

Interhemispheric insular and inferior frontal connectivity are associated with substance abuse in a psychiatric population



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ABSTRACT

Substance abuse is highly comorbid with major psychiatric disorders. While the neural underpinnings of drug abuse have been studied extensively, most existing studies compare drug users without comorbidities and healthy, non-user controls. Such studies do not generalize well to typical patients with substance abuse disorders. Therefore, we studied a population of psychiatric inpatients ($n = 151$) with a range of mental illnesses. Psychiatric disorders were diagnosed via structured interviews. Sixty-five percent of patients met criteria for at least one substance use disorder. Patients were recruited for resting state functional connectivity (RSFC) and diffusion tensor imaging (DTI) experiments to examine the interhemispheric connectivity between brain regions hypothesized to be involved in drug addiction, namely: the inferior, medial, and superior frontal gyri; insula; striatum; and anterior cingulate cortex. The World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHOA) questionnaire was used to further assess drug use. An association between use of tobacco, alcohol, cocaine, sedatives, and hallucinogens with increased insular interhemispheric connectivity was observed. In addition, increased inferior frontal gyrus interhemispheric connectivity was associated with amphetamine and inhalant use. Our results suggest that increased inter-hemispheric insula connectivity is associated with the use of several drugs of abuse. Importantly, psychiatric inpatients without a history of drug dependence were used as an ecologically valid control group rather than the more typical comparison between “mentally ill vs. healthy control” populations. We suggest that dysfunction of interhemispheric connectivity of the insula and to a lesser extent of the inferior frontal gyrus, are related to drug abuse in psychiatric populations.

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1. Introduction

Substance use disorders (SUDs) are a major public health burden and are the leading cause of premature mortality among individuals with mental disorders (Whiteford et al., 2013). SUDs are

often comorbid with other psychiatric illnesses, such as depression and anxiety, making them difficult to study in isolation (Kessler et al., 2005). Thus, studies of SUDs that do not consider comorbid conditions are potentially misleading, a common problem in neuroimaging studies. Frequently, SUD individuals are excluded from research studies due to their comorbidities, despite the high incidence of comorbid conditions with the SUD population being studied. For example, in studies of tobacco abuse, individuals who are depressed or who also use marijuana or cocaine are typically excluded when they are identified, but may inadvertently be included if participants lie about their drug use or have not been diagnosed with a psychiatric condition. Although this reductionist

Abbreviations: SUDs, Substance use disorders; RSFC, Resting state functional connectivity; DTI, diffusion tensor imaging; RDoC, Research Domains Criteria; WHOA, World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test; iFG, inferior frontal gyrus.

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approach has advanced the field's understanding of many disorders, psychiatric research as a whole is undergoing a shift towards a multi-dimensional approach to psychopathology in an effort to identify cross-cutting forms of functional impairment (e.g., The Research Domains Criteria, RDoC; (Insel et al., 2010)).

The current study invited all patients entering a single inpatient psychiatric clinic to participate without any co-morbidity exclusion criteria, ensuring a more representative sample of individuals with SUDs, in accordance with RDoC principles. Standardized clinical assessments were collected, including the Structured Clinical Interview for DSM-IV (SCIDI/II); and the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHOA). This study also collected structural and functional brain imaging data. Structural measures included high-resolution T1 anatomical images and diffusion tensor imaging (DTI) of white matter fiber pathways. Functional measures included resting state functional connectivity (RSFC).

The current case-control study examined interhemispheric functional connectivity and white matter structural connectivity among psychiatric patients with and without SUDs. Connectivity between a series of cortical and subcortical areas hypothesized to be involved in drug abuse was examined, including the insula, frontal gyri, striatum and anterior cingulate. Previous studies have demonstrated altered interhemispheric connectivity in cocaine abuse (Kelly et al., 2011) and in cannabis abuse (Orr et al., 2013). In the current study, correlations between SUD (as determined using the SCID2 and WHOA) and interhemispheric connectivity were characterized in a relatively large clinical sample of 151 patients.

