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## Influence of Compulsivity of Drug Abuse on Dopaminergic Modulation of Attentional Bias in Stimulant Dependence

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### Abstract

**Context**—There are no effective pharmacotherapies for stimulant dependence but there are many plausible targets for development of novel therapeutics. We hypothesized that dopamine-related targets are relevant for treatment of stimulant dependence, and there will likely be individual differences in response to dopaminergic challenges.

**Objective**—To measure behavioral and brain functional markers of drug-related attentional bias in stimulant-dependent individuals studied repeatedly after short-term dosing with dopamine D<sub>2</sub>/D<sub>3</sub> receptor antagonist and agonist challenges.

**Design**—Randomized, double-blind, placebo-controlled, parallel-groups, crossover design using pharmacological functional magnetic resonance imaging.

**Setting**—Clinical research unit (GlaxoSmithKline) and local community in Cambridge, England.

**Participants**—Stimulant-dependent individuals (n=18) and healthy volunteers (n=18).

**Interventions**—Amisulpride (400 mg), pramipexole dihydrochloride (0.5 mg), or placebo were administered in counterbalanced order at each of 3 repeated testing sessions.

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**Main Outcome Measures**—Attentional bias for stimulant-related words was measured during functional magnetic resonance imaging by a drug-word Stroop paradigm; trait impulsivity and compulsivity of dependence were assessed at baseline by questionnaire.

**Results**—Drug users demonstrated significant attentional bias for drug-related words, which was correlated with greater activation of the left prefrontal and right cerebellar cortex. Attentional bias was greater in people with highly compulsive patterns of stimulant abuse; the effects of dopaminergic challenges on attentional interference and related frontocerebellar activation were different between high- and low-compulsivity subgroups.

**Conclusions**—Greater attentional bias for and greater prefrontal activation by stimulant-related words constitute a candidate neurocognitive marker for dependence. Individual differences in compulsivity of stimulant dependence had significant effects on attentional bias, its brain functional representation, and its short-term modulation by dopaminergic challenges.

CHRONIC STIMULANT DRUG abuse is associated with major adverse health, social, legal, and economic consequences.<sup>1-3</sup> Yet the pharmacological and psychological treatments available for stimulant dependence are characterized by high dropout and relapse rates.<sup>4-6</sup> There is a clear need to improve treatment efficacy for the growing number of stimulant-dependent individuals.<sup>3</sup>

Advances in neuroimaging research have contributed to a better understanding of the neurobiological basis of stimulant dependence and have indicated some plausible targets for pharmacological intervention. On the hypothesis that stimulant dependence may be associated with a loss of “top-down” inhibitory control over lower-level reward processing,<sup>7,8</sup> several studies have investigated brain and behavioral responses to tasks, such as the color-word Stroop paradigm, that entail attentional control to override an automatic but incorrect response tendency.<sup>9-18</sup> In studies of stimulant dependence, a drug-related version of the Stroop test has been used to measure the degree of involuntary attention, or attentional bias, toward drug-related words compared with neutral words.<sup>19-23</sup> The increased salience of drug-related cues, as measured by attentional bias in drug-word Stroop paradigms, is thought to contribute to the maintenance of drug-taking behavior<sup>7,24</sup> and has demonstrated predictive value for the risk of relapse.<sup>12,21,25-27</sup>

The exact neurochemical mechanisms underpinning attentional bias to drug-related stimuli in stimulant-dependent individuals (SDIs) are unknown, but attentional bias on the Stroop paradigm is responsive to dopaminergic modulation.<sup>28-30</sup> Dopamine is generally released in response to reward-predicting or salient events<sup>31-33</sup> and also in response to drug-related cues in drug-dependent individuals.<sup>34,35</sup> Accumulating evidence indicates that striatal dopamine systems are disrupted in stimulant dependence.<sup>36-38</sup> For example, studies using raclopride positron emission tomography have shown that SDIs have a significantly lower binding potential of striatal dopamine D<sub>2</sub> receptors,<sup>39-41</sup> which has usually been interpreted as a marker of reduced postsynaptic receptor density.<sup>42</sup> Reduced striatal dopamine receptor density appears to be directly related to decreased metabolic activity in the orbitofrontal cortex,<sup>39,40</sup> a brain area implicated in compulsive behavior and craving.<sup>43</sup>

Collectively, these studies suggest that attentional bias predisposing to stimulant dependence could be related to abnormal dopamine transmission and could therefore be treated by drugs targeting dopamine receptors. There are rationales for both dopamine agonist and antagonist drugs, and both have been tried, but the findings are inconsistent,<sup>5,44-47</sup> in most cases providing no more than weak evidence for therapeutic efficacy. One possible explanation for this discrepancy between the theoretical strength of the target and the apparent lack of clinical benefit is that stimulant dependence is a heterogeneous syndrome. There are important psychological dimensions of difference between individuals, which may modulate

their response to treatment and attenuate the power of clinical trials involving small numbers of psychologically undifferentiated SDIs. Two psychological dimensions of particular interest in this respect are impulsivity and compulsivity: both are known to be abnormal in SDIs compared with nondependent people,<sup>24,48-50</sup> and both have been linked to dopaminergic mechanisms.<sup>51-54</sup> *Impulsivity* can be defined as loss of inhibitory control over the response to rewarding or distracting stimuli and may play a role as both a cause and a consequence of substance abuse<sup>55,56</sup>; *compulsivity* is defined as persistence or perseverance of behavior in the absence of reward or despite punishment and may be particularly important in the maintenance of drug-taking habits.<sup>54</sup> Both impulsivity and drug-related compulsivity have been linked with alterations in the dopamine system<sup>52,57,58</sup> and are thought to account for the variability of dopaminergic drug effects in SDIs.<sup>51</sup>

Herein, we tested 2 hypothetical predictions: (1) attentional bias for drug-related cues, and related brain activation, would be abnormal in people with stimulant dependence and (2) the effects of dopaminergic challenge drugs on attentional bias and related brain systems would be influenced by individual differences in impulsivity and compulsivity among a group of SDIs. We conducted a double-blind, placebo-controlled, pharmacological functional magnetic resonance imaging (fMRI) study to evaluate the effects on drug-word Stroop task performance of single doses of a dopamine D<sub>2</sub>/D<sub>3</sub> receptor agonist (pramipexole dihydrochloride, 0.5 mg) and a D<sub>2</sub>/D<sub>3</sub> antagonist (amisulpride, 400 mg) administered in a within-subjects crossover design to SDIs and healthy comparison volunteers.

