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Brief Report

BRIEF REPORT

Behavioral and Accumbal Responses During an Affective Go/No-Go Task Predict Adherence to Injectable Naltrexone Treatment in Opioid Use Disorder

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Abstract

Adherence is a major factor in the effectiveness of the injectable extended-release naltrexone as a relapse prevention treatment in opioid use disorder. We examined the value of a variant of the Go/No-go paradigm in predicting extended-release naltrexone adherence in 27 detoxified opioid use disorder patients who were offered up to 3 monthly extended-release naltrexone injections. Before extended-release naltrexone, participants performed a Go/No-go task that comprised positively valenced Go trials and negatively valenced No-go trials during a functional magnetic resonance imaging scan. Errors of commission and neural responses to the No-go vs Go trials were independent variables. Adherence, operationalized as the completion of all 3 extended-release naltrexone injections, was the outcome variable. Fewer errors of commission and greater left accumbal response during the No-go vs Go trials predicted better adherence. These findings support the clinical potential of the behavioral and neurophysiological correlates of response inhibition in the prediction of extended-release naltrexone treatment outcomes in opioid use disorder.

Keywords: opioid use disorder, extended-release naltrexone, adherence, errors of commission, nucleus accumbens

Introduction

Opioid use disorder (OUD) caused approximately 50 000 deaths worldwide and accounted for over 40% of all substance abuse-related deaths in 2013 (Naghavi et al., 2015). OUD is driven mainly by the reinforcing effects of opioid agonists mediated by the μ-opioid receptor (MOR) (Wise and Koob, 2014). A major mechanism of MOR-mediated reinforcement is the inhibition of GABAergic input into the ventral tegmental area leading to an increase in dopamine release in the nucleus accumbens (NAcc) (Fields and Margolis, 2015). Naltrexone (NTX) is an opioid antagonist that competitively binds to the MORs and blocks the

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Significance Statement

Opioid use disorder (OUD) is an acute public health problem. Injectable naltrexone (XR-NTX) is the only extended-release opioid antagonist approved for treatment of OUD in the United States. Given its high pharmacological efficacy, the outcomes of XR-NTX depend largely on adherence. Nonadherence is almost invariably associated with relapse to opioids and often a fatal opioid overdose. These facts underscore the importance of prospectively identifying OUD patients at a high risk of an early dropout from XR-NTX treatment. In the present study, we found that errors of commission and nucleus accumbens fMRI response during a modified Go/No-go paradigm predicted adherence to XR-NTX in 27 OUD patients. These findings suggest that impaired functioning of the nucleus accumbens during executive and affective processing constitute a risk factor for treatment failure in OUD.

effects of opioid agonists. Although oral NTX is used clinically for relapse prevention in detoxified OUD patients, its effectiveness has been severely limited by poor adherence (Comer et al., 2006). A monthly injectable extended-release NTX (XR-NTX) was developed to overcome this obstacle and shown to be more effective than oral NTX in reducing opioid craving and preventing relapse (Krupitsky et al., 2011; Tanum et al., 2017; Shi et al., 2018). Recent studies also show that while the overall long-term effectiveness of XR-NTX is comparable to that of the oral agonist buprenoprphine/naloxone, there is considerable individual variability in treatment response, including adherence (Krupitsky et al., 2011; Lee et al., 2018; Tanum et al., 2017). Nonadherence to XR-NTX is particularly challenging because it almost invariably indicates a relapse to opioids. Unlike agonist medication-assisted treatments (MATs), resuming XR-NTX after relapse often requires repeating the detoxification. Discontinuation of XR-NTX may also increase the risk of accidental overdose due to reduced tolerance to opioids, leading to heightened sensitivity to the dose of opioids that patients had been accustomed to prior to detoxification (White and Irvine, 1999). These facts underscore the importance of uninterrupted adherence to XR-NTX treatment and the need to identify those at high risk of an early dropout. The value of the clinical and self-report measures to prediction of XR-NTX adherence has been limited (Nunes et al., 2015). Although functional magnetic resonance imaging (fMRI) does not have recognized clinical applications in the treatment of addiction, there is a growing literature reporting its use to predict treatment outcomes in the research settings (Falk et al., 2011; Wang et al., 2015; Volkow and Boyle, 2018).

