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An intrinsic connectivity network approach to insula-derived dysfunctions among cocaine users

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Abstract

Background: Addiction is a complex phenotype, though it consistently includes characteristics of impulsivity. A number of brain regions are suggested to be involved in cocaine addiction, including the insula, which serves diverse functions including interoceptive awareness and integration of neural signals from sensory, subcortical and frontal regions. Malfunction of this integration links impulsive behavior to the insula. Objectives: This study examines intrinsic connectivity of the insula in chronic cocaine users to investigate abnormal insular circuitry, its role in cocaine addiction, and relationships to measure of impulsivity. Methods: Cocaine-dependent individuals (n = 33) and healthy controls (n = 32) completed a resting-state fMRI scan. An intrinsic connectivity network (ICN) approach generated metrics of mean network connectivity and inter-network connectivity from fMRI data. Metrics pertaining to ICNs involving insula and other structures repeatedly involved in addiction (e.g. striatum) were selected for analysis, which included the capacity to discriminate groups. Relationships between group discriminating connectivity metrics and behavioral impulsivity were examined. Results: Models demonstrated group prediction accuracy up to 75%. Accuracy of 69% was obtained by a parsimonious model of six inter-network connectivity metrics. The inter-network connectivity between an ICN involving the anterior insula and ACC, and an ICN involving the striatum, was significantly weaker in cocaine users relative to controls. The degree of reduced inter-network connectivity was significantly related to greater non-planning impulsivity in cocaine users. Conclusions: Aberrant insula-derived intrinsic connectivity patterns are observed in cocaine users and include dysfunctions in insula to striatal connectivity, which is furthermore linked to increased impulsivity pertaining to forethought.

Introduction

The insula is implicated in an array of brain functions (1–5), serves as a hub connecting subcortical, sensory, association, and frontal regions (2,6–10), and has been implicated in addiction (11–13). Tucked beneath prefrontal cortex and inside the temporal lobes, this bilateral structure responds to drug cues (11), and insular damage causes disruption in addictive behaviors (14). Nonetheless, its role in addiction remains unclear. In the present study, we examined intrinsic connectivity of the insula in cocaine-dependent individuals to investigate its involvement in cocaine addiction.

Meta-analytic and parcellation studies demonstrate functional segregation within the insula, which are potentially relevant to addiction (7,15–21). The posterior and middle insula primarily receive sensory, motor and interoceptive neural signals. The anterior insula (AI) receives and integrates this information with dually received cognitive and emotional neural signals. The insula, particularly the AI, can therefore be viewed as a hub for integration and synchronization of neural connectivity (6,22,23). In addition, the AI may support conscious awareness of the self, error-monitoring, emotions, physiological states, and interoceptive memory (3–5,24–27). Finally, the AI is a key component of the salience network, involved in bottom-up saliency detection, modulation of physiological responses, resource recruitment for modifying behavior, and facilitation of cognitive switching (22,23).

There are multiple theories as to why the insula is associated with addiction (12,28–31). A key characteristic of addiction is the inability to modulate behavior (e.g. discontinue use) despite unfavorable outcomes (e.g. negative or psychosocial or physiological consequences) (32). This characteristic highlights how drug addiction involves a “gain of function” to seek and use drugs, and a “loss of function” for modulating behavior (11,12,29). The ability to modulate behavior depends on awareness of behavior.
Thus, decreased awareness and ability to reflect on or inhibit behavior is associated with the ‘loss of function’; whereas, cravings, cue sensitivity, and subsequent withdrawal symptoms (e.g. anxiety, depression, nausea, itching and insomnia) are associated with the ‘gain of function’.

The loss of awareness and the ability to modulate behavior can lead to compulsive or automatic drug use in response to cues; however, this switch can be predicted by underlying traits of impulsivity (33,34). Individuals with cocaine dependence show high impulsivity on the Barratt Impulsiveness Scale (BIS [35,36]), which predicts degree of cocaine use (37). Additionally, while increased AI volume is associated with heightened interoceptive and emotional awareness (27), cocaine users show reduced AI volume (38), which is associated with both greater impulsivity and duration of drug use (39). Furthermore, impaired insight and awareness of drug-seeking behaviors and bodily sensations, as well as intensity of cravings, have all been linked to insular dysfunction in addicted individuals (14,28). Taken together, the insula may have a prominent role in the neural architecture of addiction.

