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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

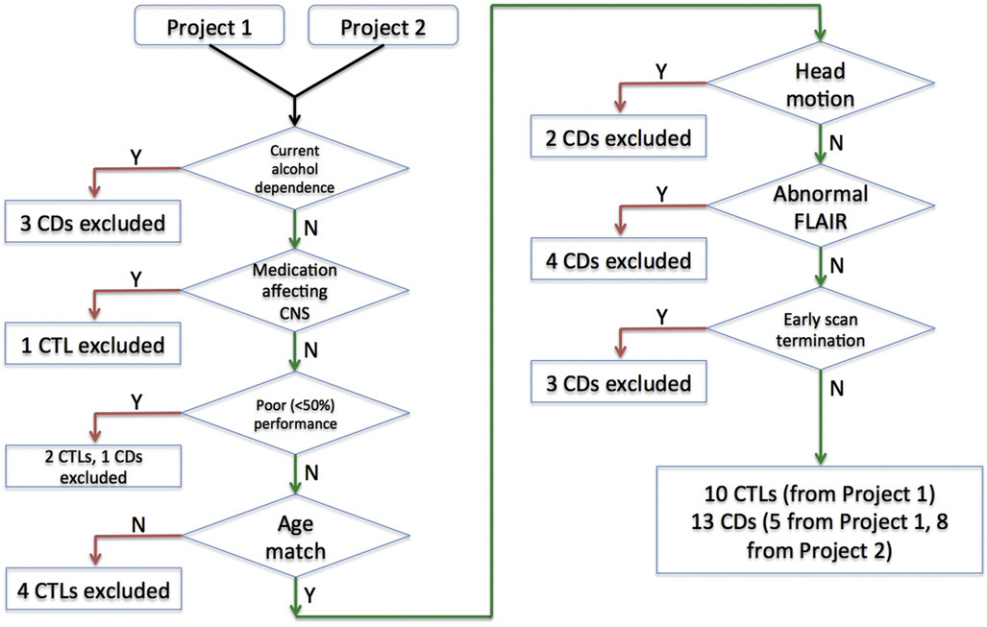

Fig. 1. Flow chart showing subject inclusion/exclusion, and which project (Project 1 and Project 2) the subjects come from. CTL denotes control subject, and CD denotes cocaine dependent subject.

performance (percentage of correct response <50%) (one subject); excessive head motion during the fMRI scan (two subjects); clinically significant abnormal results on FLAIR scan of the brain (four subjects); subject's request to terminate the scanning (three subjects); and current alcohol dependence (three subjects). See Fig. 1 for the flow chart showing subject inclusion/exclusion.

Based on the inclusion and exclusion criteria, 13 CD subjects (CD group) and 10 controls (control group) were included for final analysis. None of the control subjects had a DSM-IV diagnosis of any present or past drug abuse or dependence. All CD subjects had DSM-IV diagnoses of both current and past cocaine dependence. Please see Supplementary materials for additional diagnoses. The CD group was composed of one female and 12 males; their mean age was 37.4 ± 5.3 years (mean ± standard deviation), ranging from 27.5 to 44.1 years. The control group had three females and seven males; the mean age was 35.2 ± 7.3 years, ranging from 23.3 to 43.6 years. The educational duration of CD group was 11.8 ± 2.0 years, ranging from 7 to 15 years; and the educational duration of the control group was 13.8 ± 2.0 years, ranging from 11 to 17 years.

Fisher's exact test revealed that there was no significant difference in proportion of female and male subjects between groups ($p = 0.281$, two tail). There was no significant group difference in age ($t = 0.837$, degree of freedom [df] = 21, $p = 0.412$). The CD group had significantly lower educational durations than the control group ($t = -2.220$, df = 21, $p = 0.038$), with a 2-year difference in means.

2.2. Go/NoGo response inhibition task

A rapid-presentation event-related Go/NoGo task (Lane et al., 2007; Ma et al., 2014b) was used for analyses of response inhibition during fMRI. For all subjects, there were two Go/NoGo fMRI runs. The Go/NoGo task has been described in detail elsewhere (Lane et al., 2007; Ma et al., 2014b). In brief, during each fMRI run, 208 visual stimuli (including Go, Easy NoGo, or Hard NoGo, please see below) were sequentially presented in random order. Each stimulus was displayed for 500 ms. The neighboring stimuli in time were separated by a blank screen lasting 1900 ms, 2100 ms, or 2300 ms (jittered randomly). Each of the stimuli consisted of line segments enclosed within two boxes that were presented simultaneously side by side on the same screen. Each subject was instructed to discriminate the direction of the lines by pressing a button using their right index finger when both boxes showed parallel diagonal lines in the same direction in both boxes (Go trial). Each subject was instructed not to press the button when both boxes showed horizontal lines ("Easy" NoGo trial), or when one box contained diagonal lines that were in the opposite direction of the diagonal lines in the other box ("Hard" NoGo trial). For Go trials, a key press, completed greater than 100 ms and less than 600 ms after the stimulus, was defined as a correct response. For NoGo trials, a key press, completed within 600 ms after the stimulus, was defined as an incorrect response. Each fMRI run duration was 10 min 40 s, including 156 Go trials (75%), 26 Easy NoGo trials (12.5%), and 26 Hard NoGo trials (12.5%). There was no "null" (i.e., resting) trial in this event-related paradigm. Each subject completed a practice Go/NoGo test during a mock fMRI session in order to stabilize performance and provide familiarity with the task prior to actual MRI scanning. The discrimination accuracy measure (d′) (Forman et al., 2004; Gescheider, 1985; Lane et al., 2007) was used to measure behavioral performance on the Go/NoGo task in the scanner.

