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Inhibitory behavioral control: A stochastic dynamic causal modeling study comparing cocaine dependent subjects and controls

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ABSTRACT

Cocaine dependence is associated with increased impulsivity in humans. Both cocaine dependence and impulsive behavior are under the regulatory control of cortico-striatal networks. One behavioral laboratory measure of impulsivity is response inhibition (ability to withhold a prepotent response) in which altered patterns of regional brain activation during executive tasks in service of normal performance are frequently found in cocaine dependent (CD) subjects studied with functional magnetic resonance imaging (fMRI). However, little is known about aberrations in specific directional neuronal connectivity in CD subjects. The present study employed fMRI-based dynamic causal modeling (DCM) to study the effective (directional) neuronal connectivity associated with response inhibition in CD subjects, elicited under performance of a Go/NoGo task with two levels of NoGo difficulty (Easy and Hard). The performance on the Go/NoGo task was not significantly different between CD subjects and controls. The DCM analysis revealed that prefrontal–striatal connectivity was modulated (influenced) during the NoGo conditions for both groups. The effective connectivity from left (L) anterior cingulate cortex (ACC) to L caudate was similarly modulated during the Easy NoGo condition for both groups. During the Hard NoGo condition in controls, the effective connectivity from right (R) dorsolateral prefrontal cortex (DLPFC) to L caudate became more positive, and the effective connectivity from R ventrolateral prefrontal cortex (VLPFC) to L caudate became more negative. In CD subjects, the effective connectivity from L ACC to L caudate became more negative during the Hard NoGo conditions. These results indicate that during Hard NoGo trials in CD subjects, the ACC rather than DLPFC or VLPFC influenced caudate during response inhibition.

1. Introduction

Cocaine dependence is associated with increased impulsivity (Chamberlain and Sahakian, 2007; Moeller et al., 2001a) in humans (Colzato et al., 2007; Feil et al., 2010; Fillmore and Rush, 2002; Kaufman et al., 2003; Lane et al., 2007; Li et al., 2006b; Verdejo-Garcia et al., 2007) and animals (Anastasio et al., 2011; Anker et al., 2009; Paine et al., 2003; Paine and Olmstead, 2004; Winstanley et al., 2010). Impulsivity may serve as a premorbid trait that confers vulnerability to cocaine dependence (Buckholtz et al., 2010; Cunningham and Anastasio, 2014; Verdejo-Garcia et al., 2008; Winstanley et al., 2010). In addition, cocaine dependent (CD) subjects with higher baseline impulsivity predict reduced retention in outpatient treatment trials for cocaine dependence than CD subjects with lower baseline impulsivity (Moeller et al., 2001b). Both cocaine dependence and impulsive behavior are under the regulatory control of cortico-striatal networks (Aron, 2011; Cunningham and Anastasio, 2014; Dalley et al., 2011; Ersche et al., 2011; Fineberg et al., 2010; Ghahremani et al., 2012; Robbins et al., 2012; Volkow et al., 2011; Winstanley, 2007) with the theories of addiction (Bickel et al., 2007)

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positing that impulsivity and maladaptive drug-taking result from insufficient communication between frontocortical behavioral control centers and subcortical (striatal) incentive-motivational circuitry. However, there is no direct evidence for this putative disruption of directional information flow in cortico-striatal networks in humans, either in cocaine use disorder research or impulsivity research.

Response inhibition (ability to withhold a prepotent response) is one main measure of impulsivity (Moeller et al., 2001a). Most neuroimaging analyses of response inhibition have used either a Go/NoGo task or a Stop-Signal task (Colzato et al., 2007; Fillmore et al., 2002; Fillmore and Rush, 2002; Li et al., 2006a; 2006b, 2008a; 2008b). Meta-analyses (e.g., Buchsbaum et al., 2005; Simmonds et al., 2008; Swick et al., 2011) of Go/NoGo neuroimaging studies have shown activation of frontal, subcortical, parietal, and insular regions with right hemispheric dominance during response inhibition under the NoGo condition. It has been hypothesized that the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and pre-supplementary motor area are particularly important for response inhibition during NoGo conditions (Chikazoe, 2010).

The Go/NoGo task has revealed altered patterns of cortical recruitment under acute demands to curtail a prepotent response in subjects with cocaine dependence. For example, Kaufman et al. (2003) conducted a functional magnetic resonance imaging (fMRI) study with a Go/NoGo task and found poorer behavioral performance and lower activation in the cingulate, pre-supplementary motor cortex, and insula during response inhibition in active cocaine users compared to cocaine-naive controls. In another fMRI study using a Go/NoGo task, Connolly et al. (2012) found that although there was no group difference in behavioral performance, cocaine users with short-term abstinence had greater inhibition-elicited activation than controls in the right middle frontal gyrus (MFG), right precentral gyrus, right superior frontal gyrus, and right middle temporal region. In addition, cocaine users with long-term abstinence had greater activation than controls in the right inferior frontal gyrus (IFG), right MFG, right precentral gyrus, left superior temporal gyrus, and cerebellar tonsils.

