Response Perseveration in Stimulant Dependence Is Associated with Striatal Dysfunction and Can Be Ameliorated by a $D_{2/3}$ Receptor Agonist

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Background: Compulsivity is a hallmark of drug addiction and in animal models is measured by consecutive incorrect responses to a previously rewarded stimulus during reversal learning. The aim of this study was to measure behavioral and neural markers of compulsivity in stimulant-dependent individuals and to test whether these markers could be modulated by treatment with drugs targeting the dopamine system.

Methods: In a randomized, double-blind, placebo-controlled, crossover design, stimulant-dependent individuals (SDIs; $n = 18$) and healthy volunteers ($n = 18$) received single doses of dopamine $D_{2/3}$ receptor antagonist (amisulpride, 400 mg) and agonist (pramipexole, 0.5 mg) drugs. To examine compulsivity and its dopaminergic modulation more generally, patients with obsessive-compulsive disorder (OCD; $n = 18$) were also included in the study.

Results: SDIs made significantly more perseverative responses to the previously correct stimulus immediately following reversal, compared with both healthy volunteers and patients with OCD. Across all participants, the number of perseverative errors was negatively correlated with functional activation in right fronto-striato-parietal networks—in particular, the right caudate nucleus. In SDIs, perseveration-related caudate activation was abnormally reduced in the placebo condition, but the dopamine $D_{2/3}$ agonist pramipexole normalized both perseverative responding and related activation of the right caudate.

Conclusions: Perseveration during reversal learning was associated specifically with stimulant dependence rather than with compulsive behaviors more generally. The beneficial effects of a dopamine agonist drug challenge on both behavior and associated brain activation in SDIs may indicate new avenues for pharmacologic treatment in stimulant dependence.

Key Words: Dopamine, fMRI, obsessive-compulsive disorder, pramipexole, probabilistic reversal learning, substance dependence

A central feature of substance dependence is the persisting nature of drug-taking habits, despite the risk of job loss, family breakup, or imprisonment precipitated by further drug use (1). Such compulsive drug-taking patterns are thought to result from progressive changes to mesolimbic and nigrostriatal dopamine systems (2), and chronic stimulant dependence has been associated with orbito-fronto-striatal abnormalities in brain imaging studies of patients (3,4). We have recently shown that the dopaminergic modulation of attentional bias for stimulant drug–related words was modulated by the compulsivity of stimulant abuse, as assessed by self-report measures (5). Here, we further investigate the nature of compulsivity in stimulant dependence by using an objective, behavioral marker of compulsivity (perseverative responding) and by exploring the potential efficacy of dopaminergic drugs in modulating abnormalities of compulsive behavior and related brain functional activation.

Animal models of addiction suggest that perseveration, as measured by reversal-learning paradigms, might serve as a sensitive objective measure reflecting compulsive behavior patterns seen in drug-addicted individuals (6). The term "perseveration" describes a tendency to respond persistently to a particular stimulus, even after the response has become inappropriate or unrewarded. Indeed, both animals experimentally administered or self-administering psychostimulants, and humans chronically using cocaine, demonstrate difficulties in adjusting their behavior to changes in stimulus-reward contingencies, as reflected by perseveration to previously rewarded stimuli (7–9). Strong preclinical evidence indicates a key role for dopamine in the ability to shift behavior according to changes in reinforcement contingencies (10,11). Successful response reversal relies on the integrity of frontostriatal networks, including the dorsomedial and ventral striatum and ventral prefrontal cortex (12,13), which are known to have major dopaminergic inputs. Although dopamine D_2 and D_3 receptors are thought to play an important role in reversal learning, findings in the literature are equivocal. Both the D_2/D_3 antagonist raclopride (14) as well as the $D_{2/3}$ agonist quinpirole (15) have led to reversal deficits in experimental animals.

Because compulsive behaviors are not specific to stimulant dependence but are also implicated in other psychiatric disorders, such as obsessive-compulsive disorder (OCD) (2), we included a second control group of patients with OCD to better understand how reversal-learning performance is related to compulsivity in

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general. OCD has also been associated with orbito-fronto-striatal circuits (16,17), but the compulsive symptoms are differently expressed in OCD than in stimulant dependence—namely, by ritualistic or repetitive behaviors or mental acts, often accompanied by troubling intrusive thoughts (1).

