Enhanced Orbitofrontal Cortex Function and Lack of Attentional Bias to Cocaine Cues in Recreational Stimulant Users

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Background: Although cocaine is known to be a highly addictive drug, there appears to be a select subset of individuals who are able to use the substance recreationally without developing dependence. These individuals do not report experiencing feelings of craving for cocaine, an important distinction from dependent users. However, no prior studies have compared attentional bias with cocaine cues between these groups to confirm this difference. Additionally, previous investigations into cognitive abilities in these individuals have been conflicting, and no research has been conducted on the neurobiological processes underlying cognitive functioning in this group.

Methods: This study administered the emotional cocaine-word Stroop to 27 recreational cocaine users, 50 stimulant-dependent individuals, and 52 healthy control participants during functional magnetic resonance imaging scanning. Behavioral and functional imaging results were compared between groups to assess attentional bias and cognitive effort to resist salient cocaine stimuli.

Results: Recreational users did not exhibit attentional bias to the cocaine words and did not differ from control subjects on task performance. Conversely, stimulant-dependent individuals were significantly more impaired on the task. Recreational participants also displayed a unique pattern of activation during performance, with significant underactivation in the orbitofrontal and anterior cingulate cortices compared with both dependent users and control subjects.

Conclusions: The absence of bias to cocaine-related stimuli in recreational users indicates they do not share attentional preference for these words with dependent users. Their distinct pattern of activation suggests a decreased need for cognitive control due to diminished desire for the drug, potentially serving as a resilience factor against dependence.

Key Words: Cocaine, craving, fMRI, orbitofrontal cortex, recreational, Stroop

Every year an estimated 16.2 million people use cocaine worldwide (1). However, of these individuals, the vast majority (7 out of 8) who try the drug do not become addicted (1). Moreover, there seems to be a select subset of the population who are able to use stimulant drugs recreationally in a controlled manner without developing dependence (2). These individuals report consistent, occasional, social use of cocaine without experiencing a loss of control or exhibiting symptoms of dependence or abuse (2). They also do not report feeling cravings for cocaine, and their use is planned rather than impulsive.

Drug craving is one of the key facets of stimulant dependence, often leading to unplanned or undesired use. Attentional bias to drug-related cues can elicit feelings of craving and, combined with poor decision making and inhibitory control characteristic of stimulant-dependent individuals (SDIs), can precipitate relapse (3–6). These experiences are thought to be subserved by dysfunction in the prefrontal cortex, an area known to be impaired in stimulant dependence (7–9). Dependent stimulant users have been shown to have decreased orbitofrontal cortex (OFC) gray matter volume compared with healthy control individuals (10–16). Additionally, SDIs exhibit a significant decrease in prefrontal cortex activation on executive function tasks, often accompanied by behavioral impairments in self-control, inhibition, and working memory (17–21).

Recent evidence has emerged suggesting that some of these structural and functional traits, particularly those involved in impulse control, are abnormal predating drug abuse, potentially underlying an increased predisposition for dependence (22–26). However, there are additional abnormalities in the brains and cognitive abilities of dependent drug users that extend beyond these risk factors and are likely due to prolonged stimulant abuse itself (23,27).

Individuals who have used cocaine in a stable manner for an extended period of time without developing dependence are an intermediary group that can be used to assess these cocaine-induced abnormalities and distinguish them from traits involved in compulsive use and dependence. Recreational users would be expected to show similar, though not as severe, changes in structure and function attributed to prolonged stimulant use but not the abnormalities associated with increased premorbid risk for dependence. Furthermore, there may be additional differences between the brains of dependent and recreational stimulant users that serve as protective factors in these non-dependent individuals (2). However, it should be noted that inherent differences in cocaine exposure between the dependent and recreational users may create potential confounds when comparing cognitive function and attentional bias to drug cues. Additionally, categorization of recreational use can be problematic, as there are currently no clinical guidelines for classifying controlled occasional use of cocaine. Previous research in non-dependent stimulant users has been limited and the results are

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conflicting, with some studies demonstrating evidence of impairment on tasks of executive function compared with control subjects (28–30), while other assessments show no difference in performance (29). There have been no previous measures of attentional bias to cocaine cues in recreational stimulant users.

