Published in final edited form as:

Psychiatry Res. 2018 January 30; 271: 59–66. doi:10.1016/j.psychres.2017.10.012.

Altered anterior cingulate cortex to hippocampus effective connectivity in response to drug cues in men with cocaine use disorder

Liangsuo Ma^{a,b,*}, Joel L. Steinberg^{a,c}, Kathryn A. Cunningham^d, James M. Bjork^{a,c}, Scott D. Lane^e, Joy M. Schmitz^e, Thomas Burroughs^f, Ponnada A. Narayana^g, Thomas R. Kosten^h, Antoine Becharaⁱ, and F. Gerard Moeller^{a,c,j,k}

^aInstitute for Drug and Alcohol Studies, Virginia Commonwealth University (VCU), Richmond, Virginia, USA

^bDepartment of Radiology, Virginia Commonwealth University (VCU), Richmond, Virginia, USA

^cDepartment of Psychiatry, Virginia Commonwealth University (VCU), Richmond, Virginia, USA

^dCenter for Addiction Research and Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas, USA

^eDepartment of Psychiatry and Behavioral Sciences, University of Texas Health Science Center (UTHSC), Houston, Texas, USA

^fMcGuire VA Medical Center, Richmond, Virginia, USA

^gDepartment of Diagnostic and Interventional Imaging, UTHSC, Houston, Texas, USA

^hDepartment of Psychiatry and Department of Neuroscience, Baylor College of Medicine, Houston, Texas, USA

ⁱBrain and Creativity Institute, and Department of Psychology, University of Southern California, Los Angeles, California, USA

^jDepartment of Pharmacology and Toxicology, VCU, Richmond, Virginia, USA

^kDepartment of Neurology, VCU, Richmond, Virginia, USA

Abstract

Drug-related attentional bias may have significant implications for the treatment of cocaine use disorder (CocUD). However, the neurobiology of attentional bias is not completely understood. This study employed dynamic causal modeling (DCM) to conduct an analysis of effective (directional) connectivity involved in drug-related attentional bias in treatment-seeking CocUD subjects. The DCM analysis was conducted based on functional magnetic resonance imaging

*Correspondence: Liangsuo Ma, Ph.D. Institute for Drug and Alcohol Studies, Department of Radiology, Virginia Commonwealth University, 203 East Cary Street, Suite 202, Richmond, Virginia 23219, USA. Phone: +1 804-828-2871; Fax: +1 804-827-2565; Liangsuo.ma@vcuhealth.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(fMRI) data acquired from fifteen CocUD subjects while performing a cocaine-word Stroop task, during which blocks of Cocaine Words (CW) and Neutral Words (NW) alternated. There was no significant attentional bias at group level. Although no significant brain activation was found, the DCM analysis found that, relative to the NW, the CW caused a significant increase in the strength of the right (R) anterior cingulate cortex (ACC) to R hippocampus effective connectivity. Greater increase of this connectivity was associated with greater CW reaction time (relative to NW reaction time). The increased strength of R ACC to R hippocampus connectivity may reflect ACC activation of hippocampal memories related to drug use, which was triggered by the drug cues. This circuit could be a potential target for therapeutics in CocUD patients. No significant change was found in the other modeled connectivities.

Keywords

Cocaine use disorder; attentional bias; cue reactivity; effective connectivity; dynamic causal modeling

1. INTRODUCTION

Individuals with cocaine use disorder (CocUD) often show drug related attentional bias. This phenomenon refers to exaggerated attention to drug cues, which results in longer reaction times to drug related stimuli than to neutral stimuli (Field and Cox, 2008; Sofuoglu et al., 2013). A related concept is drug cue reactivity, a kind of learned response which is often observed in individuals with substance use disorders and involves significant reactions (physiological and subjective) to drug cues (i.e., drug-related stimuli) (Carter and Tiffany, 1999; Cunningham and Anastasio, 2014). The attentional bias and cue reactivity are commonly tested by comparing the measures obtained during exposure to drug stimuli versus neutral/non-drug-related stimuli in the same sensory domain. While visual stimuli (words and pictures) were mainly used in attentional bias studies (see Hester and Luijten, 2014, for review), stimuli used in cue reactivity studies are relatively versatile (see Jasinska et al., 2014, for review), including visual (words, pictures, and videos), auditory, audiovisual, tactile or haptic, olfactory or gustatory, or combined sensory domains. Surveys of the neuroimaging studies on attentional bias (Hester and Luijten, 2014) and drug cue reactivity (Jasinska et al., 2014) revealed that dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), insula, hippocampus, amygdala, and striatum are common brain regions critical for both drug related attentional bias and drug cue reactivity. However, we are not aware any study which directly compares the neural networks underlying attentional bias and cue reactivity. A cocaine Stroop task (Liu et al., 2011), in which drug-related words are presented intermixed with neutral words, was used in the present study. Because drug Stroop tasks are commonly used to test drug related attentional bias, we focused on attentional bias (rather than drug cue reactivity) in the remaining parts of this paper.

Based on the regional activation studies (e.g., Ersche et al., 2010; Goldstein et al., 2007; 2009a; 2009b; 2010; Hester and Garavan, 2009; Marhe et al., 2013; Smith et al., 2014) which have employed functional magnetic resonance imaging (fMRI) to investigate

attentional bias in CocUD and other substance use disorders, Hester and Luijten (2014) hypothesized that the neural correlates underlying attentional bias result from the abnormal control of prefrontal regions over the emotion/reward regions, such as amygdala, hippocampus, insula, and striatum (Hester and Luijten, 2014). A survey of these imaging studies and behavioral studies investigating attentional bias in CocUD (Leeman et al., 2014) indicates that drug cue reactivity was consistently reported in the behavioral studies, but the findings from the imaging studies are somewhat heterogeneous. Thus, more research is necessary to understand neuronal correlates underlying attentional bias in CocUD.

Cognitive processes depend on interactions among brain regions (Collette and Van der Linden 2002; Fuster 2006; Volkow, et al. 2011). Functional connectivity and effective connectivity analyses are two commonly used brain connectivity methods (Friston, 2011). Functional connectivity refers to correlations among spatially remote neurophysiological events (Friston, 2011), while effective connectivity measures the causal (hence directional) influence of the neuronal activity in one region on a second region (Friston, 2011). To date, one functional connectivity study (Kilts et al., 2014) and one effective connectivity study (Ray et al., 2015) which investigated attentional bias in CocUD subjects have been published. Kilts et al. (2014) found that attentional bias could be related to a functional connectivity network consisting of frontal, occipitotemporal, parietal, cingulate, and premotor cortex. Ray et al. (2015) reported that during exposure to cocaine-related cues, CocUD subjects showed a particular feed-forward effective connectivity pattern (the feed-forward connectivities are the connectivities that do not form a cycle using feedback) among the nodes of a network (amygdala to hippocampus to dorsal striatum to insula to medial frontal cortex, DLPFC, and ACC). This effective connectivity pattern was not observed in control subjects exposed to cocaine-associated cues.