2. Methods

Participants were drawn from a larger study of psychiatric inpatients from the Menninger Clinic in Houston, TX, USA. The majority of inpatients were admitted for treatment of co-occurring psychiatric illnesses, including major depression, anxiety disorders, personality disorders, and SUD. Patients were invited to participate during the admission process. In some cases, patients were not deemed stable enough

to participate. These patients were invited to participate once they were stabilized. All participation was voluntary with approximately 72% of those patients approached consenting to participate since study inception in December of 2012.

2.1. Participants

A total of 178 adult inpatients participated in the neuroimaging component of the study. Of those, 27 were excluded from the final analysis due to excessive movement (>2 mm during RSFC) or because they did not complete the task. The remaining sample consisted of 151 patients (66 female) between the ages of 18 and 70 (average 32 ± 1 year) and with an average length of clinic stay of $45 \text{ days} \pm 1$ day. Standardized psychiatric assessments were conducted as close to admission as possible (SCIDI/II average time: 8 ± 0.4 days post-admission). The most common diagnoses included depression, anxiety, SUDs, and other psychiatric comorbidities (Fig. 1A). To evaluate substance use and dependence, the SCIDI alcohol abuse and dependence (pooled) and substance abuse and dependence (pooled) were administered to patients along with the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHOA). The WHOA consists of a total score and sub-scores for different drugs. There were patients with high, moderate, and low scores for all drugs specified in the WHOA. Alcohol, tobacco, and cannabis were most prevalent in this sample (Fig. 1B). SUD was more prevalent in male patients than female patients (75% vs. 53% Chi-square t test $p < 0.01$). SUD and non-SUD groups were matched for ethnicity (98% Caucasian vs. 96% Caucasian, respectively) and age (30 ± 1 years vs. 33 ± 2 years, respectively). Comorbidities were roughly the same in SUD and non-SUD patients in: Depression (non-SUD 38%, SUD 40%); anxiety (non-SUD 50%, SUD 53%); bipolar (non-SUD 17%, SUD 14%); and personality disorders (non-SUD 41%, SUD 37%).

2.2. Imaging

Following informed consent, patients were scanned in a 3T Siemens Trio MR scanner in the Center for Advanced MR Imaging at Baylor College of Medicine in Houston, TX USA. An ~ 4.5 min structural MPRAGE sequence (TE = 2.66 ms, TR = 1200 ms, flip angle = 12° , 256×256 matrix, 160 one mm axial slices at $1 \times 1 \times 1$ mm voxels) was collected followed by a 5 min resting state scan (RSFC: TE = 40 ms, TR = 2 s, flip angle = 90° , $3 \times 3 \times 3$ mm voxels, eyes open or closed). A large "X" was displayed on the screen during the RSFC scan and patients were instructed to keep their eyes open or closed and to relax. RSFC data were pre-processed using the SPM8 software (The Wellcome Trust, London, UK). Pre-processing included: realignment to the first time series image, co-registration to the mean image, normalization to the MNI EPI template, and smoothing with a 6 mm full width at high maximum (FWHM) Gaussian smoothing kernel. Patients that moved more than 2 mm ($N = 27$) during the 5 min RSFC scan were not included in the final RSFC analysis.

Regions of Interest (ROIs) for inferior, medial, and superior frontal gyri (iFG, mFG, sFG), insula, striatum, and anterior cingulate cortex (ACC) were created in AFNI (Cox, 1996) using the MNI atlas. The Matlab CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) was then used to analyze RSFC data. Grey matter, white matter, and cerebrospinal fluid were segmented. Movement identified during pre-processing was included as 6 regressors of no interest. Cerebrospinal fluid and white matter were also included as regressors. After processing, the Fisher's z -transformed correlation coefficients between the different seeds for each subject were identified and analyzed.