The emotional cocaine-word Stroop is a well-established measure of cognitive control and attentional bias to cocaine-related stimuli (6). Participants are asked to ignore the content of a target word, responding instead to the color of the font. Performance is assessed via a relative increase in response latencies to cocaine cues compared with those for matched neutral words. Impairment stems from a problem with attention allocation and selective processing of more salient cues, as stimulant users become distracted by the cocaine words (4,31–33). Preoccupation with cocaine stimuli is thought to interfere with the normal cognitive processes required to name the font color of the word, resulting in higher reaction times than on emotionally neutral words (6,34). In several studies, this bias has been linked to cocaine craving scores, with longer response latencies correlating with greater self-report levels of craving (4,35).

In the current study, we investigated selective bias to cocaine-cue words on an emotional Stroop task using a functional magnetic resonance imaging paradigm. We assessed 50 stimulant-dependent individuals, 27 recreational cocaine users, and 52 healthy control volunteers, comparing both behavioral and neural responses to cocaine versus neutral stimuli. To the best of our knowledge, this is the first investigation into the neurofunctional activity of recreational cocaine users, as well as the first to assess responses to cocaine-related stimuli in this group. We predicted that recreational users would fall between stimulant-dependent and control individuals in terms of both behavioral and neurocognitive responses, given their greater familiarity with cocaine cues but nondependent patterns of use.

Methods and Materials

Participants

Fifty stimulant-dependent individuals were recruited through drug treatment centers and word of mouth; 27 recreational cocaine users and 52 healthy control volunteers were recruited from the community using local advertisements. All SDIs met DSM-IV criteria for stimulant dependence. Recreational users had been using cocaine for a minimum of 2 years without displaying any DSM-IV symptoms of physical or psychological dependence. Cocaine nondependence was screened for in these individuals, focusing not only on frequency and amount of use but also on patterns of use and associated cognitive and emotional perceptions (Ersche *et al.*, unpublished data, 2012). For example, recreational participants reported no feelings of guilt or remorse about using and stated that their occasional use did not interfere with work, school, family, or social obligations. They also reported no feelings of cravings or urges to use the drug and could "take it or leave it." The Obsessive Compulsive Drug Use Scale was also administered to assess drug use severity, measuring thoughts and obsessions regarding cocaine use, as well as success at resisting these urges (36). Drug urinalysis was collected from all participants, and control and recreational users tested negative for all substances. Conversely, 93% of SDIs tested positive for stimulants. Members from all three groups also reported either current or prior use of tobacco and cannabis (Table 1). Detailed recruitment methods have been described previously in these groups (2,22,37).

Exclusion criteria for all participants included: 1) history of psychiatric, neurological, or neurodevelopmental disorder; 2) current use of psychotropic medication; 3) traumatic head injury; and 4) color-blindness. Additional exclusion criteria for control and recreational participants included no personal or family history of substance dependence, with the exception of nicotine. This included problem drinking behaviors as assessed by the Alcohol Use Disorder Identification Test (AUDIT) (38). All participants were screened for depression using the Beck

Table 1. Demographic Information and Group Differences for 41 Dependent and 26 Recreational Stimulant Users and 47 Healthy Control Volunteers

	Control Subjects ($n = 47$)	Recreational ($n = 26$)	SDI ($n = 41$)	F/χ^2	p
Age	32.52	29.15[a]	34.28[a]	3.609	.030
Gender, *n* Male (%)[b]	33 (63.5%)	14 (51.9%)[a]	44 (88%)[a]	13.127	.001
NART (Score)	112.61	115.64[a]	110.64[a]	3.609	.030
Education (Years)[b]	12.69[c]	13.41[a]	11.58[a,c]	9.917	<.001
BDI-II (Total Score)[b]	2.27[c]	3.78[a]	18.08[a,c]	58.405	<.001
AUDIT (Total Score)[b]	3.35[c]	5.74[a]	11.14[a,c]	15.703	<.001
Tobacco Use History (%)[b]	30 (57.7%)[c,d]	23 (88.9%)[a,d]	49 (98%)[a,c]	23.640	<.001
Cannabis Use History (%)[b]	11 (21.2%)[c,d]	26 (96.3%)[d]	50 (100%)[c]	85.116	<.001
				t/χ^2	p
Last Stimulant Use (Days)[b]		100.35	2.78	−7.08	<.001
Age Cocaine Use Onset		21.26	19.56	−1.44	.155
Duration of Cocaine Use (Years)[b]		7.85	12.64	3.145	.002
OCDUS (Total Score)[b]		1.19	23.66	12.35	<.001
Current Cannabis Use, *n* (%)		11 (40.7%)	33 (66%)	4.57	.033

Differences calculated using chi square and ANOVA with Bonferroni post hoc corrections. Drug use history also provided for stimulant using groups.