However, the insula does not act alone; it is one of the several brain structures involved in addiction (30,40). To address these complications, the current investigation will be informed by recent work on intrinsic connectivity of the brain.

Intrinsic connectivity refers to the spontaneous and synchronized patterns of the brain functioning across local and distant regions while a subject is at rest. Intrinsic connectivity networks (ICNs) are currently conceptualized as the fundamental architecture of the brain (41–43); configurations do not rely on task demands, patterns closely resemble task-evoked activity, they have a biological basis, and have utility for examining individual differences (for review, see (44)).

Intrinsic connectivity of the brain can be measured multiple ways depending on the goal (45–54). Here, we will use independent component analysis (ICA) to derive ICNs by identifying the underlying signal sources within fMRI data using blind source separation (55) to estimate statistically independent non-Gaussian sources distributed across the brain. Advantages of this data-driven procedure include that: it captures wide-spanning synchronized signals with no prior information and parses overlapping signals by permitting voxels to have membership in multiple networks (for methods review, see (56)). Recently optimized methods for generating ICNs in a data-driven, replicable and reliable manner have been described elsewhere (44,57). Building on this foundation, we can apply the prescribed methods in cocaine addiction.

Although ICNs in cocaine use has been examined previously, targets typically include anterior cingulate, substantia nigra, or other subcortical areas (58,59) often using seed-based methods. Notably, the insula integrates signals from autonomic, subcortical and cortical regions, all of which are heavily modulated by cocaine use (30,60–62). At present time, only one study examined the insula, but did not test relationships with external behaviors (63). We are unaware of other empirical investigations of the importance of aberrant insular connectivity in cocaine addiction, despite the prevalence of this suggestion in the literature. To this end, the current study examined the following competing hypotheses. Cocaine users will have 1) decreased inter-network connectivity reflecting reduced awareness of behavior, risks and consequences; 2) increased inter-network connectivity, reflecting greater impact of insular activity on regions associated with decision-making and action (e.g. cravings), or 3) increased within-insula connectivity which may reflect greater sensitivity to the physiological effects of withdrawal.

Materials and methods

Participants and clinical assessment

A sample of 78 individuals over the age of 18 were scanned as part of a larger study of cocaine dependence (see (64) for recruitment details). Eight individuals were excluded due to scanning complications and five (four cocaine users and one healthy control) due to excessive head movement (mean absolute displacement above 1.5 mm or any absolute displacement (translations or rotations) over 3.0 mm/degrees) (15). There were no demographic differences between included and excluded participants. The final sample consisted of 33 chronic cocaine users (7 females) and 32 healthy controls (8 females). All participants completed a Structured Clinical Interview for DSM IV disorders (SCID) (65). Cocaine users were required to have been using for at least six months, meet criteria for cocaine dependence within the last month, and to have used at least once weekly for the past month except during the 48 h preceding the scan. Exclusion criteria included 1) medical condition with neurological sequelae; 2) contraindications to MRI scanning; 3) diagnosis of mental retardation; 4) current or lifetime diagnosis of autism, bipolar disorder, schizophrenia or any psychotic disorders except for substance-induced psychotic disorder for cocaine-dependent individuals; 5) excessive alcohol use (more than 14 drinks/week for men, more than 10 drinks/week for women), and therefore, current diagnosis of alcohol abuse or dependence; 6) controls only: current or lifetime diagnosis of dependence on drugs except nicotine or caffeine; 7) cocaine users only: current diagnosis of dependence on sedatives/hypnotics/anxiolytics, stimulants, opioids or hallucinogens. See Supplementary Table 1 for present comorbid psychiatric and substance use disorders. Participants were matched on sex, age and parental education level. Participants were matched on parental education to avoid confounds associated with pseudo-experimental designs where the disorder impacts individual educational attainment (66,67). All participants provided written informed consent and the study was approved by the institutional review board of the University of Minnesota.