## METHODS

### PARTICIPANTS

Thirty-six right-handed volunteers participated in this study: 18 individuals with a chronic history of stimulant drug abuse, satisfying the *DSM-IV-TR*<sup>59</sup> criteria for dependence on either crack cocaine (n=5), cocaine (n=5), or amphetamines (n=8) and 18 matched healthy controls. Stimulant-dependent individuals were non-treatment seeking and recruited from the local community. Prior to study enrolment, all participants had a satisfactory medical review and were screened for any other current Axis I psychiatric disorder using the Structured Clinical Interview for the *DSM-IV-TR* Axis I Disorders.<sup>60</sup> Participants were excluded on the basis of any current Axis I psychiatric disorder, other than substance dependence in SDIs. Participants were also screened for normal appearance of structural MRI scans (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>). All volunteers provided written informed consent and received monetary compensation for participation. The study was approved by the Cambridge Research Ethics Committee (REC06/Q0108/130; principal investigator, T.W.R.).

### SHORT-TERM DOPAMINERGIC DRUG TREATMENTS

Amisulpride is a selective antagonist at the dopamine D<sub>2</sub>/D<sub>3</sub> receptors. We administered a single oral dose of 400 mg of amisulpride; no serious adverse events were reported. Pramipexole is a selective agonist at the dopamine D<sub>2</sub>/D<sub>3</sub> receptors<sup>61</sup>; we administered a single oral dose of 1.5 mg of pramipexole dihydrochloride to the first 6 participants enrolled in the study (3 SDIs, 3 nondependent volunteers). However, this dose of pramipexole was poorly tolerated in the 3 nondependent volunteers, who were unable to perform the tasks at this treatment session because of nausea, vomiting, sweating, and tiredness. Subsequently, the dose of pramipexole dihydrochloride was reduced to 0.5 mg orally for all participants (ie, for 18 controls [including the 3 volunteers who did not tolerate the higher dose] and 15 SDIs). All participants were also administered 30 mg of domperidone orally at each treatment session to prevent emetic effects of dopamine receptor agonism (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>).

## BASELINE ASSESSMENTS

All participants completed the Barratt Impulsiveness Scale as a measure of self-reported impulsivity. In SDIs, drug-related compulsivity was assessed using the Obsessive Compulsive Drug Use Scale,<sup>62,63</sup> an equivalent to the Yale-Brown Obsessive Compulsive Scale<sup>64</sup> of symptom severity in obsessive-compulsive disorder. The Obsessive Compulsive Drug Use Scale measures the amount of time, interference, and distress caused by stimulant-related thoughts or urges and the efforts to resist them. Obsessive-compulsive tendencies in controls were assessed by the Yale-Brown Obsessive Compulsive Scale (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>).

## ATTENTIONAL CONTROL TASKS

We used 2 versions of the Stroop task as tests of attentional control, based on the paradigm used by Compton et al,<sup>65</sup> in which participants were asked to indicate the font color of a word displayed on the screen using a 4-button box. Each button corresponded to 1 of 4 possible font colors: red, blue, yellow, or green. The drug-word Stroop task involved 2 lists of target words: 16 amphetamine-related and 16 cocaine-related words. Both lists were matched with a list of 16 neutral words with regard to length and frequency. Equivalent to the drug-word version, the color-word Stroop task also involved 2 lists of color words, each including 8 distinct color words that were presented twice per block. Each color word was always displayed in a font color incongruent with its meaning. Both lists of color words were matched with neutral words for length and frequency (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>).

Both the drug-word and the color-word Stroop tasks were presented as a blocked periodic paradigm during fMRI (Figure 1). This design was chosen because interference effects in emotional Stroop paradigms are thought to rely on a slow disengagement process<sup>66</sup> that generalizes to drug-related words,<sup>67</sup> and the block design has therefore been the method of choice in many prior studies investigating attentional interference in an emotional context.<sup>65,68-70</sup> For each word trial, the interstimulus interval was 2.2 seconds, including the presentation of a fixation cross for 0.3 second followed by the presentation of a word for 1.9 seconds, during which time the participants had to register a response by button press. Each block of words lasted 35.2 seconds, and 2 blocks of each word type were followed by a 38-second fixation block (Figure 1). The order of the words within each block was randomized and the order of the blocks was counterbalanced across participants and testing sessions. The allocation of the font colors to the words was randomized; each of the 4 colors occurred equally often in each word category. All participants were trained on the task prior to each scanning session with a practice run of at least 1 color-word block and 1 block of different neutral words to familiarize themselves with the task and to minimize practice effects. Acute Stroop task-induced stimulant cravings were measured immediately before and after the Stroop task by asking the following question: "How would you rate your current state of craving on a scale from 0 to 100?"

Task performance was measured in terms of accuracy and latency of response to each trial. Attentional bias for drug-related words was quantified by an interference score, calculated for each individual as the median latency of correct responses to the drug-related words minus the median latency of correct responses to the neutral words. Likewise, attentional interference in the color-word Stroop task was calculated as the median latency of correct responses to color words minus the median latency of correct responses to neutral words. The median is generally more robust than the mean as a measure of central location in small samples; however, the mean interference scores were also calculated for comparative purposes (Table 1 and Table 2).

## ACQUISITION OF fMRI DATA

Whole-brain fMRI data were acquired at the Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, England, using a Siemens Magnetom Tim Trio whole-body scanner operating at 3 T (Siemens Medical Solutions, Erlangen, Germany). During the performance of each Stroop task, 32 transaxial sections of gradient echo, echoplanar imaging data depicting blood oxygen level-dependent contrast were acquired parallel to the intercommissural line with the following parameters: repetition time=2000 milliseconds, echo time=30 milliseconds, flip angle=78°, slice thickness=3 mm plus 0.75-mm interslice gap, image matrix size=64×64, and within-plane voxel dimensions=3.0 mm×3.0 mm. Prior to data analysis, the first 5 echoplanar images were discarded to account for T1 equilibration effects.