After RSFC imaging, DTI was performed (61 transversal 2 mm no gap slices with a voxel size of $2 \times 2 \times 2$ mm and phase encoding direction: A-P, FOV = 256×256 mm, TR = 9.4 s, TE = 91 ms, matrix size: 128×128 , echo spacing: 73 ms, diffusion directions: 71 unique directions at $b_0 = 1000 \text{ s/mm}^2$ with 8 repetitions at $b_0 = 0 \text{ s/mm}^2$, duration: 12:32 min). Due to FOV and slice selection, the cerebellum and posterior occipital lobes were not fully captured for every subject.

2.3. Volumetric parcellation

Freesurfer version 5.3 (<http://surfer.nmr.mgh.harvard.edu>) was used to perform segmentation and estimation of both cortical and subcortical volume (Dale et al., 1999). Freesurfer software uses automated routines to remove non-brain tissue (e.g. skull removal), Talairach transform each brain, segment subcortical grey and white matter structures, and then parcellate the cerebral cortex into anatomically defined units based on gyral and sulcal structures (Dale et al., 1999).

2.4. Tract-Based Spatial Statistics

Tract-Based Spatial Statistics (TBSS; (Smith et al., 2006)) in FSL (Smith et al., 2004) were used to calculate voxelwise statistics for whole brain FA. Diffusion weighted images (DWIs) were preprocessed, FA maps were created, and TBSS analyses were conducted using a custom analysis pipeline described elsewhere (Savjani et al., 2014). SUD patients were contrasted with non-SUD patients, adjusting for continuous demographic covariates including gender, ethnicity, and age. Categorical binary psychiatric illness status (depression, anxiety, and bipolar disorder) was also adjusted in the analysis. Covariates were mean centered across all participants. Using FSL's randomize tool (Winkler et al., 2014), a non-parametric permutation method for inference thresholding was used to analyze 10,000 permutations

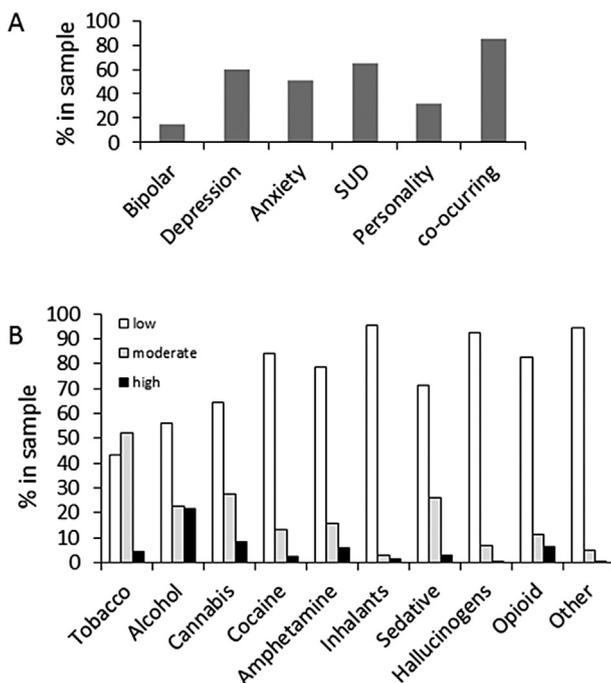


Fig. 1. Diagnoses and WHOA scores. A) The most common diagnoses among the 151 inpatient sample. B) WHOA scores (low, medium, and high levels of dependence shown as percentages of the whole sample) on the psychiatric patients at The Menninger Clinic used in this study.

to generate null distributions for the general linear model. Significance maps were clustered using threshold-free cluster enhancement (TFCE) and p -values were corrected by controlling family-wise error (FWE) and thresholded at $p < 0.05$.

2.5. Statistics

Linear regressions of WHOA scores (total or individual drugs) versus inter-hemispheric RSFC were performed. All means are expressed as mean \pm SEM. Significance was set at $p < 0.05$ with Bonferroni correction for number of regions compared.