Self-report measures

All participants completed the Barratt Impulsiveness Scale, version 11 (BIS-11), a multidimensional measure of behavioral impulsivity (35,36) and the Beck Depression Inventory (BDI), a multifaceted measure of depression (68). Cocaine users also completed the Cocaine Craving Questionnaire (CCQ), a broad measure of self-reported cravings associated with cocaine use (69). See Supplementary Section 1 for details.

Image acquisition and preprocessing

Standard image acquisition and preprocessing procedures were employed (see (44) for details). Briefly, resting-state scans
Generation of ICNs

Preprocessed data were employed in a meta-level ICA generating unbiased data-driven ICNs (44, 57). To optimize ICN consistency 25 temporal concatenation (model-free and multi-subject) group-level probabilistic ICAs (57) were completed using the MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components (70, 71)) package. Each MELODIC employed a unique, randomly generated subject order of equal proportion of cocaine and control subjects totaling 40 subjects each (all subjects were not included due to computational demands, hardware limitations, and to reduce the likelihood of overfitting). Sixty components were derived from each MELODIC based on previous work revealing the impact of dimensionality on ICN neurometrics. This work showed 60 resting-state components derived from a meta-level MELODIC, rather than lower or higher solutions, demonstrated the highest reproducibility for group-level networks (57). Subsequently, the 60 components from each MELODIC were concatenated into a single file, and employed in the single meta-level MELODIC (meta-ICA) to generate the 60 most consistent group-level components. Artifacts were visually identified using standard methods and removed; these included signals due to cardiac or respiratory sources, or movement or non-neural fluctuations located in the periphery (43, 72). Of the 60 meta-ICA derived components, 37 were identified as ICNs and 23 were artifact or white matter components. Five of the 37 included voxels within insular cortex as defined by the Harvard-Oxford Cortical Atlas (probability threshold of 25%) (15). Networks including the AI (anterior insula) were the focus of subsequent analyses; three ICNs met this criterion. To summarize, a multi-stage data-driven procedure was employed to derive 60 consistent ICNs from fMRI data collected from cocaine users and controls. From the final 60 components, those driven by irrelevant sources were excluded, and those including voxels within AI cortex were identified for analysis.

Connectivity metrics

A dual regression procedure (52, 73, 74) was employed to generate subject-specific data (connectivity maps and the respective time courses) based on the meta-ICA derived ICNs. To examine mean network connectivity at the individual level, the mean value of the connectivity strength across voxels within a mask image was calculated for each subject-specific connectivity map, for each ICN. The masks applied to the subject-specific connectivity maps were generated by normalizing group ICNs by the maximum value, then thresholding at $z > 0.30$ based on previous work indicating this threshold maximized reproducibility of ICNs for this dimensionality (57). Thresholded ICNs were binarized prior to use as masks for calculating mean network connectivity scores. Taken together, a subject’s mean network connectivity score was a measurement of the average connectivity strength across all voxels within an ICN mask, calculated for a single ICN. Mean network connectivity scores were calculated for each ICN for each subject: larger connectivity scores indicated more integrated dynamics across all voxels within the ICN, whereas lower connectivity scores reflected more disparate dynamics. Normality of these scores was tested using the Shapiro-Wilk test (75). Nearly all connectivity scores were negatively skewed to a significant degree; logarithmic transformations were applied to improve normality. To examine inter-network connectivity at the individual level, Pearson correlations between pairs of ICNs were calculated using subject-specific time courses generated for each ICN by the dual regression procedure. The Fisher $Z$-transformation was applied to all individual level Pearson correlations; group-level means were calculated using Fisher $Z$ values, this value was then back transformed to an $r$-value for reporting. Standard scores ($z$-scores) were computed across the sample for the mean network connectivity and the inter-network connectivity metrics (the latter using the Fisher $Z$-transform of scores); standard scores ($z$-scores) of the two metrics were also computed for each group separately. In summary, two types of connectivity metrics were calculated to examine the intrinsic brain functioning across groups: (1) mean network connectivity measuring within-network connectivity strength; (2) inter-network connectivity measuring between-network connectivity dynamics.

Between-group analysis

First, to determine demographic and behavioral between-group differences for cocaine users and healthy controls, and guide within-group tests, the demographic variables, three BIS-11 impulsivity factor scores, and BDI scores were examined using two-sided $t$-tests. Bonferroni correction was applied to BIS results to control for multiple comparisons for this construct.