2.3. fMRI data acquisition

MRI data were acquired on a Philips 3.0 T Intera system (Philips Medical Systems, Best, Netherlands) with an eight-channel receive head coil. Single shot spin-echo echoplanar imaging (EPI) was used for acquiring fMRI data. The spin-echo EPI sequence eliminates signal losses caused by through-slice dephasing in medial orbitofrontal cortex (Kruger et al., 2001) and is sensitive (Norris et al., 2002) to blood oxygen level dependent (BOLD) signal in fMRI. The fMRI acquisition parameters were as follows: SENSE acceleration factor 2.0, repetition time 2500 ms, echo time 75 ms, flip angle 90°, field-of-view 240 × 240 mm, in-plane resolution 3.75 × 3.75 mm, 25 axial slices, slice thickness 3.75 mm, interslice gap 1.25 mm, 256 repetitions per run after 10 dummy acquisitions. A T1-weighted 3-dimensional Spoiled Gradient Recalled (SPGR) anatomical scan (in-plane resolution 0.94 × 0.94 mm, slice thickness 1 mm) was acquired for co-registration with the fMRI images. A Fluid Attenuated Inversion Recovery (FLAIR) scan and T2-weighted spin-echo scan were acquired, and were read by a board-certified radiologist in order to rule-out incidental brain abnormalities. Although two fMRI runs were acquired for each subject, some subjects only had one usable

fMRI run. Thus we decided to use only one fMRI run for each subject in order to avoid potential bias effects. The first run was used if a subject had two usable fMRI runs.

2.4. fMRI preprocessing

During each fMRI run, individual images in which the fMRI signal exceeded plus or minus four standard deviations from the mean for the run were considered to be outliers and were replaced by the mean of the two nearest neighbors using the Analysis of Functional NeuroImages (AFNI) (Cox, 1996) software command "3dDespike" (http://afni.nimh.nih.gov/afni/). All remaining preprocessing used Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab R2007b (Mathworks Inc., Sherborn, MA, USA). Slice-timing correction was conducted first. Then, the fMRI series was realigned to the first image to correct for head motion. Runs with head motion greater than 1 voxel (3.75 mm translation on any axis) or rotation greater than 3.75° were excluded from the analysis. As an optional feature of SPM software, the head motion parameters can be regressed out in the SPM Level 1 general linear model analysis, and if so, the motion parameters can be then be regressed out from the effects of interest when generating the ROI time series for the DCM analysis. However, many studies do not enter head motion parameters as regressors because regressing out task-related head motion may eliminate much of the true signal when the movement parameters are related to the experimental task design (Ashburner and Friston, 2007). For this reason, we do not routinely include head motion parameters as regressors in our fMRI studies that involve activation tasks, including the present study. However, fMRI series with severe head movement were excluded from this study, and motion correction was conducted with the SPM8 realignment module for all included fMRI series. As noted previously, for all subjects, the first run without artifacts and without excessive motion was included in the analysis. The anatomical image was coregistered to the fMRI images and spatially transformed to Montreal Neurological Institute (MNI) standard atlas coordinates using the SPM8 Normalise module with the SPM8 T1 MNI template image. The transformation parameters were applied to the fMRI images. After that, the fMRI images were resliced to 2 mm isotropic resolution and spatially smoothed with a Gaussian filter of 8 mm isotropic full width at half maximum.

2.5. SPM univariate analysis

The univariate statistical analyses of the fMRI data were conducted using SPM8. After specifying the design matrix, the parameters for the effects of different conditions were estimated at the first level for all subjects as an event related design according to the general linear model at each voxel, using stick functions modeling the onsets of correct NoGo trials convolved with the SPM8 canonical hemodynamic response function as a basis function. Standard SPM8 basis functions for temporal and dispersion derivatives were also included in the model. Incorrect trials were entered as a separate covariate of no interest so that the remaining implicit baseline consisted only of the correct Go trials. A 1/128 Hz high-pass temporal filter was applied. One contrast image was constructed for all subjects for each of the following contrasts of parameter estimates: (1) correct Easy NoGo minus correct Go; (2) correct Hard NoGo minus correct Go; and (3) correct Hard NoGo minus correct Easy NoGo. In the remainder of this paper, for brevity the word "correct" will be omitted, but the NoGo and Go conditions will be understood to consist of correct responses only. While incorrect responses merit theoretic and clinical interest, they were too few to allow valid activation analyses.

In order to determine differences in BOLD activation between groups, a SPM8 second level Random Effects (Holmes and Friston, 1998) statistical analysis was conducted voxel-wise throughout the whole brain for each of the contrast images listed in the above paragraph. For each contrast, the SPM8 second-level two-sample t-test with the default non-sphericity correction for unequal variance between groups was used.

According to the practical steps in a typical DCM analysis suggested by Seghier et al. (2010), random effects group analysis can be used to determine the DCM nodes. Consistent with Seghier et al.'s recommendation and previous DCM studies (e.g., Bitan et al., 2005; Deserno et al., 2012; Dima et al., 2009; DiQuattro and Geng, 2011; Wang et al., 2011), we used random effects group analysis to determine the regions that significantly activated across both groups in this study, after excluding the brain regions showing group differences. A separate SPM8 second level (Random Effects) statistical analysis was conducted voxel-wise throughout the whole brain for each of the contrast images listed above. For each contrast, the SPM8 second-level one-sample t-test with the default settings was used to determine BOLD activations significantly different from zero.