As hypothesized by Hester and Luijten (2014), the abnormal control of prefrontal regions over the emotion/reward regions, could be the neural basis underlying drug related attentional bias. A previous effective connectivity study (Ray et al., 2015) reported significant effects of the emotion/reward regions over the prefrontal regions. However, there is no direct evidence supporting the critical role of the prefrontal regions over the emotion/reward regions during attentional bias. Thus, there is still a gap between theory and human imaging research regarding neuronal circuits underlying attentional bias. The present study aimed to reduce this gap through testing the effects exerted by the prefrontal regions over the emotion/reward regions. Toward that end, dynamic causal modeling (DCM) (Friston et al., 2003; Li et al., 2011) was used to measure the effective connectivity upon exposure to cocaine-related cues in CocUD subjects. Effective connectivity rather than functional connectivity was selected because the direction of connectivity is modeled in effective connectivity, but the direction of connectivity cannot be determined using functional connectivity (Friston, 2011). Thus, effective connectivity analysis can distinguish the effects exerted by the prefrontal regions over the emotion/reward regions versus the effects exerted by the emotion/reward regions over the prefrontal regions. DCM has two major advantages over other effective connectivity analytic techniques. First, disease or drugs could affect neurovascular coupling and/or hemodynamic responses (Iannetti and Wise, 2007). In DCM, the parameter for the ratio of intra- and extravascular signals in the hemodynamic model of DCM is estimated from the observed blood oxygen level dependent signal (Stephan et al.,

2007), thus accounting for the individual difference in neurovascular coupling and/or hemodynamic responses. Second, DCM can measure effective connectivity under specific experimental conditions, rather than for the experiment as a whole. For example, the present study used a cocaine-word Stroop task in which blocks of cocaine words (CW) and neutral words (NW) alternated. DCM can distinguish the effective connectivity occurring upon exposure to CW versus NW, thus allowing measurement of the differential effects exerted by exposure to CW relative to NW on effective connectivity.

Heightened drug cue salience is associated with enhanced attention (Leeman et al., 2014) and with boosted unconscious memory processing of drug cues in CocUD subjects (Ray et al., 2014). The ACC plays an important role in attention (Bush et al. 2000) and contributes to the recall of past memories (Weible, 2013). The hippocampus is necessary in processing contextual cues by which memories may be retrieved (Robbins et al., 2008). Based on these previous studies and evidence showing the involvement of ACC (Goldstein et al., 2009a; Marhe et al., 2013) and hippocampus (Fotros et al., 2013; Ray et al., 2015) in drug related attentional bias, we hypothesized that relative to NW, CW would significantly increase ACC to hippocampus effective connectivity, reflecting recall of past memory about drug use. In addition, we hypothesized that greater increases in connectivity would be associated with greater CW reaction time (relative to NW reaction time).

2. METHODS

2.1 Subjects

The study was officially approved by the local Institutional Review Board, and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from each subject. The CocUD subjects were from a treatment study, in which the majority of the participants were male (Schmitz et al, 2014). All MRI scans took place prior to the initiation of medication treatment. All subjects were screened using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) and 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 (THC), 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) met Diagnostic and Statistical Manual Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) criteria for current cocaine dependence based on the Structured Clinical Interview for DSM-IV (First et al., 1996). Exclusion criteria were: (1) 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 or MRI simulator sessions; (4) any definite or suspected clinically significant abnormalities of the brain on Fluid Attenuated Inversion Recovery (FLAIR) MRI scans; (5) positive pregnancy test result. Based on above

criteria, fifteen CocUD subjects, among the 26 CocUD subjects who were scanned, were included for final analysis. See Table 1 for the demographics and drug-use information of these subjects. This is a free-standing study; all the CocUD subjects (n=26) who were scanned were considered. Eleven CocUD subjects were excluded because of either missing behavioral performance data (n=1); excessive head motion during the fMRI scan (n=2); clinically significant abnormal results on FLAIR scan of the brain (n=4); subject's request to terminate the scanning (n=2); or current alcohol dependence (n=2). The majority of the participants were male. The one female subject who was scanned was excluded because of excessive head motion.

2.2 Cocaine-word Stroop fMRI Task

The subject was presented with ten cocaine words (CW) and ten neutral words (NW), one word at a time. The CW and NW were matched in letter length. Both CW (e.g., “cocaine”, “crack”) and NW (e.g., “kitchen”, “table”) were frequently used words in the English language. Each word when presented was randomly printed in one of three different colors (blue, green, or red). The subject was instructed to ignore the meaning of the word and to press the appropriate button to denote the color in which the word was printed. Each word was shown for a maximum duration of 1800 ms (if no response), but the display of the word was terminated by a response, after which a blank screen was shown for the remainder of the trial up to 1900 ms. The next trial immediately began with the presentation of the next word. Four CW blocks and four NW blocks alternated with a 12 s pause between blocks. Within each block (58 s per block), thirty words were presented. The effect of drug cues on the reaction times (RT) was measured by the mean reaction time during all the CW blocks minus that during all of the NW blocks, i.e., $RT = RT(CW) \text{ minus } RT(NW)$. Only the correct-response trials were included when calculating the mean reaction times. RT was treated as a measure of attentional bias at the behavioral level in the present study.

2.3 fMRI Data Acquisition

MRI data were acquired on a Philips 3.0 T Intera system with an eight channel receive head coil (Philips Medical Systems, Best, Netherlands). Single shot spin echo echoplanar imaging (EPI) was used for acquiring fMRI data. The fMRI acquisition parameters were: SENSE acceleration factor 2.0, repetition time 2500 ms, echo time 75 ms, flip angle 90 degrees, field of view 240 mm × 240 mm, in-plane resolution 3.75 mm × 3.75 mm, 25 axial slices, slice thickness 3.75 mm, interslice gap 1.25 mm, 224 repetitions per run after 10 dummy acquisitions, total duration per run was 10 min 40 s.

2.4 fMRI Preprocessing

During an fMRI run, individual scans in which the fMRI signal exceeded plus or minus four standard deviations from the mean 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 subsequent preprocessing used Statistical Parametric Mapping 12 (SPM12) software (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab R2007b (Mathworks Inc. Sherborn MA, USA). After slice timing correction, 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 degrees were removed from the analysis. The anatomical image was coregistered to the fMRI images and spatially transformed to Montreal Neurological Institute (MNI) standard atlas coordinates using the SPM12 Normalise module with the SPM12 T1 MNI template image. The transformation parameters were applied to the fMRI images, which 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

First level univariate statistical analysis of the fMRI data was conducted using SPM12. CW and NW blocks (conditions) were modeled by boxcar functions convolved with the SPM12 canonical hemodynamic response function. The parameters for each condition were estimated using the General Linear Model (Friston, 1995) at each voxel without global normalization. The fMRI time series was high-pass filtered with an optimized cut-off period of 188 s determined by the Fourier transformation of each condition's time model. Attentional bias activation was defined as the contrast at each voxel of the parameter estimate for CW blocks minus the parameter estimate for NW blocks (CW minus NW contrast). The resulting set of voxel values for this contrast constitutes a statistical parametric map for that contrast. The CW minus NW contrast image (one per subject) was then entered at the SPM12 second level (i.e., random effects) group analysis.

