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Extinction of drug cue reactivity in methamphetamine-dependent individuals

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ABSTRACT

Conditioned responses to drug-related environmental cues (such as craving) play a critical role in relapse to drug use. Animal models demonstrate that repeated exposure to drug-associated cues in the absence of drug administration leads to the extinction of conditioned responses, but the few existing clinical trials focused on extinction of conditioned responses to drug-related cues in drug-dependent individuals show equivocal results. The current study examined drug-related cue reactivity and response extinction in a laboratory setting in methamphetamine-dependent individuals. Methamphetamine cue-elicited craving was extinguished during two sessions of repeated (3) within-session exposures to multi-modal (picture, video, and in-vivo) cues, with no evidence of spontaneous recovery between sessions. A trend was noted for a greater attenuation of response in participants with longer (4–7 day) inter-session intervals. These results indicate that extinction of drug cue conditioned responding occurs in methamphetamine-dependent individuals, offering promise for the development of extinction- based treatment strategies.

Introduction

Consistent with a Pavlovian conditioning theory, cues associated with drug using (e.g. paraphernalia, locations where drug is used) acquire the capacity to elicit conditioned responses, such as craving, as a consequence of repeated pairings between the cues and the central nervous system effects of the drug (i.e., activation of reward pathways in the brain; Pavlov, 1927). This conditioned association has been systematically examined in human laboratory settings using paradigms in which participants are exposed to cues related to the use of nicotine (LaRowe, Saladin, Carpenter, & Upadhyaya, 2007; McClernon et al., 2007; Tiffany, Cox, & Elash, 2000), alcohol (Glautier & Drummond, 1994; Monti et al., 1993; Szegedi et al., 2000), heroin (Moring & Strang, 1989; Sell et al., 2000; Yu et al., 2007), and cocaine (Avants, Margolin, Kosten, & Cooney, 1995; Robbins, Ehrman, Childress, & O'Brien, 1999; Saladin, Brady, Graap, & Rothbaum, 2006), and subjective, behavioral, and physiological responses are recorded. Several studies have shown that craving is related to relapse to drug-taking behavior (Back, Brady, Sonne, & Verduin, 2006; Brady et al., 2006; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Drummond & Glautier, 1994; Killen & Fortmann, 1997; Rohsenow et al., 1994), and conditioned responses to drug cues play a critical role in relapse during abstinence, when craving is likely to be elevated (Childress, McLellan, Ehrman, & O'Brien, 1988; O'Brien, Childress, Ehrman, & Robbins, 1998; Sinha, Fuse, Aubin, & O'Malley, 2000).

While craving and reactivity to cocaine-associated cues is reliable and robust (Coffey et al., 2002; Robbins et al., 1999; Saladin et al., 2006; Sinha et al., 2000), relatively little attention has been given to methamphetamine (METH), a related psychostimulant with high abuse and dependence liability. Emerging evidence suggests that craving to METH cues can be reliably measured in METH-dependent individuals (Bruehl, Lende, Schwartz, Sterk, & Elifson, 2006; Newton et al., 2006; Tolliver et al., 2010) and cue-elicited craving is a strong predictor of subsequent METH use (Hartz, Frederick-Osborne, & Galloway, 2001). Accordingly, cue-elicited METH craving should be viewed as a clinically important phenomenon.

Animal models demonstrate that repeated exposure to drug-associated cues in the absence of drug administration leads to the extinction of conditioned responses (Barr et al., 1983; Neisewander, O'Dell, Tran-Nguyen, Castaneda, & Fuchs, 1996; See, 2002). Early work applying these principles to drug-dependent clinical populations showed promise in reducing reactivity to drug-associated

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cues and improving drug-use related outcomes (e.g. Childress, McLellan, & O'Brien, 1986; O'Brien, Childress, McLellan, & Ehrman, 1990). Nevertheless, the limited number of studies employing such techniques in clinical settings have had mixed results (e.g. Cooney et al., 1997; Drummond & Glautier, 1994; Monti et al., 1993; Rohsenow et al., 2001). Recent studies of experimentally-controlled acquisition, extinction, and renewal of conditioned appetitive responses have elucidated nuances of extinction and renewal, including the importance of context and expectation (Thewissen, Snijders, Havermans, van den Hout, & Jansen, 2006; Van Gucht, Vansteenwegen, Beckers, & Van den Bergh, 2008); however, if and how to integrate these subtleties into treatment-oriented extinction paradigms is not yet clear. A recent review of the use of cue extinction paradigms in drug-dependent clinical populations (Conklin & Tiffany, 2002) discussed the disconnect between the theoretical promise of this type of intervention and the use of extinction training in clinical practice. The authors cited the lack of clear optimal parameters for conducting cue extinction studies as one possible contribution to the inconsistent results. In addition, the time course and parameters influencing extinction may differ across substances, as use patterns tend to vary across classes of drugs of abuse. Thus, further research to characterize drug cue extinction is warranted. The purpose of this study is to explore extinction of craving response to METH-related cues following repeated exposure in METH-dependent individuals.