For all SPM second level group analyses, statistical significance was defined as family-wise error (FWE) corrected cluster probability (p) less than 0.05 (two tail). Uncorrected cluster p less than 0.05 (two tail) was used as the threshold for the brain activations used for DCM regions of interest selection. The cluster-defining threshold was $t = 2.4$. Approximate anatomical labels for regions of activation were determined using the Anatomical Automatic Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002).

2.6. Stochastic dynamic causal modeling

FMRI based DCM is a biophysical model of the underlying neuronal connectivity and of how the neuronal connectivity generates the observed BOLD signal (Friston et al., 2003). DCM12, as implemented in SPM12b, was used for effective connectivity analysis. DCM has been described elsewhere (Friston et al., 2003; Ma et al., 2012, 2014a; 2014b). In brief, the mathematical model of the underlying neuronal connectivity among an a priori selected set of brain regions (or DCM nodes) is a system of bilinear differential state equations with coefficients specified by three matrices (A matrix, B matrix and C matrix) (Friston et al., 2003). In this model, experimental conditions (e.g., Go, Easy NoGo, or Hard NoGo) can serve as inputs to the model as either driving inputs, or modulatory inputs, or both. The DCM analysis determines which particular nodes in the model exhibit effective (directional) connectivity with other specific nodes in the model, which nodes receive driving inputs from experimental conditions into the model, and which specific connectivities between nodes in the model are modulated during experimental conditions. A node in the model that receives driving inputs, as quantified by the C matrix parameters, is the brain region among the nodes in the model which first experiences a change in neuronal activity associated with experimental conditions. The node that receives the driving input then influences ("drives") the connectivity to other nodes in the model. The endogenous (or fixed) connectivity in DCM is quantified by the A matrix parameters, which measure the effective connectivity strengths (in units of Hz) between nodes, regardless of the moment-to-moment switching on and off of inputs. Experimental conditions can modulate the endogenous connectivity among nodes. These modulation effects are quantified by the B matrix parameters as increased or decreased connectivity strength compared to the endogenous connectivity at different times in the experiment that are related to the timing of changes in the particular experimental conditions. Nonlinear connectivity effects that are gated by other regions in the system can be modeled by another matrix (D matrix) (Stephan et al., 2007). In the present study, the nonlinear option was not applied, and thus the term "modulation effects" in the present paper denotes bilinear modulation effects, where "bilinear" refers to the mathematical form of the equations determining the B matrix parameters. In addition, the stochastic option for DCM was used in which random fluctuations were modeled as inputs to the system as well as the driving inputs due to

experimental conditions (Daunizeau et al., 2009, 2012a, 2012b, 2013; Li et al., 2011). The random fluctuations in physiological noise may contribute to the system connectivity input (Li et al., 2011) due to stochastic fluctuations in neuronal and vascular responses (Kruger and Glover, 2001; Li et al., 2011). Li et al. (2011) have shown that stochastic DCM can improve parameter estimation over deterministic DCM. In addition, Daunizeau et al. (2012) have validated stochastic DCM and shown that stochastic DCM is superior to deterministic DCM in terms of both model structure inference and model parameter inference.

2.6.1. Regions-of-interest

Following the procedures in Ma et al. (2012, 2014a), the regions (nodes) for the DCM analysis in the present study were chosen based on simultaneously meeting the following three criteria: (1) the region must show activation that is at least significant at the uncorrected cluster level in the present univariate SPM second-level analysis; (2) the region must also show activation (NoGo vs. Go or NoGo vs. baseline) in previous fMRI studies using Go/NoGo tasks (e.g., meta studies, Buchsbaum et al., 2005; Simmonds et al., 2008; Swick et al., 2011), and (3) the region must also be regarded to be involved in inhibitory behavior in the previous literature (e.g., Bechara, 2005; Chikazoe, 2010; Heatherton and Wagner, 2011; Volkow et al., 2011). Thus, the following seven nodes were used for the DCM analyses in the present study: (1) left (L) dorsolateral prefrontal cortex (DLPFC); (2) right (R) DLPFC; (3) L anterior cingulate cortex (ACC); (4) R ACC; (5) R ventrolateral prefrontal cortex (VLPFC); (6) L caudate (CAU); and (7) R hippocampus (HIPP). Because of uncertainty about the exact gross anatomical boundaries in humans of the DLPFC (Fuster, 2008), the DLPFC in the present paper was defined by the middle frontal gyrus, which comprises a major portion of the DLPFC in humans (Fuster, 2008). The VLPFC in the present paper was defined by inferior frontal gyrus, on which the major part of the VLPFC of the human brain lies (Petrides, 2005).