Second, ICNs including the AI (anterior insula) were employed for analyses (AI-ICNs). To interpret possible functionality of ICNs, correspondences between AI-ICNs and AI clusters from a published meta-analytic parcellation study (http://fcon_1000.projects.nitrc.org (15)) were examined. AI-ICNs were masked by the insula image from the Harvard Oxford Cortical atlas (25% probability) to isolate insula-specific voxels (15). Using these insula-masked AI-ICN images and meta-analytic AI cluster images, the proportion of insula voxels within each AI-ICN which overlapped with AI meta-analytic clusters was calculated...
separately for five of the nine published meta-analytic images. By assessing correspondence (overlap) of the two sets of maps, this technique improves capacity for reverse inference, which is the assignment of function to subregions of the brain (43,76,77), in this case insular subregions.

Third, multiple brain structures are associated with emotions and reward processing in addiction neural circuitry (30,40); in addition to the insula, these include orbital frontal cortex, medial frontal cortex, anterior cingulate cortex, amygdala, hippocampal formation, striatum, ventral tegmental area and thalamus. To examine dynamic interplay between AI-ICNs, and between AI-ICNs and the above regions, five additional ICNs were identified (using the Harvard Oxford Cortical and Subcortical atlases) and included in connectivity metric calculations. Subsequently, inter-network connectivity metrics (between-network connectivity) were only retained for the analyses if the absolute value of the Pearson correlation between the respective ICNs was equal to or greater than 0.20 in cocaine users or controls (threshold selected based on previous work (78,79)). Finally, mean network connectivity and inter-network connectivity metrics pertaining to the three AI-ICNs and five additional ICNs were entered in a multivariate general linear model to test a priori prediction of group membership. Model decomposition analyses were employed to determine a parsimonious solution; cross-validation tests were completed to validate each model using a 10-fold method. The final model identified metrics to be evaluated for between-group differences using two-tailed t-tests with Bonferroni correction. In summary, these analyses tested the overarching hypothesis of aberrant insula connectivity in cocaine users while considering the complexity of this brain connectivity. Analyses then provided the foundation for subsequent tests of the three specific hypotheses regarding insular connectivity in cocaine users.

Within-group analysis

Significant between-group differences in inter-network connectivity and mean network connectivity guided within-group analyses. Analysis of individual differences in BIS-11 scores among cocaine users was completed using stepwise regression, followed by one-sided Pearson correlations with Bonferroni correction. Connectivity metrics showing a predicted relationship with BIS-11 scores were tested for associations with weekly cocaine use, total cravings (CCQ), and current depression (BDI) to assess whether findings were driven by stated clinical factors. These analyses identified individual differences in brain-behavior relationships associated with the group differences.

Network specificity analyses

Significant group differences in inter-network connectivity and mean network connectivity guided specificity analyses. Where significant inter-network connectivity differences were observed, the mean network connectivity for the two respective ICNs was examined for group differences to rule out this influence. In addition, insula-specific regions of AI-ICNs were examined for insula specific withdrawal-driven group differences in mean network connectivity. See Supplementary Section 1 for details.

Potential movement confounds

A series of analyses were completed to rule-out influence of participant movement on the connectivity findings. The first set of analyses identified associations between metrics of interest and movement parameters considering overall displacement and specific movement in each direction. Additional analyses of time course correlations between ICNs of interest and movement parameters were completed to further assess impact of movement. See Supplementary Section 1 for details.

Results

Between-group analysis

Demographic and impulsivity differences

The individuals in this sample did not show group differences regarding gender frequency, age or parental education (see Table 1). Although, proportion of high school graduates did not differ, there was a difference in the total years of education obtained (t(46.46) = −3.03, p = 0.00395). Cocaine users showed an average chronicity of 15.5 years and on average used cocaine three times per week. Using the BDI, cocaine users showed significantly (p<0.001) greater self-reported depression symptoms. Using the BIS-11, cocaine users demonstrated significantly (p<0.001) greater self-reported attentional impulsiveness, non-planning impulsiveness, and motor impulsiveness which remained significant after correcting for three comparisons (see Table 1).