These studies collectively suggest an altered neural network underlying response inhibition in cocaine dependence. However, traditional regional activation fMRI studies have been unable to answer questions about effective neuronal connectivity and directional relationships among functionally-related brain regions, i.e., whether a particular neuronal region ("Region 1") directionally influences another region ("Region 2"), whether Region 2 directionally influences Region 1, or whether the regions reciprocally influence each other. In the present study, we addressed this limitation. We employed dynamic causal modeling (DCM) (Friston et al., 2003; Li et al., 2011) to test whether CD subjects have altered directional neuronal connectivity underlying their inhibitory behavioral control. We measured response inhibition using the Go/NoGo task (Lane et al., 2007), in which the subject was instructed to respond (Go) when a target stimulus was presented and to withhold responding (NoGo) when a non-target stimulus was presented. Unique from other analytic techniques, effective (directional) connectivity in DCM is modeled at the neuronal level rather than the observed blood oxygen level dependent (BOLD) signal level (Friston et al., 2003). This is important for fMRI studies of individuals with substance use disorders because it is known that the BOLD signal could be confounded by disruption from disease (i.e., Alzheimer's) or drug effects on neurovascular coupling and/or hemodynamic responses (Iannetti and Wise, 2007). In addition, DCM can measure effective connectivity specific to certain experimental conditions. This is attractive because sometimes disease-related impaired cognitive functions can only be observed during special experimental conditions. For example, Lane et al. (2007) used a Go/NoGo task with two-level NoGo difficulty (Easy and Hard, in terms of similarity between targets and non-targets), and found that CD subjects showed poorer behavioral performance than controls only during Hard NoGo trials rather than Easy NoGo trials. The DCM analysis in this study was conducted on fMRI data acquired from 13 CD subjects and 10 normal healthy cocaine naive controls while they performed a Go/NoGo task as used in Lane et al. (2007). Based on the hypothesis that cocaine use disorder and inhibitory behavior are regulated through top-down control of the prefrontal cortex reflective system over an amygdala–striatum impulsive system (Aron, 2011; Bechara, 2005; Cunningham and Anastasio, 2014; Dalley et al., 2011; Ersche et al., 2011; Fineberg et al., 2010; Ghahremani et al., 2012; Heatherton and Wagner, 2011; Noël et al., 2013; Robbins et al., 2012; Volkow et al., 2011; Winstanley, 2007), we hypothesized that the effective connectivity from prefrontal regions to sub-cortical regions would be altered in CD subjects compared to controls during successful response inhibition.

2. Methods

2.1. Subjects

The study was officially approved by the Committee for the Protection of Human Subjects (CPHS) in University of Texas Health Science Center, Houston, TX and University of Texas Medical Branch, Galveston, TX, and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Subjects with cocaine dependence and normal healthy controls were recruited through advertisements. Informed consent was obtained from each subject.

The subjects included in this study were from two separate projects that assessed the acute effects of medication versus placebo on brain activation and brain connectivity. Subjects received placebo or medication prior to the MRI scan. The functional MRI scans analyzed in this study were only on placebo days. Four subjects participated in both projects. Among the 23 subjects included in the final analyses, 15 subjects (five CD subjects and 10 controls) were from the first project, and eight subjects (all CD subjects) were from the second project.

All subjects were screened using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). All subjects underwent physical examination and medical history. The Addiction Severity Index (McLellan et al., 1992) was obtained to document lifetime drug and alcohol use. Female subjects were screened with a urine pregnancy test immediately prior to MRI scanning. Each subject's urine was screened for tetrahydrocannabinol, opiates, cocaine, amphetamines, and benzodiazepines (Syva Company, Deerfield, IL), and each subject was screened for alcohol with an Intoximeter Alco-Sensor III breathalyzer (Intoximeters, Inc., St. Louis, MO) immediately prior to MRI scanning.

Subject inclusion criteria were: (1) 18–55 years old; (2) right-handed; (3) free of alcohol at the time of MRI scanning; (4) CD subjects met Diagnostic and Statistical Manual Fourth Edition (American Psychiatric Association, 2000) criteria for current cocaine dependence as determined by Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), and (5) normal control subjects had no current or lifetime history of any DSM-IV substance use or psychiatric disorder. Exclusion criteria were: (1) CD subjects who met current or past DSM-IV Axis I disorder other than substance abuse or substance dependence; (2) medical disorders or taking medication that may affect the central nervous system; (3) claustrophobia experienced during MRI simulator sessions; (4) any definite or suspected clinically significant abnormalities of the brain on Fluid-Attenuated Inversion Recovery (FLAIR) MRI scans, as read prior to data analysis by a board-certified radiologist; (5) positive urine drug screen for control subjects; and (6) positive pregnancy test result.

In addition to the 10 completed control subjects analyzed in this report, seven other control subjects were excluded for the following reasons: taking medications that may affect the central nervous system (one subject); behavioral performance (percentage of correct responses <50%) (two subjects); and unmatched age (younger than 23 years old) (four subjects). In addition to the 13 completed CD subjects, 13 additional CD subjects were excluded for the following reasons: behavioral