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The influence of monetary punishment on cognitive control in abstinent cocaine-users☆

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ABSTRACT

Background: Dependent drug users show a diminished neural response to punishment, in both limbic and cortical regions, though it remains unclear how such changes influence cognitive processes critical to addiction. To assess this relationship, we examined the influence of monetary punishment on inhibitory control and adaptive post-error behavior in abstinent cocaine dependent (CD) participants.

Methods: 15 abstinent CD and 15 matched control participants performed a Go/No-go response inhibition task, which administered monetary fines for failed response inhibition, during collection of fMRI data.

Results: CD participants showed reduced inhibitory control and significantly less adaptive post-error slowing in response to punishment, when compared to controls. The diminished behavioral punishment sensitivity shown by CD participants was associated with significant hypoactive error-related BOLD responses in the dorsal anterior cingulate cortex (ACC), right insula and right prefrontal regions. Specifically, CD participants' error-related response in these regions was not modulated by the presence of punishment, whereas control participants' response showed a significant BOLD increase during punished errors.

Conclusions: CD participants showed a blunted response to failed control (errors) that was not modulated by punishment. Consistent with previous findings of reduced sensitivity to monetary loss in cocaine users, we further demonstrate that such insensitivity is associated with an inability to increase cognitive control in the face of negative consequences, a core symptom of addiction. The pattern of deficits in the CD group may have implications for interventions that attempt to improve cognitive control in drug dependent groups via positive/negative incentives.

1. Introduction

An abnormally high sensitivity to the rewarding properties of drug taking and cognitive control dysfunction are evident across substance-use dependent (SUD) populations and are predictive of poor treatment outcomes (especially relapse during abstinence; Goldstein and Volkow, 2011; Koob and Volkow, 2010). There is also evidence to suggest that this hypersensitivity extends to non-drug rewards (e.g., money) in drug-dependent populations and drug-naïve children who have familial 'risk' for SUD (Hommer et al., 2011), however, the findings are qualified by the use of paradigms that may be confounded by the requirement for temporal discounting and or risk taking (MacKillop et al., 2011). While contemporary neurobiological models highlight the importance of reward sensitivity and cognitive control in SUD (Jentsch and Taylor, 1999; Naqvi and Bechara, 2009; Paulus, 2007), it is unclear how these two features, abnormal reward sensitivity and cognitive control

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dysfunction, interact. One example of this interaction and the focus of the current study is a diminished ability to exert impulse control, and adapt behavior, in response to negative feedback (punishment).

Previous research examining the processing of non-drug rewards in SUD samples has typically focused on positive (e.g., monetary reward) rather than negative outcomes (e.g., monetary punishment; Bjork et al., 2008b; Buhler et al., 2010; Monterosso et al., 2007; Reuter et al., 2005), revealing significant differences in functional activity within the reward network, when compared to healthy controls. The changes to non-drug reward processing in addiction have been argued to result from the transient increases in dopamine induced by drugs generating overly positive reward prediction errors (Schultz, 2011). In combination with increased reward sensitivity, drug addicted individuals show a reduced sensitivity to punishment in their behavioral performance (Bechara et al., 2002). Functional MRI studies of addicted drug users have also shown a diminished neural response to monetary loss (Beck et al., 2009; Bjork et al., 2008a; Wrase et al., 2007), in both subcortical limbic regions such as the striatum and cortical regions such as the anterior cingulate and insula cortices. These studies have typically not examined the consequences on behavior of this reduced response to loss.

Cocaine addiction, and addiction more generally, is associated with significant cognitive control dysfunction (Bolla et al., 1999; Garavan and Hester, 2007; Goldstein et al., 2001; Li et al., 2008). Such dysfunction is thought to play a role in addiction because of the critical role cognitive control plays in inhibiting the immediate pursuit of rewarding stimuli and the development of maladaptive patterns of behavior (Kalivas and Volkow, 2005). For example, drug addicted individuals will consistently choose smaller immediate rewards in preference to larger, but more delayed, rewards (irrespective of whether the reward is hypothetical or real; Kirby and Petry, 2004; Petry, 2001). Given that increased sensitivity to reward and a blunted sensitivity to punishment appear to reduce drug users' control over rewarding stimuli, it is of interest whether this group shows the same punishment-related improvement in cognitive control observed in healthy controls (Simoes-Franklin et al., 2010). The use of punishment to shape appropriate behavior is also a key element of clinical (and criminal law) interventions for drug addiction, and its reduced effectiveness with drug abusers has widespread ramifications.