Insula derived connectivity differences

Three ICNs out of 37 showed voxels within bilateral AI (anterior insula) which was the focus of the investigation (see Figure 1A); one included anterior cingulate cortex (ACC), one included inferior frontal gyrus (IFG), and one included amygdala and hippocampus (Limbic). Correspondence to AI clusters from a published meta-analytic parcellation study (15) was completed for insula-specific regions of the three AI-ICNs (see Figure 1B). The AI-ACC ICN insula partition showed dominant correspondence with meta-analytic clusters localized to the dorsal anterior region associated with cognition, and demonstrated a right preference. The AI-IFG ICN insula partition showed dominant correspondence with meta-analytic clusters localized to the dorsal and middle anterior region associated with cognition and emotion and demonstrated a left preference. The AI-Limbic ICN insula partition showed dominant correspondence with meta-analytic clusters localized to the ventral anterior region associated with emotion, and showed a left preference. In summary, insular voxels of the three AI-ICNs all showed overlap with meta-analytic insula images associated with cognition and emotion, but to differing degrees. Notably, although some voxels across the three AI-ICNs overlapped with each other, each AI-ICN showed a unique configuration of insular voxels and connections to other brain regions.

The mean network connectivity metrics for – and the inter-network connectivity metrics between - the three AI-ICNs and the five additional ICNs were calculated. Out of all possible inter-network connections (18 total: five for each
AI-ICN and the three between the AI-ICNs), only six (30%) satisfied the criterion of showing a Pearson correlation (absolute value) equal to or greater than 0.20 in cocaine users or controls. Next, the mean network connectivity metrics for the eight ICNs, as well as the six inter-network connectivity metrics, were entered into a multivariate general linear model to test a priori prediction of group membership. This all-inclusive model explained 31% of the deviance and demonstrated a group prediction accuracy of 75% (see Table 2). Model decomposition was employed to derive
Table 2. Connectivity models to predict group from intrinsic connectivity network metrics.

<table>
<thead>
<tr>
<th># ICNs</th>
<th>Mean-network variables</th>
<th>Inter-network variables</th>
<th># Variables</th>
<th>% Prediction accuracy</th>
<th>% Deviance explained</th>
<th>% CV prediction</th>
<th>% Deviance of df</th>
<th>p Value b</th>
<th>Model</th>
<th>p Value a</th>
<th>Residual df</th>
<th>Mean-network connectivity of 3 AI ICNs and 5 other emotion/reward ICNs</th>
<th>Inter-network connectivity between the 3 AI ICNs and 5 other emotion/reward ICNs</th>
<th>Inter-network connectivity between the 3 AI ICNs and 5 other emotion/reward ICNs</th>
<th>Inter-network connectivity between the 3 AI ICNs and 5 other emotion/reward ICNs</th>
<th>Inter-network connectivity between the 3 AI ICNs and 5 other emotion/reward ICNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>3 AI ICNs and 5 other emotion/reward ICNs</td>
<td>4 other emotion/reward ICNs</td>
<td>6</td>
<td>95.12</td>
<td>5.44</td>
<td>0.020</td>
<td>121.90</td>
<td>56</td>
<td>0.0005</td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3 AI ICNs and 5 other emotion/reward ICNs</td>
<td>3 AI ICNs and 5 other emotion/reward ICNs</td>
<td>8</td>
<td>95.83</td>
<td>4.72</td>
<td>0.008</td>
<td>125.50</td>
<td>56</td>
<td>0.0036</td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
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<td><img src="https://static.panotrace.ai/56.png" alt="" /></td>
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<td></td>
</tr>
</tbody>
</table>

CV, Cross-Validation using 10-fold method; AI, Anterior insula; ICN, Intrinsic connectivity network; df, degrees of freedom.

b Model is significantly degraded from best model (14 variables) using analysis of deviance.

