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# Cingulo-hippocampal effective connectivity positively correlates with drug-cue attentional bias in opioid use disorder

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## Abstract

Individuals with opioid use disorder (OUD) often relapse when exposed to opioid-related cues. Previous functional magnetic resonance imaging (fMRI) studies have identified neuronal corticolimbic changes related to drug cue reactivity in OUD. However, the corresponding manner in which brain regions interact is still unclear. Effective (directional) connectivity was analyzed using dynamic causal modeling of fMRI data acquired from 27 OUD participants (13 with OUD and 14 with OUD and cocaine use disorder [OUD+CUD]), while performing an opioid-word Stroop task. Participants were shown opioid and neutral words presented in different colors and were instructed to indicate word color but ignore word meaning. The effects of opioid words relative to neutral words on effective connectivity and on behavioral reaction time were

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AUTHORS CONTRIBUTION

FGM, JLS, and KAC were responsible for the study concept and design. LM performed the data analysis and drafted the manuscript. All authors critically reviewed content and approved final version for publication.

defined as modulatory change and attentional bias, respectively. For all the 27 participants, left anterior cingulate cortex (ACC) to right hippocampus effective connectivity exhibited the largest modulatory change, which was positively correlated with attentional bias. The findings for the ACC to hippocampus EC were consistent across OUD and CUD found in a previous study.

**Keywords**

Attentional bias; cue reactivity; dynamic causal modeling; effective connectivity; opioid use disorder

## 1. INTRODUCTION

The prevalence of opioid use disorder (OUD) has increased significantly in the past decade in the United States (Martins et al., 2017). OUD is associated with altered brain function (Fareed et al., 2017) and is a significant social burden (Sharma et al., 2016). Severe consequences of OUD include overdoses, suicide attempts, higher rates of depression, increased psychiatric treatment and hospitalizations, increased concurrent cocaine use, and increased risky sexual behaviors (Sharma et al., 2016). In OUD, there is a high rate of relapse (Moningka et al., 2018), which is often related to exposure to drug cues in the patient's environment (Courtney et al., 2016). Thus, further understanding of the neuronal underpinnings of drug cue reactivity may enhance the development of pharmacotherapeutic and other approaches for relapse prevention.

Brain activation studies using functional magnetic response imaging (fMRI) have significantly contributed to knowledge about the neuronal correlates of drug cue reactivity (Langleben et al., 2008; Langleben et al., 2014; Li et al., 2015; Li et al., 2012; Lou et al., 2012; Martins et al., 2017; Mei et al., 2010; Pothineni et al., 2016; Scarpina and Tagini, 2017; Sharma et al., 2016; Shi et al., 2018; Yang et al., 2009; Zeng et al., 2018). In these studies, OUD participants looked at images or videos related to opioid use, i.e., opioid cues, and neutral images or videos (for review, Moningka et al. (2018)). In most reports, opioid cues elicited greater fMRI blood-oxygen-level dependent (BOLD) responses in anterior cingulate cortex (ACC), dorsal striatum, ventral striatum, hippocampus, and posterior cingulate cortex (PCC). The opioid cue elicited activation in PCC, ventral striatum, and dorsal striatum was related to craving (Li et al., 2012) and abstinence duration (Lou et al., 2012), implying possible clinical relevance of individual differences in these activations. Acute administration of opioid (e.g., heroin) can further enhance activation in this network (Martins et al., 2017). Conversely, therapeutic medication interventions can reduce the activation in some regions, e.g., dorsal striatum and ventral striatum (Langleben et al., 2014; Shi et al., 2018).

The drug-word Stroop task is a complimentary alternative to the image-based drug-cue reactivity tasks (Smith and Ersche, 2014). During the drug-word Stroop task, the participant is asked to indicate the color in which the drug word or neutral word was printed on the screen, but to ignore the word's meaning. Thus, there is an interference between a less automated task (color responding), and a more automated task (reading the word) (Henriksen and Willoch, 2008). The existence of the difficulty in inhibiting this more

automated task is a key difference between drug-word Stroop tasks and image-based drug-cue reactivity tasks. The difficulty in inhibiting this more automated task provides a behavioral metric of attention to drug-associated stimuli. Drug users generally show a relative latency to report the color of the drug word (Smith and Ersche, 2014). At the behavioral level, attentional bias is operationally defined as the reaction time during the drug word trials minus the reaction time during the neutral word trials.

Attentional bias, measured during the drug-word Stroop task, has been reported to be associated with drug craving (a strong desire to use the drug) and can possibly predict treatment outcomes (Smith and Ersche, 2014). Therefore, both behavioral and brain indicators of attentional bias represent a potentially useful marker of treatment effects in OUD (Zhang et al., 2018). Two studies (Wang et al., 2015; Wang et al., 2014) employed opioid-word Stroop task to investigate OUD at the behavioral level. Wang et al. (2015) reported that in heroin-dependent participants, the reaction time to respond to heroin-associated cues correlated positively with heroin craving. Wang et al. (2014) found that attentional bias, which was measured during an opioid-word Stroop task and before treatment in abstinent heroin-dependent patients, was predictive of subsequent relapses during a three-month follow-up. Although the drug-word Stroop task is potentially useful and has been used to study other substance use disorders (Hester and Luijten, 2014; Smith and Ersche, 2014), as far as we are aware, brain correlates of attentional bias on the Stroop task in OUD have not been studied with fMRI.

Because of the prevalence of concurrent cocaine use in opioid users (Christensen et al., 2016; Sharma et al., 2016), participants who had a diagnosis of OUD without and with a concurrent diagnosis of cocaine use disorder (OUD and OUD+CUD, respectively) were included in the present study. The primary aim of this study was to identify neuronal circuits underlying opioid-word related attentional bias in all included participants (OUD and OUD+CUD participants). FMRI-based dynamic causal modeling (DCM) (Friston et al., 2003; Friston et al., 2016) was used to measure the effective (directional) connectivity (EC) elicited by the opioid-word Stroop fMRI task in abstinent OUD and OUD+CUD participants. We reported previously in a study of CUD subjects who did not have OUD, that during performance of a cocaine-word Stroop task, the drug cues (cocaine words) significantly increased the strength of the ACC to hippocampus EC, and this increase in EC was associated with greater attentional bias (Ma et al., 2018). Based on the studies that suggest similarity in neurocircuit underpinnings of drug cue reactivity across abused drug classes (e.g., Hanlon et al., 2018; Zhang et al., 2018), the OUD participants and the OUD+CUD participants were pooled together for the primary analysis. Specifically, we hypothesized (1) that opioid-word-elicited ACC to hippocampus EC would be increased relative to neutral words in OUD and OUD+CUD participants, and (2) that this increase in EC would be associated with greater attentional bias.

This study differs from the Ma et al. (2018) study in four aspects: (1) all participants in the current study had OUD diagnosis *vs.* all participants in the previous study had CUD diagnosis, (2) different fMRI tasks: opioid-word Stroop task in the current study *vs.* cocaine-word Stroop task in the previous study; (3) completely different participants; and (4) fMRI data were acquired using a different scanner in the current study than the previous study.

# 2. METHODS

## 2.1 Participants

The MRI data herein were acquired from participants who received pretreatment placebo prior to being randomized to active vs. placebo arms of a clinical trial investigating medication effects in participants with OUD or OUD+CUD. This study was officially approved by the Virginia Commonwealth University Institutional Review Board, and was performed in accordance with the Declaration of Helsinki. Participant confidentiality was in no way breached, and written informed consent was obtained from each participant.