To explore further the role of dopamine in compulsive behaviors, we conducted a double-blind, placebo-controlled, pharmacologic functional magnetic resonance imaging (fMRI) study, using single doses of a dopamine $D_{2/3}$ receptor agonist and a $D_{2/3}$ antagonist, in a within-subjects crossover design in SDIs, healthy volunteers and patients with OCD. We chose these dopaminergic drugs on the basis of their selective profile for $D_{2/3}$ receptors, particularly in the striatum, where reduced receptor levels have been reported in both SDIs and OCD patients (3,4,18). We used a probabilistic reversal-learning task that has previously demonstrated sensitivity to dopaminergic modulation (19,20) and perseverative responding in cocaine-dependent individuals (8) but not in patients with OCD (21,22). We hypothesized that perseverative responding in SDIs during serial reversal learning is caused by dysfunction in frontostriatal networks, which would be ameliorated by dopaminergic agonist modulation.

Methods and Materials

Study Sample

Fifty-four right-handed participants were recruited: healthy volunteers ($n = 18$), stimulant-dependent individuals (SDIs; $n = 18$), and patients with OCD ($n = 18$). Demographic and clinical data are summarized in Table 1 and Supplement 1. SDIs had a minimum 2-year history of dependence on illicit stimulants satisfying the DSM-IV-TR (1) criteria for dependence on cocaine/crack ($n = 10$) or amphetamines ($n = 8$). Diagnoses of stimulant dependence and OCD were made using the Structured Clinical Interview for the DSM-IV (23). Data from these groups were published previously (5,24–26).

All participants were screened to exclude any other current Axis I psychiatric disorder according to the DSM-IV-TR criteria and underwent an assessment of their general health, including a physical examination and baseline clinical blood tests. Concomitant medications (except selective serotonin reuptake inhibitors in OCD patients) and the illicit use of drugs (except in SDIs) were exclusion criteria. In addition, participants were excluded if they had a current or past history of any serious medical disorder or any contraindications to MRI (see Supplement 1). One SDI was excluded because his overall task performance deviated by more than two standard deviations from both the SDI mean and the overall mean. The study was approved by the Cambridge Research Ethics Committee (REC06/Q0108/130; principal investigator: TWR), and all participants provided written informed consent.

Study Design

All participants were scanned on three occasions with a week between each session. The scan started 1 hour after a single dose of 400 mg amisulpride ($D_{2/3}$ receptor antagonist), 0.5 mg pramipexole ($D_{2/3}$ receptor agonist), or placebo, which coincided with peak plasma levels of both drugs, based on existing pharmacokinetic data (27–29). Three SDIs received a higher dose of 1.5 mg of pramipexole (see Supplement 1 for details). Subjective drug effects were serially assessed using the Bond-Lader Visual Analogue Scale (30) administered 1 and 2.5 hours after dosing in each treatment session (immediately before and after fMRI scanning). At these two time points, blood samples were also drawn for the assessment of plasma levels of the drug treatments. Plasma levels of pramipexole in one OCD patient were unavailable.

Probabilistic Reversal-Learning Task

The probabilistic reversal-learning task (31) is a serial, two-choice visual discrimination task. As shown in Figure 1, the same two stimuli were simultaneously presented on each trial; participants initially learned through trial-and-error which stimulus was correct and which was incorrect. To make a response and select a stimulus, participants pressed either the left or the right button on the response pad, depending on the position of the correct stimulus on the screen. On each trial, the two stimuli were presented for a 2000-msec period during which the response had to be made before a "too late" message was presented on the screen. Participants received immediate feedback on the accuracy of their choice, in the form of a happy green face or a sad red face, 500 msec after a response was made. After each trial, a fixation cross appeared for a variable interval, making the interstimulus interval up to 3000 msec in duration. Participants were told in advance that the response rule would reverse several times during the task, at which point the previously incorrect stimulus would become the correct stimulus, and that they should adjust their responses to the new rule as soon as they were aware it had changed. Participants were also informed that the task was of probabilistic nature, meaning that intermittently they would receive negative feedback for a correct response, which they should ignore. The change in reinforcement contingen-

Table 1. Demographic, Psychological, and Baseline Personality Measures for the Groups of Healthy Nondependent Control Volunteers ($n = 18$), SDI ($n = 17$), and Patients with OCD ($n = 18$)