3. Results

3.1. Increased interhemispheric insular and inferior frontal gyrus RSFC were associated with SUD

Left and Right RSFC coefficients were calculated for 6 ROIs for each patient: iFG, mFG, sFG, insula, striatum, and ACC. To determine if group differences in RSFC across these regions were associated with drug use, correlations between WHOA-total scores and RSFC were performed for each ROI, followed by linear regression. Significant correlations between interhemispheric RSFC and WHOA-total score were observed in iFG ($p_{\text{corrected}} < 0.05$) and insula ($p_{\text{corrected}} < 0.001$) (Fig. 2). No correlation between WHOA score and interhemispheric RSFC was observed in the other regions (mFG, sFG, striatum, and ACC) following Bonferroni correction for multiple comparisons (data not shown). While the sample contained a higher proportion of males in the SUD group, separate analysis of males and females revealed no differences in WHOA-total vs. Right/Left insular or Right/Left iFG RSFC correlations.

3.2. Group differences in insular and inferior frontal gyrus interhemispheric RSFC were associated with specific drugs of abuse

To study whether the interhemispheric RSFC of the insula and the iFG are associated with SUD in general or with specific drugs of abuse, RSFC in insula and iFG was compared against WHOA subscores for tobacco, alcohol, cocaine, sedatives, hallucinogens, amphetamines, inhalants, cannabis, opioids, and other drugs. Interhemispheric insular RSFC was significantly higher in patients with WHOA dependence subscores for: tobacco ($p_{\text{uncorrected}} < 0.01$), alcohol ($p_{\text{uncorrected}} < 0.001$), cocaine ($p_{\text{uncorrected}} < 0.02$), sedatives ($p_{\text{uncorrected}} < 0.005$), hallucinogens ($p_{\text{uncorrected}} < 0.005$), and “other”

drugs ($p_{\text{uncorrected}} < 0.05$). Increases in iFG interhemispheric RSFC were associated with use of amphetamines ($p_{\text{uncorrected}} < 0.05$) and inhalants ($p_{\text{uncorrected}} < 0.01$). Opioid or cannabinoid use did not alter RSFC correlations in insula or iFG (Table 1).

3.3. Insula and inferior frontal gyrus volume in SUD patients

Given the observed increases in insula and iFG interhemispheric RSFC in patients with SUD compared to non-SUD patients, volumetric analysis of these regions was performed using Freesurfer to determine if these connectivity differences were related to structural differences between SUD and non-SUD patients (Fig. 3). No differences in insula size were found between groups, however the right iFG was significantly smaller in SUD patients (t test, $p < 0.05$).

3.4. Lower FA in SUD

Fractional Anisotropy (FA) was measured using Tract-Based Spatial Statistics (TBSS) as a means of assessing white matter structure and connectivity in SUD and non-SUD patients. A significant reduction in FA was observed in the corpus callosum, internal capsule, corona radiata, and other white matter tracks in SUD patients once gender, ethnicity, age, depression, anxiety, and bipolar spectrum status were controlled for (Fig. 4 A–C, $p < 0.05$ FWE corrected). Remaining white matter tracks did not differ significantly between groups, although FA in SUD white matter tracks were consistently lower than FA in non-SUD patients. The corpus callosum as the major substrate of interhemispheric connectivity was further analyzed based on the discovery of interhemispheric RSFC differences in the two patient groups. WHOA-total SUD severity, however, did not correlate with corpus callosum FA (Fig. 4D).

4. Discussion

We show here that RSFC between the right and the left insula (and to a lesser extent between the right and left iFG) is positively correlated with substance use in a general inpatient psychiatric population. The primary strength of these observations is the ecological validity of the sample that derives from studying a complete psychiatric population in accordance with RDoC (Insel