All participants were screened using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) and underwent physical examination and medical history. Female participants were screened with a urine pregnancy test immediately prior to MRI scanning. Also immediately prior to MRI scanning, urine from each participant was screened for amphetamine, barbiturates (secobarbital, amobarbital, butabarbital, pentobarbital, and phenobarbital), benzodiazepines (oxazepam, alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, temazepam, and triazolam), cocaine, methamphetamine, MDMA (ecstasy), opioids (methadone, buprenorphine, morphine, codeine, 6-monoacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxycodone, and oxymorphone), phencyclidine, propoxyphene, tricyclic antidepressants, and $\Delta^9$-tetrahydrocannabidiol. Each participant was also screened for breath alcohol immediately before MRI scanning.

Participant inclusion criteria were: (1) 18–55 years old; (2) negative alcohol breath test at the time of MRI scanning; (3) met Diagnostic and Statistical Manual Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) criteria for current opioid dependence (for OUD participants) or both opioid dependence and cocaine dependence (for OUD+CUD participants), based on the Structured Clinical Interview for DSM-IV (First et al., 1996). Participants were excluded from this study if one or more of the following criteria were met: (1) current 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 urine drug screen result at the time of scanning; (6) positive pregnancy test result, and (7) unusable MRI scans due to artifacts such as head motion artifacts. Based on the above criteria, two out of the 29 participants who were scanned were excluded because of unusable MRI scans.

See Table 1 for the demographic information and substance use data of the included participants ($n$=13 for OUD, and $n$=14 for OUD+CUD). In Table 1, mean and standard deviation were reported for the continuous variables. There were no significant differences between OUD and OUD+CUD participants in age, education, lifetime opioid use, past 30-day opioid use, opioid abstinence duration, lifetime alcohol use, lifetime cigarette use, number of cigarettes used per day, sex, ethnicity, and handedness. A paired Student $t$-test indicated that for the OUD+CUD participants, the duration of abstinence from cocaine use vs. opioid use was not significantly different ($t$=1.26, degree of freedom [$df$]=13, $p$=0.23).

For the reminder of the paper, the "abstinence duration" refers to duration of abstinence from opioid use for simplicity.

### 2.2 Opioid-word Stroop fMRI Task

The within-scanner opioid-word Stroop task is similar to the cocaine-word Stroop task previously described (Ma et al., 2018). Specifically, participants saw opioid words (OWs) and neutral words (NWs) within four alternated 30-s OW blocks and NW blocks. Each presented word was randomly printed in **blue, green, or red**. The participant was instructed to ignore the meaning of the word and to press a button to denote the word color. For each participant, the mean reaction times (RTs) during the OW blocks and during the NW blocks were computed after removing the RT outliers using the RT trimming method (Van Selst, 1994), as implemented in the R code downloaded from (http://figshare.com/articles/RT_Trimming_ToolBox_zip/717189). The effect of opioid cues on the reaction time (ΔRT) was measured by the mean RT during all the correct-response trials in the OW blocks minus the mean RT during all the correct-response trials in the NW blocks, i.e., ΔRT = RT (OW) minus RT (NW). ΔRT was treated as the behavioral measure of attentional bias.

### 2.3 Assessment of craving

To assess subjective effects, visual analogue scales (VAS) were completed immediately before the MRI scanning. Each participant reported current opioid craving by marking on a 100 mm line between 0 (NOT AT ALL) and 10 (EXTREMELY), as the answer of "*How much do you currently crave opioids?*"

### 2.4 fMRI Data Acquisition

MRI scans were acquired using the Philips Medical Systems (Best, Netherlands) Ingenia wide-bore dStream 3T MRI scanner, with 32-channel receive head coil. Single shot spin echo echoplanar imaging (EPI) was used for acquiring fMRI data. The fMRI acquisition parameters were: parallel imaging SENSE acceleration factor 2.0, repetition time 2500 ms, echo time 75 ms, flip angle 90 degrees, field of view 240 mm (anterior-to-posterior) × 240 mm (left-to-right) × 123.75 mm (foot-to-head), in-plane resolution 3.75 mm × 3.75 mm, 25 axial slices, slice thickness 3.75 mm, interslice gap 1.25 mm, 112 repetitions per run after 10 dummy acquisitions, and total duration approximately 5 min.

### 2.5 fMRI Preprocessing

fMRI volumes in which the signal exceeded plus or minus four standard deviations from the mean of the run were considered to be outliers and data were imputed as the mean of the two nearest neighbors using the Analysis of Functional NeuroImages (AFNI) (Cox, 1996) module "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 R2015b (Mathworks Inc. Sherborn MA, USA). After slice timing correction, the fMRI series was realigned 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 the Montreal Neurological Institute (MNI) standard

atlas coordinates using the SPM12 Normalise module with the SPM12 tissue probability maps. The transformation parameters were applied to the fMRI images, which were then resliced to 2 mm isotropic resolution and spatially smoothed with a Gaussian filter of 8 mm isotropic full width at half maximum.

### 2.6 Evaluation of head motion

Six motion correction parameters (x, y, z translations [mm] and x, y, z translations [degree]) were output by the realignment during the fMRI preprocessing. Each of these six head motion parameters was quantified using cumulative value (Haller et al., 2014) and maximal value. Specifically, for each motion parameter and each participant, the corresponding cumulative value and maximal value were computed as the summation and the maximum respectively, of the absolute values of this motion parameter across the entire fMRI run. Because some previous studies (e.g., Ardekani et al., 2001) investigating head motion used summed values across the x/y/z axes, the summed x/y/z translations and the summed x/y/z rotations were therefore computed based on the six original motion parameters.

### 2.7 SPM univariate analysis

The first-level univariate statistical analysis of the fMRI data was conducted using SPM12. OW 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 at each voxel without global normalization. The fMRI time series was high-pass filtered with an optimized cut-off period of 144 s determined by the Fourier transformation of each condition's time model. At each voxel, attentional bias related activation was measured as the contrast of the parameter estimate for OW blocks minus the parameter estimate for NW blocks (OW minus NW contrast). The resulting set of voxel values for this contrast constitutes a statistical parametric map for that contrast. The OW minus NW contrast image (one per participant) was then entered at the SPM12 second level (i.e., random effects) group analysis.

To determine the main effects of blood-oxygen-level dependent (BOLD) activation common to both groups (OUD and OUD+CUD), an SPM12 second level Random Effects one-sample *t*-test was conducted voxel-wise throughout the whole brain for the OW minus NW contrast image. To determine the preliminary group difference (OUD vs. OUD+CUD) in BOLD activation, an SPM12 second level Random Effects two-sample *t*-test was conducted voxel-wise throughout the whole brain for the contrast image. Regional brain activation was defined as the family-wise error (FWE) corrected cluster probability ($p$) less than 0.05 (two tail). For all second-level analyses, the cluster-defining threshold (CDT) was $t=2.4$, corresponding to $p=0.01$. More conservative CDT ($p\leq 0.001$) as suggested by Eklund et al. (2016) was not used in this study because the brain activations were only used to constrain the DCM nodes. It is commonly accepted that less conservative statistical criteria can be used when brain activations are used for determining DCM nodes (Friston et al., 2003; Friston et al., 2011). Anatomical labels for regions of activation were determined using the Anatomical Automatic Labeling (AAL2) toolbox (Rolls et al., 2015).

The brain activations found by the SPM univariate analyses (both one-sample *t*-test and two-sample *t*-test analyses) were only used to constrain the DCM nodes in this study.

## 2.8 Dynamic causal modeling

Bilinear DCM (Friston et al., 2003) with the deterministic option, as implemented in SPM12 (Revision 7219), was used for EC analysis. DCM has been described elsewhere (Ma et al., 2018). In brief, the bilinear DCM rests on some a priori selected brain regions (nodes), and the EC (in units of Hz) among these nodes are termed as endogenous (or fixed) connectivity. The experimental conditions (i.e., OW and NW) can serve as either driving inputs (to one or more DCM nodes), or modulator (factor eliciting change in EC), or both. The changes on the EC in response to the modulator are termed as modulation effects. The DCM parameters are optimized by minimizing the difference between the observed BOLD signal and the signal predicted by DCM and a hemodynamic model (Friston et al., 2003).