Substance use disorders are characterized by repeated and compulsive seeking of drug rewards despite acknowledged negative consequences (Moeller and Goldstein, 2014). Inhibitory control deficits that significantly contribute to the development and maintenance of such a behavioral pattern have been studied using the "Go/No-go" paradigm (Donders, 1868/1969; Luijten et al., 2014; Smith et al., 2014). In this paradigm, a response prepotency is created by requiring participants to respond to frequently presented "Go" stimuli and to inhibit such prepotent response to infrequently presented "No-go" stimuli. Prior studies have shown deficits in response inhibition in cocaine and tobacco users compared with healthy controls (Luijten et al., 2014; Smith et al., 2014). Moreover, inhibitory training has been shown to reduce future alcohol intake in drinkers (Houben et al., 2011). However, it remains inconclusive whether impaired inhibitory control is associated with OUD and its treatment (Luijten et al., 2014; Smith et al., 2014).

In the present study, we used a previously reported modified Go/No-go paradigm, in which the affectively positive and potentially rewarding stimuli (e.g., flowers) require the frequent Go response and the affectively negative and potentially aversive stimuli (e.g., snakes) signal the infrequent No-go trials (Goldman et al., 2015). This modification made the task more intuitive than the original version because humans are predisposed to approach positively valenced stimuli and avoid negatively valenced ones (Chen and Bargh, 1999; Goldman et al., 2015). It mitigates technical difficulties that individuals with substance use disorders exhibit on tasks involving abstract stimuli, such as low motivation to perform accurately and difficulty following instructions. In the modified Go/No-go task, more errors of commission (i.e., false-alarm responses on No-go trials) are associated with more aggressive behavior, inattention, and hyperactivity problems among adolescents at high risk for substance use disorders (Goldman et al., 2015). Similar tasks are also able to differentiate between patients with mood disorders (e.g., depression, mania) and healthy controls (Elliott et al., 2004; Erickson et al., 2005). These findings support the external validity of the modified paradigm.

The present study is the first to our knowledge to apply a Go/No-go paradigm to the prediction of adherence to XR-NTX treatment in OUD patients and to use fMRI to explore the underlying neural mechanisms. We hypothesized that OUD patients who made fewer errors of commission at baseline would show better adherence to subsequent XR-NTX treatment. Adherence was operationalized as the completion of a 3-month XR-NTX treatment program (Tanum et al., 2017; Shi et al., 2018). Another goal of the study was to explore the neural mechanisms of adherence using fMRI during the performance of our modified affective Go/No-go task. We focused on the following regions of interest given their significant role in addiction as well as their involvement in affective or reward processing and executive functions: the NAcc (Zink et al., 2006; Fields and Margolis, 2015), the amygdala (Koob and Le Moal, 2008), the right inferior frontal gyrus (IFG) (Goldstein and Volkow, 2011; Aron et al., 2014), and the dorsal anterior cingulate cortex (dACC) (Goldstein and Volkow, 2011; Shackman et al., 2011).

Methods

Participants

Twenty-nine individuals with OUD were enrolled. Two were excluded due to excessive errors of omission on the Go/No-go task (>99% missed response on Go trials). The demographic characteristics of the remaining 27 participants are summarized in Table 1. All participants gave written informed consent to participate in the protocol, which was approved by the University of Pennsylvania Institutional Review Board. See the Supplementary Information: inclusion and exclusion criteria.

Procedure

After the informed consent procedure, participants completed baseline assessments including the Structured Clinical Interview for DSM-IV-TR (American Psychiatric Association,

Table 1. Participant Characteristics (mean ± SD)

Variable	All	Adherent vs Nonadherent	*P* Value
N	27	14 vs 13	
Years of age	28.74 ± 9.71	32.00 ± 11.60 vs 25.23 ± 5.73	.069
Sex	20 M, 7 F	9 M, 5 F vs 11 M, 2 F	.228[a]
Race	24 Cau, 3 AA	12 Cau, 2 AA vs 12 Cau, 1 AA	.247[a]
Ethnicity	3 Hispanic	2 Hispanic vs 1 Hispanic	.586[a]
Years of education	14.04 ± 1.65	14.00 ± 1.71 vs 14.08 ± 1.66	.907
Using prescription opioids	27	14 vs 13	1.000[a]
Using heroin	11	7 vs 4	.309[a]
Errors of commission (%)	39.38 ± 18.15	30.83 ± 13.98 vs 48.58 ± 18.03	.008
Errors of omission (%)	3.76 ± 4.65	3.57 ± 3.81 vs 3.97 ± 5.57	.828
Left NAcc response	3.20 ± 3.29	4.70 ± 2.58 vs 1.58 ± 3.29	.011
Right NAcc response	3.62 ± 3.41	4.55 ± 3.16 vs 2.61 ± 3.51	.144

Abbreviations: Cau/AA, Caucasian/African American; M/F, male/female; NAcc, nucleus accumbens.
P values were obtained from 2-sample *t* tests, except as below.
a χ^2 test with df = 1.

