Drug and Alcohol Dependence 132 (2013) 195–201

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Impact of DCS-facilitated cue exposure therapy on brain activation to cocaine cues in cocaine dependence

James J. Prisciandaro*, Hugh Myrick, Scott Henderson, Aimee L. McRae-Clark, Elizabeth J. Santa Ana, Michael E. Saladin, Kathleen T. Brady

Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, Clinical Neuroscience Division, 67 President Street, MSC861, Charleston, SC 29425, United States

ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form 28 January 2013
Accepted 2 February 2013
Available online 14 March 2013

Keywords:
D-Cycloserine
DCS
Cocaine dependence
fMRI
Cue reactivity
Exposure therapy

ABSTRACT

Background: The development of addiction is marked by a pathological associative learning process that imbues incentive salience to stimuli associated with drug use. Recent efforts to treat addiction have targeted this learning process using cue exposure therapy augmented with D-cycloserine (DCS), a glutamatergic agent hypothesized to enhance extinction learning. To better understand the impact of DCS-facilitated extinction on neural reactivity to drug cues, the present study reports fMRI findings from a randomized, double-blind, placebo-controlled trial of DCS-facilitated cue exposure for cocaine dependence.

Methods: Twenty-five participants completed two MRI sessions (before and after intervention), with a cocaine-cue reactivity fMRI task. The intervention consisted of 50 mg of DCS or placebo, combined with two sessions of cocaine cue exposure and skills training.

Results: Participants demonstrated cocaine cue activation in a variety of brain regions at baseline. From the pre- to post-study scan, participants experienced decreased activation to cues in a number of regions (e.g., accumbens, caudate, frontal poles). Unexpectedly, placebo participants experienced decreases in activation to cues in the left angular and middle temporal gyri and the lateral occipital cortex, while DCS participants did not.

Conclusions: Three trials of DCS-facilitated cue exposure therapy for cocaine dependence have found that DCS either increases or does not significantly impact response to cocaine cues. The present study adds to this literature by demonstrating that DCS may prevent extinction to cocaine cues in temporal and occipital brain regions. Although consistent with past research, results from the present study should be considered preliminary until replicated in larger samples.

1. Introduction

Recent animal research has demonstrated that repeated drug use leads to the development of increasingly habitual drug-seeking and using behavior that is promoted by the transfer of incentive salience from the drug itself to a wide variety of cues associated with drug reward via associative learning (Robinson and Berridge, 1993). Animal models have shown that this process is marked by shifts in drug cue processing from ventral to more dorsal regions of the striatum (Everitt and Robbins, 2005). The neurobiologic underpinning of this pathological associative learning is believed to be dysfunctional glutamate-mediated long-term potentiation processes (Kalivas, 2009). Because of the central role of associative learning in the development and maintenance of addiction, there have been a number of efforts to evaluate the clinical utility of therapies that target extinction of conditioned responses by exposing individuals to drug cues in the absence of drug reward. Unfortunately, such therapies have not consistently demonstrated high clinical efficacy (Conklin and Tiffany, 2002). Recent efforts to strengthen the efficacy of cue exposure therapies have focused on using D-cycloserine (DCS), a partial glutamate N-methyl-D-aspartate receptor agonist, to enhance extinction learning of conditioned drug-seeking and using behavior (Myers and Carlezon, 2012). The success of these attempts has been mixed; whereas some have found a beneficial effect of DCS on facilitating cue extinction in nicotine dependence (Santa Ana et al., 2009), others have demonstrated that DCS may increase cue-induced craving in cocaine dependence (Price et al., 2009, 2012). These inconsistent findings suggest that DCS may influence extinction differently based on the substance under consideration. One potentially fruitful approach to characterizing the varied effects of DCS on addictive behavior may be to study the underlying

* Corresponding author. Tel.: +1 843 792 1433; fax: +1 843 792 0528.
E-mail address: priscian@musc.edu (J.J. Prisciandaro).

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http://dx.doi.org/10.1016/j.drugalcdep.2013.02.009

neural signature of DCS-facilitated cue exposure treatment using contemporary imaging methods.