2.6.2. Volumes of interest and time series extraction

We followed the method that was described in Ma et al. (2012, 2014a; 2014b) to construct the volumes of interest (VOIs). The atlas-derived binary masks corresponding to the aforementioned seven nodes were obtained from the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) which was implemented in the WFU (Wake Forest University) PickAtlas SPM toolbox (Maldjian et al., 2003; Maldjian et al., 2004). The binary mask of VLPFC was defined as the set-theoretic union of the atlas-based binary masks of inferior frontal gyrus (pars opercularis, pars triangularis, and pars orbitalis). Each VOI was obtained by the set-theoretic intersection of the atlas-based binary masks and the activation clusters (at least significant at uncorrected cluster level) that were determined by the second-level random effects univariate SPM analysis. The standard SPM procedure in which NoGo and Go conditions were explicitly modeled was conducted by using the principal eigenvariate of each VOI as a summary of the functional activity time-series in that VOI (Ma et al., 2014a), and each principal eigenvariate time series was also adjusted for the F-contrast of effects of interest (Stephan et al., 2010). The same VOIs were used for each subject. The number of voxels, volume, and center of mass of the seven VOIs used as nodes for the DCM analysis are shown in Table 1. These VOIs did not overlap with the regions showing significant group difference (See the Results section).

Table 1
Number of voxels, volume, and center of mass of each of the seven VOIs used as nodes in the DCM analysis.

VOI	Number of voxels	Volume (mL)	Center of Mass MNI coordinates [x, y, z] (mm)
L DLPFC	78	0.624	−23, 20, 41
R DLPFC	128	1.024	43, 39, 21
L ACC	21	0.168	−0, 38, 3
R ACC	25	0.200	4, 37, 0
R VLPFC	185	1.480	46, 16, 29
L CAU	53	0.424	−14, −3, 21
R HIPP	253	2.024	24, −18, −21

2.6.3. DCM network discovery

DCM structure inference, as applied to task-fMRI experiments such as this study, searches for a model of the underlying neuronal connectivity among an a priori selected set of brain regions, in which the combined presence of some endogenous connectivities (and/or modulation/driving input effects) and the absence of some other endogenous connectivities (and/or modulation/driving input effects) best explain the observed fMRI data. In this study, DCM structure inference was conducted using DCM Network Discovery (DND) (Friston et al., 2011; Friston and Penny, 2011). The rationale for us to conduct DCM structure inference using DND has been described elsewhere (Ma et al., 2014b).

DND was conducted using the post-hoc optimization (spm_dcm_post_hoc routine) as implemented in the SPM12b software. Before the DND analysis was conducted, an initial single "full" model (Friston et al., 2011) was specified for all subjects. The term "full" is used here in the sense that (1) each of the three experimental conditions (i.e., Go, Easy NoGo, and Hard NoGo conditions) can be a driving input and a modulatory input; (2) each of the putative driving inputs entered all of the seven nodes; (3) each node was putatively interconnected to all other nodes, and (4) each of the modulatory inputs putatively modulated all of the 42 interconnectivities between nodes. Only stimuli corresponding to correct responses were included in the DCM analysis because the incorrect responses were very few and sporadic for all included subjects. The full models were inverted (estimated) for all subjects. For each group, group level post-hoc optimization was conducted by selecting all inverted "full" models (one per subject). The group level optimal sparse model was found at the group level, using Bayesian parameter averaging (BPA), which is integrated in the spm_dcm_post_hoc routine.

2.7. Statistical analyses

Student's t-test and Fisher's exact test were used to assess group differences on continuous and categorical demographic variables, respectively. Linear mixed models analysis, as implemented in IBM SPSS Version 22 (Chicago, IL) for Windows (Microsoft Corp., Redmond, WA), was used to analyze the main effects of the two factors and their interaction effects on the behavioral performance. The between-subjects factor in this analysis was group (CD and control groups), and the within-subjects factor was levels of NoGo difficulty (Easy and Hard). If main effects or interactions were statistically significant, then post-hoc analyses were conducted with the Bonferroni correction for multiple comparisons.

3. Results

3.1. Behavioral results

The mean and standard deviation of the discrimination accuracy measure (d′) and percentage of correct response in each group during Easy NoGo and Hard NoGo are shown in Table 2. The SPSS linear mixed model analysis revealed significant main effects of difficulty level (Hard or Easy NoGo) ($F = 18.810$; $df = 1, 35.13$; $p < 0.001$). The main effects of group ($F = 0.014$; $df = 1,35.13$; $p = 0.905$) and

Table 2
Mean and standard deviation of the behavioral performance (discrimination accuracy d′, and percentage of correct response) in each group during different NoGo trials.

	Correct Easy NoGo		Correct Hard NoGo	
	d′	Percentage	d′	Percentage
CD	3.501 ± 0.767	0.979 ± 0.030	2.275 ± 0.831	0.778 ± 0.149
Control	3.457 ± 0.604	0.992 ± 0.016	2.232 ± 0.835	0.808 ± 0.148

the interaction of group × difficulty ($F = 0.111$; df = 1,35.13; $p = 0.741$) were not statistically significant. Post-hoc comparisons showed that d′ during Easy NoGo was significantly greater than during Hard NoGo for both groups (CDs and controls) ($p < 0.001$), suggesting that the behavioral performance during Hard NoGo trials was less accurate than that during Easy NoGo trials.

3.2. Contrast-elicited brain activation

The SPM8 univariate second level GLM analysis of the fMRI data revealed a statistically significant cluster ($p = 0.038$, two tail, FWE-corrected) showing a group difference in activation (CD group less than control group) for the Easy contrast. This cluster (Fig. 2 and Table 3) was found in portions of R middle frontal gyrus (g), R precentral g, R middle cingulate cortex, R superior frontal g, and R paracentral lobule. No significant cluster was found for the reverse direction of comparison (control group less than CD group) for the Easy contrast. No significant cluster was found for the other contrasts (Hard and Hard-Easy contrasts).