## ANALYSIS OF DEMOGRAPHIC, PSYCHOMETRIC, AND BEHAVIORAL DATA

Using data from both groups, attentional interference scores, error, and craving data were each analyzed separately using a repeated-measures analysis of covariance (ANCOVA) model with drug treatment (3 levels: placebo, amisulpride, and pramipexole) as the within-subject factor and group (2 levels: nondependent volunteers and SDIs) as the between-subject factor. Using data from the patient group only, attentional interference was also analyzed using a repeated-measures ANCOVA model with drug treatment (3 levels: placebo, amisulpride, and pramipexole) as the within-subject factor and compulsivity subgroup (2 levels: high and low) as the between-subject factor. In all analyses of attentional interference scores, only data on correctly performed trials were included. To control for group differences in depressive mood, education, and dose of pramipexole, we included the Beck Depression Inventory scores, years of education, and plasma levels of pramipexole as covariates in all analyses involving SDIs and controls; the subgroup analyses (involving SDIs only) included plasma levels of pramipexole as a covariate. Statistical tests were conducted using SPSS (version 13; SPSS Inc, Chicago, Illinois) and were reported as significant if  $P < .05$ .

## ANALYSIS OF fMRI DATA

Details of the fMRI data analysis procedures are briefly summarized herein (full details, <http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>). We first identified by whole-brain analysis those brain regions where functional activation was specifically related to the contrast of drug-related vs neutral words and strongly correlated with the behavioral measure of attentional interference (as defined earlier). At each voxel of these behaviorally relevant frontal and cerebellar regions, we tested the factorial effects of diagnostic group and dopaminergic drug challenge by ANCOVA using all data on both groups. Finally, we also tested each voxel of this frontocerebellar system to investigate factorial effects of compulsivity (high or low) and dopaminergic drug challenge by ANCOVA in the patient group only. These anatomically focused factorial analyses of the fMRI data are formally analogous to parallel factorial analyses of behavioral data on attentional interference (described earlier).

All data sets from both Stroop tasks for SDIs and controls under all drug conditions were initially preprocessed to correct for effects of subject motion, differential slice timing, and differences in global means.<sup>72-74</sup> At the first single-subject level of analysis, a time series regression model specified 2 key contrasts between correctly performed trials: (1) drug-related words vs neutral words in the drug-word blocks and (2) color words vs neutral words in the color-word blocks. These contrasts are equivalent to those used to generate attentional interference scores in the behavioral data and are therefore most specific to the cognitive control processes of interest. This design matrix, convolved with a hemodynamic response function,<sup>75</sup> was regressed at each voxel onto the corrected time series. The resulting maps of

the model coefficients normalized by their standard errors for each individual were mapped into the standard space of the Montreal Neurological Institute echo-planar imaging template by linear affine transformation to obtain a group activation map. These activation maps included all participants under all drug treatments to identify brain regions that were significantly activated by contrast 1 (drug-word Stroop task) and by contrast 2 (color-word Stroop task) using a permutation test on spatial statistics (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>).

We used the activation map of the drug-word Stroop task contrast to define a mask (shown as red voxels in Figure 2) and regressed the median attentional interference score for each individual on the individual activation statistics at each voxel in this mask. This procedure identified a set of voxels that were both generically activated by the task and significantly associated with variability in attentional interference (shown as yellow voxels in Figure 2). The mean activation statistic over all voxels associated with attentional interference was calculated for each participant and used as a dependent variable in ANCOVA models that tested the effects of group, drug, and drug×group interaction on brain activation in these regions. The same regional activation statistics were also used as dependent variables in ANCOVA models that tested the effects of subgroup (eg, high or low compulsivity), drug, and drug×subgroup interaction on brain activation.

## RESULTS

### BASELINE IMPULSIVITY, COMPULSIVITY, AND MOOD

As expected from previous research,<sup>49</sup> SDIs reported significantly higher levels of impulsivity on the Barratt Impulsiveness Scale than controls. Stimulant-dependent individuals also generally reported high levels of compulsivity of stimulant abuse on the Obsessive Compulsive Drug Use Scale, whereas healthy controls did not show strong obsessive-compulsive traits, as assessed by the Yale-Brown Obsessive Compulsive Scale (Table 3). Although participants with clinical depression were excluded from the study, SDIs reported higher scores on depressive mood, as assessed at baseline by the Montgomery-Asberg Depression Rating Scale<sup>77</sup> and corroborated by serial scores on the Beck Depression Inventory–II<sup>71</sup> before each treatment session ( $F_{2,34}=21.50$ ;  $P<.001$ ).

### SUBJECTIVE EFFECTS OF DRUG TREATMENT

Dopaminergic challenge drugs had no significant effects on subjective alertness, contentedness, or calmness scales. There were also no significant group differences or drug×group interactions on any of these measures (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>). There was no evidence for induction of craving by performance of the drug-word Stroop task and no effect of dopaminergic challenge drugs on self-reported craving.

### BEHAVIORAL DATA FOR THE STROOP TASKS

In the drug-word Stroop paradigm, SDIs showed a marked attentional bias toward drug-related cues compared with controls (Figure 2A). Thus, across all 3 short-term treatment conditions, SDIs demonstrated significantly longer latency than controls in correctly identifying the font colors of drug-related words compared with their responses to neutral words (Table 1). Drug users did not make more errors on the drug-word Stroop task than controls. The significant drug×group interaction for accuracy was driven by controls who showed a tendency to make fewer errors while taking amisulpride relative to placebo ( $F_{1,14}=3.48$ ;  $P=.08$ ). On the color-word Stroop paradigm, no main effect of group and no drug×group interaction were identified (Table 1).

## fMRI DATA FOR THE DRUG-WORD AND COLOR-WORD STROOP TASKS

The brain regions activated by drug words (relative to neutral words) included the left ventral and dorsal prefrontal cortex and precentral cortex; anterior cingulate, medial prefrontal, and premotor cortex; posterior cingulate and medial posterior parietal cortex; bilateral middle and inferior temporal cortex; left thalamus and caudate nucleus; and right cerebellum (Table 4 and <http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>). Within this pattern of brain activation, attentional bias for drug words was most strongly associated with greater activation of the left ventral prefrontal cortex (Montreal Neurological Institute coordinates [x, y, z] in millimeters: -46, 26, 12; -44, 22, -8; and -40, 6, 30) and right cerebellum (x, y, z: 22, -80, -40) (Figure 2B and C). We fitted an ANCOVA model to test for significant main and interactive effects of group and dopaminergic drug challenge on these regions of activation. Only the effect of group was significant: SDIs had greater task-related activation of the left ventral prefrontal cortex and right cerebellum compared with controls ( $F_{1,31}=6.40$ ;  $P<.05$ ) (Figure 2D and <http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>).