**2.8.1 DCM nodes—**DCM nodes were selected based on (1) theories about altered neurocircuits in substance use disorders (e.g., Fareed et al., 2017; Koob and Volkow, 2016), (2) a survey of neuroimaging studies of drug cue reactivity (e.g., Courtney et al., 2016; Hester and Luijten, 2014), (3) a review of previous fMRI studies using opioid cue reactivity tasks (see Introduction), and (4) the DCM nodes in the current analysis were selected if they fell within the areas that showed a difference in activation between groups (cluster $p < 0.05$, uncorrected). As suggested by one of the DCM developers in SPM archive (https://www.jiscmail.ac.uk/cgi-bin/webadmin?A2=spm;bba77b5a.1904), it is feasible to use a contrast of between-group differences to select DCM nodes if different scientific questions were asked and answered with the generalized linear model (GLM). Here, the GLM answered where in the brain is there a between-group difference in neural responses, whereas the DCM connectivity analysis answered which connectivities common to all the participants were more altered during the OW period than the NW period, and whether these connectivities were associated with the attentional bias. these criteria, the following six regions were selected as DCM nodes. Each node was a sphere with 6 mm radius, and the x, y, z values in mm are the MNI coordinates of the center of each node determined by the local t-test maximum of the fMRI activation cluster corresponding to that node: (1) left (L) anterior cingulate cortex (ACC) (x=−6, y=24, z=22); (2) right (R) medial orbitofrontal cortex (MOFC) (x=14, y=56, z=−4); (3) R posterior cingulate cortex (PCC) (x=6, y=−44, z=22); (4) L insula (x=−26, y=22, z=6); (5) R hippocampus (x=32, y=−6, z=−22); and (6) R caudate (x=16, y=0, z=22). The MOFC and ACC were selected as the prefrontal DCM nodes, consistent with a recent study showing their reliable role in cue reactivity in different substance use disorders (Hanlon et al., 2018).

**2.8.2 Driving input and EC modulator—**Following the procedure as described in (Ma et al., 2018), two parametric regressors, called “All Words” and “OW minus NW,” respectively, were created for the DCM analysis. The “All Words” regressor, which reflects the common features of the OW and NW, was used as the driving input to the DCM. The OW minus NW regressor, which reflects the special effect of OW over NW on EC, was used as a putative modulator of EC (i.e., an experimental factor eliciting change in EC). In the present study, the changes of ECs (relative to the endogenous connectivities) in response

to the modulator are termed as modulatory changes. By definition, a modulatory change reflects the change in an EC during the OW trials minus the change in EC during the NW trials.

**2.8.3 DCM Parametric Empirical Bayes (PEB) analysis—**The Parametric Empirical Bayes (PEB) analysis (Friston et al., 2016) was used to conduct group level analyses for the modulatory changes. Two primary PEB analyses were conducted using all the participants (pooled OUD and OUD+CUD participants): (1) testing the mean of each modulatory change across all the participants; and (2) testing the linear relationship (linear regression) between each modulatory change and the attentional bias across all participants. Given the paucity of study investigating the difference between the OUD and OUD+CUD individuals, we believe that it is scientifically and clinically important to investigate if the OUD individuals and the OUD+CUD individuals show different response or not when exposed to opioid cues. Thus, a preliminary PEB analysis (3) testing the group difference in each modulatory change between the OUD and OUD+CUD participants was conducted too. In order to evaluate the effects of alcohol use and cigarette smoking, above PEB analyses #2 and #3 were conducted again with alcohol use and amount of cigarette smoking as covariates. Note that alcohol use and cigarette smoking were not included as covariates in the first primary PEB analysis because such an analysis would test the linear relationship between EC and the first covariate while controlling the other covariates. Therefore, in order to evaluate the effects of alcohol use and cigarette smoking, PEB analyses #2 and #3 were repeated with alcohol use and amount of cigarette smoking as covariates. The advantage of the linear regression analysis within the DCM PEB framework is that the covariance among DCM parameters is automatically taken into consideration.

DCM PEB computes group level analyses using Bayesian posterior inference (Friston and Penny, 2003). Its key advantage is the lack of false positives, thus removing the need to contend with the multiple-comparison problem (Friston and Penny, 2003). In these posterior inferences, posterior probability (PP) is used as an indicator of the confidence in whether or not a modulatory change in a group is different from zero (or different compared to another group) or the confidence in the degree of linear relationship between variables. The PP ($0 \leq PP \leq 1$) is the conditional probability of the posterior density that is computed by DCM PEB using Bayes rule after the available information (the likelihood function and the prior probability density of the model's parameters) is taken into account (Friston and Penny, 2003). The higher the PP, the greater the confidence.

## 3. RESULTS

### 3.1 Task behavioral performance and abstinence

The in-scanner behavioral performance on the Stroop task and the abstinence duration are summarized in Table 1. As shown in Table 1, there were no significant differences between OUD and OUD+CUD participants in task behavioral performance (in terms of accuracy on OW or NW), nor attentional bias. The mean of the attentional bias was 12.8 ms and −2.8 ms for the OUD group and the OUD+CUD group respectively. The lack of group difference in the attentional bias could be related to the small sample size for the group

comparison (see Discussion) or the large variation (standard deviation was 31.02 ms and 30.07 ms respectively for the two groups). Only some of participants (9/13 OUD participants and 7/14 OUD+CUD) showed attentional bias (ΔRT > 0) during the task. At the group level, the average attentional bias was not significantly different from zero for the OUD ($t$=1.40, $df$=12, $p$=0.18), OUD+CUD ($t$=0.11, $df$=13, $p$=0.91), or all participants ($t$=0.73, $df$=26, $p$=0.47).

The duration of abstinence was not significantly different between OUD and OUD+CUD participants. Across all participants, Spearman correlation analysis found a significant negative correlation between attentional bias and abstinence duration ($rho$=−0.4535, uncorrected $p$=0.0175, Bonferroni corrected $p$=0.0350). A non-parametric (i.e., Spearmen) correlation analysis was used because the abstinence duration was found to be non-Gaussian distributed using the Anderson-Darling Normality Test (Test-Statistic: 1.4485, $p$=0.0017). A scatter plot of abstinence duration (weeks), and the attentional bias ΔRT (ms) during the Stroop task is shown in Figure 1 for the 27 participants.

### 3.2 Self-report craving

The measure of “current craving” (craving data from one OUD+CUD participant was missing) is summarized in Table 1. As shown in Table 1, craving was not significantly different between the OUD and OUD+CUD participants. There was no correlation between attentional bias and craving (Pearson correlation: $rho$=−0.0257, $p$=0.9007; Spearman correlation: $rho$=−0.0313, uncorrected $p$=0.8793, Bonferroni corrected $p$=1). The lack of significant correlation could be due to the fact that many participants reported zero craving (11 of 26 participants, evenly distributed among OUD and OUD+CUD participants). The craving measure was not used for testing the relationship with the EC measures due to this observation.

### 3.3 Head motion

For each motion parameter and each quantification method (cumulative or maximum), the mean and standard deviation are demonstrated in Table 2 for all the participants, OUD group, and OUD+CUD group. As shown in Table 2, none of the differences between groups for the cumulative head motion value was statistically significant after Bonferroni correction (corrected $p$≥0.48). In addition, none of the differences between groups for the maximal head motion value was statistically significant after Bonferroni correction (corrected $p$=1). For all the participants, the maximum of the summed head motion across x/y/z translations was 2.77 mm, and the maximum of the summed head motion across x/y/z rotations was 0.062 degree.