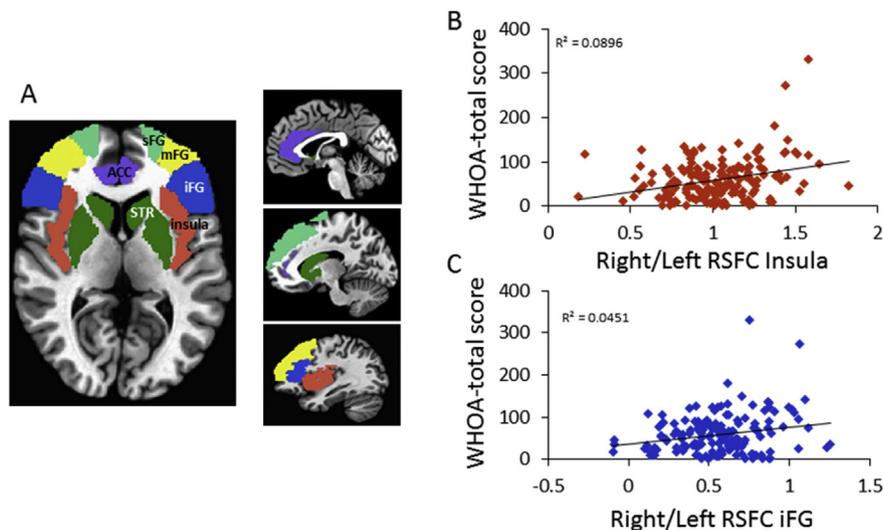


Fig. 2. A) ROIs: bilateral anterior cingulate cortex (ACC), insula, striatum, and superior (sFG), medial (mFG), and inferior (iFG) frontal gyri. Left panel, transversal view. Right panels, sagittal views (more medial on top, more lateral on bottom). B, C) Positive correlations between WHOA-total score and the RSFC between right and left B) insula ($p < 0.001$) and C) inferior frontal gyrus ($p < 0.05$). p values were obtained from linear regression analyses and Bonferroni-corrected for 6 comparisons.

Table 1
Results of linear regression analysis between Interhemispheric RSFC and WHOA drug-specific scores. Ins: insula; iFG: inferior frontal gyrus. Tob: tobacco, Alc: alcohol, Cann: cannabinoids, Coc: cocaine, Amp: amphetamine, Inh: inhalants, Sed: sedatives, Hal: hallucinogens, Opi: opioids, Other: “other” drugs. r^2 : linear regression goodness of fit. p : linear regression p value. Bold p values denote $p < 0.05$.

		Tob	Alc	Cann	Coc	Amp	Inh	Sed	Hal	Opi	Other
Ins	r^2	0.045	0.0691	0.005	0.037	0.0067	0.0059	0.0605	0.0305	0.02	0.025
	p	0.007	0.0008	0.37	0.015	0.3	0.3	0.0018	0.0028	0.07	0.045
iFG	r^2	0.023	0.01	0.0096	0.014	0.027	0.0476	0.0079	0.0146	0.016	0.01
	p	0.054	0.2	0.22	0.13	0.036	0.006	0.27	0.13	0.11	0.21

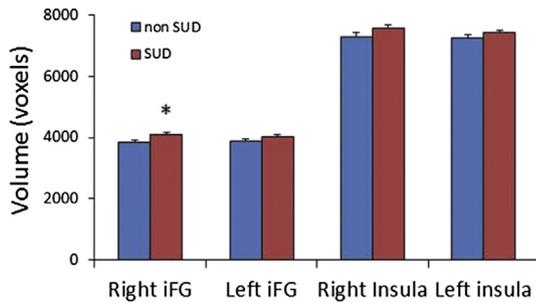


Fig. 3. Volumetric analysis of iFG and insula in nonSUD and SUD patients. The right iFG was significantly larger in SUD patients. No other comparison was significant. (* $p < 0.05$).

et al., 2010). Our final sample of 151 patients represented a mix of several different diagnoses and comorbidities, including mood and anxiety disorders, substance abuse disorders, and personality disorders. Interpretation of data involving comorbidities is more difficult, but makes the results more relevant to typical populations found in psychiatric facilities.