Methods

Subjects

Men and women aged 18–50 who met DSM-IV criteria for METH dependence within the past six months were eligible to participate. The study was approved by the Institutional Review Board of the Medical University of South Carolina. All participants provided written informed consent after being fully informed of potential risks of participation before any study assessments/procedures were undertaken. Both treatment-seeking and nontreatment-seeking participants were recruited through referrals from local substance abuse treatment clinics or advertisements in the community and were compensated with vouchers for their participation. All subjects were required to maintain abstinence from METH, alcohol, and all other drugs of abuse except nicotine as confirmed by breathalyzer and urine drug screening on the day of test assessments. Exclusion criteria included a history of or current psychotic disorder, bipolar affective disorder, or major depressive disorder requiring antidepressant pharmacotherapy or presenting with significant suicidal risk. Subjects with current severe anxiety disorders including panic disorder, posttraumatic disorder, or generalized anxiety disorder were excluded due to potential interference with the measurement of cue reactivity. Current treatment with benzodiazepines, β-blockers, anti-arrhythmic agents, psychostimulants or any other agents known to interfere with heart rate and skin conductance monitoring was exclusionary. Subjects with significant hematologic, endocrine (including diabetes mellitus), cardiovascular, pulmonary, renal, gastrointestinal, or neurological disease were also excluded.

Study design

All study procedures were conducted at the research clinic of Behavioral Health Services in Pickens, South Carolina, a NIDA Clinical Trials Network site. After giving informed consent, potential participants were screened using the MINI International Neuropsychiatric Interview (Sheehan et al., 2003), a structured interview based on the DSM-IV for assessment of psychiatric and substance use symptoms. Quantitative METH and other substance use data for the past 90 days were assessed using the Time-Line Follow-Back (TLFB), a calendar-based instrument used to assess daily self-reported substance use (Sobell & Sobell, 1992) and breathalyzer and urine drug screening was conducted to assess recent substance use. Once all inclusion/exclusion criteria were satisfied, subjects were eligible to begin cue exposure sessions.

Cue reactivity procedures

Participants were administered three 20-min sequences of multi-modal METH cue exposure over each of two 1-h sessions, resulting in exposure to a total of six cue exposure sequences. Multi-modal METH cues were counterbalanced for order of presentation, and consisted of photographs and video of individuals procuring and using METH and "in vivo" paraphernalia and simulated METH. Baseline craving ratings and physiologic measures were collected 20 min and 5 min prior to initial cue exposure for each session and subsequently during each cue sequence. The intervals between the two cue exposure sessions varied from 1 day to 7 days. Subjects were required to provide a negative urine drug screen prior to each cue exposure session. Self-reported baseline and cue-induced craving were assessed using a modification of the Within-Session Rating Scale (Childress et al., 1986), a visual analog scale (0–10) assessment of subjective desire to use METH. Physiologic data [heart rate (BPM) and skin conductance (micro-Seimans)] were collected using Ag/AgCl electrodes interfaced to a Biopac MP-100 data acquisition system and analyzed using AcKnowledge software (Biopac, Goleta, CA). Two electrodes were placed on the second phalanx of the first and third fingers of the non-dominant hand for the measurement of skin conductance, and additional electrodes were placed on the anterior chest and left abdomen to record heart rate; participants were instructed not to move during recordings to limit movement artifact.

Statistical analysis

Standard descriptive statistics were used to summarize the general demographic and clinical data. Descriptive statistics are denoted as Mean ± Standard Error of the Mean (SEM) for continuous variables and percentages for categorical variables. Demographic and clinical characteristics were tabulated for all subjects and were also compared between individuals who reported METH craving (>0) during the initial baseline assessment and those who did not. The comparisons were done using the Wilcoxon 2-Sample Rank Sum Test Statistic for continuous variables and the Pearson Chi-Square test for categorical characteristics.

In order to establish that the selected cues were effective in eliciting a conditioned craving response, the Wilcoxon Signed Rank test was used to analyze the difference between craving scores at baseline and those reported during the first cue sequence. The first and second session baseline values were also compared to assess whether non-cue-elicited craving was reduced across sessions.

Extinction of craving response was assessed via covariance pattern models, which account for the correlation across repeated measures as well as data that are missing at random. A type III sums of squares *F*-test for the sequence effect was used to determine whether significant decreases in conditioned craving occurred over the course of the six cue sequences. To assess whether baseline craving level impacted extinction, secondary analyses included a between-group comparison between those participants who did and those who did not report craving at baseline (i.e., prior to cue presentations in session 1). These comparisons were made by fitting repeated measures ANOVA with craving Group assignment,