Within-group analysis

A stepwise regression was used to explore relationships between the three BIS-11 factors and the inter-network connectivity metric that significantly differed between the groups. The BIS-11 non-planning impulsivity factor was identified by this procedure. An inverse relationship between the AI-ACC and striatum inter-network connectivity metric and the BIS-11 non-planning impulsivity factor in cocaine users was demonstrated, which remained significant after correcting for three comparisons ($r(31) = -0.41, p = 0.009$) (see Figure 2B). The inter-network connectivity explained 16.8% of the variance in non-planning impulsivity; robust regression to down weight an outlier confirmed the inverse relationship ($r = -2.1906, p = 0.018$). To better understand this finding, we explored the associations between the AI-ACC and striatum inter-network connectivity metric and clinical variables. Non-significant correlations were found for weekly cocaine use (# days of use per week) ($r(31) = -0.24, p = 0.089$), total cravings (CCQ) ($r(31) = -0.09, p = 0.317$), and severity of depression (BDI) ($r(31) = 0.004, p = 0.509$).

In summary, we identified a brain-behavior relationship associated with the primary group difference; weaker AI-ACC and striatum inter-network connectivity was related to greater non-planning impulsivity in cocaine users and unrelated to other clinical factors.

Given psychiatric and/or substance comorbidity and variation of depression within the sample, confirmatory analyses were completed to test potential influence of these characteristics on present findings (see Supplementary Section 2 and Supplementary Table 2 for details). In summary,
between- and within-group findings from the full sample (n = 65) were replicated using a confirmatory sample with reduced comorbidity (n = 58, exclusions included three cocaine users with current depression not otherwise specified, two cocaine users with current dysthymia, one cocaine user with current cannabis dependence, and one control subject with current abuse of sedatives/hypnotics/anxiolytics). Thus, the current findings do not appear to be primarily the product of comorbid affective disorders or other substance use disorders.

Network specificity analyses

To rule-out major contributions of within-network connectivity to the main findings, between-group analyses of mean network connectivity metrics were completed for the AI-ACC and the striatum ICNs. Cocaine users showed significantly greater mean connectivity compared to controls for the AI-ACC ICN (t(49.42) = 2.41, p = 0.020), but not for the striatum ICN (t(54.85) = 1.48, p = 0.151). However, mean network connectivity of the AI-ACC ICN did not show an association with BIS-11 non-planning within cocaine subjects (p > 0.15), and thus could not be driving the observed relationship described above. For additional specificity findings, see Table 4 and Supplementary Section 1 for details. Taken together, these analyses aid in clarifying findings associated with the three competing hypotheses. They also rule out confounding factors for the primary group difference finding and its relationship to impulsivity.
gender and chronicity of cocaine use (58,59,63,87). Another exclusion criteria; otherwise, these samples are similar in age, may be sample characteristics such as substance inclusion/exclusion for the AI (58,59,87); only increased connectivity between AI cocaine users have generally not suggested an important role in cocaine addiction. Previous studies of resting-state connectivity in cocaine users. Most investigations of insula functioning in addiction have been performed using seed-based or interhemispheric methods to assess connectivity using a whole-brain approach. In contrast, the present study, and the one other study demonstrating insula and striatal abnormalities in cocaine users (63) employed ICA to derive networks across voxels, and then a priori selection of networks for analysis. The ICA approach captures distributed synchronized signals, allows voxels to be considered as an isomorphic whole representing one source (as in seed-based methods), and also allows voxels to have membership in multiple statistically independent sources (44,56). This empirically parses heterogeneity of a region. For the insula, which is known for its heterogeneity (1–5), ICA could provide a methodological advantage over seed-based methods for the stated reasons. Taken together, the present findings converge with other literature sources to highlight; 1) the insula and striatum as structures exhibiting aberrant intrinsic connectivity in cocaine addiction and 2) the utility of ICA methods for examining intrinsic connectivity in addiction.

Other insular abnormalities, such as reduced gray matter volume, have been reported in cocaine-dependent individuals (38,39,88). Additionally, reduced insular gray matter shows negative correlations with impulsivity in cocaine users (39). Similarly, reduced insular and putamen gray matter volumes show negative correlations with a lack of premeditation in cocaine users (88). Furthermore, decreased activity and volume of AI is associated with reduced interoceptive and emotional awareness (27,89), which may contribute to impaired overall awareness and insight (28). These findings further converge with current results to suggest that reductions in insular measurements or functioning are associated with cocaine use and greater impulsivity with diminished awareness and forethought.