To determine the group level blood-oxygen-level dependent (BOLD) activation, a SPM12 second level Random Effects (Holmes and Friston, 1998) one-sample t-test was conducted voxel-wise throughout the whole brain for the contrast image (CW minus NW). Statistical significance was defined as family-wise error (FWE) corrected cluster probability (p) less than 0.05 (two tail). The brain activations found by this analysis were used for DCM nodes (regions of interest) selection, but the statistical significance was defined as uncorrected cluster p less than 0.05 (two tail). It is commonly accepted to use uncorrected cluster p less than 0.05 (two tail) for determining DCM nodes (Friston et al., 2003). For all SPM12 second level analyses, the cluster-defining threshold was $t = 2.4$. Anatomical labels for regions of activation were determined using the Anatomical Automatic Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002).

2.6 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). DCM with stochastic option, as implemented in SPM12 (Revision 6906), was used for effective connectivity analysis. DCM has been described elsewhere (Friston et al., 2003, Ma et al., 2015a; 2015b). In brief, the mathematical model of the underlying neuronal connectivity among an a priori selected set of brain regions 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, the experimental conditions (i.e., CW and NW) 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 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 (i.e., changed in connectivity strength, in units of Hz) under experimental conditions. A node (driving input location) 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. 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 (CW and NW) 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.

2.6.1 DCM nodes—DCM node selection criteria were: (1) the brain activations found in this study, (2) previous fMRI studies using cocaine stimulus Stroop tasks (e.g., Ersche et al., 2010; Goldstein et al., 2007; 2009a; 2009b; Hester and Garavan, 2009; Fotros et al., 2013; Ray et al., 2015), and (3) theories about attentional bias (e.g., Robbins et al., 2008; Weible, 2013; Hester and Luijten, 2014). Based on meeting the combined presence of all of the above three criteria, the following five regions served as nodes for the DCM analysis: (1) left (L) anterior cingulate cortex (ACC) ($x=-8$, $y=46$, $z=-4$); (2) R ACC ($x=10$, $y=26$, $z=24$); (3) right (R) insula ($x=42$, $y=-10$, $z=-6$); (4) R hippocampus ($x=36$, $y=-18$, $z=-14$); and (5) L caudate ($x=-18$, $y=-8$, $z=22$). The x , y , z values are the MNI coordinates of the center of each node, which were defined as a sphere with 5 mm radius and centered at local maximum of the regional fMRI activation corresponding to that node. For each node, the functional activation BOLD time-series, which was used for DCM analysis, was extracted using the methods described in Ma et al. (2015a; 2015b).

2.6.2 Driving input and modulatory input—The CW and NW experimental conditions were not directly used as inputs. Following Buchel et al. (1998) and Hillebrandt et al. (2014), we created a parametric regressor for “All Words” contrast, and another parametric regressor for CW minus NW contrast. The method of constructing these regressors can be found online (https://github.com/HaukeHillebrandt/SPM_connectome). The “All Words” contrast, which reflects the common features of the CW and NW, was used as a single input to the DCM (driving input). The CW minus NW contrast, which reflects the special effect of CW over NW, was used as a putative modulator (modulatory input) of effective connectivity (the factor causing changes in the effective connectivities). In the present study, the changes of effective connectivities (relative to the endogenous connectivities) caused by the CW minus NW modulator are termed as modulatory changes. By definition, a modulatory change reflects the change in an effective connectivity caused by the CW minus the change in this effective connectivity caused by the NW. Thus the effects of drug cues (CW) on the behavioral performance (reaction time), brain activation, and effective connectivity were all assessed relative to NW in the present study.

2.6.3 DCM inference—Given the nodes of the model, a DCM post-hoc optimization analysis (Friston and Penny, 2011) was used for model structure inference. Starting from a

fully-connected model, the post hoc optimization analysis systematically searches for an optimal “sparse” model that determines which particular nodes exhibit effective connectivity with other nodes (i.e., endogenous connectivity), which nodes first experience a change in neuronal activity associated with the “All Words” input (i.e., driving input effects), and which effective connectivities showed modulatory changes associated with the CW minus NW modulator. Based on the results of the post hoc optimization analysis, a Bayesian model averaging (BMA) analysis (Penny et al., 2010) was conducted for DCM parameter inference, with a model space consisting of the fully-connected model and the optimal sparse model. BMA averages each DCM parameter across models (and across subjects) such that the contribution of each model (of each subject) for that parameter was weighted by the model’s posterior probability.

3. RESULTS

3.1 Behavioral results

During the performance of the cocaine-word Stroop task, the RT was 1.2 ± 30.7 ms (mean $\pm$ standard deviation [STD]) for the 15 CocUD subjects. The mean of RT was not significantly different from zero ($t=0.15$, DoF=14, $p=0.88$). The accuracy was $92\% \pm 4\%$ and $91\% \pm 6\%$ for the CW and NW periods, respectively. The difference in the accuracy was not significant between the CW period and the NW period ($t=0.5371$, DoF=28, $p=0.5955$). Eight subjects had RT greater than zero. Among these subjects, two had positive cocaine UDS and positive THC UDS, four had positive cocaine UDS, and two had negative UDS. Seven subjects had RT less than zero. Among these subjects, one had positive cocaine UDS and positive THC UDS, three had positive cocaine UDS, one had positive THC UDS, and one had negative UDS. Among the seven subjects with positive cocaine UDS, four subjects had RT greater than zero, and the other three subjects had RT less than zero.

3.2 Brain activation results

No significant regional brain activation (FWE corrected two-tailed cluster p greater than 0.10) was found for the CW minus NW contrast. However, several clusters were found with the uncorrected two-tailed cluster level p less than 0.05 (uncorrected, two-tail), in portions of ACC, hippocampus, insula, caudate and other brain regions. See Figure 1 and Table 2 for the detailed information about these clusters. The results of the regional activation analysis were used along with the other selection criteria (see Methods section) to select the nodes for DCM analysis.

