sessions for each participant were scheduled at least one week apart.

### 2.3. Study session timeline

Fig. 1 outlines the study session timeline; the time of naloxone administration is marked as $T = 0$. Prior to the MRI, ondansetron or saline placebo was administered as an IV bolus at $T = -165$. Thirty minutes later, $T = -135$, morphine was administered as an infusion over 10 min. Participants remained in the lab under observation and were offered music or video entertainment and caffeine-free meals or snacks ad lib until they were transported to the MRI scanner. The MRI scan commenced at $T = -41$, and high-resolution structural scan was acquired. Acquisition of resting state data began at $T = -9$, and at $T = 0$, naloxone was administered as an IV bolus. Scanning continued for a further 15 min and then participants were removed from the scanner. The total study session time was 185 min.

### 2.4. Objective and subjective opioid withdrawal symptoms

The Objective Opioid Withdrawal Scale (OOWS) and Subject Opioid Withdrawal Scale (SOWS) ratings – validated by Handelsman et al. (1987) – were used during study sessions to assess withdrawal symptoms and possible modulation of opioid withdrawal by ondansetron. The OOWS consists of 13 observable physical symptoms that are assessed over a five-minute observation period and scored as present (score of 1) or absent (score of 0). The total OOWS score is determined by summing scores for the 13 physical symptoms. Lacrimation and mydriasis were unable to be assessed during the eyes-closed resting state scan and were