### 3.4 Brain activation used for constraining DCM nodes

The SPM12 second level two-sample $t$-test analysis, showed that compared to the OUD+CUD participants, the OUD participants had greater activation (Family-Wise-Error [FWE] corrected two-tailed cluster level $p < 0.05$) during opioid words relative to neutral words in a cluster which extended into portions of prefrontal, insular and striatal regions. See Figure 2 and Table 3 for the detailed information about this cluster. There was no significant positive or negative correlation between activation and abstinence duration for

the OUD group, for the OUD+CUD group, or for both groups combined (FWE corrected two-tailed cluster level $p > 0.9$). The second level SPM12 one-sample *t*-test analysis of the main effects across both groups combined did not reveal any significant positive (OW minus NW > 0) or negative (OW minus NW < 0) activation clusters (FWE corrected two-tailed cluster level $p > 0.1$), probably due to the significant difference in activation between the two groups.

## 3.5 DCM connectivity

**3.5.1 PEB analysis testing the modulatory changes against zero—**This analysis tested the modulatory changes against zero for all the participants combined (n=27). For each EC modulatory change, the mean modulatory changes and the corresponding PPs are shown in Table 4. This analysis found that the L ACC to R hippocampus EC (mean modulatory change [M] = 0.7398 Hz, PP = 1), and the L ACC to R PCC EC (M = 0.6779 Hz, PP = 1) had the largest modulatory changes.

**3.5.2 PEB linear regression analysis—**This analysis tested the linear regression between the EC modulatory changes and the attentional bias across all participants. Both a simple model (relationship between OUD and connectivity without alcohol use and amount of cigarette smoking as covariates) and a comprehensive model (with alcohol use and amount of cigarette smoking as covariates) were considered. In linear regression analysis, the *beta* coefficient is the slope of the linear relationship, i.e., the degree of change in the outcome variable per unit of the predictor variable. For example, a *beta* of 0.0092 indicates a change of 0.0092 Hz in modulatory change per each ms change of attentional bias. For each situation (simple model *vs.* comprehensive model) and each modulatory change, the *beta* and corresponding PP are shown in Table 4. These analyses found that when the simple model was used, the modulatory changes in L ACC to R hippocampus (*beta* = 0.0092, PP = 1) and the L ACC to R PCC EC (*beta* = 0.0046, PP = 1) were positively associated with the attentional bias. Notably, these were the two ECs that had the largest modulatory changes as found by the above analysis. After the alcohol use and amount of cigarette smoking were controlled in the comprehensive model, the positive linear relationship between the modulatory change on L ACC to R hippocampus was still reliable (*beta* = 0.0084, PP = 1); but the positive linear relationship between the modulatory change on L ACC to R PCC was no longer reliable (*beta* = 0.0034, PP = 0.7527).

**3.5.3 Preliminary PEB group difference analysis—**This preliminary analysis tested for a group difference in the EC modulatory change between the OUD participants (n=13) and the OUD+CUD participants (n=14). Again, both a simple model (without alcohol use and amount of cigarette smoking as covariates) and a comprehensive model (with alcohol use and amount of cigarette smoking as covariates) were considered. For each model (simple model and comprehensive model) and each modulatory change, the group difference, i.e., ΔM = M from OUD+CUD minus M from OUD, and the corresponding PP are shown in Table 4. This preliminary analysis found that whether the alcohol use and amount of cigarette smoking were entered as covariates or not, the OUD individuals had the same modulatory change in the L ACC to R hippocampus EC as the OUD+CUD participants (ΔM= 0 Hz, PP = 0).

**3.5.4 PEB analyses without left-handed participants—**To exclude the potential confounding effects of the participants with left-handedness, the above three analyses were similarly conducted by including the non-left-handed participants only. The results of these three analyses are shown in Table 5. When the simple model (without alcohol use and amount of cigarette smoking as covariates) was used, these analyses found similar results for the L ACC to R hippocampus EC. When the comprehensive model (with alcohol use and amount of cigarette smoking as covariates) was used, the PEB analyses did not converge, possibly because of model overfitting (a statistical situation in which too many parameters are included in the model such that the model cannot be justified by the data) (Everitt and Skrondal, 2010).

## 4. DISCUSSION

Using an opioid-word Stroop task and DCM, we investigated the directional neuronal connectivity related to drug-related attentional bias in OUD and OUD+CUD participants. To the best of our knowledge, these are the first observations to demonstrate that within the modeled DCM network, the L ACC to R hippocampus EC had the largest modulatory change (averaged across OUD and OUD+CUD participants) and that the modulatory change of this EC was positively associated with the attentional bias.

### 4.1 Attentional bias

The OUD participants were not significantly different from the OUD+CUD participants in behavioral performance, as reflected by both task accuracy and attentional bias (ΔRT). At the group level, the average ΔRT measure was not significantly greater than zero for OUD participants, OUD+CUD participants, or all participants combined, although some of the participants (n=9 for OUD, and n=7 for OUD+CUD) showed attentional bias (ΔRT>0) during the task. The lack of average attentional bias at the group level could be related to the relatively long abstinence duration (more than 10 weeks in average). This interpretation is supported by the significant negative correlation between the attentional bias and the abstinence duration. Specifically, the attentional bias measure was positive for participants in earlier abstinence, but negative (faster responses to OW than NW) in participants in later abstinence, resulting in an overall average that was not significantly different from zero at the group level. Notably, other research on attentional bias (Field et al., 2009) suggests that in some individuals in recovery (or even in some epochs of the task session within-participant), drug-connotations may be negatively-valenced. A similar correlation (negative correlation between the attentional bias and the abstinence duration) has been reported (Constantinou et al., 2010).

No significant correlation was found between the attentional bias and the participant craving measure in the present study. A meta-analysis (Field et al., 2009), however, showed that the correlation between attentional bias and craving was statistically significant but weak (rho=0.19), and was weaker when attentional bias was inferred indirectly by RT and when craving strength was low (Field et al., 2009). In the current study, the attentional bias was measured indirectly, and the craving strength was low (1.92 ± 2.68, with 10 as the maximum); thus these two factors may underlie the lack of association between the

attentional bias and the self-report craving. The low craving is not surprising for the OUD and OUD+CUD participants who were abstinent for approximately 12 weeks.

### 4.2 DCM effective connectivity

Within the modeled DCM network, the two ECs with the largest modulatory changes (averaged across all participants) originated from L ACC. The involvement of L ACC (rather than R ACC) was also reported in previous studies (Li et al., 2015; Li et al., 2012) investigating opioid cue reactivity. Importantly, the modulatory change of one of these two ECs (i.e., L ACC to R hippocampus EC) was significantly correlated with attentional bias. Consistent with multiple functions of the ACC (Bush et al., 2002), these results suggest ACC involvement in drug cue reactivity in OUD and OUD+CUD.

Consistent with our hypothesis, the primary DCM analysis found that the modulatory change in the L ACC to R hippocampus EC showed a significant positive correlation with attentional bias. We previously reported that during the cocaine-word Stroop task in CUD participants who did not have OUD, the modulatory change in the R ACC to R hippocampus EC was positive, and also was positively correlated with attentional bias (Ma et al., 2018). Thus, the findings with regard to the ACC to hippocampus EC are consistent across OUD, OUD+CUD, and CUD without OUD. In our previous study (Ma et al., 2018), we proposed that the increased strength of ACC to hippocampus EC may reflect ACC activation of hippocampal memories related to drug use, which was triggered by the drug cues. Alternatively, Dacher and Nugent (2011) suggested that there is a strong link between environmental cues and drug use, which could take place through drug induced signaling and plasticity in the hippocampus. Thus, the drug-word cue related increase in ACC to hippocampus EC may also be a factor in drug cue related signaling in the hippocampus. Given the consistency in findings across OUD participants (current study), OUD+CUD (current study), and CUD without OUD (Ma et al., 2018), an interesting question is whether the ACC to hippocampus EC is a common neurocircuit related to drug cue reactivity in all substance use disorders.