In the color-word Stroop task, the only brain area activated in all participants was the left cerebellum (x, y, z: -4, -46, -40) (Table 5). We did not find a significant relationship with attentional interference scores in this locus of activation and therefore did not investigate it any further.

## EFFECTS OF IMPULSIVITY AND COMPULSIVITY ON STIMULANT DEPENDENCE

To investigate possible effects of individual differences in baseline measurements of impulsivity on drug-related attentional bias, we divided the SDIs into low- and high-impulsivity subgroups by a median split on their total Barratt Impulsiveness Scale scores. The high- and low-impulsivity subgroups were not significantly different on any other demographic or clinical variables (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>). There were no significant differences between impulsivity subgroups in latency or accuracy of response to the drug-word Stroop test and there were no significant drug $\times$ impulsivity subgroup interactions (Table 2).

Likewise, we also divided the SDIs into high- and low-compulsivity subgroups by a median split on their total Obsessive Compulsive Drug Use Scale scores; the compulsivity subgroups were not significantly different on any other baseline variables (<http://www.neuroscience.cam.ac.uk/directory/profile.php?ke220>). However, there was a significant subgroup effect on attentional interference during the drug-word Stroop test; the high-compulsivity subgroup demonstrated significantly greater attentional bias to drug-related related words (Figure 3A) (Table 2). There was also a significant drug $\times$ compulsivity subgroup interaction whereby the dopaminergic agents had markedly different effects on attentional bias in high- and low-compulsivity subgroups. Post hoc analysis indicated that this interaction was due to different effects of pramipexole in the 2 subgroups: low-compulsivity SDIs showed no attentional bias, whereas in high-compulsivity SDIs, response latencies for drug-related words were increased ( $F_{1,15}=9.80$ ;  $P<.05$ ).

The effects of compulsivity on attentional bias for drug-related words were followed up by an analysis of subgroup effects on brain activation in the frontocerebellar regions previously defined. We found a significant drug $\times$ compulsivity subgroup interaction on brain activation in the left ventral prefrontal cortex and right cerebellum ( $F_{2,30}=3.36$ ;  $P<.05$ ) (Figure 3B). Post hoc analysis showed that this interaction also was mainly driven by pramipexole, which caused a significant reduction in frontocerebellar activation compared with placebo in the low-compulsivity subgroup ( $t_8=2.34$ ;  $P<.05$ ) and the opposite effect of increased prefrontal activation, in the high-compulsivity subgroup ( $t_8=-0.77$ ;  $P>.05$ ).

## COMMENT

Using 2 versions of the Stroop paradigm for testing attentional control, we confirmed that SDIs had significantly greater attentional bias in favor of drug-related cues,<sup>20,21,23,63,80</sup> reflected in greater attentional interference scores on the drug-word Stroop test (Figure 2A). Moreover, this impairment of attentional control in people with stimulant dependence was specific to drug-related cues and did not generalize to their performance on the color-word Stroop task. Thus, it seems that there is a clinically relevant impairment of attentional control in stimulant dependence<sup>21</sup> that does not simply reflect the global impairment in attentional function that has been associated with stimulant dependence.<sup>81,82</sup>

We were also able to show, using fMRI, that greater attentional bias for drug-related words was associated with greater activation of the right cerebellum, a brain area that is implicated in Stroop task interference control,<sup>83-86</sup> and the left ventral prefrontal cortex or inferior frontal gyrus, a brain area that is implicated in the retrieval of semantic knowledge<sup>87-89</sup> and the processing of word meaning.<sup>90-92</sup> This neurocognitive association was demonstrated by the contrast between SDIs and controls: SDIs had significantly greater frontocerebellar activation (Figure 2D) as well as significantly greater attentional interference scores (Figure 2A) and attentional interference was positively correlated with frontocerebellar activation over all subjects in both groups (Figure 2C). Although abnormal inferior frontal gyrus activation during the disorder-related Stroop paradigm has been identified in various groups of psychiatric patients,<sup>68,69,93</sup> overactivation of left inferior frontal gyrus when identifying font colors of drug-related words might be specific for stimulant dependence. Left inferior frontal gyrus overactivation in stimulant users has also been reported in response to cocaine-related videos<sup>94</sup> or imagery<sup>95</sup> relative to neutral cues or when a stimulant drug was administered unexpectedly.<sup>96</sup>

## COMPULSIVITY OF DRUG ABUSE AND FRONTOCEREBELLAR SYSTEMS

We also found that SDIs with a highly compulsive pattern of stimulant drug abuse generally had greater attentional bias for drug-related words (Figure 3A). Moreover, the high- and low-compulsivity subgroups differed markedly in their response to single-dose challenges of pramipexole and amisulpride: most saliently, pramipexole increased attentional interference and frontocerebellar activation in highly compulsive SDIs, whereas in low-compulsivity SDIs, pramipexole had the opposite effect, tending to reduce or “normalize” attentional interference and frontocerebellar activation. How can we explain the different effects of these drugs on attentional interference and related brain activation in high- and low-compulsivity subgroups of SDIs?

At a mechanistic level, the normalizing effect of pramipexole on attentional bias and related frontocerebellar systems in low-compulsive SDIs could be achieved by 1 of 2 main actions. If there is relatively deficient striatal dopamine neurotransmission in this subgroup, consistent with findings recently reviewed by Narendran and Martinez,<sup>97</sup> that impairs the function of the associated corticostriatal “loops,” the dopamine D<sub>2</sub>/D<sub>3</sub> agonist could restore normal function via its postsynaptic action.<sup>98</sup> Alternatively, given that the SDIs were not in a withdrawal state, it is conceivable that they were exhibiting upregulation of striatal dopamine neurotransmission at the synapse and that the relatively low dose of the dopamine agonist restored normal functioning by its presynaptic action at dopamine D<sub>2</sub> autoreceptors.<sup>99,100</sup> However, the D<sub>2</sub>/D<sub>3</sub> receptor antagonist, amisulpride, generally had opposite effects to those of pramipexole, perhaps favoring the former hypothesis.