SPM8 second-level random-effects one-sample t-test analysis across both groups combined revealed several clusters for Easy, Hard, and Hard–Easy activations with the cluster level p less than 0.05 (uncorrected, two tail) in portions of frontal, subcortical, and other brain regions. These clusters were used to select regions (or nodes) for DCM analysis. Please see Supplementary materials for the detail of these regions.

3.3. DCM network discovery analysis

Post-hoc optimization found a group-level optimum sparse model structure for each subject group. For the CD group, R HIPP, L ACC, and R VLPFC were reliable (posterior probability > 0.9999) driving input locations for all three driving inputs (Go, Easy NoGo, and Hard NoGo). In addition, L caudate was a reliable driving input location for Easy NoGo and Go inputs. Furthermore, R ACC was a reliable driving input location for the Go input. For the control group, R HIPP, L ACC, L caudate, and R DLPFC were reliable driving input locations for all three driving inputs (Go, Easy NoGo, and Hard NoGo). There was no other driving input locations for the control group. The posterior mean strength of each driving input effect is shown in Supplementary Table 1.

The group level sparse structure regarding the endogenous connectivities is shown in Supplementary Table 2, which also shows the posterior mean strength of each endogenous connectivity. Three connectivities (R DLPFC to R ACC, R ACC to R DLPFC, and R ACC to L DLPFC) among the 42 connectivities were switched off (posterior probability = 0) by the post-hoc optimization for the CD group. Two connectivities (R VLPFC to R ACC, and R ACC to R VLPFC) among the 42 connectivities were switched off (posterior probability = 0) by the post-hoc optimization for the control group.

The group level sparse structure regarding the modulation effects is shown in Supplementary Table 3. The group level optimum sparse structure regarding NoGo modulation effects is shown in Fig. 3, for both CD group (left panel) and control group (right panel). The mean strength of each endogenous connectivity modulated during NoGo conditions is also shown in Fig. 3. For the CD group, only one (L ACC to L caudate) of the 42 connectivity was reliably (posterior probability > 0.9999) modulated during NoGo conditions, and this connectivity was modulated during both Easy (modulation effect = −0.0584 Hz) and Hard (modulation effect = −0.0822 Hz) NoGo conditions. For the control group, three of the 42 connectivity were reliably (posterior probability > 0.9999) modulated during NoGo conditions. One connectivity (L ACC to L caudate) was only modulated during the Easy NoGo condition (modulation effect = −0.0229 Hz). The other two connectivity, i.e., R DLPFC to L caudate, and R VLPFC to L caudate, were only modulated during the Hard NoGo condition, with modulation effect = 0.2016 Hz for the DLPFC–caudate connectivity, and modulation effect = −0.2418 Hz for the VLPFC–caudate connectivity.

A post-hoc analysis (using Student's t-test) was conducted to determine whether the two groups were significantly different in the modulation effects exerted by the NoGo conditions. A t-test was conducted based on the posterior means and posterior standard deviations obtained from the two groups. There was no group difference (uncorrected p = 0.3640, 2-tail) in the modulation effects exerted by the Easy NoGo condition (on the connectivity from L ACC to L caudate). All the modulation effects exerted by the Hard NoGo condition were significantly different between the groups ($p < 0.0008$, Bonferroni corrected). These modulation effects were on the connectivities from L ACC to L caudate (CD group: −0.0822 Hz; control group: 0 Hz), from R DLPFC to L caudate (CD group: 0 Hz; control group: 0.2016 Hz), and from R VLPFC to L caudate (CD group: 0 Hz; control group: −0.2418 Hz).

4. Discussion

The present study provides evidence that cortico-striatal circuits activated in CD subjects during inhibition of a prepotent response are distinct from those employed by normal healthy controls responding under the same task with similar performance. When the task demands were high (Hard NoGo trials), CD subjects demonstrated ACC connectivity to the caudate during successful response inhibition instead of the control subjects' DLPFC or VLPFC connectivity to the caudate which was also during successful response inhibition. These data support the use of DCM to measure effective connectivity specific to certain experimental conditions. In the DCM analysis, a single optimum model

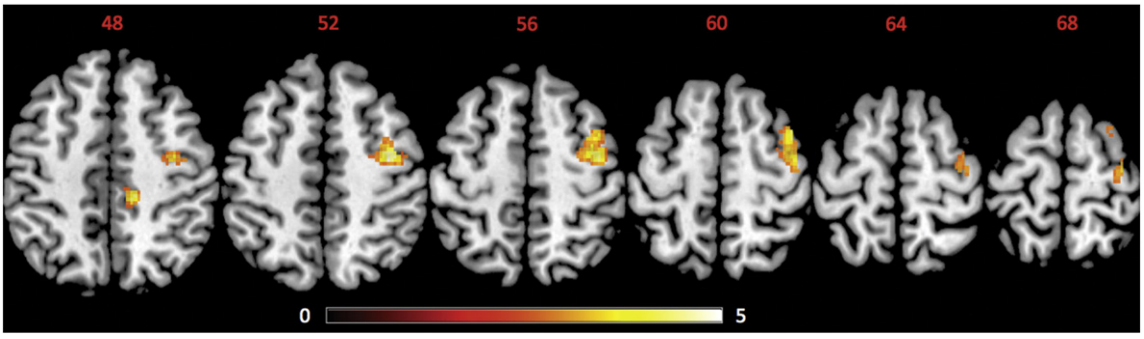

Fig. 2. FWE corrected significant cluster detected by the SPM8 second-level random effects analysis. In the cluster, the control group had significantly greater activation (FWE corrected two-tailed p = 0.038) than the CD group for the E contrast (Easy NoGo BOLD signal minus the Go BOLD signal). The cluster is overlaid in color on axial slices of the MNI brain template image in gray. The number above each slice indicates slice location (mm) of the MNI z coordinate. Scale on color bar represents voxel t values. The reader's left (L) side of each slice is the subjects' left brain hemisphere.