Consistent with our hypothesis, the preliminary DCM analysis showed that the modulatory change in the L ACC to R hippocampus EC was not different between OUD and OUD+CUD participants, supporting our speculation that the ACC to hippocampus EC may be a common neurocircuit related to drug cue reactivity across substance use disorders.

### 4.3 Clinical implications

The modeled DCM network has overlap with the central opioidergic pathways (Henriksen and Willoch, 2008). Methadone (Langleben et al., 2008), naltrexone (Langleben et al., 2014), and buprenorphine (Mei et al., 2010) can reduce drug cue-elicited activation of hippocampus in heroin users. Thus, further research would be needed to show whether these medications have effects on the ACC to hippocampus EC, and whether these effects may be related to therapeutic benefit for OUD and/or OUD+CUD patients.

### 4.4 Strengths and limitations

Strengths of this study include the use of the opioid-word Stroop task, which provides an objective behavioral measurement of cue reactivity (i.e., attentional bias), as well as the DCM PEB approach in the linear regression and group comparison analyses, in which the covariance among EC parameters was taken into account. Furthermore, this study focused on the modulatory change which reflects the effect of opioid cues on neurocircuitry. Limitations include: (1) Both within-group design (Goldstein et al., 2007; Hester and Garavan, 2009; Ma et al., 2018; Marhe et al., 2013) and between-group design (Li et al., 2015; Ray et al., 2015; Wang et al., 2014; Yang et al., 2009) have been used to study drug cue reactivity. Because data and participants were from a clinical trial of medication effects on OUD or OUD+CUD individuals, this study used a within-group design and focused on differences in connectivity among OUD individuals as they relate to attentional bias as a mechanism for OUD. The lack of controls could have increased the difficulty in interpreting the results. However, in light of findings that individual differences in attentional bias have been predictive of treatment dropout and relapse within treatment populations (Smith and Ersche, 2014; Zhang et al., 2018), we contend that our findings clinically meaningful. Moreover, our primary findings (related to the ACC to hippocampus EC) are consistent with the results found in a separate CUD population (Ma et al., 2018) and previous studies (e.g., Hanlon et al., 2018; Zhang et al., 2018) suggesting a similarity in mechanisms of drug cue reactivity across abused drug classes. These consistencies can improve confidence in the interpretation of the primary findings. (2) The sample size was small for the preliminary between-group analysis. However, the primary findings (related to the ACC to hippocampus EC) are consistent with the results found in a separate population of CUD patients performing a cocaine-word stroop tasks (Ma et al., 2018). This consistency reduces the likelihood that the primary results (related to ACC to hippocampus EC) were chance findings. We nevertheless conducted preliminary analyses testing the group differences between the OUD participants (n=13) and OUD+CUD participants (n=14), which did not find a group difference on the ACC to hippocampus EC. On the other hand, this preliminary DCM analysis suggested that the OUD individuals were different from the OUD+CUD participants in several ECs. These preliminary differences can be confirmed by future studies with larger sample size. (3) The EC modulatory changes were based on the contrast between OW and NW trials, and thus may have been slightly confounded by the sporadic incorrect responses (less than 6% for all trials). This limitation is inherited from the block design, which is a common design for the drug-related Stroop studies (Smith and Ersche, 2014). (4) Because computation time increases quadratically with the number of nodes in task-based DCM (Seghier and Friston, 2013), we had to carefully select nodes a priori based on preponderance of previous findings. Thus, left (but not right) ACC, and right (but not left) hippocampus were selected as DCM nodes. The involvement of L ACC (rather than R ACC) is consistent with previous studies on OUD (Li et al., 2015; Li et al., 2012). It is possible that cross-hemisphere connectivities rather intra-hemisphere connectivities are found to be relevant. For example, Zhang et al. (2017) reported that it was the cross-hemisphere (but not the intra-hemisphere) functional connectivity between PCC and temporal parietal junction showed significant correlation with consciousness. Other neural interconnectivities may also be important for opioid cue reactivity but may not have been identified in the current study because the connecting regions were not included as

DCM nodes. Future analyses with quantum computing and other technological advances will enable more comprehensive analyses. (5) fMRI runs with head motion less than 1 voxel (3.75 mm translation on any axis) were allowed for inclusion in the analysis. Thus, the head motion could have confounded the imaging results. A previous empirical study (Ardekani et al., 2001), however, indicated that SPM can effectively correct up to 10 mm initial misalignment (summed across x/y/z translations) without significant confounding effect. Our analysis on the head motion data indicated that the maximum of the summed head motion across x/y/z translations was only 2.77 mm, and all head motion was corrected using standard SPM techniques during the preprocessing of the fMRI data. Furthermore, there was no significant difference in any of the motion parameters (Table 2) between the OUD participants and the OUD+CUD participants. Based on the (Ardekani et al., 2001) finding and the results of our head motion analysis, we believe that the effect of head motion is unlikely to be a major factor in the results of this study. And (6) Attentional bias was inferred from reaction-time, and was not directly indexed by actual gaze-fixation as captured by eye-tracking. Future EC studies with a larger sample size, healthy control participants, and additional measures of attentional bias are warranted.

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## HIGHLIGHTS

- This study investigated drug-related attentional bias in opioid use disorder.
- Dynamic causal modeling was used to assess underlying neural circuits.
- Opioid cues caused increase in anterior cingulate cortex (ACC) to hippocampus effective connectivity.
- Greater increase of this connectivity was associated with greater attentional bias.
- The findings were consistent across opioid use disorder and cocaine use disorder.

