Drug and Alcohol Dependence 168 (2016) 52–60

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

A preliminary study of longitudinal neuroadaptation associated with recovery from addiction

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ARTICLE INFO

Article history:
Received 25 March 2016
Received in revised form 24 July 2016
Accepted 15 August 2016
Available online 9 September 2016

Keywords:
fMRI
Treatment outcome
Decision-making
Balloon analogue risk task
Anterior cingulate cortex
Ventromedial prefrontal cortex
Monetary reward

ABSTRACT

Background: Few studies have explored longitudinal change in event-related brain responses during early recovery from addiction. Moreover, existing findings yield evidence of both increased and decreased signaling within reward and control centers over time. The current study explored reward- and control-related signals in a risky decision-making task and specifically investigated parametric modulations of the BOLD signal, rather than signal magnitude alone. It was hypothesized that risk-related signals during decision-making and outcome evaluation would reflect recovery and that change in specific signals would correspond with improved treatment outcomes.
Methods: Twenty-one substance dependent individuals were recruited upon enrollment in community-based substance use treatment programs, wherein they received treatment-as-usual. Participants completed functional neuroimaging assessments at baseline and 3-month follow-up while performing the Balloon Analogue Risk Task (BART). Risk- and reward-sensitive signals were identified using parametric modulators. Substance use was tracked throughout the 3-month study interval using the timeline follow-back procedure.
Results: Longitudinal contrasts of parametric modulators suggested improved formation of risk-informed outcome expectations at follow-up. Specifically, a greater response to high risk (low-likelihood) positive feedback was identified in caudal anterior cingulate cortex (ACC) and a greater response to low risk (low-likelihood) negative feedback was identified in caudal ACC and inferior frontal gyrus. In addition, attenuation of a ventromedial prefrontal cortex (vmPFC) "reward-seeking" signal (i.e., increasing response with greater reward) during risky decisions at follow-up was associated with less substance use during the study interval.
Conclusions: Changes in risk- and reward-related signaling in ACC/vmPFC appear to reflect recovery and may support sobriety.

1. Introduction

Changes within primary reward circuitry and prefrontal control networks underlie the neurobiological instantiation of substance use disorders (SUDs), resulting in a disturbance of salience attribution and response inhibition that drives compulsive use (Goldstein and Volkow, 2002, 2011). Interventions for SUDs should restore functioning within these neural systems, but few studies explore longitudinal neuroadaptation during early recovery.

In a recent meta-analysis, both pharmacologic and cognitive-behavioral interventions affected the ventral striatum, orbitofrontal cortex, and inferior frontal gyrus (IFG) – regions associated with reward-learning, reward-seeking, and response inhibition, respectively (Konova et al., 2013). Cognitive-behavioral interventions also recruited control-related brain areas (e.g., anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and middle frontal gyrus) – suggesting an added benefit of these approaches. Konova et al. primarily considered acute treatment effects and were unable to target neuroadaptive change over the longer term because few longitudinal neuroimaging studies have been conducted.

A few studies have explored longitudinal change in brain function during recovery from SUDs. DeVito et al. (2012) studied a mixed sample of substance dependent individuals

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http://dx.doi.org/10.1016/j.drugalcdep.2016.08.626
0376-8716/

(SDIs) receiving treatment-as-usual (with or without adjunctive cognitive-behavioral therapy) and found improved Stroop performance and reduced control-related activation in regions including ACC, IFG, and midbrain following 8 weeks of treatment – consistent with enhanced processing efficiency in these regions. Increased activation has also been reported following treatment for cocaine dependence in midbrain and thalamus – both in response to neutral and drug Stroop stimuli (Moeller et al., 2012) and during reward anticipation in a monetary incentive delay task (Balodis et al., 2016). Moeller et al. also identified a trend toward increased ACC activation to drug words, specifically. Taken together, these results suggest restoration of dopaminergic neurotransmission within the midbrain and improved recruitment and/or efficiency of dopaminergically-innervated regions associated with cognitive control and motivational salience.

Moeller et al. (2012) also report a relationship between increased midbrain activity at follow-up, reduced drug-seeking in a simulated cocaine choice paradigm, and fewer days of use during recovery – while increased dorsolateral prefrontal cortex activity was associated with less spending on cocaine during treatment. Balodis et al. (2016) also found that an increased midbrain response at follow-up was associated with reduced use, while a greater ventral striatum response during loss anticipation was associated with fewer negative urine drug screens. Correlations with treatment outcome were also explored by DeVito et al. (2012) but no significant effects were identified.