Previous research has linked the insula to drug use. For example, patients with bilateral insular lesions tend to spontaneously quit smoking tobacco (Naqvi et al., 2007). Whether these patients would also spontaneously quit other drugs at a higher rate than the general population is an open question. Insular activity also predicts non-relapse smoking episodes or “slips”; as measured by fMRI, brain responses to smoking-related images in brain areas related emotion, including the insula, were higher in subjects who

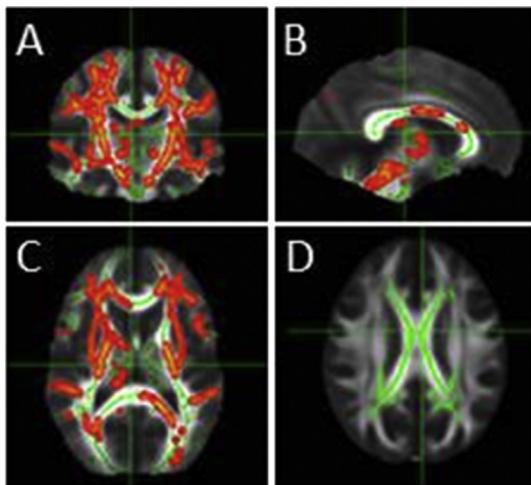


Fig. 4. TBSS analysis reveals lowered FA in SUD patients compared to non-SUD patients. A–C) Brain regions showing decreased FA in SUD patients (FWE corrected, $p < 0.05$). D) Corpus callosum skeletonized mask used for inter-hemispheric analysis. No significant correlations were found between FA values within the corpus callosum and substance use measures (WHOA scores).

relapsed (Janes et al., 2010). Use of other drugs of abuse has also been linked to the insula. For example, in a meta-analysis of fMRI studies of alcohol use disorder, it was found that alcohol cues elicit activity in the right insula and this effect is stronger in alcohol-dependent subjects (Schacht et al., 2013). Cocaine, methamphetamine, and heroin may have physiologic effects on the insula. Cocaine-dependent individuals have been reported to have lower gray and white matter volume in the insula and inferior frontal gyrus (Moreno-Lopez et al., 2012), methamphetamine users who also smoke tobacco were shown to have smaller insular gray matter when compared to non-smoker controls (Morales et al., 2012), and heroin users were shown to have reduced right posterior insular cortex volume (Gardini and Venneri, 2012).

Interestingly, the right/left cue-elicited connectivity of the insula has been shown to be correlated with severity of nicotine dependency (Claus et al., 2013). The insula is important for the integration of internally generated states (for example related to homeostasis) and emotion regulation (Naqvi et al., 2014). Thus, it is not surprising that the insula is involved in the mechanisms of drug abuse. Drugs of abuse produce strong emotional states (i.e. when present in the body, when presented as available, or during withdrawal) that are coupled with strong internal states (e.g. altered cardiac rhythms). Through altered insular function, drugs of abuse could help regulate negative emotion. Since we found a positive correlation between insular interhemispheric RSFC and several drugs of abuse, we postulate that drug abuse lead to a state of enhanced insular connectivity that in turn leads to stronger associations between the abused drug and the user's emotional state.

The iFG has also been shown to be involved in drug abuse. An fMRI study of heroin use revealed decreased activation of the iFG during a go/no go cognitive control task (Schmidt et al., 2013). In a separate go/no go task involving abstinent methamphetamine users, the iFG, insula, and anterior cingulate cortex were less activated by incongruent Stroop conditions (Nestor et al., 2011). In another report, years of cocaine use were correlated with decreases in local gray matter volume in the iFG and the insula (Connolly et al., 2013). Thus, the iFG may play an important role in drug addiction, especially as related to inhibitory control.

In the context of the current study, the drugs of abuse specified on the WHOA questionnaire show a specific pattern of association with the ROIs investigated in this study. Insular interhemispheric RSFC was associated with tobacco, alcohol, cocaine, sedatives, hallucinogens, and “other” drug use while the iFG interhemispheric RSFC was associated with amphetamines and inhalants. Two drugs, cannabinoids and opioids, were not associated with brain connectivity as measured by RSFC in either the insula or the iFG. Although drugs of abuse have been hypothesized to alter dopamine levels in striatal areas (Di Chiara and Imperato, 1988), the specific mechanisms of drug action may differ. We postulate that specific drugs of abuse act upon anatomic, metabolic, or molecular pathways in the insula and iFG, resulting in the observed changes in functional and structural connectivity. It is also possible that cannabis and opioid use may induce long-term anatomical changes in other brain regions not observed in the current study.