3.3 DCM connectivity results

The group level mean and STD of each DCM parameter were obtained from the outputs of the BMA analysis. The mean and STD of each modulatory change are shown in Table 3. The mean and STD of each driving input effect and endogenous connectivity are shown in Table 4 and Table 5, respectively. The BMA analysis revealed that the modulatory change of the R ACC to R hippocampus effective connectivity (caused by the CW minus NW modulator) was 0.0444 ± 0.0121 Hz. A Student t-test showed that the modulatory change on the R ACC to R hippocampus effective connectivity was significantly different from zero (Bonferroni corrected $p < 0.0020$). The modulatory changes on the remaining 19 effective

connectivities in the network were not significantly different from zero (Bonferroni corrected $p > 0.7569$). A BMA analysis was conducted separately in the subjects showing attentional bias (AB+) and the subjects not showing attentional bias (AB-) respectively. The mean and STD of each modulatory change are shown in Table 3. The modulatory change of the R ACC to R hippocampus effective connectivity (caused by the CW minus NW modulator) was 0.0684 ± 0.0272 Hz for the AB+ subjects, and 0.0149 ± 0.0282 Hz for the AB- subjects. This modulatory change was significantly greater than zero for the AB+ subjects (Bonferroni corrected $p = 0.0038$), but not significantly different from zero for the AB- subjects (uncorrected $p = 0.2116$). In addition, this modulatory change was marginally different between the AB+ subjects and the AB- subjects (Bonferroni corrected $p = 0.0507$). The modulatory changes on the remaining 19 effective connectivities in the network were not significantly different from zero for the AB+ subjects (Bonferroni corrected $p > 0.7716$) and AB- subjects (Bonferroni corrected $p > 0.7182$), and did not show significant (or marginally significant) difference between the AB+ subjects and AB- subjects (Bonferroni corrected $p = 1$).

3.4 Correlation results

A Spearman partial correlation analysis was used to test the *a priori* hypothesis that the modulatory change in the R ACC to R hippocampus effective connectivity would correlate with the RT in CocUD subjects. The parameters measuring drug use, i.e., lifetime cocaine use (years), past 30 days usage (days), total KMSK score [Kreek-McHugh-Schluger-Kellogg score (Kellogg et al., 2003)], and UDS results, were included in the analysis as covariates. The correlation between RT and the modulatory change on the R ACC to R hippocampus was statistically significant ($\rho = 0.7525$, $p = 0.0120$), with greater increase in strength of R ACC to R hippocampus effective connectivity associated with greater RT. The scatter plot illustrating the modulatory change in this effective connectivity vs. the RT is shown in Figure 2. A full Spearman correlation analysis (i.e., no covariates) yielded a similar result: the modulatory change on the R ACC to R hippocampus was significantly and positively correlated to RT ($\rho = 0.6393$, $p = 0.0123$).

4. DISCUSSION

Drug related attentional bias was evaluated in fifteen CocUD subjects using behavioral data, regional brain activation, and effective connectivity. Although no significant results were found in the behavioral data analysis and the brain regional activation analysis, the DCM analysis found that relative to the neutral word condition, the cocaine word condition caused a significant increase in the strength of the R ACC to R hippocampus effective connectivity. In addition, the increase of this connectivity was positively associated with the cocaine word condition reaction time (relative to neutral word condition reaction time). These results support the hypothesis that the abnormal control of prefrontal regions over the emotion/reward regions, such as the amygdala, hippocampus, insula, and/or striatum, could be the neural basis underlying attentional bias (Hester and Luijten, 2014). Different from a previous effective connectivity study (Ray et al., 2015) which reported significant effects of the emotion/reward regions over the prefrontal regions, the present study revealed that the inverse circuit, i.e., the ACC to hippocampus effective connectivity, may also be important

for drug related attentional bias as well. The identification of this circuit (R ACC to R hippocampus effective connectivity) reduces the gap between the existing theories regarding drug related attentional bias and current human imaging research. Activation of brain circuits associated with attentional bias could serve as a predictor or a target of treatment outcome in CocUD (Schoenmakers et al., 2010; Marhe et al., 2013). Thus, the circuit found in this study could serve as a potentially novel target for treatment and preclinical studies.

The DCM analysis revealed that the CW minus NW modulator was related to a significant increase in the R ACC to R hippocampus effective connectivity during the cocaine-word Stroop task. In addition, the modulatory change in this effective connectivity associated positively with RT in the CocUD subjects. These findings are similar to the results of a previous fMRI study (Janes et al., 2010) in which the investigators found that in smokers there was a positive correlation between attentional bias to smoking words and brain activation (based on the contrast of smoking stimuli minus neutral stimuli) in the hippocampus and other brain regions (amygdala, parahippocampal gyrus, insula, and occipital cortex). Janes et al. (2010) suggested that smoking cues may trigger smoking-affiliated memories, leading to the mental rehearsal of past smoking experiences. This suggestion was based on the role of hippocampus in memory recollection (Manns and Eichenbaum, 2006; Weible, 2013), which was defined as “the recovery of qualitative associations prompted by a critical cue” (Eichenbaum et al., 2007). While DCM based effective connectivity does not require direct structural (or anatomical) connectivity (Stephan et al. 2009), a recent study (Fani et al., 2016) has found a direct structural connection (cingulum bundle) between ACC and hippocampus in humans. The ACC is a cortical region found to be important in recall of past memory (see Weible, 2013 for review). As concluded by Weible et al. (2013), the ACC supports attention to and recognition of the cues that are most relevant to successful recall of behaviors learned in the past. Thus, based on the results reported by Janes et al. (2010) and the function of ACC in past memory recall (Weible, et al., 2013), our DCM finding provides further support for the importance of the ACC and hippocampus in drug cue related memories. The positive correlation between the modulatory change of the R ACC to R hippocampus effective connectivity and RT supports this interpretation and implies that memories associated with drug use may be relatively more easily triggered by drug cues in the CocUD subjects with greater attentional bias.

Our results of increased connectivity between the R ACC to R hippocampus differ from a previous effective connectivity study (Ray et al., 2015). These between-study differences could be related to the nodes analyzed as well as differences in visual stimuli (words vs. pictures), study design (within group vs. between-group), and/or effective connectivity analysis methods. The present study focused on the modulatory changes in effective connectivities exerted by the CW minus NW modulator, which reflects the differential effect of CW over NW. Ray et al. (2015) assessed effective connectivities during the cocaine-stimuli period only. Thus the effects of the neutral-stimuli were not accounted for in that study.

In the current study, for the CocUD group as a whole, the average difference between the reaction time during CW and the reaction time during NW was not statistically different.

The results of previous fMRI studies are mixed with regard to whether CocUD subjects show greater reaction time when exposed to drug stimuli than when exposed to neutral stimuli. Two studies (Goldstein et al., 2007; 2009a) did not find a significant difference in reaction time between cocaine stimuli and neutral stimuli, unlike the results from five other studies (e.g., Ersche et al., 2010; Hester and Garavan, 2009; Marhe et al., 2013; Smith et al., 2014; Kilts et al., 2014). In addition, reaction time results were not reported in several other studies (Goldstein et al., 2009b; 2010; Ray et al.; 2015). These data suggest that the CocUD subjects may not always show attentional bias when exposed to drug cues. This is particularly true for the in-scanner version of the cocaine-stimuli Stroop task, as opposed to the consistent findings of attentional bias for the cocaine-stimuli Stroop tasks used in behavioral laboratory studies in the absence of concurrent fMRI analyses (Leeman et al., 2014).