Group	Controls	SDI	OCD	*F*	*df*	*p*
Age (years)	32.7 (±6.9)	34.3 (±7.4)	35.4 (±9.8)	.49	2,50	.618
Gender Ratio (male:female)	15:3	14:3	7:11			.318[a]
Ethnic Ratio (Caucasian:Afro-Caribbean)	17:1	15:2	18:00			.308[a]
Verbal Intelligence Quotient (NART)	108.4 (±6.0)	108.0 (±8.3)	107.9 (±8.8)	.06	2,50	.938
Years of Education	12.4 (±1.8)	11.2 (±1.0)	12.3 (±2.0)	2.06	2,50	.082
Dysphoric Mood, BDI-II (total score at baseline)	1.1 (±2.4)	9.8 (±11.2)	18.5 (±10.0)	18.07	2,50	<.001
Impulsivity, BIS-11 (total score)	62.0 (±7.2)	81.7 (±9.7)	66.9 (±9.7)	22.83	2,49	<.001
Compulsivity, Y-BOCS (total score)	.1 (±.5)	—	24.11 (±13.0)	—	—	—
Compulsivity, OCDUS (total score)	—	26.0 (±7.8)	—	—	—	—
Age of Onset (years) of Stimulant Abuse or of OCD	—	20.5 (±5.4)	17.1 (±11.0)	—	—	—
Duration (years) of Stimulant Abuse or OCD	—	11.7 (±7.4)	18.3 (±10.6)	—	—	—

BDI-II, Beck Depression Inventory, version 2 (32); BIS-11, Barratt Impulsiveness Scale, version 11 (33); NART, National Adult Reading Test (34); OCD, obsessive-compulsive disorder; OCDUS, Obsessive-Compulsive Drug Use Scale (35); SDI, stimulant-dependent individuals; Y-BOCS, Yale–Brown Obsessive-Compulsive Scale (36).

[a]Fisher's Exact Test.

