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Temporal profile of fronto-striatal-limbic activity during implicit decisions in drug dependence

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ABSTRACT

Background: Substance dependence is associated with impaired decision-making and altered fronto-striatal-limbic activity. Both greater and lesser brain activity have been reported in drug users compared to controls during decision-making. Inconsistent results might be explained by group differences in the temporal profile of the functional magnetic resonance imaging (fMRI) response. While most previous studies model a canonical hemodynamic response, a finite impulse response (FIR) model measures fMRI signal at discrete time points without assuming a temporal profile. We compared brain activity during decision-making and feedback in substance users and controls using two models: a canonical hemodynamic response function (HRF) and a FIR model.

Methods: 37 substance-dependent individuals (SDI) and 43 controls performed event-related decision-making during fMRI scanning. Brain activity was compared across group using canonical HRF and FIR models.

Results: Compared to controls, SDI were impaired at decision-making. The canonical HRF model showed that SDI had significantly greater fronto-striatal-limbic activity during decisions and less activity during feedback than controls. The FIR model confirmed greater activity in SDI during decisions. However, lower activity in SDI during feedback corresponded to a lower post-stimulus undershoot of the hemodynamic response.

Conclusions: Greater activity in fronto-striatal-limbic pathways in SDI compared to controls is consistent with prior work, further supporting the hypothesis that abnormalities in these circuits underlie impaired decision-making. We demonstrate for the first time using FIR analysis that lower activity during feedback may simply reflect the tail end of the hemodynamic response to decision, the post-stimulus undershoot, rather than an actual difference in feedback response.

1. Introduction

Substance dependent individuals (SDI) display deficits in decision-making. One of the most consistently observed effects is poor performance relative to healthy controls on the Iowa Gambling Task (IGT; Bechara et al., 2001; Grant et al., 2000; Verdejo-Garcia et al., 2006) which was developed to measure decision-making under conditions of uncertainty (Bechara et al., 1994). Drug users preferentially choose options yielding immediate large rewards despite long-term losses over options yielding immediate small rewards that result in long-term gains. In a modified version of the IGT designed to remove potential confounds of search strategy, Thompson et al. (2012) found deficits in avoidance learning in SDI; patients did not learn to avoid losing decks in order to minimize losses. Such results may be clinically relevant because deficits in learning to avoid bad choices may lead to long-term negative outcomes and increase relapse risk.

Poor performance of SDI on the IGT is associated with altered activity in the orbital-frontal cortex (OFC), striatum, and anterior cingulate cortex (ACC), areas important for processing habit learning, reward, and emotional stimuli (Tanabe et al., 2013; Verdejo-Garcia et al., 2006; Wesley et al., 2011). Positron emission tomography (PET) studies have shown that, compared to controls, SDI have greater OFC activity during decision-making (Bolla et al., 2003; Ersche et al., 2005). Given the importance of OFC in

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reward processing and adaptive learning (Schoenbaum et al., 2009; Tsuchida et al., 2010), the PET studies suggest that portions of the neural systems underlying these processes are altered in SDI.

A drawback of PET imaging is the relatively low temporal resolution as compared to fMRI. It is not possible to separately measure brain activity during the early compared with late phases of decision-making. In contrast, event-related fMRI can model brain activity during different phases of the decision-making process. By inserting a delay between the decision and outcome, investigators have separated neural activity during these phases of the decision-making process (Hyatt et al., 2012; Jia et al., 2011; Nestor et al., 2010; Wesley et al., 2011). One study showed greater striatal activity in drug users compared to controls during the early phase of decision-making, suggesting that drug users had a heightened sensitivity to reward anticipation (Nestor et al., 2010). Others found no group differences in striatal activity during the early phase of decision-making (Bjork et al., 2008; Jia et al., 2011). Results have also been inconsistent for the feedback phase. Compared to controls, drug users showed less activity in striatal-limbic regions during feedback (Hyatt et al., 2012; Nestor et al., 2010; Wesley et al., 2011), suggesting that drug users have *less* sensitivity to reward outcomes. In contrast, other studies report greater striatal and insula activity in drug (Jia et al., 2011) and alcohol (Bjork et al., 2008) users compared to controls during outcomes, suggesting the opposite possibility, namely that drug users have *greater* sensitivity to reward outcomes. Clearly, there is a need to reconcile these differences in direction of activity across groups.

One possible source of this inconsistency may be differences in the temporal profile of the fMRI signal between the groups. fMRI models deconvolve the blood-oxygen-level-dependent (BOLD) signal associated with different phases of decision-making. Generally this is accomplished by temporal jitter, in which varying time delays are imposed between the different phases. While jitter improves the ability to resolve the brain response during different phases of the decision-making process, there are some tradeoffs. First, jittering lengthens scan time, which can necessitate reducing the number of trials leading to a decrease in power. Second, since feedback must follow decision there is always an effective correlation between them. Third and perhaps most important, the time allotted to make a decision influences task performance (Cella et al., 2007). For the IGT, longer decision times introduce a bias toward deliberative and explicit cognitive processing when, in fact, implicit emotion-based processes are thought to underlie the sensitivity of the task.