Regional activation analyses were also conducted in the present study. No significant clusters (FWE corrected two tailed cluster $p > 0.10$) were found at the group level (for the CW – NW contrast). This lack of statistical significance and the hypoactivation (uncorrected two-tailed cluster $p < 0.05$) in R ACC, R insula, and R lingual gyrus are consistent with the findings in one previous study (Goldstein et al., 2007). The similarity between the present study and Goldstein et al. (2007) is the use of the cocaine word Stroop task and within-group design. Significant clusters were reported in another within-group design study which used a working memory task with neutral and cocaine pictures as distractors (Hester and Garavan, 2009). This across-study difference supports the opinion of Leeman et al. (2014) that the task employed to test attentional bias is a factor which contributes to the variation in results across studies.

A strength of the present study is the use of the CW minus NW modulator in DCM. By definition, the modulatory change on the R ACC to R hippocampus effective connectivity reflects the influence of drug cue on the neurocircuitry (the effect of CW relative to NW). In contrast, the functional connectivity in Kilts et al. (2014) was measured using the time series as a whole (including both CW and NW), while in a second study (Ray et al., 2015), the effective connectivity was assessed solely during the cocaine-stimuli period.

One of the limitations of the present study is the lack of drug cue related attentional bias at the averaged group level. The lack of attentional bias may be related to our inclusion/exclusion criteria (i.e., CocUD participants were included regardless of their UDS results). However, among the seven subjects with positive cocaine UDS, four showed attentional bias, and the other three subjects did not show attentional bias, suggesting that in the present study, the attentional bias could not be further evidenced by including only those who had positive UDS. Thus, the inclusion/exclusion criteria are unlikely to account for the null finding in group averaged behavioral performance. Nevertheless, the present study and previous studies (Goldstein et al., 2007; 2009a) indicated that in some cases, there was no average attentional bias for the CocUD group during the in-scanner versions of the Stroop tasks. Even in studies (e.g., Kilts et al., 2014) reporting average group level attentional bias, not all the CocUD subjects showed attentional bias during the drug cue related Stroop tasks (See Figure 1 in Kilts et al., 2014 as an example). These findings in the previous studies reflect individual difference in attentional bias among the CocUD individuals. Indeed,

individual difference in attentional bias (or approach tendency bias) has been reported in CocUD (Marhe et al., 2013; Kilts et al., 2014) and other substance use disorders (Kang et al., 2012; Cousijn et al., 2011; 2014). Focusing on individual differences associated with altered cognitive function has been suggested to be a strategy to improve the effectiveness of therapeutic interventions (Sofuoglu et al., 2013). As suggested by Sofuoglu et al., (2013) and consistent with our findings, the presence of attentional bias could be an individual variable to consider for the evaluation of cognitive treatment in CocUD. The preliminary post-hoc analysis revealed that during the cocaine Stroop task, the CocUD subjects showing attentional bias and those not showing attentional bias had marginally different effective connectivity. Another limitation of the present study is the variance in the UDS results, which reflect recent drug use. As discussed above, the variance in the UDS results is unlikely to account for the lack of attentional bias in the present study. In addition, the correlation between the effective connectivity and RT was significant whether the UDS results were included as covariates or not included, suggesting that the variance in the UDS results did not affect the relationship between the effective connectivity and RT. However, we cannot exclude a negative effect of the variance in the UDS results on the replicability of the fMRI results. The third limitation is the limited number of analyzed ROIs (nodes). It is possible that other neural interconnectivities are also important for attentional bias 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 is study feasibility. With the increase in the number of nodes, the time needed for the DCM analysis increases quadratically (Seghier and Friston, 2013). Thus, node selection criteria were used to control the number of nodes. Another reason was diminished statistical power for fMRI activation due to the variance in UDS results and the small sample size, which is another limitation of the present study. Future studies with more subjects and more strict inclusion/exclusion criteria will be helpful in providing greater insight into the altered neuronal effective connectivity underlying attentional bias in the CocUD subjects.

Acknowledgments

This work is financially supported by National Institute on Drug Abuse (NIDA) Grant# P50DA033935 (KAC; LM; FGM; JS).

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders fourth edition, text revision. Psychiatric Association; Washington, DC: 2000.
- Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci.* 2005; 8(11):1458–1463. [PubMed: 16251988]
- Buchel C, Holmes AP, Rees G, Friston KJ. Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *Neuroimage.* 1998; 8:140–148. [PubMed: 9740757]
- Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci.* 2000; 4:215–222. [PubMed: 10827444]
- Carter BL, Tiffany ST. Cue-reactivity and the future of addiction research. *Addiction.* 1999; 94:349–351. [PubMed: 10605863]
- Collette F, Van der Linden M. Brain imaging of the central executive component of working memory. *Neurosci Biobehav Rev.* 2002; 26:105–125. [PubMed: 11856556]

- Courtney KE, Schacht JP, Hutchison K, Roche DJ, Ray LA. Neural substrates of cue reactivity: association with treatment outcomes and relapse. *Addict Biol.* 2016; 21:3–22. [PubMed: 26435524]
- Cousijn J, Goudriaan AE, Wiers RW. Reaching out towards cannabis: approach-bias in heavy cannabis users predicts changes in cannabis use. *Addiction.* 2011; 106:1667–1674. [PubMed: 21518067]
- Cousijn J, Luijten M, Wiers RW. Mechanisms underlying alcohol-approach action tendencies: the role of emotional primes and drinking motives. *Front Psychiatry.* 2014; 5:44. [PubMed: 24834057]
- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996; 29(3):162–173. [PubMed: 8812068]
- Cunningham KA, Anastasio NC. Serotonin at the nexus of impulsivity and cue reactivity in cocaine addiction. *Neuropharmacology.* 2014; 76(Pt B):460–478. [PubMed: 23850573]
- Ersche KD, Bullmore ET, Craig KJ, Shabbir SS, Abbott S, Muller U, Ooi C, Suckling J, Barnes A, Sahakian BJ, Merlo-Pich EV, Robbins TW. Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. *Arch Gen Psychiatry.* 2010; 67:632–644. [PubMed: 20530013]
- Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci.* 2007; 30:123–152. [PubMed: 17417939]
- Fani N, King TZ, Shin J, Srivastava A, Brewster RC, Jovanovic T, Bradley B, Ressler KJ. Structural and Functional Connectivity in Posttraumatic Stress Disorder: Associations with Fkbp5. *Depress Anxiety.* 2016; 33:300–307. [PubMed: 27038411]
- Field M, Cox WM. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend.* 2008; 97(1–2):1–20. [PubMed: 18479844]
- First, MB., Spitzer, RL., Gibbon, M., Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders--Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute; New York, NY: 1996.
- Fotros A, Casey KF, Larcher K, Verhaeghe JA, Cox SM, Gravel P, Reader AJ, Dagher A, Benkelfat C, Leyton M. Cocaine cue-induced dopamine release in amygdala and hippocampus: a high-resolution PET [(1)(8)F]fallypride study in cocaine dependent participants. *Neuropsychopharmacology.* 2013; 38:1780–1788. [PubMed: 23546387]
- Friston KJ. Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping.* 1995; 2:189–210.
- Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage.* 2003; 19(4):1273–1302. [PubMed: 12948688]
- Friston KJ. Functional and effective connectivity: A review. *Brain Connectivity.* 2011; 1:13–36. [PubMed: 22432952]
- Friston K, Penny W. Post hoc Bayesian model selection. *Neuroimage.* 2011; 56:2089–2099. [PubMed: 21459150]
- Fuster JM. The cognit: a network model of cortical representation. *Int J Psychophysiol.* 2006; 60:125–132. [PubMed: 16626831]
- Hillebrandt H, Friston KJ, Blakemore SJ. Effective connectivity during animacy perception--dynamic causal modelling of Human Connectome Project data. *Scientific reports.* 2014; 4:6240. [PubMed: 25174814]
- Goldstein RZ, Tomasi D, Rajaram S, Cottone LA, Zhang L, Maloney T, Telang F, Alia-Klein N, Volkow ND. Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience.* 2007; 144:1153–1159. [PubMed: 17197102]
- Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proc Natl Acad Sci U S A.* 2009a; 106:9453–9458. [PubMed: 19478067]
- Goldstein RZ, Tomasi D, Alia-Klein N, Honorio Carrillo J, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. Dopaminergic response to drug words in cocaine addiction. *J Neurosci.* 2009b; 29:6001–6006. [PubMed: 19420266]
- Goldstein RZ, Woicik PA, Maloney T, Tomasi D, Alia-Klein N, Shan J, Honorio J, Samaras D, Wang R, Telang F, Wang GJ, Volkow ND. Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. *Proc Natl Acad Sci U S A.* 2010; 107:16667–16672. [PubMed: 20823246]

