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The neurobiology of cognitive control in successful cocaine abstinence

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ABSTRACT

Introduction: Extensive evidence demonstrates that current cocaine abusers show hypoactivity in anterior cingulate and dorsolateral prefrontal cortex and respond poorly relative to drug-naïve controls on tests of executive function. Relatively little is known about the cognitive sequelae of long-term abstinence in cocaine addicts.
Methods: Here, we use a GO–NOGO task in which successful performance necessitated withholding a prepotent response to assay cognitive control in short- and long-term abstinent cocaine users (1–5 weeks and 40–102 weeks, respectively).
Results: We report significantly greater activity in prefrontal, cingulate, cerebellar and inferior frontal gyrii in abstinent cocaine users for both successful response inhibitions and errors of commission. Moreover, this relative hyperactivity was present in both abstinent groups, which, in the presence of comparable behavioral performance, suggests a functional compensation.
Conclusions: Differences between the short- and long-abstinence groups in the patterns of functional recruitment suggest different cognitive control demands at different stages in abstinence. Short-term abstinence showed increased inhibition-related dorsolateral and inferior frontal activity indicative of the need for increased inhibitory control while long-term abstinence showed increased error-related ACC activity indicative of heightened behavioral monitoring. The results suggest that the integrity of prefrontal systems that underlie cognitive control functions may be an important characteristic of successful long-term abstinence.

1. Introduction

Addiction is characterized by an uncontrollable, compulsive drive to obtain and consume an abused drug, despite the profound negative health and social consequences likely to ensue (Everitt et al., 2001; Garavan and Stout, 2005; Goldstein and Volkow, 2002). Substance dependent individuals preferentially select actions that yield short-term gains, though they may lead to long-term losses (Bechara and Damasio, 2002). They are more likely to engage in risky behavior (Lane and Cherek, 2000) and show less consideration of the consequences of their actions (Petry et al., 1998). Arguably, these traits are related to executive dysfunction (Lyvers, 2000) wherein chronic cocaine users show deficits in the brain structures implicated in cognitive control of behavior, in particular, in regions thought to be the seat of higher executive brain functions (Miller and Cohen, 2001). Indeed, chronic cocaine users consistently demonstrate impairments on neuropsychological tests of executive function (Ardila et al., 1991; Di Sclafani et al., 2002; Yücel et al., 2007).

Two important aspects of executive control implicated in addiction are inhibitory control and performance monitoring (Garavan and Hester, 2007). Performance monitoring processes (e.g., error detection and conflict monitoring) have been ascribed to the anterior cingulate cortex (ACC) (Botvinick et al., 1999, 2001; Kiehl et al., 2000; MacDonald et al., 2000; Menon et al., 2001; Ruchsow et al., 2002; Ullsperger and von Cramon, 2001; van Veen and Carter, 2002).

One model of cognitive control asserts that when erroneous or conflicting behavior is detected by the ACC, it signals to lateral prefrontal cortex (PFC) regions responsible for maintaining goal-oriented behavior that greater levels of control are necessary to successfully perform a task (Botvinick et al., 2001 see Silton

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et al., 2010 for an alternative interpretation). Increased top-down control should reduce conflict by biasing the system away from the incorrect, conflict-causing response and towards the correct, conflict-reducing response (Botvinick et al., 2001; Fassbender et al., 2009). With regard to addiction and specifically abstinence, this monitoring process may be important in detecting risky situations or behaviors that increase the likelihood of relapse (Garavan and Stout, 2005).

Previous investigations of inhibitory control in cocaine addicts have shown reduced prefrontal activity relative to controls (Fillmore and Rush, 2002; Goldstein et al., 2001; Kaufman et al., 2003) and there is evidence that cocaine addicts appear to rely more heavily on a suboptimal cerebellar pathway to successfully inhibit a prepotent response (Hester and Garavan, 2004). These findings are consistent with theories implicating cocaine-induced damage to the mesencephalic dopamine (DA) system (Franken et al., 2005; Spanagel and Weiss, 1999). It is thought that blockade of dopamine transporters produces elevated synaptic DA levels, chronic exposure to which may account for both the reduced DA receptors and metabolism seen in users (Koob and Le Moal, 1997; Volkow et al., 1993). Inhibitory control has also been identified as a risk factor for addiction that precedes drug use (Dalley et al., 2007; Tarter et al., 2003; Verdejo-García et al., 2008). Performance and neuroimaging data on Stroop and decision-making tasks have been shown to predict likelihood of completing treatment in substance abusers (Brewer et al., 2008; Paulus et al., 2005; Streeter et al., 2008) as has cognitive functioning (Aharonovich et al., 2006; Turner et al., 2009). As these tasks are known to activate the neuronal circuits underlying cognitive control, this indicates that these circuits may play an important role in abstinence.

Previous studies of abstinent drug users have typically investigated short-term abstinence and have revealed many persistent deficits, which are more pronounced in heavy users, in the regions associated with cognitive control and reward anticipation (Bolla et al., 2004, 2003). Relative to controls, abstinent cocaine abusers have been shown to have reduced metabolism in left ACC and right dorsolateral prefrontal cortex (DLPFC), and greater activation in right ACC. Indeed, activity in some of these regions predicts relapse in both abstinent cocaine and methamphetamine abusers (Kosten et al., 2006; Paulus et al., 2005; Wexler et al., 2001) with individuals showing more ACC activity at the onset of abstinence being less likely to relapse subsequently. It has previously been suggested that the general pattern of prefrontal hypoactivity in drug users may ameliorate with increasing abstinence from drug consumption (Volkow and Fowler, 2000) and indeed abstinence from cocaine use has been shown to reduce high-risk responses on a gambling task (Bartzokis et al., 2000). GO/NOGO tasks in which the GO/NOGO ratio is low thereby creating a prepotent response that is difficult to inhibit on NOGO trials provide a useful assay of cortical activity underlying inhibitory control and action monitoring. Indeed cocaine addicts have shown impaired performance in these tasks (Fillmore and Rush, 2002; Fillmore et al., 2002). We hypothesized that such a task would be useful for evaluating any functional change that may occur in the cortical circuits underlying inhibitory control and action monitoring over abstinence.