The present investigation was a sub-study of a clinical trial investigating the use of DCS to facilitate extinction of responses elicited by cocaine cues. All participants were randomized to receive either DCS or placebo prior to each of two days of cocaine cue (i.e., paraphernalia) exposure. Extinction procedures included skills training designed to reduce reactivity to cocaine cues during the post-cue exposure consolidation period in the hope that DCS would enhance consolidation of reduced craving to cocaine cues learned within cue exposure sessions. Participants of the sub-study ($n = 25$) additionally completed a cocaine-cue reactivity fMRI paradigm prior to and following the cue extinction sessions. We hypothesized that all participants would experience decreased brain activation to drug cues across MRI scans, but this decrease would be greater in the DCS-treated participants relative to placebo-treated participants.

2. Methods

2.1. Participants

Twenty-five cocaine-dependent men and women aged 18–65 were recruited from a larger ($n = 47$) clinical trial of DCS facilitation of cocaine-cue extinction (Santa Ana et al., 2012) through media advertisements and clinical referrals in the local Charleston, SC area. All trial participants were invited to participate in the present fMRI sub-study. Trial participants who did not participate in the fMRI sub-study were excluded for having ferrous metal implants (37%), claustrophobia (5%), left-handedness (5%), or for unknown reasons (53%; primarily lack of interest in participating). Individuals who participated in the parent trial, but not in the fMRI sub-study, were approximately evenly split between DCS (53%) and placebo (47%) treatment groups. All study procedures were performed in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, with approval from the Medical University of South Carolina (MUSC) Institutional Review Board.

All participants met DSM-IV criteria for cocaine dependence within 3 months preceding the study and indicated cocaine as their primary drug of choice. Participants were right-handed. Exclusionary criteria included medications for addiction (e.g., topirimate, naltrexone, suboxone), major medical (e.g., diabetes, HIV) and psychiatric conditions (e.g., affective disorders, posttraumatic stress disorder), pregnancy or nursing, ferrous metal implants or pacemakers, and DSM-IV criteria for non-cocaine substance dependence (except caffeine, nicotine, marijuana, or alcohol) within the past 60 days. Participants were required to maintain at least 72 h of abstinence from cocaine, alcohol, and all other drugs of abuse as confirmed by breathalyzer, urine drug screen (UDS), and self report, prior to each study appointment; positive UDS for tetrahydrocannabinol (THC) was acceptable as long as subjects denied marijuana use within the preceding 72 h. This testing strategy ensured that participants were abstinent from cocaine and other drugs of abuse for at least 72 h preceding their first MRI session through the completion of their second MRI session.

2.2. Procedure

Following a phone or in-person screening, participants were scheduled for a baseline diagnostic visit during which they completed a diagnostic interview for DSM-IV disorders along with a number of self-report measures (see Section 2.3 below). Once all inclusion and no exclusion criteria were met, participants were scheduled for their first fMRI visit within one-week. Participants with positive breath alcohol or urine drug screens at the first MRI visit were rescheduled; participants with positive screens at any subsequent visit were excluded. One week following their first MRI visit, participants completed a second, identical MRI scan; scans typically occurred on two consecutive Fridays. Between MRI visits, on intervening Mondays and Wednesdays, participants underwent two outpatient cocaine-cue extinction sessions (described fully in Santa Ana et al., 2012), separated by one day. Each cocaine-cue extinction session included 4 brief alternating blocks of pre-recorded cognitive behavioral therapy skills training and in vivo handling of paraphernalia and simulated cocaine. Skills training included guided imagery for craving reduction, urge surfing, coping with automatic thoughts to use cocaine, and distraction techniques (Santa Ana et al., 2010). After learning each skill, participants were encouraged to apply the skill to managing their craving during cue exposures. Participants' subjective craving and physiological reactivity to cocaine cues were recorded during and following each cue exposure block. Fifteen minutes preceding the first cue exposure block, on each day of the extinction sessions, participants were randomly assigned to receive either 50 mg of DCS or matched placebo. Participants received the same medication before both cue extinction session. Medication was compounded and packaged by the Investigational Drugs Services (IDS) at MUSC in identical capsules within blister packs. Both study personnel and participants were blind to group assignment.

2.3. Measures

Substance use disorders (SUD) were assessed using the SUD module of the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Other axis I psychiatric disorders were assessed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Cocaine use in the three months preceding the first visit, as well as throughout the study, was assessed using the Timeline Follow-back method (Sobell and Sobell, 1996). Demographics and cocaine use history (e.g., years of use) were assessed using an in-house questionnaire.