- Hester R, Garavan H. Neural mechanisms underlying drug-related cue distraction in active cocaine users. *Pharmacol Biochem Behav.* 2009; 93(3):270–277. [PubMed: 19135471]
- Hester R, Luijten M. Neural correlates of attentional bias in addiction. *CNS Spectr.* 2014; 19(3):231–238. [PubMed: 23919984]
- Holmes AP, Friston KJ. Generalisability, random effects and population inference. *NeuroImage.* 1998; 7:S754.
- Iannetti GD, Wise RG. BOLD functional MRI in disease and pharmacological studies: room for improvement? *Magn Reson Imaging.* 2007; 25(6):978–988. [PubMed: 17499469]
- Janes AC, Pizzagalli DA, Richardt S, de BFB, Chuzy S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biol Psychiatry.* 2010; 67:722–729. [PubMed: 20172508]
- Jasinska AJ, Chen BT, Bonci A, Stein EA. Dorsal medial prefrontal cortex (MPFC) circuitry in rodent models of cocaine use: implications for drug addiction therapies. *Addict Biol.* 2015; 20:215–226. [PubMed: 24620898]
- Kang OS, Chang DS, Jahng GH, Kim SY, Kim H, Kim JW, Chung SY, Yang SI, Park HJ, Lee H, Chae Y. Individual differences in smoking-related cue reactivity in smokers: an eye-tracking and fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012; 38:285–293. [PubMed: 22542509]
- Kellogg SH, McHugh PF, Bell K, Schluger JH, Schluger RP, LaForge KS, Ho A, Kreek MJ. The Kreek-McHugh-Schluger-Kellogg scale: a new, rapid method for quantifying substance abuse and its possible applications. *Drug Alcohol Depend.* 2003; 69:137–150. [PubMed: 12609695]
- Kilts CD, Kennedy A, Elton AL, Tripathi SP, Young J, Cisler JM, James GA. Individual differences in attentional bias associated with cocaine dependence are related to varying engagement of neural processing networks. *Neuropsychopharmacology.* 2014; 39:1135–1147. [PubMed: 24196947]
- Leeman RF, Robinson CD, Waters AJ, Sofuoglu M. A critical review of the literature on attentional bias in cocaine use disorder and suggestions for future research. *Exp Clin Psychopharmacol.* 2014; 22:469–483. [PubMed: 25222545]
- Li B, Daunizeau J, Stephan KE, Penny W, Hu D, Friston K. Generalised filtering and stochastic DCM for fMRI. *Neuroimage.* 2011; 58:442–457. [PubMed: 21310247]
- Liu S, Lane SD, Schmitz JM, Waters AJ, Cunningham KA, Moeller FG. Relationship between attentional bias to cocaine-related stimuli and impulsivity in cocaine-dependent subjects. *Am J Drug Alcohol Abuse.* 2011; 37:117–122. [PubMed: 21204739]
- Ma L, Steinberg JL, Hasan KM, Narayana PA, Kramer LA, Moeller FG. Working memory load modulation of parieto-frontal connections: Evidence from dynamic causal modeling. *Hum Brain Mapp.* 2012; 33:1850–1867. [PubMed: 21692148]
- Ma L, Steinberg JL, Hasan KM, Narayana PA, Kramer LA, Moeller FG. Stochastic dynamic causal modeling of working memory connections in cocaine dependence. *Hum Brain Mapp.* 2014; 35:760–778. [PubMed: 23151990]
- Ma L, Steinberg JL, Cunningham KA, Lane SD, Kramer LA, Narayana PA, Kosten TR, Bechara A, Moeller FG. Inhibitory behavioral control: a stochastic dynamic causal modeling study using network discovery analysis. *Brain Connect.* 2015a; 5:177–186. [PubMed: 25336321]
- Ma L, Steinberg JL, Cunningham KA, Lane SD, Bjork JM, Neelakantan H, Price AE, Narayana PA, Kosten TR, Bechara A, Moeller FG. Inhibitory behavioral control: A stochastic dynamic causal modeling study comparing cocaine dependent subjects and controls. *NeuroImage Clinical.* 2015b; 7:837–847. [PubMed: 26082893]
- Ma L, Steinberg JL, Moeller FG, Johns SE, Narayana PA. Effect of cocaine dependence on brain connections: clinical implications. *Expert review of neurotherapeutics.* 2015; 15:1307–1319. [PubMed: 26512421]
- Manns JR, Eichenbaum H. Evolution of declarative memory. *Hippocampus.* 2006; 16:795–808. [PubMed: 16881079]
- Marhe R, Luijten M, van de Wetering BJ, Smits M, Franken IH. Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. *Neuropsychopharmacology.* 2013; 38:1085–1093. [PubMed: 23303067]

- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat.* 1992; 9:199–213. [PubMed: 1334156]
- Mitchell MR, Balodis IM, Devito EE, Lacadie CM, Yeston J, Scheinost D, Constable RT, Carroll KM, Potenza MN. A preliminary investigation of Stroop-related intrinsic connectivity in cocaine dependence: associations with treatment outcomes. *Am J Drug Alcohol Abuse.* 2013; 39:392–402. [PubMed: 24200209]
- Moeller FG, Steinberg JL, Schmitz JL, Ma L, Liu S, Kjome KL, Rathnayaka N, Kramer LA, Narayana PA. Working memory fMRI activation in cocaine dependent subjects: association with treatment response. *Psychiatry Research Neuroimaging.* 2010; 181:174–182. [PubMed: 20153142]
- Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends Neurosci.* 2009; 32:56–67. [PubMed: 18986715]
- Noel X, Brevers D, Bechara A. A neurocognitive approach to understanding the neurobiology of addiction. *Curr Opin Neurobiol.* 2013; 23:632–638. [PubMed: 23395462]
- O'Brien CP, Childress AR, Ehrman R, Robbins SJ. Conditioning factors in drug abuse: can they explain compulsion? *J Psychopharmacol.* 1998; 12:15–22. [PubMed: 9584964]
- Penny WD, Stephan KE, Daunizeau J, Rosa MJ, Friston KJ, Schofield TM, Leff AP. Comparing families of dynamic causal models. *PLoS Comput Biol.* 2010; 6:e1000709. [PubMed: 20300649]
- Ray S, Pandina R, Bates ME. Memory for drug-related visual stimuli in young adult, cocaine-dependent polydrug users. *Am J Drug Alcohol Abuse.* 2014; 40:170–175. [PubMed: 24588421]
- Ray S, Haney M, Hanson C, Biswal B, Hanson SJ. Modeling Causal Relationship Between Brain Regions Within the Drug-Cue Processing Network in Chronic Cocaine Smokers. *Neuropsychopharmacology.* 2015; 40(13):2960–2968. [PubMed: 26038158]
- Robbins TW, Ersche KD, Everitt BJ. Drug addiction and the memory systems of the brain. *Ann N Y Acad Sci.* 2008; 1141:1–21. [PubMed: 18991949]
- Rowe JB. Connectivity analysis is essential to understand neurological disorders. *Front Syst Neurosci.* 2010; 4.
- Schmitz JM, Green CE, Stotts AL, Lindsay JA, Rathnayaka NS, Grabowski J, Moeller FG. A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: modafinil, levodopa-carbidopa, naltrexone. *Drug Alcohol Depend.* 2014; 136:100–107. [PubMed: 24424425]
- Schoenbaum G, Shaham Y. The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. *Biol Psychiatry.* 2008; 63:256–262. [PubMed: 17719014]
- Schoenmakers TM, de Bruin M, Lux IF, Goertz AG, Van Kerkhof DH, Wiers RW. Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug Alcohol Depend.* 2010; 109:30–36. [PubMed: 20064698]
- Seghier ML, Friston KJ. Network discovery with large DCMs. *Neuroimage.* 2013; 68:181–191. [PubMed: 23246991]
- Smith DG, Simon Jones P, Bullmore ET, Robbins TW, Ersche KD. Enhanced orbitofrontal cortex function and lack of attentional bias to cocaine cues in recreational stimulant users. *Biol Psychiatry.* 2014; 75:124–131. [PubMed: 23809860]
- Sofuoglu M, DeVito EE, Waters AJ, Carroll KM. Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology.* 2013; 64:452–463. [PubMed: 22735770]
- Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ. Comparing hemodynamic models with DCM. *Neuroimage.* 2007; 38:387–401. [PubMed: 17884583]
- Stephan KE, Tittgemeyer M, Knosche TR, Moran RJ, Friston KJ. Tractography-based priors for dynamic causal models. *Neuroimage.* 2009; 47:1628–1638. [PubMed: 19523523]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* 2002; 15:273–289. [PubMed: 11771995]
- Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Quantification of Behavior Sackler Colloquium: Addiction: Beyond dopamine reward circuitry. *Proc Natl Acad Sci U S A.* 2011; 108:15037–15042. [PubMed: 21402948]

- Walton ME, Behrens TE, Buckley MJ, Rudebeck PH, Rushworth MF. Separable learning systems in the macaque brain and the role of orbitofrontal cortex in contingent learning. *Neuron*. 2010; 65(6): 927–939. [PubMed: 20346766]
- Weible AP. Remembering to attend: the anterior cingulate cortex and remote memory. *Behav Brain Res*. 2013; 245:63–75. [PubMed: 23453992]
- Worhunsky PD, Stevens MC, Carroll KM, Rounsaville BJ, Calhoun VD, Pearson GD, Potenza MN. Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors*. 2013; 27:477–488. [PubMed: 22775772]

Highlights

- This study investigated attentional bias in cocaine use disorder.
- Dynamic causal modeling was used to assess underlying neural circuits.
- Drug cues caused increase in anterior cingulate cortex to hippocampus effective connectivity.
- Greater increase of this connectivity was associated with greater reaction time during drug cues.
- May reflect anterior cingulate cortex activation of hippocampal memories related to drug use.

Figure 1.

Results of the regional activation analysis. The clusters with the cluster level p less than 0.05 (uncorrected, two-tail) were shown in red ($CW - NW > 0$) or blue ($CW - NW < 0$). For the axial and coronal views, the reader's left side of the slice is the subjects' left brain hemisphere.

Figure 2.

Scatter plot of the modulatory change of the R ACC to R hippocampus effective connectivity (Hz), and RT (ms) in the 15 CocUD subjects. Both Spearman partial correlation analysis ($\rho=0.7525$, $p=0.0120$) and Spearman correlation analysis ($\rho=0.6393$, $p=0.0123$) found a significant positive correlation between these two measures.

Table 1

Demographic and drug-use information of the CocUD subjects. F=female, M=male, L=left, R=and right, THC=tetrahydrocannabinol. KMSK [Kreek-McHugh-Schluger-Kellogg score (Kellogg et al., 2003)] measures severity of cocaine dependence.

Parameter	CocUD (n=15)
Age [years] mean and standard deviation (range)	39.1 ± 8.0 (27.5 – 54.3)
Sex	0 F, 15 M
Handedness	0 L, 15 R
Education [years] mean and standard deviation (range)	12.9 ± 1.4 (12 – 16)
Life time usage [years] mean and standard deviation	14.6 ± 10.3
Past 30 days usage [days] mean and standard deviation	12.9 ± 9.8
Total KMSK score	11.7 ± 3.7
Number of subjects with negative cocaine UDS before scanning	3
Number of subjects with positive cocaine UDS before scanning	7
Number of subjects with positive THC UDS before scanning	2
Number of subjects with positive cocaine & THC UDS before scanning	3

Table 2

Results of the regional activation analysis. The regions shown in the table had FWE cluster $p > 0.1$ (two tail) but uncorrected cluster $p < 0.05$ (two tail). SMA = supplementary motor cortex, g = gyrus, c = gyrus, L = left, and R = right. The letters x, y, and z are the MNI coordinates.