Table 3
The SPM8 second-level random effects two-sample t-test analysis result. The CD group had significantly lower activation than the control group for Easy NoGo contrast. x, y, and z = MNI standard space coordinates (mm). Negative x = Left hemisphere. FWE = family-wise error corrected cluster probability. L = left. R = Right. g = Gyrus. The MNI coordinates and locations are listed for the five largest t values within the significant cluster (with the exception that small regions with number of voxels <10, or regions that were not labeled by AAL, are not shown in the table). The number of voxels in each brain region was determined by counting the number of labeled voxels for each region within the intersection of the significant cluster with the set of labeled voxels in the AAL atlas.

Cluster label	Cluster P [2-tailed FWE-corrected]	Relative maximal voxel t values within the cluster	MNI coordinates [x, y, z] of relative maximal voxel t locations	Number of voxels in brain region	Brain region containing the relative maximal voxel t location
1	0.038	4.72	36, −10, 52	232	R precentral g
		4.46	36, −8, 52	157	R middle frontal g
		4.20	14, −30, 44	90	R middle cingulate cortex
		3.95	36, −6, 58	66	R superior frontal g
		4.14	12, −32, 48	21	R paracentral lobule

with reliable driving input effects and modulatory effects was identified for each group. In the optimum model, endogenous connectivities, modulatory effects, and driving input effects with high posterior probability were retained, and those with low posterior probability were eliminated by the network discovery analysis. A modulation effect measures increased or decreased effective connectivity strength relative to the endogenous connectivity at different times in the experiment that are related to the timing of changes in a particular experimental condition.

Subjects in both groups performed the Go/NoGo tasks similarly well and demonstrated several commonalities during the NoGo conditions. Specifically, only prefrontal–caudate connectivity was modulated during the NoGo condition for both groups. This is consistent with the theories of top-down regulation (Bechara, 2005; Heatherton and Wagner, 2011; Noël et al., 2013; Volkow et al., 2011) and the involvement of the caudate (Aron et al., 2003) in response inhibition. Furthermore, the Easy NoGo condition modulated only L ACC to L caudate effective connectivity. These modulation effects were not significantly different between the two groups and support a previous study that reported similar inhibitory behavioral performance in CD and control groups during the Easy NoGo condition (Lane et al., 2007). Interestingly, control and CD subjects also achieved similar successful response inhibition during the Hard NoGo condition. This is in contrast to the poorer performance by CD subjects during Hard NoGo trials reported previously (Lane et al., 2007).

We have used DCM to demonstrate differential modulation of effective cortico-striatal networks during Hard NoGo condition for CD vs. control subjects. Specifically, performance during the Hard NoGo condition was associated with modulation of the effective connectivity of the R VLPFC to L caudate and R DLPFC to L caudate in control subjects only, and the L ACC to L caudate in CD subjects only. The DCM analyses showed negative modulation of the effective connectivity from R VLPFC to L caudate during the Hard NoGo condition in control subjects. This supports cumulative evidence suggesting that the R VLPFC functions as a "brake" during inhibitory responding (Aron et al., 2014). As previously noted, response inhibition may be driven by reduced striatal activity and subsequent medial globus pallidus disinhibition and thalamocortical suppression via the direct pathway of the basal ganglia (Aron et al., 2003; Beiser et al., 1997). Thus, our results may reflect that normal healthy subjects achieve successful response inhibition during Hard NoGo trials due to effective "brake" mechanisms afforded by the R VLPFC that appear altered in the CD group.

The DCM analyses further showed positive modulation of the effective connectivity from R DLPFC to L caudate during the Hard NoGo condition in control subjects. This result may reflect that healthy subjects achieve executive control through DLPFC activation during the Hard NoGo condition. While the effective connectivity from the R DLPFC to L caudate was modulated during the Hard NoGo condition, this pathway was not modulated during the Easy NoGo condition. This finding is similar to a previous study showing significant DLPFC activation during a complex, but not a simple, NoGo task (Mostofsky et al., 2003). The results are also consistent with a previous study that demonstrated right hemisphere lateralization during executive control in healthy subjects (Tranel et al., 2005). Further, the modulation of two inter-hemisphere