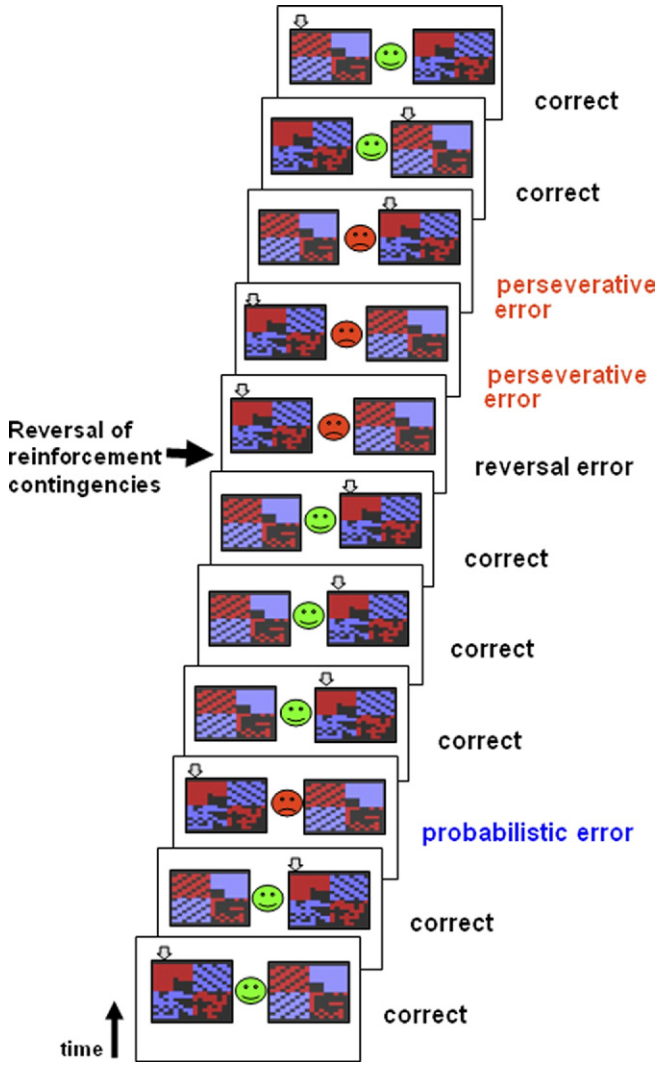

Figure 1. Schematic of the probabilistic reversal task. On each trial, participants are shown two abstract stimuli of which they should select one by pressing the right or left key on a button box. Participants are told that one pattern is correct and the other is wrong, which is indicated by a green smiling face or a red sad face presented immediately after they have made a choice (here indicated by a white arrow above the chosen pattern). Participants are instructed to select the correct stimulus on each trial. Participants are also informed that on some trials, they will receive misleading feedback following a correct response, which should not deter them from continuing to select the correct pattern. They are also told that at some point during the task the response rule may change, that is, that the stimulus that had been correct will no longer be correct (reversal). When they notice that the rule has changed, they should follow the new rule by reversing their responses. If participants fail to reverse their responses following the rule change, they perseverate on the previously correct response (perseverative errors). On each trial, the two stimuli were presented for a 2000-msec period during which the response had to be made before a "too late" message was presented on the screen. After each trial, a fixation cross appeared for a variable interval, making the interstimulus interval up to 3000 msec in duration.

cies was dependent on participants' performance. Participants had to make at least 10 cumulative correct responses before reversal occurred; this learning criterion differed from sequence to sequence from 10 to 15 to avoid participants' anticipating the reversal of reinforcement contingencies. However, if participants failed to reach the required cumulative number of correct responses, the task would stop after the 200th trial of that run.

The key behavioral measure was perseveration, that is, consecutive choices of the previously correct stimulus immediately after the rule had changed, excluding the error on reversal itself (Figure 1). The average number of consecutive errors within a preservative sequence was reflected in the perseverative error rate. This represents the number of errors made in a perseverative sequence (see Table 2 for further details). In addition, participants could also make two other types of errors: spontaneous errors (i.e., switching to the alternative, nonrewarded stimulus without having received misleading negative feedback) and probabilistic switches (i.e., switching to the nonrewarded stimulus following misleading negative feedback to a correct response, which was provided on about 15% of correct trials). This event-related fMRI task was presented in two runs of 10 learning sequences, generating a possible total of 18 response reversals. Before entering the scanner, all participants were trained on the task with a 30-trial practice run to familiarize themselves with the task and to minimize practice effects on task performance.

Acquisition of fMRI Data

Whole-brain fMRI data were acquired at the Wolfson Brain Imaging Centre, University of Cambridge, United Kingdom, using a Siemens Magnetom Tim Trio whole-body scanner operating at 3 Tesla (http://www.medical.siemens.com). During task performance, 32 transaxial sections of gradient-echo, echoplanar imaging (EPI) data depicting blood oxygen level–dependent contrast were acquired parallel to the intercommissural line with the following parameters: repetition time = 2000 msec, echo time = 30 msec, flip angle = 78°, slice thickness = 3 mm plus .75 mm interslice gap, image matrix size = 64 × 64, within-plane voxel dimensions = 3.0 × 3.0 mm. Before data analysis, the first five images were discarded to account for T_1 equilibration effects.

Analysis of Behavioral, Demographic, and Psychometric Data

Behavioral data were analyzed using repeated-measures analysis of covariance (ANCOVA) with drug treatment (three levels: placebo, amisulpride, pramipexole) as the within-subject factor and group (three levels: control volunteers SDIs, OCD patients) as the between-subject factor. Subjective drug effects rated before and after scanning were also analyzed using repeated-measures ANCOVA models. The summary Beck Depression Inventory—II score of the three testing sessions and plasma levels of pramipexole were included as covariates in these models to control for group differences on these variables. For post hoc analysis, univariate ANCOVA models were fit separately to the placebo and pramipexole data. Where significant group-by-drug interactions were identified, we calculated the Pearson's correlation coefficient, *r*, between the drug-related response and self-reported measures of compulsivity in each group separately, while controlling for pramipexole plasma levels. If not otherwise specified, the least significant difference test was used if variances were equivalent between groups or the Tamhane procedure if variances differed. Statistical tests were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics, V13) and were reported as significant if $p < .05$.