ANOVA, analysis of variance; AUDIT, Alcohol Use Disorder Identification Test; BDI-II, Beck Depression Inventory-II; NART, National Adult Reading Test; OCDUS, Obsessive Compulsive Drug Use Scale; SDI, stimulant-dependent individuals.

[a]Significance between SDI and recreational groups in Bonferroni post hoc test at $p < .01$.

[b]Significant group difference at $p < .01$.

[c]Significance between SDI and control groups in Bonferroni post hoc test at $p < .01$.

[d]Significance between recreational and control groups in Bonferroni post hoc test at $p < .01$.

Depression Inventory-II (BDI-II) and verbal IQ with the National Adult Reading Test (39,40).

Fifteen individuals were excluded from analysis, resulting in 114 total participants. Reasons for exclusion included incomplete dataset, excessive head motion during scanning, poor understanding of task requirements, and neurological abnormalities discovered post hoc.

Behavioral Measures

All participants completed the cocaine-word Stroop task during functional magnetic resonance imaging scanning. The task consisted of two 16-trial blocks of either common cocaine-related words (i.e., coke, line, snort) or neutral words that were matched for length and frequency of use (i.e., song, band, piano). Each trial lasted 2.2 seconds, the target word presented for 1.9 seconds followed by an intertrial interval of .3 seconds. Word order was randomized within each block and blocks were counterbalanced between participants. Individuals were asked to respond to the font color of the word using a four-button box, with each button corresponding to one of the four font colors. Participants were trained on the task and button color allocation before entering the scanner. Performance was measured using response latencies and accuracy. Interference scores were calculated as the difference between response times on cocaine and neutral trials.

Behavioral Analysis

Data were analyzed using the Statistical Package for Social Science (SPSS v.18; IBM SPSS Statistics, Chicago, Illinois). Demographic information and error scores were analyzed using analysis of variance, chi-square, and independent sample *t* tests. Response times and interference scores were compared between groups using general linear model (GLM) multivariate and repeated-measures analyses, controlling for age, gender, education, smoking status, and BDI-II and AUDIT scores. Post hoc analyses were conducted using Bonferroni tests. Pearson correlation coefficients were used to assess relations between variables, and paired samples *t* tests compared categorical differences in response times within groups. Median values were used for response latency analyses, and only correct trials were included; significance levels were set at $p < .05$.

Imaging Acquisition and Preprocessing

Scanning took place at the Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, United Kingdom, using a Siemens Magnetom Tim Trio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). Whole-brain images were collected using gradient echo, echo planar imaging with blood oxygen level–dependent (BOLD) contrast. Thirty-two transaxial sections parallel to the intercommissural line were acquired using the following parameters: slice thickness = 3 mm, interslice gap = .75 mm, repetition time = 2000 msec, echo time = 30 msec, flip angle = 78°, image matrix = 64 × 64 with field of view = 192 × 192, in-plane resolution = 3 × 3 mm.

Imaging Analysis

Functional magnetic resonance imaging data were analyzed using Cambridge Brain Analysis software (CamBA) (http://www-bmu.psychiatry.cam.ac.uk/software/; Cambridge, United Kingdom). The first five images were discarded to account for T1 equilibration. Images were motion-corrected and registered to Montreal Neurological Institute standard stereotactic space using affine transformation (http://www.fil.ion.ucl.ac.uk/spm) and were spatially smoothed in-plane with a Gaussian kernel of .5 voxels full-width at half maximum.

The presentation time of each word was modeled as an event onset, with the duration of time until response. Each event was convolved with a canonical BOLD hemodynamic response function in CamBA to assess brain activation up to the time of response on all trials. A comparison of BOLD responses during cocaine versus neutral word trials was conducted, first among all participants and then comparing contrast activation between groups. Analyses were repeated using the inferior frontal gyrus (IFG) as a region of interest. Previous studies have identified the IFG as an area commonly found to be abnormal in stimulant-dependent individuals (18), as well as a region involved in Stroop task performance (25,32). Significance levels were set at family-wise error correction $p < .05$ for all analyses.

Whole-brain imaging analysis compared activation during cocaine and neutral word conditions on successful trials among all participants, creating a group contrast map of significant voxel-wise responses of the cocaine–neutral contrast. Significant clusters were then exported to SPSS and compared between groups using GLM multivariate analysis and Bonferroni post hoc corrections, including the demographic covariates listed above.