Clearly, neither of these hypotheses could account for the opposite effects of pramipexole in the high-compulsivity subgroup. One hypothesis that might explain this is that highly compulsive individuals have developed a dopamine receptor sensitivity that could lead to an



exaggerated and pathological response to pramipexole. Similar observations of postsynaptic supersensitivity have been described in patients with Parkinson disease who compulsively overdose their dopamine agonist medication.<sup>58</sup> The consistent finding of reduced D<sub>2</sub>/D<sub>3</sub> receptor binding in stimulant dependence<sup>36,38,97,101</sup> argues against this interpretation. However, recent preclinical studies have demonstrated that a long-term regimen of amphetamine exposure does lead to an increase in activation of the high-affinity state of striatal D<sub>2</sub> receptors.<sup>102</sup> Regardless of these considerations, it is evident that heterogeneity in response to dopaminergic agents clearly has to be taken into account when interpreting the studies of dopamine neurotransmission in stimulant abusers and indeed may help to resolve some of the inconsistencies in the field.<sup>97</sup>

## THERAPEUTIC IMPLICATIONS

One general therapeutic implication of these results is that dopaminergic drugs might have value in controlling the attentional bias toward stimulant-related cues that has previously been shown to predict relapse following a period of abstinence.<sup>21</sup> For example, dopaminergic agents could reduce the risk of attentional capture by relapse-provoking cues and thereby promote maintenance of abstinence. The observation that we did not find a relationship between attentional bias and self-reported craving may not be unusual given that many aspects of compulsive drug taking occur through automatic or habitual processes.<sup>54,103,104</sup> Our data further suggest that the therapeutic effects of dopaminergic drugs could be strongly influenced by the baseline compulsivity of stimulant drug use (which can vary considerably within a group homogeneously defined as satisfying *DSM-IV* criteria for stimulant drug dependence). This finding also has potential implications for early clinical trial design in the development of new candidate therapeutics for stimulant dependence: greater statistical power for tests of therapeutic efficacy might be achieved by sampling psychologically stratified, eg, high- or low-compulsivity, groups of patients.

## METHODOLOGICAL ISSUES

Strengths of the study include the balanced, parallel-groups, crossover design; the use of psychological test paradigms theoretically focused on cognitive mechanisms of special relevance to drug dependence; the choice of pharmacologically contrasting dopaminergic challenge drugs; and the well-characterized group of stimulant users. Weaknesses of the study include modest sample size, which has probably constrained the statistical power of the experiment, although the repeated-measures design generated 108 (36×3) behavioral and neuroimaging observations to assess factorial effects of interest. This is a large number of observations by comparison with other neuroimaging studies of stimulant dependence. The dose of pramipexole dihydrochloride was reduced during the course of the experiment, from 1.5 mg to 0.5 mg, because of the occurrence of adverse effects at the starting dose. This difference in dose was associated with proportional changes in pharmacokinetic measures of exposure, which were subsequently included as covariates in ANCOVA models to control for any effects of dose on behavioral or brain functional differences between groups.

Although SDIs were carefully selected according to eligibility criteria that excluded comorbid Axis I disorders and alcohol and opiate dependence, there was still a degree of heterogeneity within the SDI group in terms of their stimulant drug of choice (cocaine or amphetamine) and its source (3 amphetamine users were prescribed amphetamine for harm reduction). This clinical heterogeneity motivates our analysis of individual differences in compulsivity and impulsivity of drug use; however, it also presents a constraint on the generalizability of our results. The observation that high- and low-compulsivity SDIs did not differ in terms of drug-taking histories or clinical symptoms may seem surprising but similar observations have been made with regard to craving in the presence of drug-related cues,

which seems not to be reflected in clinical or demographic variables but in biological differences of cue-induced dopamine release in the striatum.<sup>35</sup>