Drug addicted participants have also been shown to have diminished feedback-related activity during cognitive errors, principally in the anterior cingulate and insula cortices (Franken et al., 2007; Hester et al., 2009b; London et al., 2005). Error-related activity in these regions is known to be critical to post-error processes such as conscious error detection and post-error adaptation of performance (Hester et al., 2009a; Kerns et al., 2004), with the diminished error-related activity in addiction linked to poor error awareness (Hester et al., 2009b; Moeller et al., 2010). Previous studies have not manipulated punishment to examine how this influences the level of error-related hypoactivity, or the potential consequence of diminished responsivity to punishment on adaptation of performance

The aim of the current study was to examine how these two features – abnormal punishment sensitivity and cognitive control dysfunction, interact via the administration of Go/No-go response inhibition task that indexes the ability to exert impulse control, and adapt behavior, in response to negative feedback (punishment). Response inhibition performance was assessed during differing levels of monetary feedback (neutral and punishment) for inhibition failures, and the association of this response to subsequent behavioral adaptations and cognitive control performance. We hypothesized that CD participants would show significantly poorer inhibitory control performance when compared to control participants, particularly under conditions of monetary punishment (relative to neutral). And, further, that the poorer performance under punishment conditions would be associated with a hypoactive error-related response in CD participants, particularly in regions critical to post-error adaptive behavior such as the dACC. The rationale for recruiting abstinent cocaine users was to assess neurocognition in this domain without the acute influence of recent cocaine use.

2. Methods and materials

2.1. Subjects

Fifteen abstinent cocaine dependent (CD) participants (2 female, mean age = 38.2, range = 24–51) were recruited from in-patient and outpatient addiction treatment centers located in New York State. 15 matched control participants (2 female, mean age 42.7, range: 23–55) were recruited from the Volunteer Recruitment Pool at Nathan S. Kline Institute for Psychiatric Research. Groups were also matched for educational attainment (Cocaine: 13.1 years, Control: 13.0) and Wide Ranging Achievement Test (WRAT) estimated IQ (CD: 98.9, Control: 102.8). All 15 patients received a primary Axis I diagnosis of Cocaine Dependence and from the onset of treatment were closely monitored for continued abstinence with random urine toxicology testing for multiple substances at least two times a week for at least the 4 weeks prior to participating in the study. Patients would also meet at least once a week with a personal counselor who was accredited through the state of New York as an alcoholism and substance abuse counselor. The duration of abstinence, as assessed through negative biweekly random urine screens for the durations noted, was confirmed with the counselors at the addiction treatment centers. Exclusion criteria are provided in the supplementary materials.[1]

The average time since last use of cocaine was self-reported at 335 days (range 30–1825 days), and participants reported using cocaine for an average of 5.12 years (range = 1–16 years). The duration of lifetime use and self-reported abstinence duration were not significantly related ($r = -.19$, $p = .53$). The duration of cocaine use and period of abstinence were not significantly related to the other demographic variables (i.e., age, education, WRAT IQ).

2.2. Inhibition punishment task

We examined response inhibition performance (see Fig. 1; Simoes-Franklin et al., 2010), via a motor Go/No-go response inhibition task that alternates between neutral and punishment conditions. The Punishment Go/No-go (PGNG) task presents a serial stream of cycling shapes (square, circle, triangle), each presented for 900 ms followed by a 100 ms inter-stimulus interval. Participants were trained to respond to each of the stimuli with a single 'Go trial' button press, and withhold this response whenever a shape repeated on consecutive trials. The task alternated between neutral and punishment conditions every 30 trials. In the neutral condition the symbols were presented in white and participants were instructed to perform the task as accurately as possible. In the punishment condition stimuli were presented in red and participants were instructed that they would lose 15c (from an initial amount of $20) for each commission error during a No-go trial. Four blocks of 360 trials, divided into 12 alternating runs of neutral and punishment conditions (30 trials per run), were administered to participants. The blocks included 144 No-go trials (72 per condition).

2.3. Data analysis

The fMRI data acquisition and pre-processing analysis is detailed in the supplementary materials.[2] A mixed regression group fMRI analysis was employed comprising five regressors. A square-wave regressor, convolved with a standard hemodynamic response function, coded for the neutral-punishment pattern in a block design manner, using the Neutral condition as a baseline and the punishment condition as the On period (block regressor). Group activation maps for event-type (stops, errors) and the punishment block were determined with one-sample t-tests against the null hypothesis of zero event-related activation changes (i.e., no change relative to baseline). Significant voxels passed a voxelwise statistical threshold ($t = 4.31$, $p \leq .001$) and were required to be part of a larger 142 μl cluster of contiguous significant voxels.

The primary comparison of interest was group differences in activation between the punishment and neutral conditions, for both stops and errors. For instance, the activation clusters from the whole-brain analyses of stops from each group and each condition were used to create a map for the purposes of a functionally defined ROI analysis. This map includes the voxels of activation indicated as significant in any

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