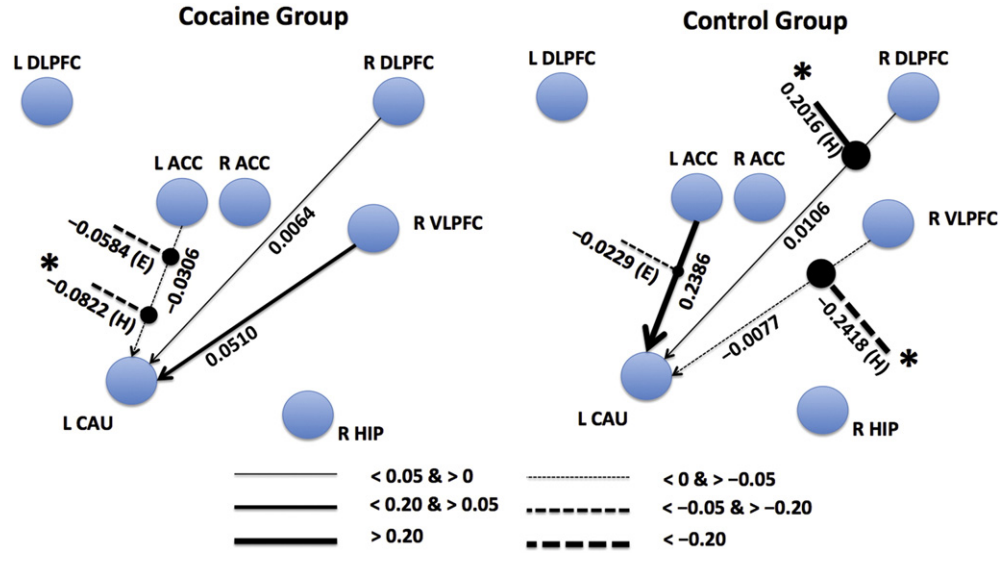

Fig. 3. Schematic diagram representing effective connectivity only modulated by the NoGo conditions. The endogenous connectivities are denoted by line with arrow. The modulation effects are depicted by lines ending with solid dot. The mean strengths (in units of Hz) of the modulation effects exerted by the Easy (E) or Hard (H) NoGo condition are separately shown. For clarity, not all nodes or endogenous connectivities are shown in this figure. The modulation effects showing significant group difference are indicated by asterisks. All the significant group differences in modulation effect occurred during Hard NoGo condition. L = Left. R = right.

prefrontal–striatal connectivities (R DLPFC to L caudate and R VLPFC to L caudate) during the Hard NoGo condition in the control group is consistent with the hypothesis that DLPFC and VLPFC are essential for Go/NoGo response inhibition tasks and that the right PFC dominates the left PFC during response inhibition in healthy subjects (Chikazoe, 2010).

The present study demonstrates the unique finding that the Hard NoGo condition modulates different prefrontal–striatal networks in CD subjects compared to control subjects. Particularly, the effective connectivity from L ACC to L caudate was negatively modulated during the Hard NoGo condition in the CD group but unaffected in the control group. The ACC is a critical region for both behavioral monitoring (Botvinick et al., 1999; MacDonald et al., 2000), an important aspect of executive control (Garavan and Hester, 2007), and emotional response inhibition (Albert et al., 2012). Thus, instead of employing the "brake" functionality of the VLPFC and executive control functionality of the DLPFC as in control subjects, the CD subjects may complete the task through the behavior monitoring functionality of the ACC. Alternatively, the difficulty level of the Hard NoGo trials may arouse frustration and consequently activate emotion-responsive neural nodes (e.g., ACC; Albert et al., 2012) during response inhibition, particularly as observed in the CD subjects. The results also may suggest that CD subjects employ an intact intra-hemisphere connectivity (L ACC to L caudate) to compensate for an altered inter-hemisphere connectivity (R VLPFC to L caudate) to achieve successful response inhibition. While the key connectivity underlying response inhibition in CD subjects (L ACC to L caudate) seems inconsistent with a previous study (Kaufman et al., 2003) that found the ACC to be hypoactive in cocaine users during a Go/NoGo task, it is important to consider that the current study showed no group differences in success during the NoGo condition as opposed to the study that demonstrated ACC hypoactivity concurrent with impairments in behavioral performance in CD subjects (Kaufman et al., 2003). Nonetheless, the present study shows group differences in modulation of prefrontal–striatal effective connectivity during Hard NoGo condition consistent with other studies (e.g., Hanlon et al., 2011; Wilcox et al., 2011; Ma et al., 2014a) and theories (e.g., Volkow et al., 2011) in CD subjects.

The groupwise difference in brain signaling that underlies overtly similar task performance (here discriminability) is in keeping with perhaps a dominant finding in the task fMRI of addiction (Connolly et al., 2012; Ma et al., 2014a; Tomasi et al., 2007; Wilkinson and Halligan, 2004). We contend that these altered brain signatures may be indicative of reduced effective function in real world settings that may be infused with emotional context or may otherwise lack the vigilance-inducing conditions of observed behavior in a novel laboratory setting. The interpretive advantage of normative performance is that differences are not likely due to any differences in experience, perception of task errors, or frustration.