While a relatively large clinical sample (151 patients) was included in the present study, several limitations should be noted. First, Only a small number of regions were tested using *a priori* hypotheses, including brain regions hypothesized to be involved in drug addiction, such as the inferior, medial, and superior frontal gyri; insula; striatum; and anterior cingulate cortex. Of these regions, significant RSFC changes in SUD versus non-SUD patients were observed in the insula and iFG. Interhemispheric connectivity in other brain regions not examined in the current study may also be associated with SUD. The decision to focus on a limited number of ROIs was based on the heterogeneous nature of the sample: Selecting a limited set of ROIs avoided superimposing a multiple comparisons problem on top of a sample heterogeneity problem. A whole-brain data driven approach, rather than hypothesis-driven examination of a few brain ROIs, increases the probability of identifying false positives.

A second limitation is the lack of correlation between FA values in the DTI analysis and WHOA scores. Although FA was diminished in SUD patients across several white matter tracts, no correlation was observed between white matter pathways and WHOA scores. Additional experiments should be performed to more thoroughly examine the current finding that FA is decreased throughout the brains of SUD patients when compared to non-SUD patients and to clarify the biological implications for a change in FA among SUD patients (Alba-Ferrara and de Erausquin, 2013).

While the current study attempted to gather a heterogeneous inpatient psychiatric sample complete with comorbidities, and thus more reflective of the general psychiatric population, inpatients at the Menninger Clinic in Houston, TX are treated for a much longer period of time (typically for several weeks) than those inpatients at many other psychiatric facilities. As such, most Menninger Clinic inpatients are likely to have sought psychiatric treatment prior to the Menninger Clinic. Patients in the current study could thus be considered “treatment resistant”, although this categorization is also quite heterogeneous in the studied population. Additionally, patients in the Menninger Clinic are allowed to smoke tobacco products, but are encouraged to quit and provided with treatments including nicotine patches, Chantix, and other smoking cessation aids. Thus, the current sample of Menninger Clinic patients was likely in various states of tobacco withdrawal during study participation. This range of withdrawal adds another layer of heterogeneity to the study and could influence brain activity (as measured by RSFC) or even brain structure (as measured by DTI). Within the Menninger Clinic sample, tobacco and alcohol use were more common than use of other drugs of abuse, such as inhalants or hallucinogens. This patient distribution was expected, but may bias the results in that associations between alcohol use and measures of brain structure/function may be more readily apparent in the larger sub-samples of the population, rather than in the few patients abusing for example inhalants. This concern is unlikely to affect the overall study results as use of both high prevalence drugs (e.g. tobacco and alcohol) and low prevalence drugs (inhalants and hallucinogens) were tied to specific increases in RSFC. No associations between use of cannabis (high prevalence) or opioids (medium prevalence) and changes in brain structure/function were observed.

A forth limitation of all correlational studies, including the current study, is the chicken-and-egg problem: Drug use or abuse may cause increases in interhemispheric connectivity or people with high interconnectivity may be more prone to abusing drugs. Nonetheless, correlational studies in clinical populations are an important tool for understanding relationships between the brain and drug use and for speculating about the underlying mechanisms.

In conclusion, the current study demonstrates that increased interhemispheric RSFC in the insula and inferior frontal gyri are

present in a comorbid psychiatric population and that these increases correlate with abuse of specific drugs. The current patient sample reflects the general incidence of drug abuse and psychiatric disorders in the broader psychiatric population and thus suggests that studies of heterogeneous patient samples can reveal significant changes in brain structure and function even in highly comorbid samples. As additional patients are recruited to this cohort for future studies, we expect to identify even more fine-grained relationships between specific drugs of abuse and brain structure, function, and connectivity in psychiatric conditions.

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