Analysis of fMRI Data

The event-related fMRI data were statistically analyzed using CamBA software, version 2.3.0 (http://www-bmu.psychiatry.cam.ac.uk/software). Full details of the fMRI data analysis procedures are provided in Supplement 1 and briefly summarized here. Data sets from all three groups under all three drug conditions were initially preprocessed to correct for effects of subject motion, differential

Table 2. Performance Data During Probabilistic Reversal Learning

	Healthy Volunteers		Stimulant Users		OCD Patients	
Performance Measures	Mean	SD	Mean	SD	Mean	SD
Number of Trials per Sequence	15.3 (±1.0)		17.7 (±3.4)		15.8 (±1.3)	
Number of Perseverative Errors	20.1 (±6.1)		17.7 (±6.5)		16.2 (±6.2)	
Number of Sequences on Which Criterion for Perseveration Was Met[a]	15.2 (±3.3)		11.8 (±4.7)		12.4 (±4.9)	
Perseverative Error Rate[a]	1.3 (±.3)		1.6 (±.6)		1.4 (±.3)	
Number of Spontaneous Errors	5.5 (±3.7)		15.8 (±10.3)		9.0 (±10.2)	
Number of Probabilistic Switches	3.5 (±5.0)		5.7 (±5.1)		8.6 (±7.0)	

Because the reinforcement contingencies did not reverse until participants had made a minimum number of cumulative correct responses (between 10 and 15), the number of trials per sequence varied across participants. The key behavioral measure was perseveration, that is, consecutive choices of the previously correct stimulus immediately after the rule had changed, excluding the error made on reversal itself. Participants could also make two other types of errors in addition to perseverative errors: spontaneous errors (i.e., switching to the alternative, nonrewarded stimulus without having received misleading negative feedback) and probabilistic switches (i.e., switching to the nonrewarded stimulus following misleading negative feedback to a correct response).

OCD, obsessive-compulsive disorder; SD, standard deviation.

[a]The perseverative error rate is calculated by dividing the number of perseverative errors by the number of sequences on which criterion for perseveration was met. To meet criterion for perseveration, participants had to make at least one consecutive response to the previously rewarded stimulus immediately following reversal, excluding the reversal error itself.

slice timing and differences in global means. Scanning data of one OCD patient during one scanning session (amisulpride condition) were lost because of technical reasons. To maintain the balanced design necessary for permutation testing of two-way ANCOVA models, a replacement data set was imputed on a voxel-wise basis using the mean and sampling the variance of the fMRI data acquired from the other OCD patients following amisulpride treatment (37). The task had two runs; functional activation was estimated from each run separately and then combined before construction of group activation maps by simple addition of statistics on a voxelwise basis. Responses under simulated conditions of the null hypothesis were similarly combined for subsequent significance testing by permutation methods.

The first-level fMRI time-series model was specified using the following regressors: 1) correct (correct responses followed by positive feedback), 2) probabilistic errors (correct responses followed by misleading negative feedback), and 3) perseverative errors (consecutive incorrect responses immediately following the change in reinforcement contingencies, excluding the error immediately following reversal). These regressors, convolved with a hemodynamic response function, formed the design matrix, which was fit to the subject motion-corrected time series at each voxel. The regressors were combined in two orthogonal contrasts: 1) negative versus positive feedback (−2 correct, +1 probabilistic errors; +1 perseverative errors), and 2) perseverative errors versus probabilistic errors (0 correct, −0.5 probabilistic errors; +0.5 perseverative errors). 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 by affine transformation. Conditions under the null-hypothesis of no stimulus-related response were simulated by wavelet permutation and then processed in an identical manner as the observed data and used for statistical inference 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 (negative feedback) and by contrast 2 (perseverative errors) using a permutation test on spatial statistics (38) and a statistical threshold controlling multiple comparisons such that the expected number of false positive clusters <1 (equivalent $p < .00057$).

We focused our analysis on those brain regions where functional activation was specifically associated with perseveration, controlling for negative feedback (contrast 2). This analysis allowed us to dissociate responses associated with receiving negative feedback per se from responses associated with using negative feedback to guide subsequent responses adaptively. To investigate the effects of drug and group on brain regions specifically associated with perseverative responding, we used the activation map (as described in Table 2) to define a mask and regressed the mean number of perseverative errors for each individual on the individual activation statistics at each voxel in this mask. At each voxel of these behaviorally relevant regions, we tested the factorial effects of diagnostic group and dopaminergic drug challenge by ANCOVA across all three groups.