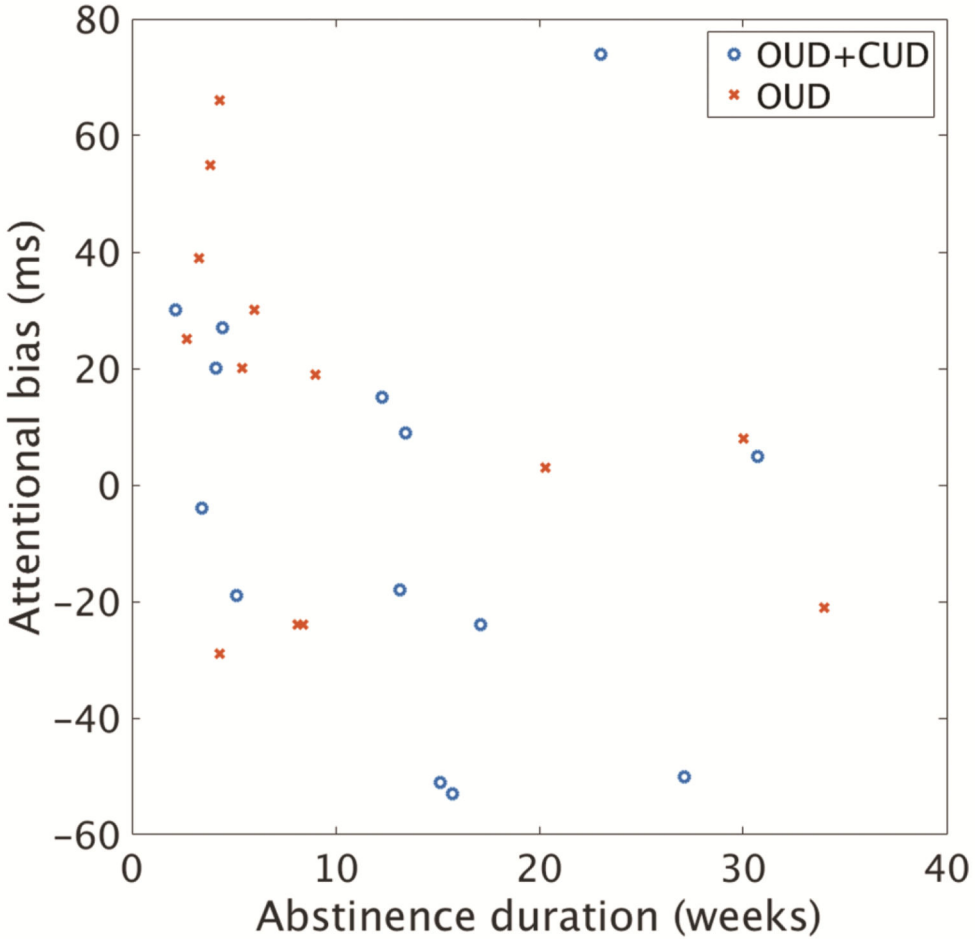


**Figure 1:**
Scatter plot of abstinence duration (weeks), and the attentional bias (ΔRT) (ms) during the opioid-word Stroop task for the 27 participants. Spearman correlation analysis found a significant negative correlation between these two measures (rho=−0.4535, uncorrected $p$=0.0175, Bonferroni corrected $p$=0.0350).

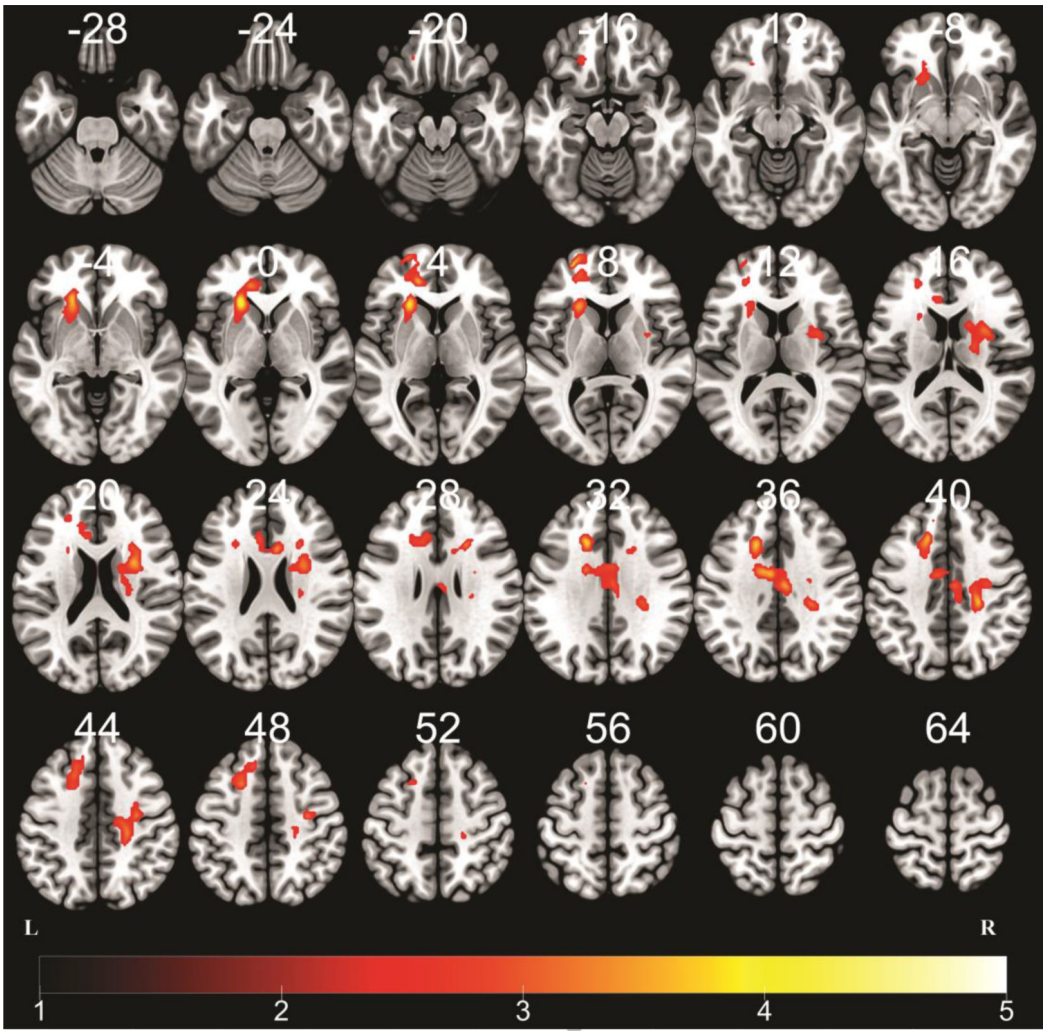


**Figure 2:**

Results of the SPM12 second level Random Effects two-sample t-test analysis, based on the OW minus NW contrast. The OUD participants had significantly greater (FWE corrected two-tailed cluster level $p < 0.05$) activation in this cluster than the OUD+CUD participants. Brain activations are overlaid in color on axial slices of the MNI template brain. The number above each slice indicates slice location (mm) of the MNI z coordinate. Scale on the color bar represents voxel t values. Left (L) side of each slice is left hemisphere of the brain, and right (R) side of each slice is right hemisphere of brain. The DCM nodes were constrained by the activations found by this analysis with uncorrected two-tailed cluster level $p < 0.05$.

**Table 1:**

Demographic data, substance use data, in-scanner behavioral performance, abstinence duration, and craving score of the subjects. AA=African American, C=Caucasian, F=female, M=male, L=left, R=right, AMBI=ambidextrous. Mean and standard deviation were reported for the continuous variables. The Fisher's exact test on handedness was for the portion of L-handed participants. The *p* values were two-tail. Alcohol and smoking use data from two OUD+CUD participants was missing due to technical problems. OW=opioid words. NW=neutral words.

| Parameter | All (n=27) | OUD (n=13) | OUD+CUD (n=14) | Statistics (OUD vs. OUD+CUD) |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age (years) (range) | 32 ± 8 (19 – 47) | 32 ± 8 (22 – 46) | 32 ± 8 (19 – 47) | $t$=0.01, $p$=0.99 |
| Ethnicity | 7 AA, 20 C | 4 AA, 9 C | 3 AA, 11 C | Fisher's exact test $p$=0.68 |
| Sex | 8 F, 19 M | 4 F, 9 M | 4 F, 10 M | Fisher's exact test $p$=0.99 |
| Handedness | 5 L, 2 AMBI, 20 R | 3 L, 10 R | 2 L, 2 AMBI, 10 R | Fisher's exact test $p$=1 |
| Education (years) (range) | 13 ± 2 (11 -18) | 13 ± 1 (11 -15) | 13 ± 2 (12 -18) | $t$=1.16, $p$=0.25 |
| **Substance use data** | | | | |
| Lifetime opioid use (years) | 7.7 ± 6.0 | 9.3 ± 6.9 | 6.1 ± 4.8 | $t$=1.41, $p$=0.17 |
| Past 30 days opioid use (days) | 5.6 ± 8.1 | 6.2 ± 8.0 | 5.1 ± 8.4 | $t$=0.34, $p$=0.73 |
| Lifetime cocaine use (years) | N/A | N/A | 4.2 ± 5.4 | N/A |
| Past 30 days cocaine use (days) | N/A | N/A | 2.9 ± 7.0 | N/A |
| Lifetime alcohol use (kg) | 112.8 ± 196.0 | 78.0 ± 96.7 | 150.4 ± 265.9 | $t$=0.92, df =23, $p$=0.37 |
| Lifetime cigarette use (years) | 12.5 ± 6.5 | 12.4 ± 6.4 | 12.6 ± 7.0 | $t$=0.07, df =23, $p$=0.94 |
| Number of cigarettes used per day | 12.6 ± 6.5 | 13.9 ± 5.6 | 11.3 ± 7.1 | $t$=1.02, df =23, $p$=0.32 |
| **In-scanner behavior** | | | | |
| Accuracy (OW) | 95% ± 5% | 95% ± 7% | 96% ± 3% | $t$=0.49, $p$=0.63 |
| Accuracy (NW) | 95% ± 7% | 94% ± 9% | 95% ± 4% | $t$=0.38, $p$=0.71 |
| Attentional bias (ms) | 4.74 ± 34.03 | 12.85 ± 31.02 | −2.79 ± 30.07 | $t$=1.33, $p$=0.20 |
| **Abstinence duration** | | | | |
| Opiate (weeks) | 12.1 ± 9.7 | 10.7 ± 10.5 | 13.4 ± 9.1 | $t$=0.72, $p$=0.48 |
| Cocaine (weeks) | N/A | N/A | 14.8 ± 12.6 | N/A |
| **Craving** | | | | |
| Current craving | 1.92 ± 2.68 | 1.05 ± 1.40 | 2.78 ± 3.37 | $t$=1.71, df =24, $p$=0.10 |