Between-group activation differences were also assessed using a three-way GLM omnibus analysis in CamBA, identifying clusters that significantly differed between groups on the cocaine versus neutral contrast. These results were then exported into SPSS for further analysis, comparing group differences in activation in the significant clusters using GLM multivariate analysis.

A within-group GLM was conducted in CamBA, regressing behavioral interference scores onto the group activation contrast map. This identified regions in which BOLD contrast activity levels directly correlated with cocaine interference scores. These regions were further analyzed in SPSS using Pearson correlation and GLM multivariate analyses. Within-group GLM and between-group GLM omnibus analyses were repeated after application of a restricted small volume mask of the IFG taken from Hammers *et al.* (41) probabilistic atlas.

Results

The three groups significantly differed in terms of age and gender, with recreational users being younger than stimulant-dependent individuals and more female subjects in the control and recreational groups (Table 1). Stimulant-dependent individuals also had significantly lower verbal IQ scores than recreational users and fewer years of education than both control and recreational participants. There were higher rates of tobacco and cannabis use in the stimulant-dependent and recreational users, as well as higher alcohol and depression scores in SDIs. As such, age, gender, education, smoking status, and BDI-II and AUDIT scores were controlled for in all analyses.

Behavioral Performance

Stimulant-dependent individuals were more impaired than both recreational and control participants on the cocaine-word Stroop task, demonstrated via a greater number of errors committed on both cocaine (Kruskal-Wallis $\chi^2 = 23.01$, $p < .001$) and neutral trials ($\chi^2 = 6.62$, $p < .036$) and increased interference scores ($F_{2,105} = 3.017$, $p = .053$), though this lost significance after controlling for demographic variables. Conversely, recreational users did not differ from control subjects on any behavioral measure (Table S1 in Supplement 1). In a mixed-model analysis of variance with participant group and word type (cocaine versus neutral), SDIs had significantly slower response times compared with the other two groups ($F_{2,105} = 3.787$, $p = .026$). Stimulant-dependent individuals also demonstrated attentional bias to

cocaine cues, with significantly increased response latencies to cocaine over neutral stimuli ($t_{40} = 3.665$, $p = .001$). Neither recreational users nor control subjects had an increase in response times from cocaine to neutral words (control: $t_{46} = 1.238$, $p = .222$; recreational: $t_{25} = -1.561$, $p = .131$).

Functional Imaging

Six clusters emerged that demonstrated significantly different activation during cocaine versus neutral trials among all participants (Figure 1; Table S2 in Supplement 1). This included increases in left orbitofrontal and inferior frontal gyrus activity, as well as bilaterally in the superior medial frontal lobe and anterior cingulate cortices. A significant decrease in activation was also seen in the right cuneus/precuneus and superior and inferior parietal lobe. Activity in these regions did not differ between groups.

Two clusters in the right orbitofrontal/anterior cingulate cortex and right angular gyrus/posterior cingulate cortex significantly differed between groups during a second-level GLM omnibus contrast comparing activation to cocaine–neutral trials between participants. In both of these areas, recreational users demonstrated a significant decrease in activity compared with SDIs and control participants. There were no differences in activation levels between control subjects and SDIs in these regions (Figure 2; Table S3 in Supplement 1).

After restricting analyses to the inferior frontal gyrus, three additional clusters emerged that significantly differed between participants in the cocaine–neutral word GLM omnibus contrast (Table S3 in Supplement 1). These three areas spanned across the right IFG, including the insula and operculum. Control participants showed a significant underactivation in the first cluster compared with both dependent and recreational users; these two groups did not differ from each other in this area. In the second cluster, there was again a significant decrease in activity in the recreational participants compared with both stimulant-dependent and control individuals, whereas in the third cluster, the dependent stimulant users had significantly greater activation compared with recreational users (Figure 3).

When interference scores were regressed against activation levels among all groups on the cocaine–neutral contrast, no significant clusters arose. However, upon application of a mask of the IFG, three areas in the right IFG emerged where activity significantly correlated with cocaine interference scores in all participants. These were centered in the right IFG pars triangularis and pars orbitalis. The trend again remained of recreational users showing a comparative underactivation of these regions, while dependent stimulant users exhibited a relative overactivation (Figure S1 in Supplement 1); however, these differences were only significant in the cluster centered on the right IFG pars orbitalis. Activity levels in control participants fell between the other two groups. Activation in all three regions significantly negatively correlated with interference scores in all groups, with greater impairment associated with greater activity on cocaine versus neutral trials ($r = .377, .405, .381$, $p < .001$ all correlations).