Just as not all people with a propensity to develop addiction do so, not all addicts successfully complete treatment. Indeed, treatment programs typically have very high dropout rates (Carroll et al., 1994; Simpson et al., 1999) reflecting the relapsing nature of the disease. This means that very little is known about the neurobiology of successful long-term abstinence as the high attrition and relapse rates of longitudinal studies pose significant impediments to assessing long-term abstinence effects prospectively. Another research approach is to recruit and characterize individuals known to have been abstinent for varying durations. While this approach cannot reveal whether neurobiological differences in abstinent users preceded or arose from that abstinence, it can nonetheless characterize the functioning of those who have demonstrated the ability to abstain for either short or long periods. Here, we investigate what role cognitive control may play in abstinence, both short- and long-term. We hypothesized that any changes that may occur with prolonged abstinence or any pre-existing differences that might facilitate successful abstinence would be reflected in functional brain measurements of cognitive control.

2. Materials and methods

2.1. Participants and task design

Twenty-seven volunteers (21 male; mean age 33.2 years, range: 22–45) participated in this study, which was approved by the Institutional Review Board of the Nathan Kline Institute for Psychiatric Research (NKI). Participants gave informed written consent and were compensated for their participation.

Abstinent cocaine dependent (CD) users were patients in the Daytop Village Inc., a large therapeutic community with multiple treatment sites in the New York City area. Controls were recruited from the community via the NKI volunteer program and had no history of substance abuse disorders. Participants were recruited over the course of 5 months by a psychiatrist (JN) visiting the treatment site to make a presentation about the study. Interested participants were prescreened and signed a consent form to be enrolled in the study. The protocol described here was part of a larger study investigating the effects of abstinence on grey and white matter. All participants were screened with the Structural Clinical Interview for the DSM-IV – TR (SCID) by a psychiatrist (JN) or a SCID-certified research assistant (First et al., 2002). CD participants had no lifetime history of substance dependence (other than cocaine and nicotine) but were eligible for the study if they met criteria for abuse (lifetime or current) of other substances. Participants with any history of neurological disorders, psychiatric illness, head trauma, contra-indications for MRI, or HIV seropositivity were excluded. CD participants were excluded if they did not have continuous treatment or tested positive during the reported abstinence period. Participants early in treatment were monitored on a 24-h basis, were subject to periodic random urine toxicology screens, and were not permitted to leave the facility without an escort. Those later in treatment were allowed leave the facility on their own recognizance but were evaluated by clinical staff (including urine toxicology) upon their return. Subjective data on drug use and abstinence history (including date of last use) were collected from participants and corroborated with records from clinical charts, lab tests and interviews with clinical staff. On the day of scanning, representatives of the Daytop Village transported participants to and from NKI where all behavioral and MRI measurements occurred.

Abstinent CD participants were divided into two groups depending on length of abstinence from their last cocaine consumption. The long-term abstinent (LA) group ($n = 9$) had not consumed cocaine for on average 69 weeks (SD = 17.49, range: 40–102). The short-term abstinent (SA) group ($n = 9$) had refrained from consumption for on average 2.4 weeks (SD = 1.34, range: 1–5.1) prior to scanning. Average length of use prior to abstinence for the LA group was 10.67 years (SD = 7.63, range: 1.5–23) and for the SA group was 12.11 years (SD = 5.01, range: 1–18). This difference was not significant (Welch $t(13.81) = -0.47$, $p > 0.05$). A further group of nine cocaine-naïve participants constituted the control group (see Table 1).

Handedness (Oldfield, 1971) and socio-economic status (Hollingshead, 1975) of participants was assessed and participants were administered the Barratt Impulsivity test (Patton et al., 1995), the Buss Perry aggression test (Buss and Perry, 1992) and the Kreek–McHugh–Schluger–Kellogg (KMSK) scale (Kellogg et al., 2003) to assess drug use history. These assessments were included to characterize the participants and evaluate whether these traits would change with abstinence. Socioeconomic status (which includes educational status) has previously been linked with attrition rates from treatment programs (Alterman et al., 1996) and consumption of drugs of abuse (Miech and Chilcoat, 2007), as has aggression (Brook et al., 1995) and impulsivity (de Wit, 2009; Verdejo-García et al., 2008).

Participants completed a GO/NOGO task based on our earlier work (Garavan et al., 1999) and which has been shown previously to reveal functional hypoactivity in current cocaine users (Kaufman et al., 2003). The letters X and Y were serially presented, alternating at 1 Hz and participants were required to make a button press response to each letter. Responses and reaction times were recorded. Participants were instructed to withhold their response on NOGO trials, that is, trials in which the alternating pattern was broken. For example, in the stimulus train X Y X Y Y X, participants were to withhold their response to the fifth letter. The stimuli were presented for 900 ms followed by a 100 ms blank screen. Participants were instructed to respond while the letter was on the screen. Participants completed four runs each containing 315 GO and 20 NOGO stimuli totaling 1260 GO trials and 80 NOGO trials.

2.2. Scanning parameters and data analysis

Functional images were acquired in contiguous 5 mm transverse slices using a blipped gradient-echo echo-planar pulse sequence (TE = 50 ms, TR = 2000 ms,