The strongest case-control difference in the present study showed cocaine users had significantly decreased connectivity between the AI-ACC ICN and striatal ICN, which predicted increased non-planning impulsivity. Considering these findings and related literature, this aberrant connectivity could be interpreted as reduced inhibition from the AI-ACC on the striatum and conceptualized as an underlying risk factor for cocaine use. Although the correlation between this connectivity and weekly cocaine use was non-significant, it was in the predicted direction and therefore, consistent with

### Table 4. Group differences in the mean-network connectivity for each insula ICN for a given partition.

<table>
<thead>
<tr>
<th>ICN structures and partition</th>
<th># Voxels</th>
<th>CU mean</th>
<th>HC mean</th>
<th>Direction</th>
<th>T-stat</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI-ACC ACC only</td>
<td>2223</td>
<td>24.33</td>
<td>19.06</td>
<td>CU &gt; HC</td>
<td>2.0768</td>
<td>0.0432</td>
</tr>
<tr>
<td>AI-ACC Insula only</td>
<td>140</td>
<td>9.59</td>
<td>8.74</td>
<td>CU &gt; HC</td>
<td>0.5888</td>
<td>0.5582</td>
</tr>
<tr>
<td>AI-IFG Insula only</td>
<td>454</td>
<td>22.03</td>
<td>18.32</td>
<td>CU &gt; HC</td>
<td>1.4611</td>
<td>0.1496</td>
</tr>
<tr>
<td>AI-Limbic Insula only</td>
<td>420</td>
<td>24.02</td>
<td>21.79</td>
<td>CU &gt; HC</td>
<td>1.0034</td>
<td>0.3196</td>
</tr>
</tbody>
</table>

CU, cocaine user; HC, healthy control; AI, anterior insula; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus. Number of insular voxels calculated using Harvard Oxford Cortical Atlas image of the partition structure (probability 25%).

### Discussion

Resting-state data from 33 chronic cocaine users and 32 healthy controls produced three ICNs involving AI, an integrative brain region thought to be implicated in addiction. Using within- and between-network connectivity metrics we identified aberrant connectivity in cocaine users. Specifically, cocaine users showed greater mean network connectivity (within-network) for an ICN including AI and ACC; in contrast, cocaine users showed significantly weaker inter-network connectivity (between-network) between the AI-ACC ICN and a striatal ICN. Moreover, this reduced inter-network connectivity predicted greater self-reported impulsivity and diminished forethought in cocaine users. In summary, we report novel findings which contribute to the neural understanding of cocaine addiction.

Most investigations of insula functioning in addiction have measured brain activity during cognitive control, drug-cue, or emotional/reward regulation tasks (58,80–86). The current results expand this work by showing intrinsically weaker connectivity between the insula and striatum among chronic cocaine users. Previous studies of resting-state connectivity in cocaine users have generally not suggested an important role for the AI (58,59,87); only increased connectivity between AI and a primary motor seed (59). Underlying these differences may be sample characteristics such as substance inclusion/exclusion criteria; otherwise, these samples are similar in age, gender and chronicity of cocaine use (58,59,63,87). Another cause of study differences may be methodology. Only one previous study also used ICA to examine cocaine users at rest, and similarly found group differences involving the insula, despite sample differences in substance inclusion/exclusion criteria (63). Thus, variant findings may be due to the methodological factors rather than sample characteristics. The aforementioned studies which did not find insula differences employed seed-based or interhemispheric methods to assess connectivity using a whole-brain approach. In contrast, the present study, and the one other study demonstrating insula and striatal abnormalities in cocaine users (63) employed ICA to derive networks across voxels, and then a priori selection of networks for analysis. The ICA approach captures distributed synchronized signals, allows voxels to be considered as an isomorphic whole representing one source (as in seed-based methods), and also allows voxels to have membership in multiple statistically independent sources (44,56). This empirically parses heterogeneity of a region. For the insula, which is known for its heterogeneity (1–5), ICA could provide a methodological advantage over seed-based methods for the stated reasons. Taken together, the present findings converge with other literature sources to highlight; 1) the insula and striatum as structures exhibiting aberrant intrinsic connectivity in cocaine addiction and 2) the utility of ICA methods for examining intrinsic connectivity in addiction.