Results

Baseline Assessment

The groups were well matched on most demographic variables (Table 1), but both patient groups reported higher levels of dysphoric mood compared with control volunteers ($p < .001$). The SDI group scored significantly higher on the Barratt Impulsiveness Scale (33) 11 than the other two groups ($p < .001$). Both patient groups also reported relatively high levels of compulsivity, as reflected in mean Obsessive Compulsive Drug Use Scale (35) and Yale–Brown Obsessive Compulsive Scale (36) scores for the SDIs and patients with OCD, respectively.

Behavioral Responses During Serial Probabilistic Reversal Learning

The groups differed significantly in terms of the number of trials per sequence before reversal [$F(2,47) = 6.74$, $p = .003$]; the SDIs needed significantly more trials to reach criterion compared with both controls and OCD patients (both $ps < .05$). There was no main effect of drug [$F(2,94) = 4.34$, $p = .151$] and no drug-by-group interaction [$F(4,94) = .43$, $p = .786$]. The groups also differed significantly in terms of spontaneous errors [$F(2,47) = 6.92$, $p = .002$], with SDIs making more such errors than both control volunteers and OCD patients (both $ps < .05$). Spontaneous errors were unaffected by drug administered [$F(2,94) = 2.44$, $p = .093$] and no group-by-drug interaction was identified [$F(4,94) = 1.60$, $p = .181$]. There was no main effect of group [$F(2,47) = 1.23$, $p = .303$] or drug [$F(2,94) = .97$, $p = .382$] on probabilistic switches, and no group-by-drug interaction [$F(4,94) = .48$, $p = .748$; see also Table 2].

Figure 2. Brain functional and behavioral markers of perseveration in the probabilistic reversal-learning task. The regression of perseverative responses within the pattern of brain activation revealed four significant clusters, which were subsequently analyzed to explore the effects of drug and drug-by-group interactions. **(A)** The red voxels indicate brain regions activated by the contrast between perseverative errors versus probabilistic errors; the blue voxels indicate regions deactivated by perseverative errors; and the yellow voxels indicate regions where activation was negatively correlated with perseverative errors during probabilistic reversal learning. **(B)** Mean perseverative error rates are shown for each group of participants in each treatment condition. **(C)** Scatter plot between perseverative errors and brain activation in the right caudate nucleus. The correlation remained significant when the participant with high perseverative errors was removed from the analysis ($r = -.33$, $p < .05$). **(D)** Mean regional activation of right caudate nucleus by perseverative responses is shown for each group of participants in each treatment condition. Stimulant users show greater perseverative errors and reduced activation of right caudate, compared with healthy volunteers and obsessive compulsive disorder (OCD) patients following placebo and amisulpride, but both behavioral and brain functional markers are normalized in stimulant drug users following treatment with pramipexole. The coordinates are in Montreal Neurological Institute space. BOLD, blood oxygen level– dependent; L, left; R, right.

Analysis of perseverative error rates revealed no main effect of group [$F(2,47) = 2.18$, $p = .125$] but a significant effect of drug [$F(2,94) = 3.24$, $p = .044$]. However, this drug effect was qualified by a highly significant drug-by-group interaction [$F(4,94) = 5.52$, $p < .001$]. Post hoc analysis of perseveration separately on placebo and on pramipexole revealed a significant group difference for the placebo [$F(2,49) = 5.34$, $p = .005$] and amisulpride [$F(2,49) = 3.63$, $p = .034$] conditions but not for pramipexole [$F(2,47) = .63$, $p = .538$]. Post hoc comparisons between performance in the three groups on placebo showed greater perseveration in SDIs compared with control volunteers ($p = .032$) and with OCD patients ($p = .005$), confirming our previous findings (8). As shown in Figure 2B, pramipexole decreased perseverative responding relative to placebo in SDIs [$t(16) = 2.42$, $p = .02$] but did not affect performance in the other two groups [controls: $t(17) = -1.39$, $p = .183$; OCD: $t(17) = -1.17$, $p = .260$]. Moreover, SDI performance after pramipexole did not differ from performance in the control volunteers [$t(33) = -.17$, $p = .863$]. Thus, pramipexole improved performance in SDIs but had no effect in the other two groups. Amisulpride, in contrast, did not change performance relative to placebo in any of the groups [controls: $t(17) = -1.03$; $p = .316$; SDIs: $t(16) = .17$, $p = .871$; OCD: $t(17) = 1.25$, $p = .228$]. The perseverative error rate did not change over the course of the task: there was no main effect of run [$F(2,42) = .57$, $p = .456$] and no run-by-group interaction [$F(2,42) = .20$, $p = .822$]. Self-reported compulsivity in each of the patient groups was not associated with the degree of perseveration in the placebo condition (Obsessive Compulsive Drug Use Scale in SDIs: $r = -.14$, $p > .05$, Yale–Brown Obsessive Compulsive Scale in OCD patients: $r = -.24$, $p > .05$), or with the pramipexole-induced change in perseverative responding (SDIs: $r = .38$, $p > .1$; OCD: $r = -.06$, $p > .1$).