In relation to the cognitive tests, one may argue that a lack of familiarity of drug words in controls may have affected the results. This seems unlikely since previous research has shown that the interference effect for the drug-word Stroop task is specific to drug-dependent individuals and independent from the familiarity of words.<sup>105,106</sup> It is still not clear whether drug-related compulsivity is similar to compulsive behavior observed in patients with obsessive-compulsive disorder, a disorder that has also been associated with dopamine dysfunction.<sup>107-109</sup> In our healthy controls, however, the Yale-Brown Obsessive Compulsive Scale has been shown to be insensitive for obsessive-compulsive behaviors at a subclinical level. Further studies may consider using other measures such as the Padua Inventory,<sup>110</sup> which assesses the spectrum rather than the severity of obsessive-compulsive symptoms. Moreover, behavioral measures of compulsivity in stimulant dependence need to be developed to validate the individual differences in compulsivity of drug use measured herein by a self-report instrument (Obsessive Compulsive Drug Use Scale). For example, future studies of SDIs might usefully also include more general cognitive measures of attentional set shifting or reversal learning as more objective markers of compulsive perseveration.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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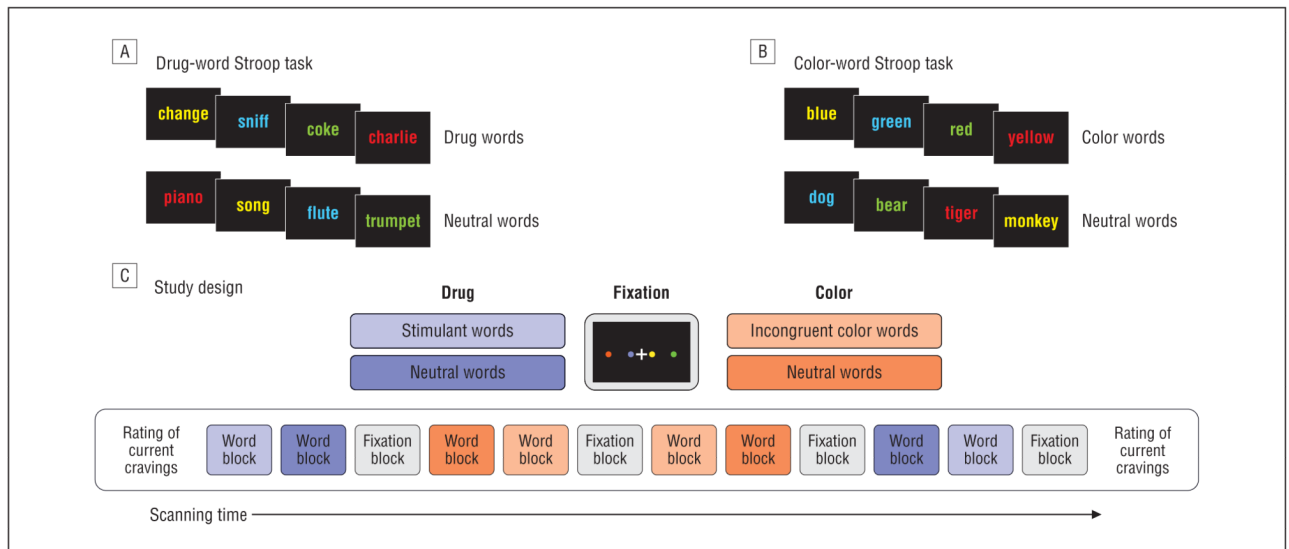
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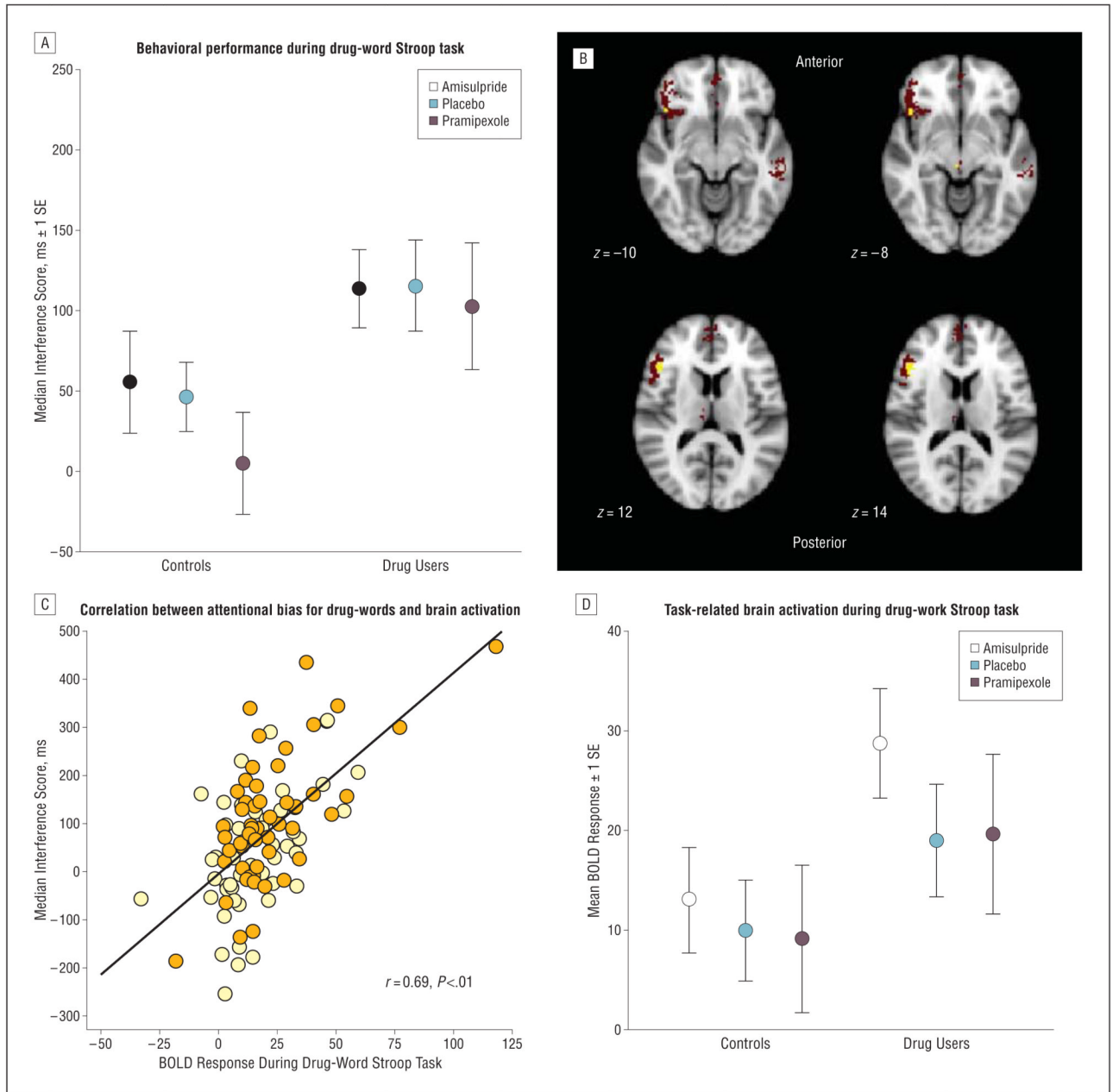
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**Figure 1.**

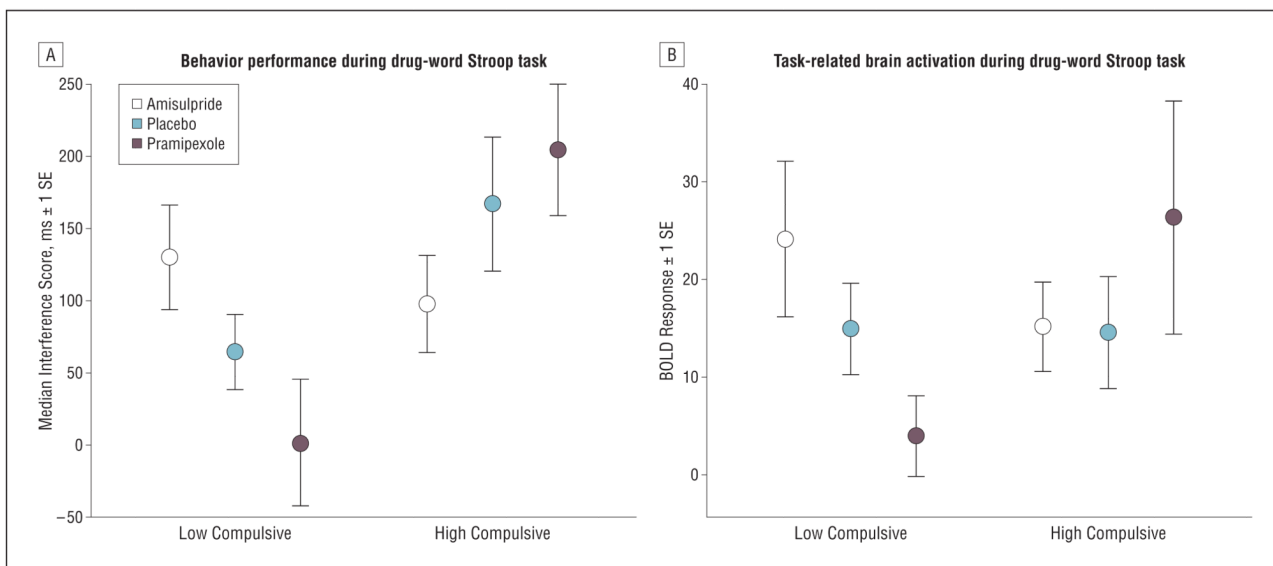
Schematic of the Stroop paradigms. A, In the drug-word Stroop task, participants were asked to identify the font colors of the drug-related words and the neutral words. B, In the color-word Stroop task, participants were asked to identify the font colors of the color words and the neutral words. C, Blocks of drug-related words, color words (which were always incongruent with their font color), and neutral words were interspersed with blocks of fixation for task presentation during functional magnetic resonance imaging.