Normal healthy controls exhibited the ability to adapt dynamic neuronal connectivity dependent upon the difficulty level of the response inhibition task, while CD subjects demonstrated the same intra-hemispheric (L ACC to L caudate) connectivity regardless of the difficulty level of the response inhibition task. This pattern of neuronal connectivity could directly result from chronic cocaine use associated with alterations in functional connectivity (Albein-Urios et al., 2013, 2014; Bednarski et al., 2011; Cisler et al., 2013; Gu et al., 2010; Hanlon et al., 2011; Lu et al., 2014; McHugh et al., 2013, 2014; Mitchell et al., 2013; Murnane et al., 2015; Velez-Hernandez et al., 2014; Verdejo-Garcia et al., 2014; Wilcox et al., 2011; Wisner et al., 2013; Worhunsky et al., 2013; Zhang et al., 2014) and dysregulation within key brain regions (e.g., prefrontal cortex) involved in cognitive processing (Fuster, 1997). These alterations may be attributable to a combination of perfusion deficits (Holman et al., 1991, 1993; Levin et al., 1994; Strickland et al., 1993; Volkow et al., 1991), altered gray/white matter structure (Barros-Loscertales et al., 2011; Ma et al., 2009; Moeller et al., 2005), and/or changes in metabolic activity (Volkow et al., 1991). Furthermore, chronic cocaine use is characterized by a multitude of alterations in neurotransmitter function, particularly in the dopamine (DA), serotonin (5-HT), and glutamate systems that may occur consequent to or independent of the aforementioned changes (Cunningham and Anastasio, 2014; Volkow et al., 2011). Monoaminergic DA and 5-HT neurons projecting from the mid-brain regions densely innervate the cortical and subcortical systems (Kosofsky and Molliver, 1987; Vertes and Linley, 2008). Both neurotransmitters interact profoundly at strategically localized receptor proteins (e.g., 5-HT_{2A} receptor (5-HT2AR), 5-HT2CR, DA D_1 and D_2 receptors) within the complex cortico-striatal circuits, including those localized to the microcircuitry of the frontal cortex and dorsal striatum (for review, Howell and Cunningham, 2015). Particularly, the 5-HT2AR and 5-HT2CR abundantly localize to pyramidal and GABAergic neurons within the frontal and cingulate cortex (Cornea-Hebert et al., 1999; Liu et al., 2007; Pompeiano et al., 1994; Santana et al., 2004), dopaminergic and GABAergic neurons of the caudate–putamen (Eberle-Wang et al., 1997; Lopez-Gimenez et al., 1997), and ascending dopaminergic mesolimbic neurons innervating the cortico-striatal networks (Bubar and Cunningham, 2007; Doherty and Pickel, 2000; Nocjar et al., 2002). Serotonin exerts tonic and phasic neuromodulatory control over both DA and glutamate neurotransmission through these receptors in the mesocortical and nigrostriatal pathways (for reviews, Alex and Pehek, 2007; Howell and Cunningham, 2015) that govern cognitive/executive processes and motor/inhibitory response behaviors (Carli and Invernizzi, 2014; Cunningham and Anastasio, 2014). While there is an extensive body of literature supporting the role of these receptors in cocaine-related behavioral alterations (Cunningham and Anastasio, 2014; Bubar and Cunningham, 2008), it is unknown whether the altered top-down control in the CD subjects may be mediated, in part, by compromised 5-HT system interactions with DA and glutamate.

Several limitations of the present study do exist. (1) It is possible that other neural interconnectivities are similarly important for inhibitory control but were not identified because the connecting regions were not included as nodes for the DCM analysis. One reason for the exclusion of potential nodes was the lack of sufficient statistical power on fMRI activation due to the small sample size in this study. Future studies with more subjects will be helpful in providing greater insight into the altered neuronal effective connectivity underlying inhibitory control in CD subjects. (2) All subjects in the present study received a placebo capsule as part of two larger studies in which they were enrolled. Although unlikely, this may have contributed to unknown sources of variability in both the behavioral and fMRI data. (3) While we have shown modulation of effective connectivity during the NoGo conditions, the present study was unable to determine which brain regions mechanistically caused these modulation effects. This question could be answered in future studies through the utilization of non-linear DCM (Stephan et al., 2007). (4) Although the Go/NoGo paradigm has been frequently used to investigate response inhibition mechanisms, regional brain activation elicited by Go/NoGo tasks may not be directly related to response inhibition (Criaud and Boulinguez, 2013). To avoid the emergence of trivial strategies (for example, repeated responses to stimuli resulting in 75% correct performance), we motivated subjects by setting reward-values for NoGo trials three times that of Go trials (either in terms of gain or loss), thereby balancing the relative value of Go and NoGo trials. Therefore, the connectivity observed in the present study may reflect the engagement of other cognitive processes (e.g., attention, reward, and/or motivation) in addition to response inhibition, which could confound our interpretations. (5) The mean education of control subjects was higher (by about 2 years) than that of CD subjects. Although differences in education level could theoretically affect the study, it is unlikely since behavioral performance was the same in both groups. (6) These findings were from a small sample size (23 total subjects). Thus, one should be cautious when generalizing these findings or interpreting effect sizes (Button et al., 2013).

In summary, the control and CD subjects had similar levels of performance on the Go/NoGo task. Given the nodes in our network model, the DCM Network Discovery analysis revealed that prefrontal–striatal

connectivities were modulated during the NoGo conditions for both groups, consistent with the theory that successful inhibition is related to top-down control by a prefrontal, reflective system over a subcortical, impulsive system. While the effective connectivity from L ACC to L caudate was similarly modulated during the Easy NoGo condition for both groups, differences in connectivity were observed during Hard NoGo trials between groups. In the control group, the effective connectivity from R VLPFC to L caudate was negatively modulated while the R DLPFC to L caudate was positively modulated during the Hard NoGo condition; there were no modulation effects on these two connectivities during the Hard NoGo condition in the CD group. In the CD group, the effective connectivity from L ACC to L caudate was negatively modulated during the Hard NoGo condition; there was no modulation effect on this network during the Hard NoGo condition in the control group. These results indicate that CD subjects use different patterns of connectivity to achieve behavioral performance similar to control subjects during Hard NoGo trials.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.03.015.

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