To determine if the temporal profile of neural activity during implicit decision-making differs between SDI and controls, we had both groups perform a modified IGT in the magnet and analyzed the data using a canonical hemodynamic response function (HRF) and a finite impulse response (FIR) model. A FIR model has been used to characterize the onset and shape of the fMRI signal and makes minimal assumptions about the hemodynamic response (Lindquist et al., 2009; Pomares et al., 2013; Reynolds et al., 2006). Here, the two complementary models determine not only whether there are differences in the *degree* of neural activity (as provided by the HRF approach) but also whether there are differences in the *temporal profile* of those responses (as provided by the FIR approach). To the best of our knowledge, no study has yet used FIR and HRF models in parallel to examine brain response during implicit decision-making in substance dependence.

2. Methods

2.1. Subjects

Ninety-nine subjects were recruited for this study. Four substance dependent individuals (SDI) and 15 controls were excluded for head motion exceeding 2 mm. Data are reported on 37 SDI (18M/19F) and 43 controls (23M/20F). SDI with DSM-IV stimulant (cocaine and/or amphetamine) dependence were recruited from a residential treatment program at the University of Colorado Denver Addiction Research and Treatment Service. SDI were abstinent an average of 14 months (mean = 14 months, range = 2–65, standard deviation = 14.33). Control subjects were recruited from the community and excluded for abuse or dependence on any substance other than tobacco. Six controls were dependent on tobacco. Exclusions for all subjects included neurological illness, schizophrenia, bipolar disorder or current major depression (within last 2 months), prior significant head trauma, or IQ ≤ 80. All participants provided written informed consent approved by the Colorado Multiple Institutional Review Board.

2.2. Behavioral measures

2.2.1. Screening assessment. Drug dependence was assessed in SDI and controls using the computerized Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM; Cottler et al., 1989). DSM-IV dependence diagnoses were determined for amphetamine, cocaine, marijuana, alcohol, tobacco, hallucinogens, opioids, inhalants, sedatives, club drugs, and phencyclidine. Controls were excluded if they met criteria for dependence on any substance other than tobacco. The Computerized Diagnostic Interview Schedule-Version IV (C-DIS-IV) was given to exclude schizophrenia, bipolar disorder, and current major depression (<2 months). IQ < 80 was exclusionary (Wechsler Abbreviated Scale of Intelligence, 2-subtest version; Psychological Corporation, 1999).

2.2.2. Modified Iowa Gambling Task. Subjects played a modified version of the Iowa Gambling Task during fMRI scanning as described previously (Thompson et al., 2012). Subjects were shown 4 decks of cards and instructed to try to earn as much money as possible. For each trial, the computer selected a deck and subject was asked to "Play" or "Pass" by pressing the appropriate response button. If subject chose "Play" the outcome showed a single positive or negative monetary value, along with the running total. If subject chose "Pass" the running total remained the same. The decks were balanced in their frequency and magnitude of gains and losses. To perform well, subjects had to learn to "play" on the two good decks that resulted in net gain and "pass" on the two bad decks that resulted in net loss over time. Importantly, "Pass" was not the default response if subject failed to respond; rather, a null response was recorded thus enabling us to measure subjects' decisions to deliberately pass on certain decks. To encourage implicit over explicit decision-making (Cella et al., 2007), the subject was given 2 s to make a decision, followed immediately by feedback of 4 s duration. Sixty-five 6-s fixation trials were interspersed throughout the task. Each deck was presented 50 times for a total of 200 trials in pseudorandom order. Total task scan time was 26 min, divided into 2 runs of 13 min each. The task was programmed in E-prime 2.0 (Psychology Software Tools, 2010).

2.3. MRI acquisition

Images were acquired on a 3.0 T scanner (General Electric, Milwaukee, WI) with an 8-channel head coil. Functional images were acquired with gradient-echo T2* blood-oxygenation-level-dependent (BOLD) contrast, with TR 2000 ms, TE 30 ms, field-of-view 220 mm^2, 64 × 64 matrix, 35 slices, 3 mm thick, 1 mm gap. Head motion was minimized using a VacFix head-conforming vacuum cushion (Par Scientific A/S, Odense, Denmark). MR-compatible goggles were used for visual stimuli and responses recorded with a 2 button response device.

2.4. Pre-processing

The first three image volumes from each run were excluded for saturation effects. Data were processed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional data were realigned to the first volume. Data were excluded for head motion exceeding 2 mm. Realigned images were normalized to Montreal Neurological Institute (MNI) space. Data were smoothed with a 6 mm full-width-half-maximum Gaussian kernel. Final smoothness of the data after pre-processing was 8.2 mm × 8.4 mm × 7.9 mm and was used in the Monte Carlo simulations to determine cluster-wise corrected threshold levels.

2.5. fMRI data analysis

2.5.1. Canonical hemodynamic response function (HRF).

2.5.1.1. First level model. fMRI data analysis consisted of filtering low frequency noise, correcting for temporal autocorrelation, and convolving the stimulus function with a canonical HRF. Nine conditions were modeled: decision and outcome for each of the four decks plus fixation. We defined the early phase of the decision as the first 2 s of the task, when the computer selected a card from a specific deck and subject was required to play or pass. Outcome was defined as the 4 s when feedback was given (win, lose, or no change). Two contrast maps were generated for each subject (decision > fixation and outcome > fixation).