Brain Responses Associated with Perseverative Errors

The brain regions activated by perseverative responding (controlling for negative feedback) included bilateral inferior, medial,

and superior frontal lobe structures and anterior and middle cingulate cortex, insular, caudate, thalamus, parietal, and occipital lobe structures (see Figure 2 and Table 2 for anatomical details), as previously reported with regard to reversal learning (31,39). In four of these regions, the strength of activation was negatively associated with perseverative errors across all participants (averaged across the three drug sessions), including right ventral caudate (Montreal Neurological Institute x, y, z coordinates [4, 6, 0] mm; right middle frontal gyrus [40, 48, 26] mm; and bilateral superior parietal gyrus [−20, 66, 60] and [16, 74, 52], as indicated by yellow voxels in Figure 2A. In other words, in these striatal, frontal, and parietal regions, increased frequency of perseverative errors was associated with decreased strength of brain functional activation during perseveration.

The regional mean activation statistics for each of these four behaviorally relevant regions were then estimated for each individual and used as dependent variables in ANCOVA models to assess drug effects. These models tested the effects of drug and group, and the drug-by-group interaction on brain activation in these regions. This analysis revealed significant main effects of drug in bilateral superior parietal gyrus [right: $F(2,94) = 4.30$, $p = .016$; left: $F(2,94) = 4.59$, $p = .013$], as both amisulpride ($p = .028$) and pramipexole ($p = .001$) reduced task-related activation in the right superior parietal gyrus in all participants. We also identified significant main effects of group in the right caudate nucleus [$F(2,47) = 4.35$, $p = .019$] and right middle frontal gyrus [$F(2,47) = 5.12$, $p = 0.010$]. Post hoc analysis revealed a significant reduction of activation in the caudate ($p = .006$) and the middle frontal gyrus ($p = .003$) in SDIs compared with control volunteers. OCD patients also showed significant underactivation in the right middle frontal gyrus compared with control volunteers ($p = .024$).

This underactivation in the right caudate in SDIs was qualified by a significant drug-by-group interaction [$F(4,94) = 2.55$, $p = .044$], as shown in Figure 2D. Post hoc analysis showed that SDIs underactivated the caudate on placebo relative to control volunteers [$t(33) = 2.89$, $p = .007$], but there was no difference on pramipexole [$t(33) = -.41$, $p = .685$)]. Moreover, the difference in activation between the pramipexole and placebo conditions was only significant in SDIs [$t(16) = -2.48$, $p = .025$] and not in controls [$t(17) = 1.58$, $p = .133$] or OCD patients [$t(17) = .39$, $p = .703$]. There was also a significant relationship between pramipexole-induced change in perseveration and the associated change in blood oxygen level–dependent response in the right caudate across all participants. As shown in Figure 2C, increased activation of the right caudate nucleus following pramipexole was associated with reduced perseverative responding in SDIs.

Discussion

We report that compulsive behavior in stimulant dependence, as reflected by response perseveration and associated brain activation during reversal learning, can be normalized by a single dose of the $D_{2/3}$ agonist pramipexole. Thus, under placebo, the stimulant-drug-dependent group exhibited greater difficulty in adjusting their behavior following a rule change compared with healthy volunteers and patients with OCD (Figure 2B), a finding that is consistent with previous research in both humans and experimental animals (8,9). However, the $D_{2/3}$ receptor agonist pramipexole reversed this perseverative behavior in the SDI group (Figure 2B), as well as normalizing an associated reduction of brain functional activation in the caudate nucleus in this group (Figure 2D).