**Figure 2.**

Behavioral performance during the drug-word Stroop paradigm and task-related activation of a frontocerebellar system associated with attentional bias for drug words (in all participants). A, Drug users showed a significant attentional bias for drug-related words, as reflected in higher attentional interference scores compared with the healthy comparison volunteers. Attentional bias was measured by each volunteer's median response latency of correctly identified colors of drug-related words minus the median response latency of correctly identified colors of matched neutral words. Pramipexole was given as pramipexole dihydrochloride. B, The red voxels indicate brain regions activated by the contrast between drug-related words and neutral words; yellow voxels indicate brain regions within this system where activation was positively correlated with attentional interference scores on the

drug-word Stroop task. C, Scatterplot of median attentional interference score (y-axis) vs functional activation of the brain regions associated with attentional bias for drug words (x-axis), which are the left ventral prefrontal cortex (Montreal Neurological Institute coordinates [x, y, z] in millimeters: -46, 26, 12; -44, 22, -8; and -40, 6, 30) and right cerebellum (22, -80, -40). The spatial coordinates refer to the peak voxel where the effect size is greatest. BOLD indicates blood oxygen level dependent. D, Comparison of mean task-related (BOLD) activation in brain regions associated with attentional bias between stimulant-dependent individuals and healthy volunteers. Stimulant users show overactivation in the left ventral prefrontal cortex and right cerebellum compared with controls.



**Figure 3.**

Behavioral performance and task-related activation of a frontocerebellar system during the drug-word Stroop task in high- and low-compulsivity drug users. Pramipexole was given as pramipexole dihydrochloride. A, High-compulsivity drug users showed a different profile in response to short-term dopaminergic treatment compared with low-compulsivity drug users, as reflected in greater attentional bias for drug-related words relative to neutral words. Attentional bias was measured by each volunteer's median response latency of correctly identified colors of drug-related words minus the median response latency of correctly identified colors of matched neutral words. B, Dopaminergic drug effects on the left prefrontal cortex during the drug-word Stroop task are modulated by compulsivity of stimulant dependence. Box plots show functional activation associated with attentional bias for drug-related words in the left prefrontal cortex (Montreal Neurological Institute coordinates [x, y, z] in millimeters:  $-46, 26, 12$ ;  $-44, 22, -8$ ; and  $-40, 6, 30$ ) and right cerebellum ( $22, -80, -40$ ) in high- and low-compulsivity subgroups, indicating differential effects of pramipexole. The spatial coordinates refer to the peak voxel where the effect size is greatest.

**Table 1**

Task Performance on the Drug-Word Stroop and Color-Word Stroop Tests in Stimulant-Dependent Individuals and Healthy Comparison Volunteers<sup>a</sup>

Dependent Variable	Effect	df	F	P Value
Drug-word Stroop task				
Attentional interference score (median latency)	Drug	2, 62	1.75	.18
	Drug×group	2, 62	0.28	.97
	Group	1, 31	10.87	.02 <sup>a</sup>
Attentional interference score (mean latency)	Drug	2, 62	1.24	.30
	Drug×group	2, 62	0.27	.77
	Group	1, 31	10.87	.002 <sup>a</sup>
Error rate, %	Drug	2, 62	1.32	.27
	Drug×group	2, 62	4.04	.02 <sup>a</sup>
	Group	1, 31	3.82	.06
Color-word Stroop task				
Attentional interference score (median latency)	Drug	2, 62	6.14	.004 <sup>a</sup>
	Drug×group	2, 62	0.74	.48
	Group	1, 31	0.24	.63
Attentional interference score (mean latency)	Drug	2, 60	3.08	.053
	Drug×group	2, 60	0.86	.43
	Group	1, 30	0.01	.94
Error rate, %	Drug	2, 62	0.05	.96
	Drug×group	2, 62	1.19	.31
	Group	1, 31	3.01	.09

Abbreviation: BDI-II, Beck Depression Inventory–II.<sup>71</sup>

<sup>a</sup>Analysis of covariance modeling of factorial effects on attentional interference and accuracy (covariates: BDI-II total scores, years of education, and plasma levels of pramipexole dihydrochloride).

<sup>b</sup>Significant.

**Table 2**

Task Performance on the Drug-Word Stroop Test in High- and Low-Compulsivity and High- and Low-Impulsivity Subgroups of Stimulant-Dependent Individuals<sup>a</sup>

Dependent Variable on Drug-Word Stroop Task	Effect	<i>df</i>	<i>F</i>	<i>P</i> Value
Compulsivity				
Attentional interference score (median latency)	Drug	2, 30	1.97	.16
	Drug×group	2, 30	4.35	.02 <sup>b</sup>
	Group	1, 15	7.84	.01 <sup>b</sup>
Attentional interference score (mean latency)	Drug	2, 30	3.23	.053
	Drug×group	2, 30	5.55	.009 <sup>b</sup>
	Group	1, 15	9.14	.009 <sup>b</sup>
Error rate, %	Drug	1.5, 22.1	1.42	.24
	Drug×group	1.5, 22.1	0.38	.71
	Group	1, 15	2.07	.17
Impulsivity				
Attentional interference score (median latency)	Drug	2, 30	1.42	.26
	Drug×group	2, 30	1.36	.27
	Group	1, 15	1.27	.28
Attentional interference score (mean latency)	Drug	2, 30	2.44	.11
	Drug×group	2, 30	1.94	.16
	Group	1, 15	1.39	.26
Error rate, %	Drug	1.5, 21.8	1.79	.20
	Drug×group	1.5, 21.8	1.44	.25
	Group	1, 15	0.20	.66

<sup>a</sup>Analysis of covariance modeling of factorial effects on attentional interference and accuracy (covariate: plasma levels of pramipexole dihydrochloride).