Other insular abnormalities, such as reduced gray matter volume, have been reported in cocaine-dependent individuals (38,39,88). Additionally, reduced insular gray matter shows negative correlations with impulsivity in cocaine users (39). Similarly, reduced insular and putamen gray matter volumes show negative correlations with a lack of premeditation in cocaine users (88). Furthermore, decreased activity and volume of AI is associated with reduced interoceptive and emotional awareness (27,89), which may contribute to impaired overall awareness and insight (28). These findings further converge with current results to suggest that reductions in insular measurements or functioning are associated with cocaine use and greater impulsivity with diminished awareness and forethought.

The strongest case-control difference in the present study showed cocaine users had significantly decreased connectivity between the AI-ACC ICN and striatal ICN, which predicted increased non-planning impulsivity. Considering these findings and related literature, this aberrant connectivity could be interpreted as reduced inhibition from the AI-ACC on the striatum and conceptualized as an underlying risk factor for cocaine use. Although the correlation between this connectivity and weekly cocaine use was non-significant, it was in the predicted direction and therefore, consistent with
the finding. It also underscores that the relationship between connectivity and impulsivity was not purely driven by current cocaine use. Additionally, aberrant connectivity was not related to current cravings. Furthermore, this finding could not be explained by increased within-insula connectivity driven by potential withdrawal symptoms, nor by symptoms of depression. In turn, although the cross-sectional sample precludes examination of causes, results are consistent with the interpretation that the observed decrease in inter-network connectivity represents reduced awareness, and thus a predisposition to engage in addictive behavior. Work over the last ten years supports this interpretation. It suggests compulsive drug use is linked to striatal control rather than prefrontal control, with this change accompanied by a switch from ventral to dorsal striatal involvement, and the corresponding behavior becoming more automatic and habitual (33,84,90). Given automatic behavior often operates outside of awareness, this could further contribute to diminished insight into non-planning impulsivity in chronic cocaine users (28).

In consideration of the model by Bechara, Naqvi and colleagues (11,12,29), the present findings may provide novel biological evidence of the “loss of function,” to have awareness of and modulate behavior. Not only was connectivity degraded between the AI-ACC ICN and striatal ICN in cocaine users, but this degraded connectivity was associated with a form of impulsivity marked by decreased planning and forethought, and therefore, awareness of behavior. The current findings do not provide evidence for a “gain of function” which is an appetitive phenomenon and may require subjects being confronted by internal or external drug-related stimuli (13).

One limitation of the present study may be the currently unknown reliability of inter-network connectivity metrics. We point out, however, that this method is similar to the graph theory principles of edges, which is a method shown to be at least modestly reliable (45,51). A second limitation may be the use of a single dimensionality for the ICA, when a range of solutions could be informative. This is possible, however, we based the present work on findings that a dimensionality of 60 for resting-state produced ICNs with higher reproducibility than other dimensionality solutions (57). Third, the data was limited to a single case-control sample; therefore, prediction models could not be validated on independent data. Fourth, artifact identification involved manual methods rather than automated methods; however, the rater employed standard methods (43,72) to identify artifacts derived from the entire sample as a single group. Finally, cognitive functions do not stop in the absence of external stimuli; as such the differences in ICN metrics between groups may reflect differences in ongoing complex thoughts while subjects lay at rest. Further work will be needed to unravel this possibility.

In conclusion, the present investigation built upon work regarding the intrinsic connectivity of the brain as well as fundamental work in addiction, to examine insula-derived connectivity abnormalities within chronic cocaine users. This study expands previous findings by reporting novel intrinsic connectivity patterns derived by ICA, insula-based inter-network connectivity dysfunctions in cocaine users, and a link between non-planning impulsivity and inter-connectivity dysfunctions in cocaine users. Although additional analyses will be needed to probe the mechanisms underlying these observations, they could include glutamate mediated neuroplasticity induced by chronic cocaine use (40,91,92). As such, addiction research may be a prime target for cross-modality investigations to form a cohesive understanding of the neuroscientific basis of addiction.

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Declaration of interest

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