Despite the apparent importance of decision-making in substance use recovery (Larimer et al., 1999; Redish et al., 2008; Reske and Paulus, 2008), no previous work has addressed change in reward- and control-related signaling in this context. The current study specifically targeted recovery-related change in neural activation during risky decision-making in a mixed sample of SDIs during the three months following treatment engagement. Specifically, the Balloon Analogue Risk Task (BART) was selected due to its good test-retest reliability (Weafer et al., 2013; White et al., 2008), external validity with respect to real-life risky behavior (including substance use; Bogg et al., 2012; Fernie et al., 2010; Lejuez et al., 2002), and existing framework for disentangling reward-seeking, loss aversion, and infrequency effects, previously developed by our lab (please see Fukunaga et al., 2012; for details).

Our previous work identified BART-related activation in mPFC/ACC that was associated with uncontrolled substance use and substance abuse risk factors in alcohol-using undergraduates (Bogg et al., 2012). Specifically, high-risk substance use was associated with reduced mPFC/ACC signal in relation to increasingly risky decision-making and increased mPFC/ACC signal in relation to unexpected, high-risk reward. This is consistent with the notion that control-related mPFC/ACC activity biases decisions away from riskier options (Fukunaga et al., 2013, 2012; Krawitz et al., 2010) and signals predictions errors based on risk appraisal (Alexander and Brown, 2011).

We specifically hypothesized that individuals with improved recovery outcomes would exhibit remediation of these event-related signals over time (i.e., increased mPFC/ACC activity during risky decision-making and reduced signal to high-risk reward). Further, unlike previous longitudinal imaging studies of recovery, the current study investigated parametric modulations of the BOLD response that reflect dynamic sensitivity to task context (specifically, trial-to-trial variation in risk and reward). Such signals provide unique insight into the neural representation of relapse-relevant constructs (e.g., reward sensitivity, loss aversion) and may be robust to changes in processing efficiency that complicate interpretation of findings from main effect contrasts.

2. Methods

2.1. Participants and design

Twenty-six SDIs were enrolled upon treatment engagement at one of two community-based clinics; 21 completed baseline and follow-up assessments and are included in the current sample (6 female; see Table 1 for demographic and recruitment data). Participants were (1) diagnosed with alcohol, drug, or polysubstance dependence using DSM-IV criteria, (2) 18–50 years of age, (3) 1–4 weeks abstinent at time of baseline assessment, and (4) actively participating in substance use treatment. Individuals receiving replacement pharmacotherapy and those reporting contraindications to magnetic resonance imaging or a history of traumatic brain injury, other neurocognitive disorders, Bipolar disorder, or psychotic illness were excluded.

Participants received treatment-as-usual in an intensive outpatient or residential treatment program. Both programs were abstinence-oriented and utilized a twelve-step facilitation approach, as well as routine urinalysis (see Supplementary materials for additional details). Participants completed a baseline assessment and follow-up fMRI assessment at 3-months. The timeline follow-back procedure (Sobell et al., 1988) was conducted at monthly intervals to track drug and alcohol use during the 3-month period and additional narrative details (e.g., subjective intoxication) were also collected (see Supplementary materials for additional information). A breathalyzer test (AlcoSensor IV, Intoximeters, Inc., St. Louis, MO) and 6-panel urine drug screen (Alere Toxicology, Portsmouth, VA) were conducted prior to baseline and 3-month assessments. Participants who resumed use during the study were required to maintain abstinence for 48 hours prior to testing and were evaluated for signs of intoxication. Study assessments were not conducted if urinalysis results were positive for recent substance use or blood alcohol content was greater than 0.000 percent by volume. Two participants screened positive for use at 3-month follow-up; both were rescheduled and completed this assessment after providing negative urine specimen and breathalyzer results.

Lifetime problems with alcohol and other substances were assessed at baseline using the Semi-structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994). Data from the timeline follow-back were used to compute a substance use metric (SUM),[1] summarizing days of use (with and without intoxication) for each participant; values were arcsine-transformed to better approximate the normal distribution. Additional self-report (including measures of social investment, craving, anxiety, depression, and coping) and cognitive-behavioral (i.e., Go/No-Go, Delay Discounting, and Brown-Peterson tasks) measures of recovery are described in Supplementary materials and Supplementary Table 1.

2.2. fMRI procedure

Imaging datasets were acquired at baseline and 3-month follow-up using a Siemens Magnetom Trio 3-T MRI scanner and 32-channel head coil. We used a version of the BART (see Fig. 1), previously validated in neuroimaging studies of healthy individuals (Fukunaga et al., 2012), substance users (Bogg et al., 2012), and at-risk youth (Hulvershorn et al., 2015), developed from the original implemen-

[1] A substance use metric (SUM) was computed to differentially weight excessive or uncontrolled use resulting in intoxication (e.g., relapse) versus less serious use without intoxication (e.g., slip) using the following formula: [Days Alcohol Used without Intoxication + 2*(Days Alcohol Used with Intoxication) + Days Drugs Used without Intoxication + 2*(Days Drugs Used with Intoxication)]/4*Total Days (See Supplementary materials for additional information.)