<sup>b</sup>Significant.

**Table 3**

Demographic, Psychological, and Baseline Personality Measures for the Groups of 18 Stimulant-Dependent Individuals and 18 Healthy Volunteers

Group	Mean (SD) [range]		F	df	P Value
	Healthy Comparison Volunteers	Stimulant-Dependent Individuals			
Age, y	32.7 (6.9)	34.3 (7.2)	0.47	1, 34	.498
Sex ratio (male:female)	15:3	15:3	<i>a</i>	<i>a</i>	>.99
Ethnic ratio (white:Afro Caribbean) <sup>b</sup>	17:1	16:2	<i>a</i>	<i>a</i>	>.99
Employment ratio (employed:unemployed)	17:1	9:9	<i>a</i>	<i>a</i>	.007
Verbal intelligence quotient (NART)	108.4 (6.0)	109.0 (8.1)	0.55	1, 34	.82
Education, y	12.4 (1.8)	11.2 (1.0)	6.85	1, 34	.01
BIS-11 total score	62.0 (7.2)	82.0 (9.5)	50.4	1, 34	>.001
MADRS total score	0.9 (2.4)	5.6 (8.2)	5.49	1, 34	.03
BDI-II total score	1.1 (2.4)	9.3 (11.1)	9.50	1, 34	.004
YBOCS total score	0.1 (0.5)				
OCDUS total score		26.5 (7.9)			
Duration of stimulant abuse, y		11.7 (7.4) [2-26]			
Frequency of stimulant abuse, d/wk		5.4 (2.0)			
Age at onset of stimulant abuse, y		20.5 (5.4) [14-35]			

Abbreviations: BDI-II, Beck Depression Inventory–II<sup>71</sup>; BIS-11, Barratt Impulsiveness Scale<sup>76</sup>; MADRS, Montgomery-Asberg Depression Rating Scale<sup>77</sup>; NART, National Adult Reading Test<sup>78</sup>; OCDUS, Obsessive Compulsive Drug Use Scale<sup>62</sup>; YBOCS, Yale-Brown Obsessive Compulsive Scale.<sup>64</sup>

<sup>a</sup>Fisher exact test.

<sup>b</sup>Ethnicity was recorded according to the standard practices of the study funder and sponsor. Ethnic background was neither an inclusion nor an exclusion criterion.

**Table 4**

Brain Regions Differentially Activated During the Drug-Word Stroop Task in Drug Users and Healthy Volunteers, Irrespective of Drug Treatment

Size (Voxel)	Max $F^a$	x, y, z Max Coordinates, mm <sup>b</sup>	AAL Regions
<b>Regions Associated With Greater Activation During Indication of Font Color of Drug-Related Words vs Neutral Words</b>			
1030	44.67	-46, 42, -12	Bilateral inferior frontal gyrus (orbital, opercula, and triangular parts), left middle frontal gyrus (orbital part), rolandic operculum, insula, and superior temporal gyrus
722	6.29	-2, 50, -14	Bilateral middle frontal gyrus (orbital part), superior frontal gyrus (medial part), rectus gyrus, and anterior cingulate gyrus
221	2.99	22, -80, -46	Right cerebellum
150	3.81	-4, -52, 30	Bilateral posterior cingulate gyrus, precuneus, and left median cingulate gyrus
139	6.59	0, -22, -4	Left thalamus and caudate nucleus
100	3.89	-62, -46, 4	Left middle temporal gyrus
88	6.19	50, -32, -6	Right middle temporal gyrus and inferior temporal gyrus
87	4.29	-52, 12, 36	Left precentral gyrus, middle frontal gyrus, and inferior frontal gyrus (opercula part)
79	6.55	0, 22, 64	Bilateral supplementary motor area and superior frontal gyrus (medial part)
<b>Regions Associated With Deactivation During Indication of Font Color of Drug-Related Words vs Neutral Words</b>			
1402	-5.36	2, 8, 10	Bilateral caudate, thalamus, hippocampus, posterior cingulate, precuneus, calcarine gyrus, left parahippocampus, left lingual gyrus, left fusiform gyrus, and right cuneus
639	-3.21	44, -8, -8	Right superior temporal gyrus, inferior frontal gyrus, rolandic operculum postcentral gyrus, supramarginal gyrus, Herschel gyrus, insula, and putamen
427	-2.47	-2, -2, 48	Bilateral cingulate gyrus, supplementary motor area, and paracentral lobule
188	-2.71	8, -72, 54	Right precuneus, cuneus, superior parietal gyrus, and superior occipital gyrus
130	-3.34	54, -36, 52	Right inferior parietal gyrus, postcentral gyrus, and supramarginal gyrus
119	-2.97	-22, -12, 72	Left precentral gyrus, superior frontal gyrus, paracentral lobule, and postcentral gyrus

Abbreviations: AAL, Automated Anatomical Labeling<sup>79</sup>; Max, maximum.

<sup>a</sup>Max  $F$  denotes the maximum  $F$  statistic (test statistics for task-related activation) over all voxels in each region.

<sup>b</sup>Coordinates are given in Montreal Neurological Institute space.



**Table 5**

Brain Regions Differentially Activated During the Color-Word Stroop Task in Drug Users and Healthy Volunteers, Irrespective of Drug Treatment

Size (Voxel)	Max $F^a$	x, y, z Max Coordinates, mm <sup>b</sup>	AAL Regions
<b>Regions Associated With Greater Activation During Indication of Font Color of Incongruent Color Words vs Neutral Words</b>			
126	5.69	-4, -46, -40	Left cerebellum and vermis
<b>Regions Associated With Deactivation During Indication of Font Color of Incongruent Color Words vs Neutral Words</b>			
431	-4.09	2, 56, -10	Bilateral middle frontal gyrus (orbital part), superior frontal gyrus (medial part), gyrus rectus, and anterior cingulate gyrus

Abbreviations: AAL, Automated Anatomical Labeling<sup>79</sup>; Max, maximum.

<sup>a</sup>Max  $F$  denotes the maximum  $F$  statistic (test statistics for task-related activation) over all voxels in each region.

<sup>b</sup>Coordinates are given in Montreal Neurological Institute space.