Discussion

Recreational cocaine users were unimpaired on a cognitive control task measuring attentional bias to cocaine-related stimuli, performing on par with nondrug using control participants. Conversely, stimulant-dependent individuals were significantly impaired compared with the other two groups, registering longer response times, higher interference scores, and more errors committed. Recreational users also demonstrated very different patterns of activation during task performance, including significantly underactive prefrontal and orbitofrontal regions compared with both stimulant-dependent and control individuals.

The absence of a significant increase in response times among recreational users to cocaine-related stimuli indicates that they do not share an attentional bias to these words with dependent users. Drug-related attentional bias has been linked to increased motivation to obtain the substance, as well as heightened emotional salience for these cues (6,42). The absence of preferential attention to cocaine cues in the recreational users suggests an inherent difference in automatic drug-related stimulus

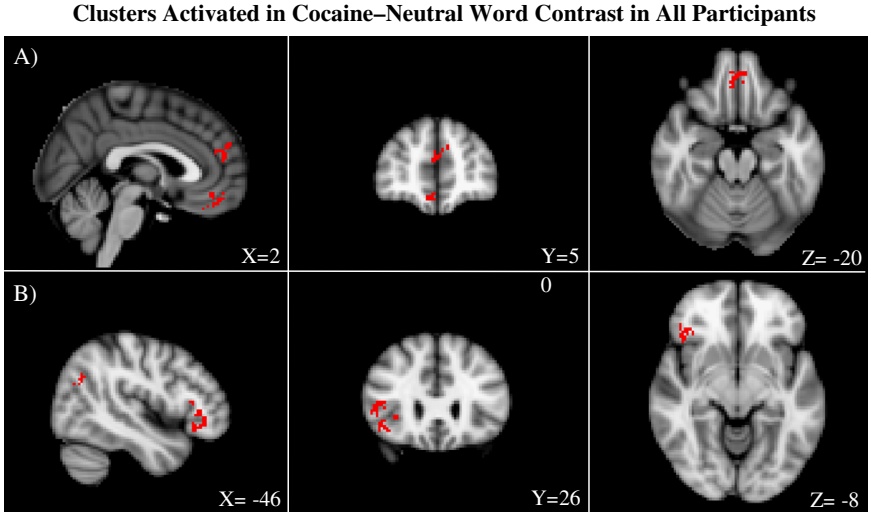

Figure 1. Significant clusters identified during the first-level functional magnetic resonance imaging contrast, comparing activation with cocaine and neutral words among all participants. Six significant clusters were identified; regions shown include increases in activation on cocaine compared with neutral trials in the **(A)** left orbitofrontal cortex, bilateral superior medial frontal gyrus, and bilateral anterior cingulate cortex, and **(B)** left inferior frontal gyrus, and left angular gyrus. Activation in these areas did not differ between participant groups. Significance set at $p < .05$ family-wise error correction for multiple comparisons. Coordinates listed are in Montreal Neurological Institute standard space.