**Table 2.**

Mean and standard deviation of the head motion parameters, for the included participants. The mean and the standard deviation were quantified in terms of cumulative value (see the text) and the maximal value (see the text). Student t-test was used to test group difference in each of the parameters. For each test, the degree of freedom was 25. All the p values were Bonferroni corrected (uncorrected p×8).

| | | **x translation (mm)** | **y translation (mm)** | **z translation (mm)** | **Summed x/y/z translation (mm)** | **y translation (mm)** | **z translation (mm)** | **z rotation (degree)** | **Summed x/y/z rotation (degree)** |
|---|---|---|---|---|---|---|---|---|---|
| Cumulative | All | 9.6±6.0 | 10.5±9.7 | 23.5±26.3 | 43.67±34.02 | 0.45±0.58 | 0.23±0.17 | 0.19±0.14 | 0.86±0.73 |
| | OUD | 10.3±7.3 | 12.1±11.9 | 29.3±35.2 | 51.66±44.10 | 0.63±0.80 | 0.29±0.20 | 0.22±0.18 | 1.13±0.95 |
| | OUD+CUD | 9.0±4.7 | 9.0±7.3 | 18.2±13.3 | 36.25±19.9 | 0.28±0.17 | 0.17±0.13 | 0.16±0.10 | 0.61±0.32 |
| | Statistics | $t$=0.55; $p$=0.58 | $t$=0.82; $p$=0.42 | $t$=1.10; $p$=0.28 | $t$=1.19; $p$=0.25 | $t$=1.60; $p$=0.12 | $t$=1.86; $p$=0.07 | $t$=1.08; $p$=0.29 | $t$=1.94; $p$=0.06 |
| Maximal | All | 0.19±0.13 | 0.21±0.16 | 0.50±0.52 | 0.90±0.67 | 0.009±0.009 | 0.004±0.003 | 0.004±0.003 | 0.016±0.012 |
| | OUD | 0.18±0.12 | 0.24±0.20 | 0.56±0.65 | 0.98±0.83 | 0.011±0.012 | 0.005±0.004 | 0.004±0.003 | 0.020±0.016 |
| | OUD+CUD | 0.20±0.15 | 0.19±0.11 | 0.44±0.38 | 0.83±0.50 | 0.007±0.004 | 0.003±0.002 | 0.004±0.003 | 0.013±0.007 |
| | Statistics | $t$=0.38; $p$=0.71 | $t$=0.81; $p$=0.42 | $t$=0.59; $p$=0.56 | $t$=0.57; $p$=0.57 | $t$=1.18; $p$=0.25 | $t$=1.66; $p$=0.11 | $t$=0.00; $p$=1.00 | $t$=1.49; $p$=0.15 |

**Table 3.**

Results of the SPM12 second level Random Effects two-sample *t*-test comparison between the OUD and OUD+CUD groups, based on the OW minus NW contrast. A significant cluster (two-tail FWE corrected cluster $p < 0.05$) was found which spanned portions of the listed anatomical regions. Also shown in the table are the AAL2 atlas index of each anatomical region, the number of voxels within each anatomical region that belong to the significant cluster, the relative maximum voxel T value within each region, and the MNI coordinates (x, y, and z, in mm) of the relative maximum voxel T. OFC = orbitofrontal cortex, SFG = Superior frontal gyrus, L = left, and R = right.

| Anatomical region | AAL2 index | number of voxels | max T | x | y | z |
|---|---|---|---|---|---|---|
| R precentral gyrus | 2002 | 34 | 3.12 | 34 | −12 | 46 |
| L SFG, dorsolateral | 2101 | 362 | 4.13 | −28 | 58 | 6 |
| L middle frontal gyrus | 2201 | 94 | 3.61 | −30 | 56 | 8 |
| L OFC in posterior orbital gyrus | 2821 | 14 | 2.87 | −20 | 32 | −16 |
| L insula | 3001 | 45 | 3.41 | −26 | 22 | 6 |
| R insula | 3002 | 18 | 2.97 | 34 | 0 | 14 |
| L anterior cingulate cortex | 4001 | 92 | 3.98 | −6 | 24 | 22 |
| R anterior cingulate cortex | 4002 | 20 | 3.40 | 8 | 16 | 24 |
| L middle cingulate cortex | 4011 | 168 | 3.61 | −6 | −6 | 36 |
| R middle cingulate cortex | 4012 | 251 | 3.51 | 6 | −14 | 34 |
| L caudate | 7001 | 34 | 3.42 | −18 | 24 | −2 |
| R caudate | 7002 | 64 | 3.84 | 16 | 0 | 22 |
| L putamen | 7011 | 114 | 3.25 | −20 | 20 | −2 |
| R putamen | 7012 | 53 | 2.96 | 30 | 2 | 14 |

**Table 4.**

The results of the DCM PEB analyses for all participants. M = mean of the modulatory change in EC (Hz), ΔM = M from OUD+CUD minus M from OUD. PP = Posterior Probability. *beta* = regression coefficient (slope) of the linear regression of EC on attentional bias (ΔRT). For example, a *beta* of 0.001 indicates a change in EC of 0.001 Hz per each ms change of attentional bias.