Brain region	# voxels	max T	x	y	z
CW – NW > 0					
L precentral g	21	3.9805	-58	-2	32
R superior frontal g	32	3.6691	14	12	46
L SMA	31	2.9437	2	10	50
R SMA	129	3.8483	12	10	46
R medial superior frontal g	88	4.2014	6	44	32
R middle cingulate c	21	3.8655	14	12	44
L posterior cingulate c	23	2.9548	-10	-50	32
L calcarine fissure	68	3.3418	-18	-72	4
R calcarine fissure	136	3.4360	10	-74	6
L cuneus g	16	2.7805	-14	-66	20
R cuneus g	25	3.1380	8	-88	16
L lingual g	106	3.8493	-32	-88	-14
R lingual g	59	3.3583	16	-66	0
L middle occipital g	114	3.6144	-36	-90	-4
L inferior occipital g	55	4.0166	-34	-90	-12
R inferior occipital g	83	5.2152	32	-92	-8
L fusiform g	25	3.5955	-36	-6	-32
L postcentral g	13	3.3502	-60	-4	34
R angular g	59	3.5804	54	-52	28
L precuneus	155	4.2827	-8	-42	60
R precuneus	14	2.9073	28	-52	2
L superior temporal g	31	3.4889	-50	-26	10
L inferior temporal g	16	4.9885	-40	-4	-32
R interior temporal g	39	3.9975	60	-12	-30
CW – NW < 0					
L medial orbital frontal c	48	4.9235	-10	50	-4

Brain region	# voxels	max T	x	y	z
L rectus g	24	3.2125	-10	28	-20
R insula	46	3.6084	42	-10	-6
L anterior cingulate c	12	3.1782	-8	46	-4
R anterior cingulate c	35	3.6381	10	26	24
R hippocampus	93	4.2382	36	-18	-14
R parahippocampal g	22	4.3554	30	-14	-26
R lingual g	12	2.9350	6	-42	-2
R inferior parietal g	22	3.1349	46	-50	54
L supramarginal g	22	2.8993	-48	-50	30
R supramarginal g	38	3.7838	58	-24	40
L caudate	15	5.0610	-18	-8	22
L superior temporal g	30	2.9751	44	-10	-6
R middle temporal g	37	4.3484	54	-6	-20

Table 3

The mean and STD of modulatory changes revealed by DCM BMA analysis, for all the CocUD subjects (All), the subjects showing attentional bias (AB+) and subjects not showing attentional bias (AB-) respectively. The unit is Hz.

CONNECTIVITY	All (mean $\pm$ STD)	AB+ (mean $\pm$ STD)	AB- (mean $\pm$ STD)
LACC→RACC	0.0040 $\pm$ 0.0127	0.0047 $\pm$ 0.0158	0.0043 $\pm$ 0.0162
LACC→ R insula	0.0075 $\pm$ 0.0145	-0.0124 $\pm$ 0.0238	0.0119 $\pm$ 0.0237
L ACC→ R hippocampus	-0.0112 $\pm$ 0.0149	-0.0139 $\pm$ 0.0217	-0.0048 $\pm$ 0.0222
L ACC→ Lcaudate	0.0044 $\pm$ 0.0134	0.0043 $\pm$ 0.0200	0.0051 $\pm$ 0.0194
RACC→ LACC	0.0070 $\pm$ 0.0104	0.0063 $\pm$ 0.0111	0.0096 $\pm$ 0.0113
RACC→ R insula	-0.0123 $\pm$ 0.0157	-0.0135 $\pm$ 0.0174	-0.0122 $\pm$ 0.0178
R ACC→ R hippocampus	0.0444 $\pm$ 0.0121	0.0684 $\pm$ 0.0272	0.0149 $\pm$ 0.0282
R ACC → L caudate	-0.0065 $\pm$ 0.0101	-0.0070 $\pm$ 0.0123	-0.0037 $\pm$ 0.0151
R insula→ L ACC	-0.0134 $\pm$ 0.0150	-0.0125 $\pm$ 0.0266	-0.0145 $\pm$ 0.0265
R insula→ R ACC	-0.0144 $\pm$ 0.0188	-0.0113 $\pm$ 0.0220	-0.0214 $\pm$ 0.0220
R insula→ R hippocampus	0.0018 $\pm$ 0.0137	0.0013 $\pm$ 0.0222	0.0024 $\pm$ 0.0221
R insula→ L caudate	0.0121 $\pm$ 0.0179	0.0143 $\pm$ 0.0340	0.0008 $\pm$ 0.0321
R hippocampus→ L ACC	-0.0053 $\pm$ 0.0150	-0.0020 $\pm$ 0.0266	-0.0067 $\pm$ 0.0268
R hippocampus→ R ACC	0.0129 $\pm$ 0.0164	0.0124 $\pm$ 0.0138	0.0228 $\pm$ 0.0224
R hippocampus→ R insula	0.0047 $\pm$ 0.0144	0.0033 $\pm$ 0.0251	0.0080 $\pm$ 0.0245
R hippocampus→ L caudate	-0.0026 $\pm$ 0.0188	-0.0018 $\pm$ 0.0357	-0.0034 $\pm$ 0.0339
L caudate→ L ACC	0.0084 $\pm$ 0.0093	-0.0004 $\pm$ 0.0133	0.0100 $\pm$ 0.0140
L caudate→ R ACC	0.0099 $\pm$ 0.0196	0.0136 $\pm$ 0.0169	0.0096 $\pm$ 0.0123
L caudate→ R insula	0.0083 $\pm$ 0.0138	0.0088 $\pm$ 0.0246	0.0074 $\pm$ 0.0245
L caudate→ R hippocampus	0.0027 $\pm$ 0.0154	0.0022 $\pm$ 0.0255	0.0042 $\pm$ 0.0256

Table 4

The mean and STD of driving input effects revealed by DCM BMA analysis. The unit is Hz.

LOCATION	MEAN	STD
L ACC	−0.0009	0.0009
R ACC	−0.0007	0.0009
R insula	−0.0063	0.0013
R hippocampus	−0.0062	0.0013
L caudate	0.0064	0.0010

Table 5

The mean and STD of endogenous connectivities revealed by DCM BMA analysis. The unit is Hz.

CONNECTIVITY	MEAN	STD	CONNECTIVITY	MEAN	STD
L ACC → R ACC	0.0902	0.0041	R insula → R hippocampus	0.1838	0.0037
L ACC → R insula	0.1086	0.0056	R insula → L caudate	0.0314	0.0037
L ACC → R hippocampus	-0.0347	0.0051	R hippocampus → L ACC	-0.0314	0.0033
L ACC → L caudate	0.0560	0.0043	R hippocampus → R ACC	0.0183	0.0031
R ACC → L ACC	0.0939	0.0041	R hippocampus → R insula	0.2008	0.0039
R ACC → R insula	0.0227	0.0054	R hippocampus → L caudate	0.0540	0.0035
R ACC → R hippocampus	0.0507	0.0052	L caudate → L ACC	0.0475	0.0033
R ACC → L caudate	0.0830	0.0043	L caudate → R ACC	0.0678	0.0035
R insula → L ACC	0.0686	0.0034	L caudate → R insula	0.0508	0.0044
R insula → R ACC	0.0118	0.0030	L caudate → R hippocampus	0.0531	0.0043