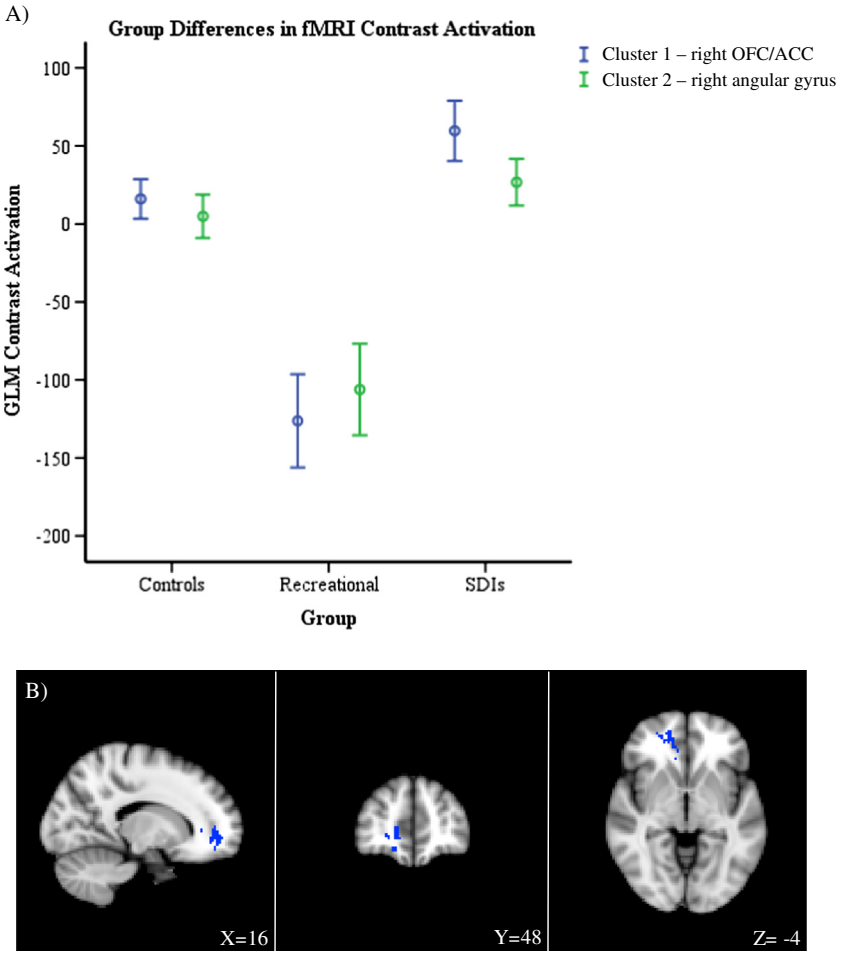

Figure 2. Second-level group contrast, comparing activation between groups during cocaine–neutral word contrast. Significant differences emerged in two significant clusters: the right orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), and the right angular gyrus and posterior cingulate cortex. **(A)** Recreational cocaine users significantly underactivated these two regions in comparison with the other two groups, while dependent stimulant users showed a relative increase in activation, though this was not significant when compared with control participants. **(B)** Task activation differences between groups in the right OFC and ACC. Coordinates listed are in Montreal Neurological Institute standard space. Cluster significance set at $p < .05$ family-wise error correction for multiple comparisons. Group comparisons made using analysis of covariance models, controlling for age, gender, years of education, smoking status, and Beck Depression Inventory-II depression and Alcohol Use Disorder Identification Test alcohol scores, with Bonferroni post hoc correction $p < .05$. fMRI, functional magnetic resonance imaging; GLM, general linear model; SDIs, stimulant-dependent individuals.

processing between the two participant groups, underlying an intrinsic difference in the pattern and type of drug use. Similar results have been reported in dependent and recreational cannabis users, with more severe users reporting greater drug craving and increased attentional bias on a cannabis-modified Stroop task (43). Similarly, light social drinkers had less attentional bias to alcohol cues than heavy drinkers (44,45). In the current assessment, SDIs were impaired on all aspects of the task, registering significantly slower responses on both trial conditions. This is suggestive of a more globalized inefficiency in these individuals that is not unique to the cocaine-related stimuli, potentially relating to increased age, lower IQ, or general cognitive impairment from prolonged stimulant use. However, the higher interference scores in these participants, demonstrating significantly slower responses on cocaine versus neutral trials, is indicative of greater content-specific impairment as well.

Resistance to drug-related attentional bias as measured by the Stroop has been cited as an indicator of successful abstinence efforts in treatment seekers (31,46,47). In the brain, these impairments manifested as abnormal activation in the frontal pole and cingulate cortex, thought to correspond with the increased cognitive demand required to override an initial emotional reaction to the words (32,48–50). The inferior frontal gyrus in particular has been found to exhibit increased activation in response to drug words and is known to be associated with cognitive control and inhibition of prepotent responses (32,51). The decrease in IFG/OFC activation seen in the recreational users suggests that these words do not hold the same salience as they do for the dependent users. The IFG is thus not equivalently recruited in the recreational users, as the need to inhibit an initial attentional bias is less prevalent in these individuals. Increased activation in the SDIs could reflect greater effort being exerted to resist the distracting cocaine words, represented via increased interference scores on the task. Higher prefrontal activity in these participants could also be due to the increased salience of the words for these individuals, resulting in greater neuronal excitation.

Previous work with these participant groups has shown differences in cortical structure, with recreational users having significantly greater volume in the OFC, while dependent users showed a significant reduction in OFC gray matter, as well as in the posterior insula (2,22). Similar dissociation in OFC activation during the cocaine-word Stroop task may reflect the structural differences in this area, which could be serving as a protective factor against development of dependence in recreational users. Increased frontal volume has previously been associated with more efficient cognitive processing (25), and it is possible that the enlarged OFC in the recreational users caused them to recruit less cortical activity during task performance, rendering the task less cognitively demanding.