| EC | Group mean across all participants | | Linear regression of EC on ΔRT across all participants without alcohol and smoking as covariates | | Linear regression of EC on ΔRT across all participants with alcohol and smoking as covariates | | Group difference between OUD+CUD and OUD participants without alcohol and smoking as covariates | | Group difference between OUD+CUD and OUD participants with alcohol and smoking as covariates | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **M** | **PP** | **beta** | **PP** | **beta** | **PP** | **ΔM** | **PP** | **ΔM** | **PP** |
| L ACC to R OFC | 0.3728 | 1 | −0.0058 | 1 | −0.0024 | 0.6866 | 0 | 0 | 0.1122 | 1 |
| L ACC to R PCC | 0.6779 | 1 | 0.0046 | 1 | 0.0034 | 0.7527 | −0.1688 | 1 | −0.2264 | 1 |
| L ACC to L INS | 0.2821 | 1 | 0.0028 | 1 | 0.0058 | 1 | −0.0768 | 1 | 0 | 0 |
| **L ACC to R HIPP** | **0.7398** | **1** | **0.0092** | **1** | **0.0084** | **1** | **0** | **0** | **0** | **0** |
| L ACC to R CAU | 0 | 0 | 0.0128 | 1 | 0.0073 | 1 | −0.2403 | 1 | −0.3551 | 1 |
| R OFC to L ACC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| R OFC to R PCC | 0 | 0 | −0.0030 | 1 | 0 | 0 | 0.1235 | 1 | 0.1674 | 1 |
| R OFC to L INS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.1255 | 1 |
| R OFC to R HIPP | 0 | 0 | 0 | 0 | 0.0050 | 1 | −0.1775 | 1 | −0.1352 | 1 |
| R OFC to R CAU | 0 | 0 | −0.0019 | 0.8211 | −0.0042 | 1 | 0.0631 | 0.8919 | 0 | 0 |
| R PCC to L ACC | −0.0864 | 0.7809 | 0 | 0 | 0 | 0 | 0 | 0 | −0.0910 | 1 |
| R PCC to R OFC | 0 | 0 | 0.0044 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| R PCC to L INS | −0.1666 | 0.9995 | 0.0017 | 0.7240 | 0 | 0 | 0 | 0 | 0 | 0 |
| R PCC to R HIPP | −0.1416 | 0.9643 | 0 | 0 | −0.0052 | 1 | 0 | 0 | 0 | 0 |
| R PCC to R CAU | 0.0855 | 0.7622 | −0.0047 | 1 | −0.0035 | 1 | 0 | 0 | 0 | 0 |
| L INS to L ACC | 0 | 0 | 0.0022 | 0.9927 | 0.0047 | 1 | 0 | 0 | 0 | 0 |
| L INS to R OFC | 0 | 0 | 0.0049 | 1 | 0 | 0 | −0.0418 | 0.6677 | 0.1006 | 1 |
| L INS to R PCC | −0.3836 | 1 | 0.0098 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| L INS to R HIPP | 0 | 0 | 0.0043 | 1 | 0 | 0 | −0.0342 | 0.4874 | −0.1869 | 1 |
| L INS to R CAU | −0.2578 | 0.9999 | −0.0065 | 1 | 0 | 0 | 0.1439 | 1 | 0.1367 | 1 |

| EC | Group mean across all participants | | Linear regression of EC on ΔRT across all participants without alcohol and smoking as covariates | | Linear regression of EC on ΔRT across all participants with alcohol and smoking as covariates | | Group difference between OUD+CUD and OUD participants without alcohol and smoking as covariates | | Group difference between OUD+CUD and OUD participants with alcohol and smoking as covariates | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **M** | **PP** | **beta** | **PP** | **beta** | **PP** | **ΔM** | **PP** | **ΔM** | **PP** |
| R HIPP to L ACC | 0.0615 | 0.6641 | 0 | 0 | 0 | 0 | 0.0382 | 0.9346 | 0 | 0 |
| R HIPP to R OFC | 0 | 0 | −0.0035 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| R HIPP to R PCC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| R HIPP to L INS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | −0.0622 | 0.8204 |
| R HIPP to R CAU | 0 | 0 | 0.0024 | 1 | 0 | 0 | 0 | 0 | 0.0947 | 1 |
| R CAU to L ACC | −0.2860 | 1 | 0 | 0 | 0 | 0 | −0.1670 | 1 | −0.1082 | 1 |
| R CAU to R OFC | 0 | 0 | −0.0030 | 1 | 0 | 0 | 0.1655 | 1 | 0 | 0 |
| R CAU to R PCC | 0 | 0 | −0.0083 | 1 | 0 | 0 | 0.1745 | 1 | 0.1650 | 1 |
| R CAU to L INS | 0 | 0 | −0.0055 | 1 | −0.0055 | 1 | 0 | 0 | 0 | 0 |
| R CAU to R HIPP | −0.3622 | 1 | −0.0064 | 1 | −0.0050 | 1 | 0.0315 | 0.4916 | 0.1925 | 1 |

**Table 5.**

The results of the DCM PEB analyses for all non-left-handed participants. M = mean of the modulatory change in EC (Hz), ΔM = M from OUD+CUD minus M from OUD. PP = Posterior Probability. *beta* = regression coefficient (slope) of the linear regression of EC on attentional bias (ΔRT). For example, a *beta* of 0.001 indicates a change in EC of 0.001 Hz per each ms change of attentional bias.

| EC | Group mean across all non-left-handed participants | | Linear regression analysis of EC on ΔRT across all non-left-handed participants without alcohol and smoking as covariates | | Group difference between non-left-handed OUD+CUD and non-left-handed OUD participants without alcohol and smoking as covariates | |
|---|---|---|---|---|---|---|
| | **M** | **PP** | ***beta*** | **PP** | **ΔM** | **PP** |
| L ACC to R OFC | 0 | 0 | −0.0102 | 1 | 0.1525 | 1 |
| L ACC to R PCC | 0.4210 | 1 | 0.0077 | 1 | −0.1274 | 1 |
| L ACC to L INS | 0 | 0 | 0.0025 | 1 | 0 | 0 |
| **L ACC to R HIPP** | **0.4087** | **1** | **0.0128** | **1** | **0.0990** | **1** |
| L ACC to R CAU | −0.1236 | 0.8453 | 0.0128 | 1 | −0.2584 | 1 |
| R OFC to L ACC | 0 | 0 | −0.0018 | 0.6325 | −0.0552 | 1 |
| R OFC to R PCC | 0.4527 | 1 | 0 | 0 | 0.0956 | 1 |
| R OFC to L INS | 0.1252 | 0.9073 | 0.0018 | 0.6811 | 0.1256 | 1 |
| R OFC to R HIPP | 0.0750 | 0.5659 | −0.0028 | 1 | −0.1562 | 1 |
| R OFC to R CAU | 0.3338 | 1 | 0.0071 | 1 | 0 | 0 |
| R PCC to L ACC | 0 | 0 | 0 | 0 | 0 | 0 |
| R PCC to R OFC | 0.1231 | 0.9907 | 0.0060 | 1 | −0.0687 | 1 |
| R PCC to L INS | −0.0968 | 0.9029 | 0 | 0 | 0 | 0 |
| R PCC to R HIPP | 0 | 0 | 0 | 0 | −0.0467 | 1 |
| R PCC to R CAU | 0 | 0 | −0.0057 | 1 | 0 | 0 |
| L INS to L ACC | 0 | 0 | 0.0026 | 1 | 0.1467 | 1 |
| L INS to R OFC | 0 | 0 | 0.0052 | 1 | 0 | 0 |
| L INS to R PCC | −0.7274 | 1 | 0.0058 | 1 | −0.0433 | 0.9935 |
| L INS to R HIPP | −0.1422 | 0.8427 | −0.0024 | 0.8360 | −0.0588 | 1 |
| L INS to R CAU | −0.2302 | 1 | −0.0029 | 1 | 0.0805 | 1 |
| R HIPP to L ACC | 0 | 0 | −0.0016 | 0.5628 | 0.0172 | 0.6152 |
| R HIPP to R OFC | 0 | 0 | −0.0060 | 1 | 0.0876 | 1 |
| R HIPP to R PCC | 0 | 0 | −0.0033 | 1 | 0 | 0 |
| R HIPP to L INS | 0 | 0 | 0 | 0 | 0.0329 | 0.9801 |
| R HIPP to R CAU | −0.1315 | 0.9845 | −0.0020 | 0.6863 | 0 | 0 |
| R CAU to L ACC | −0.1939 | 1 | 0 | 0 | −0.2216 | 1 |
| R CAU to R OFC | 0.1900 | 1 | 0 | 0 | 0.0719 | 1 |
| R CAU to R PCC | 0.3434 | 1 | −0.0035 | 1 | 0.1302 | 1 |
| R CAU to L INS | 0 | 0 | −0.0028 | 1 | 0 | 0 |
| R CAU to R HIPP | −0.2936 | 1 | −0.0027 | 1 | 0.0967 | 1 |