2000). See the Supplementary Information: additional clinical assessments.

The fMRI session was conducted after detoxification and before the first XR-NTX injection. The Go/No-go fMRI task was adopted from previous research (Goldman et al., 2015). The Go stimuli included 122 positively valenced pictures (e.g., sweets), and the No-go stimuli were 38 negatively valenced pictures (e.g., snakes). Each trial consisted of a stimulus displayed for 300 milliseconds, followed by a 1700-millisecond baseline period during which a crosshair was displayed. Pseudo-random order of the stimuli and baseline periods was generated using optseq2 (https://surfer.nmr.mgh.harvard.edu/optseq).

Twenty-three participants received the first XR-NTX injection 2.22 ± 7.54 (mean ± SD) days after the fMRI session (range = 0–36). Seventeen received the second injection 31.53 ± 3.04 days after the first injection (range = 28–41). Fourteen received the third injection 30.29 ± 5.61 days after the second injection (range = 23–47). See the Supplementary Information: study medication.

Data Analyses

fMRI data were preprocessed and subjected to individual-level analysis of the "No-go vs Go" contrast. Group-level *t* tests were applied to anatomically defined left NAcc, right NAcc, left amygdala, right amygdala, right IFG, and dACC masks to identify significant voxels at the threshold of family-wise error-corrected $\alpha < 0.05/6 = 0.0083$. See the Supplementary Information: MRI data acquisition and analysis.

Adherence to XR-NTX was operationalized as the completion of all 3 XR-NTX injections and treated as the outcome variable (1 = completion; 0 = otherwise). A logistic regression model was tested for each of the 7 predictors: rate of errors of commission, and the neural responses of the left NAcc, right NAcc, left amygdala, right amygdala, right IFG, and dACC. The neural responses were extracted from the peak activation voxel in the masks. Because 7 predictors were tested, *P* values were corrected for false discovery rate (FDR) following the Benjamini–Hochberg procedure with $\alpha = 0.05$ (Benjamini and Hochberg, 1995). Receiver operating characteristic (ROC) analysis was conducted to evaluate each model. Predictive accuracy was expressed as the area under the ROC curve (AUC) and its 95% bootstrap confidence interval (BootCI). The maximum prediction accuracy (MaxAcc) was calculated at the optimal cut point. Significant models were validated using a leave-one-out cross-validation. Commonality analysis was conducted to determine the unique and common contributions of the significant predictors in terms of the proportions of the explained variance of the outcome variable. See the Supplementary Information: prediction analyses.

Results

Participant demographic and clinical characteristics are summarized in Table 1. There were greater responses during No-go vs Go trials in the left NAcc (k = 64, Z = 4.18, x/y/z = –6/12/–2), right NAcc (k = 79, Z = 4.44, x/y/z = 6/6/–4), right IFG (k = 45, Z = 3.49, x/y/z = 48/34/18; k = 2, Z = 3.34, x/y/z = 52/16/32), and dACC (k = 534, Z = 4.98, x/y/z = 2/42/16; k = 391, Z = 4.88, x/y/z = –4/34/–8; k = 31, Z = 3.94, x/y/z = –2/–14/38; k = 31, Z = 3.89, x/y/z = 2/–14/34). The bilateral amygdala responses did not differ between the No-go and Go conditions. The number of errors of commission was negatively correlated with the left NAcc response (r = –0.39, *P* = .04) and marginally positively with the dACC response (r = 0.34, *P* = .08), but not with the responses of other regions of interest (Ps > .30).

Logistic regression revealed that fewer errors of commission predicted better treatment adherence (ROC-AUC = 0.79, 95% BootCI = [0.58,0.93], MaxAcc = 74.04%, $\chi^2(1) = 7.69$, uncorrected *P* = .006, FDR-corrected *P* = .025; see Figure 1A). Greater left NAcc activity during the No-go vs Go trials also predicted better adherence (ROC-AUC = 0.82, 95% BootCI = [0.53,0.96], MaxAcc = 88.89%, $\chi^2(1) = 7.22$, uncorrected *P* = .007, FDR-corrected *P* = .025; see Figure 1B). Neural activity at the right NAcc, bilateral amygdala, right IFG, and dACC was not significantly associated with adherence (ROC-AUC = 0.49 to 0.71, MaxAcc = 55.56% to 70.37%, $\chi^2(1) = 0.03$–2.36, uncorrected Ps > .12, FDR-corrected Ps > .29). The predictive power of errors of commission and left NAcc response were validated by leave-one-out cross-validation (cross-validated ROC-AUC = 0.73 & 0.76, Ps < .01, MaxAcc = 74.07% and 85.19%).