The relative decrease in OFC activity in the recreational users could also be linked to an absence of craving. The OFC has been implicated in reward valuation and motivation for a stimulus (52), and craving for cocaine cues has been linked to increased OFC activity (7,53). A higher value placed upon cocaine for dependent users could result in greater activation in this region, and activity in the area has been correlated with self-report craving scores in dependent users (7,54,55). The relative decrease in OFC activity in

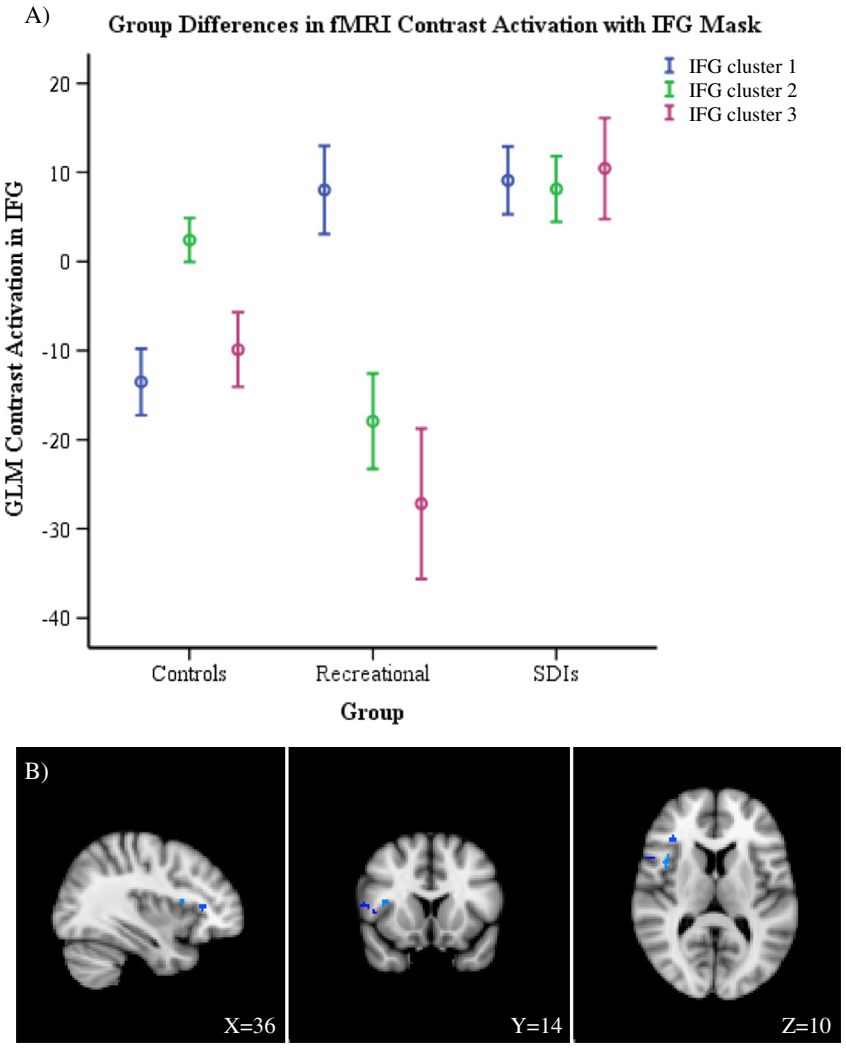

Figure 3. Between-group differences in contrast activation in the lateral inferior frontal gyrus (IFG) upon application of a small-volume correction mask. **(A)** Stimulant-dependent individuals (SDIs) demonstrated a significant increase in activity throughout the IFG, whereas recreational users showed a relative decrease in activity in two of the three clusters but had equal levels to dependent users in the third. Control participants typically fell between the two stimulant using groups in terms of activation. **(B)** Three clusters in the right IFG that significantly differed between groups. Coordinates listed are in Montreal Neurological Institute standard space. Cluster significance set at $p < .05$ family-wise error correction for multiple comparisons. Group comparisons made using analysis of covariance models, controlling for age, gender, years of education, smoking status, and Beck Depression Inventory-II depression and Alcohol Use Disorder Identification Test alcohol scores, with Bonferroni post hoc correction $p < .05$. fMRI, functional magnetic resonance imaging; GLM, general linear model.

recreational users suggests they are not experiencing cue-induced craving for cocaine in a similar manner as the SDIs and instead may have a resiliency against these types of addictive behaviors.