2.4. Cocaine cue-reactivity paradigm

The present investigation utilized a cocaine cue-reactivity fMRI paradigm adapted from an established alcohol-cue reactivity paradigm (George et al., 2001; Myrick et al., 2008). Subjects were shown pictures of cocaine and related objects (e.g., crack pipe), neutral objects (e.g., furniture), and visual control images that lack object recognition over six 90-s epochs. Of the 30 cocaine images, 13 pictured crack cocaine, 14 pictured powder cocaine, and 3 pictured both crack and powder cocaine. Fourteen of the 30 pictures contained both cocaine and cocaine paraphernalia (e.g., lighter, crack pipe, rolled paper money, razor), 12 contained cocaine only, and 4 depicted cocaine use. Each 90-s epoch contains three 24-s blocks (cocaine images, neutral objects, control images), containing five pictures displayed for 4.8 s each, and one 18-s rest block (i.e., cross-hair). The image blocks are balanced with respect to luminosity (i.e., brightness). Blocks and stimuli within blocks are presented in pseudorandom order. During the task, participants were asked to rate their craving, from zero ("none") to four ("severe"), after each block using a handpad. Participants' cocaine craving scores were computed by taking their average craving rating following cocaine blocks and subtracting from it their average craving rating following neutral object blocks. This cocaine cue-reactivity paradigm was developed for a placebo-controlled trial of N-acetylcysteine (NAC) for cocaine dependence (LaRowe et al., 2005, 2007). A recent examination of the association between motivation/treatment status and brain activation to cocaine cues utilizing the present fMRI cocaine cue paradigm provided further support for the validity of the paradigm (Prisciandaro et al., 2012).

2.5. Image acquisition

Participants underwent two identical MRI scans separated by one week. MRI scans were performed in a Siemens 3.0T Trio (Erlangen, Germany) MR scanner with a 12-channel head coil. Following localizer and anatomical scans, the cue reactivity scan was acquired using an echo-planar gradient-echo pulse sequence (TR = 2200 ms, TE = 35 ms, flip angle = 90%). Images were acquired with approximate AC-PC alignment. Each brain volume consisted of 36 transverse slices (64×64 matrix, 3.0 mm thickness, no gap). Voxel size was 3.0 mm $\times$ 3.0 mm $\times$ 3.0 mm.

2.6. Image analysis

fMRI analyses were conducted using Statistical Parametric Mapping software 8 (SPM8, The Wellcome Department of Cognitive Neurology, London). All volumes within the cue reactivity scan were realigned to the first volume. Images were stereotactically normalized into a standard space, with a resolution of 3 mm $\times$ 3 mm $\times$ 3 mm voxels using a Montreal Neurological Institute (MNI) template. Data were smoothed with an isotropic 8 mm Gaussian kernel and were high-pass filtered with a cut off period of 240 s (i.e., twice the task cycle duration). Following preprocessing, fMRI data were analyzed within a general linear model (GLM) mixed effects framework. Within-task data from individual participants were analyzed using fixed-effects GLM, with cocaine-cue activity modeled as a box-car function convolved with the standard canonical hemodynamic response function; six movement parameters (3 rotation values in radian and 3 translation values in mm) were included as covariates to control for the influence of residual head motion. Autocorrelation was statistically controlled using an AR(1) model. Following these intra-individual GLM analyses, cocaine minus neutral image contrast maps were generated and entered into inter-individual random-effects analyses. To identify brain regions that activated significantly more to cocaine cues relative to neutral objects, we performed a one-sample t-test on participants' cocaine minus neutral image contrast maps from the first MRI session. To examine the relationship between participants' subjective craving and their brain activation to cocaine versus neutral cues, the above one-sample t-test was repeated with participants' cocaine craving scores entered as a covariate. To examine the effects of cue-extinction treatment and medication (DCS vs. placebo) on brain activation to cocaine cues, we performed a 2×2 mixed effects ANOVA. The impact of cue-extinction treatment was assessed via the within-subjects main effect of MRI session (pre-scan vs. post-scan) on brain activation to cues, and the effect of medication was assessed via the interaction of MRI session and medication group on brain activation to cues. All group-level statistical maps were thresholded using cluster-level inference in SPM8. For the MRI session $\times$ medication group interaction effect, we used