Commonality analysis showed that 15.66% of variance in adherence was uniquely accounted for by errors of commission, 13.93% uniquely by left NAcc response, and 17.39% commonly by both, leaving 53.03% of variance unexplained.

Discussion

Our findings are consistent with the hypothesis that OUD patients who were better able to inhibit prepotent Go responses

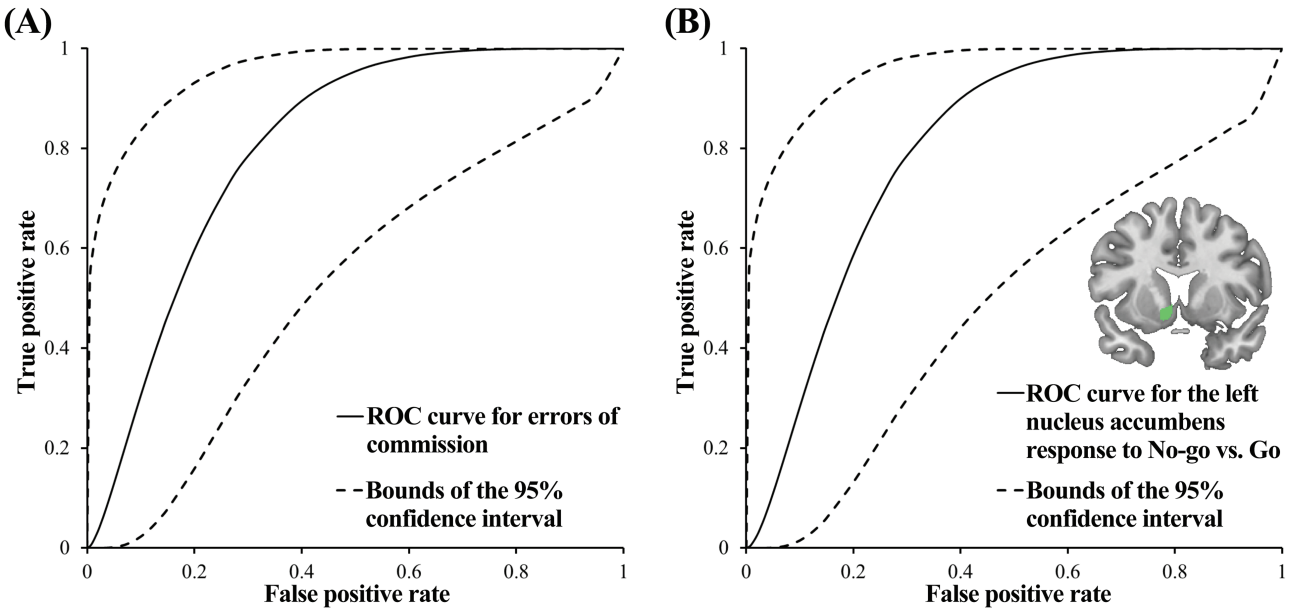

Figure 1. Receiver operating characteristic (ROC) curves for the logistic regression models predicting adherence to 3 months of extended-release naltrexone (XR-NTX) treatment in opioid use disorder. (A) Fewer errors of commission predicted better adherence to XR-NTX; area under the ROC curve (ROC-AUC) = 0.79, 95% bootstrap confidence interval (BootCI) = [0.58,0.93]. (B) Greater left nucleus accumbens response to the No-go vs Go trials predicted better adherence to XR-NTX; ROC-AUC = 0.82, 95% BootCI = [0.53,0.96].

on the No-go trials were more adherent to XR-NTX treatment. fMRI data showed that the No-go condition induced greater NAcc, right IFG, and dACC responses compared with the Go condition and that left NAcc response was positively associated with XR-NTX adherence. The behavioral performance and left NAcc response achieved 74% and 85% accuracy in predicting adherence, respectively, suggesting that if these findings are confirmed, the affective Go/No-go paradigm may be of clinical interest in predicting XR-NTX treatment outcomes in OUD.