Decision-making abilities have also been linked to the OFC, with patients with ventromedial prefrontal cortex lesions exhibiting severe impairment on a decision-making task (56). Dependent drug users show similar dysfunction on decision-making assessments, potentially due to drug-induced abnormalities in this region (57,58). The underactivation of recreational users in this area, combined with larger structural volumes, suggests they may exert greater self-control and demonstrate improved decision-making abilities, particularly compared with dependent individuals. This could be particularly applicable in situations involving myopia for the future where long-term consequences must be weighed against short-term rewards. Drug users are typically impaired when making these types of decisions (59), particularly involving drug use. However, the recreational users' anecdotal ability to prioritize work or school above drug taking suggests they may have improved self-control and future planning.

Finally, the OFC is commonly implicated in habitual repetitive behaviors characteristic of obsessive-compulsive disorder, and impairment in this region in drug-dependent individuals is thought to contribute to the compulsive drug-seeking and drug-taking behaviors present in addiction (7). Several studies investigating patients with obsessive-compulsive disorder have demonstrated an increase in glucose metabolism in the OFC, indicating hyperactivity in this region (60,61). The contrasting decrease in activity in the recreational users in this area may act as a potential protective factor against compulsive behaviors (2), thus making them less likely to develop drug dependence.

Rather than being at an earlier stage in the development toward dependence, we believe that these individuals are able to maintain a recreational pattern of cocaine use without devolving into full-fledged dependency. The cognitive, behavioral, structural, and functional data all point to a unique pattern of use in these individuals that is distinct from those who are dependent on cocaine (2). Additionally, previous data from the biological siblings of SDIs show very different results, displaying cognitive, personality, and structural traits that are most similar to those of their dependent siblings, despite never being dependent on drugs (22,23,37). Thus, these findings suggest two possible important qualitative differences between dependent and recreational stimulant users. Underlying and potentially predisposing factors for stimulant dependence, such as decreased cognitive efficiency and impaired impulse control, may be present in the former, as well as in their nondrug abusing siblings, while these potentially predisposing factors are not present in recreational users. Conversely, recreational users may exhibit resilience against the development of dependence, including neurobiological changes such

as increased orbitofrontal cortex size and efficiency that are not evident in dependent users or their siblings. This pattern of qualitative differences would seem to make it unlikely that recreational users are merely at an earlier stage on an ultimate trajectory to dependence.

Shortcomings of the study include the significant demographic differences between groups, including age and gender between the recreational and dependent users. It would perhaps be optimal to have more closely matched groups of participants; however, some of the demographic differences may be inherent to their classification. Comorbidities with depression or other drug and alcohol abuse are common in SDIs, and it would be prohibitive to the study to exclude those who met these qualifications. As such, we have tried to control for these types of differences during statistical analyses. Also, recreational cocaine use is not precisely defined. We used criteria based on the quantity and quality of use, as well as an absence of a family history of dependence, to make these classifications. These inclusion criteria may help to explain the difference in findings reported here compared with prior investigations of nondependent stimulant users (28,30). A universal definition and qualification for this type of use would be highly beneficial when making these sorts of distinctions between recreational, abusive, and dependent behaviors. In the current cocaine-word Stroop task, it is difficult to parse out whether the differences between recreational and dependent users are due to impaired executive control in the SDIs in response to cocaine stimuli or a global increase in cognitive control in the recreational users. Future studies should include a nondrug related evocative word condition to test whether the difference is specific to cocaine-related words or is also present for other salient emotional stimuli. Finally, the Stroop paradigm has been shown to have poor internal reliability (62), and studies employing objective indices of attentional bias, such as eye-tracking, should be administered to test the reproducibility of this effect.

Summary

In a study of dependent and recreational stimulant users and healthy control volunteers, stimulant-dependent individuals were significantly more impaired on a cognitive inhibition task involving cocaine cues, demonstrating significant attentional bias to the salient cocaine words. Recreational users did not differ from control subjects on this task; however, they did display significantly different patterns of activation, with a decrease in prefrontal/orbitofrontal cortical activity, suggesting their attentional control was more efficient and not overly effortful. Conversely, SDIs showed an increase in activation in these regions. These findings suggest that regular occasional users of cocaine do not experience similar attentional bias to cocaine cues as SDIs, and their neural activation reflects this lack of distraction and emotional salience for these words. This indicates that there may be inherent behavioral and neurobiological differences between those who can use a class A drug such as cocaine recreationally without making the transition to dependence and those who have become dependent upon the substance.

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