The affective Go/No-go task probes 2 different behavioral components: an affective component that requires processing the positive and negative stimuli, and an executive component that involves inhibiting the prepotent behavioral response. Deficits in both domains are characteristic of substance use disorders (American Psychiatric Association, 2000). Clinically, patients frequently encounter the challenge of recognizing aversive consequences of drug use and suppressing compulsive drug-seeking behavior. The design of the current Go/No-go task maximizes its external validity by making it congruent with the fact that these deficits often co-occur. Indeed, errors of commission on this task were associated with OUD treatment adherence in the current study. The external validity is also evidenced by a previous study, which showed that the rate of errors of commission on this task was associated with aggressive behavior, inattention, and hyperactivity symptoms in adolescents at high risk for substance abuse (Goldman et al., 2015).

The activation of the NAcc during the affective Go/No-go task is consistent with its role in action monitoring/selection (Floresco, 2015) and processing of salient stimuli (Zink et al., 2006). Prior research has elucidated drug-induced neuroplasticity in the NAcc and its association with the maintenance and relapse of drug use (Volkow and Morales, 2015; Scofield et al., 2016). The current study complemented the literature by showing that baseline left NAcc response positively predicted XR-NTX adherence in OUD. Similarly, Kober et al. (2014) found that baseline NAcc response in treatment-seeking cannabis users during the Stroop task predicted posttreatment abstinence. It is possible that substance use-induced changes in the brain, such as abnormal dopamine signaling in the NAcc and other mesocorticolimbic regions, contribute to the vulnerability to nonadherence. Development of adjunct interventions to restore NAcc functioning may help to improve adherence in those vulnerable individuals.

Our commonality analysis showed that errors of commission and left NAcc activity each accounted for a substantial proportion of unique variance in XR-NTX adherence, suggesting that behavioral and neural measures are complementary in the prediction of adherence. Nevertheless, 53% of variance remained unexplained by either predictor or their combination, suggesting that there is room for improvement in the prediction of XR-NTX adherence. This is consistent with the concept of addiction as a multi-determined disorder that involves several domains of neurocognitive alterations. Examples of such alterations not captured in the current study include elevated reactivity to drug-related cues (Shi et al., 2018) and denial of illness and need for treatment (Moeller and Goldstein, 2014). Individual differences in these domains may account for the unexplained variance. Another approach to improving prediction of adherence is to apply state-of-the-art statistical techniques. Recent advances in statistical methods such as machine learning (Orrù et al., 2012) and network analysis (Pariyadath et al., 2016) has enhanced the power of fMRI in addiction research. These analytical techniques have the potential to advance our understanding of the neurobiological mechanisms of XR-NTX adherence.

Our study also has a number of caveats. First, the affective Go/No-go task design did not allow dissociating the affective and executive contributions to the task response. The absence of amygdala activation in the No-go vs Go contrast suggests that the participants may have reduced sensitivity to aversive stimuli. We hope that our initial findings will enable future research on the mechanisms probed by the task to determine the relative contributions of its affective and executive components. It is also important for future research to examine whether and to what extent our findings can be attributed to individual

differences in learning and memory deficits or associated with concurrent disorders, such as concomitant stimulant abuse or depressive disorders. Second, we did not find significant differences in the demographic and clinical characteristics between adherent and nonadherent patients. This is consistent with previous findings that experimental cognitive and neural variables may be more sensitive predictors of health-related outcomes than the observational measures based on self-report (Falk et al., 2011). However, these negative findings may also have been due to the limited sample size of our preliminary study, which was not designed to detect small effects. Particularly, we found that the adherent patients were marginally ($P = .069$) older than the nonadherent ones (see Table 1), a trend-level difference that could nevertheless be associated with higher levels of brain maturation and lower impulsivity. Future research with larger samples may determine more accurately how neural and cognitive measures combined with advanced statistical techniques compare with demographic, clinical, and other self-report measures (Volkow and Boyle, 2018). Finally, our results raise the question of whether our approach could be applied to the prediction of XR-NTX adherence at pretreatment time points further away from the time of last opioid use (e.g., 2 weeks or more after detoxification). Although we expect that intact cognitive and affective processes probed by the current paradigm will remain important for treatment adherence regardless of the duration of opioid abstinence before treatment is initiated, this would require experimental confirmation.

In conclusion, fewer pretreatment errors of commission and greater left NAcc activity during the affective Go/No-go task were associated with better subsequent adherence to 3 months of XR-NTX treatment in patients with OUD. These findings point to the potential mechanisms of adherence that could inform the development of clinically relevant behavioral and neurophysiological predictors of adherence.

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Interest Statement

Dr Langleben has served as a consultant to Controlled Chemicals, Inc. and Alkermes plc. Other authors declare no conflicts of interest.

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