Our finding that pramipexole reduced perseveration in SDIs to levels seen in healthy volunteers is consistent with previous evidence that the ability to detect changes in reinforcement contingencies, and to adjust behavior accordingly, is modulated by dopaminergic neurotransmission in the ventral striatum (19,40). Research in both animals and humans indicates that dopamine challenges modulate reversal learning, and these modulatory effects can be localized to the striatum (41). Caudate activation during response reversal has also been reported in human research studies (19,42,43): activation in the right ventral caudate predicts repetitive responding to the correct stimulus following a rule change; conversely, caudate lesions or pathology have been associated with increased perseveration (12,44). In keeping with these prior studies, we identified a significant group-by-drug interaction in the perseveration-related activation of the right ventral part of the caudate (Figure 2D): perseverative responding in SDIs was associated with underactivation in the caudate on placebo, which was normalized by pramipexole. The dopamine precursor levodopa has previously been shown to alter reversal-related activation in the ventral striatum (19), but the beneficial effects of dopamine agonist treatment on reversal-learning performance depend on baseline levels of dopamine $D_{2/3}$ receptor availability in the caudate (41). Pramipexole has high affinity for dopamine D_3 receptors (45), which are abundant in the ventral striatum (46), raising the possibility that this dopamine agonist pharmacologically compensated for pathologically reduced dopamine transmission in the midbrain in SDIs (47). This result is thus consistent with previous findings of reduced $D_{2/3}$ receptor binding in the caudate nucleus of chronic stimulant users and with its link to reductions in orbitofrontal cortex metabolism (4,48), especially given the known role of the orbitofrontal cortex in reversal learning in animal models (12,49,50) and human lesion studies (51,52). Presumably, the $D_{2/3}$ agonist restores activity in a frontostriatal loop, which is conducive to efficient reversal learning. In contrast, amisulpride had no effect on perseverative responding; possibly the dose used was insufficient to cause impairment.

Both SDIs and OCD patients reported high subjective levels of compulsivity, but we were unable to find any evidence for perseveration in OCD patients, which is also consistent with previous studies using probabilistic reversal learning for this disorder (21,22). Despite the evidence of phenomenological overlap in compulsive behaviors, the neuropathology associated with some aspects of compulsivity in OCD may differ from that associated with stimulant dependence (42,53). However, compulsivity is a complex construct with several facets, none of which is completely captured by a single measure. Nonetheless, our findings suggest that perseveration during reversal learning is associated with chronic stimulant abuse and may therefore be a possible predictor of the habitual use of stimulant drugs.

Clinical Implications and Study Limitations

There is compelling evidence for significant disruption of mesostriatal dopamine transmission in stimulant dependence associated with an apparent downregulation of $D_{2/3}$ receptors (54). Our data confirm that such a downregulation may be associated with increasing perseverative behavior, which can be ameliorated by treatment with a $D_{2/3}$ receptor agonist. Several studies have shown that SDIs perform significantly better on cognitive tests under the acute influence of cocaine (55–57) or methylphenidate (58,59); likewise, in our study, a single dose of pramipexole was sufficient to abolish perseverative tendencies in the SDIs. These findings suggest that dopamine agonists could counterbalance disruptions in neural networks underlying the disorder. However, in SDIs the effects of dopamine agonists on compulsivity seem to be context-dependent (60), which may explain why compulsivity affects the

Table 3. Brain Regions Differentially Activated by Perseverative Responses to an Incorrect Stimulus Versus Probabilistic Errors (i.e., correct responses that yield negative feedback)

Size (voxel)	Coordinates (mm)[a] x	y	z	AAL Regions
Regions Activated by Perseverative Errors				
2562	2	20	62	Bilateral middle frontal gyrus (orbital part), superior frontal gyrus (medial part), precentral gyrus, cingulum (anterior and middle parts), **supplementary motor area**
777	38	48	28	Right inferior frontal gyrus (orbital, operculum, and triangular parts), **middle frontal gyrus**, superior frontal gyrus, precentral gyrus
557	−32	60	10	Left inferior frontal gyrus (orbital, opercula, and triangular parts), **middle frontal gyrus**, superior frontal gyrus, precentral gyrus
493	−16	−72	54	Left **parietal gyrus** (inferior and **superior parts**), supramarginal gyrus, angular gyrus, precuneus, cuneus, occipital gyrus (superior part)
361	−4	0	10	Bilateral caudate, left thalamus
311	−40	16	−16	Left inferior frontal gyrus (operculum and triangular parts), insula, **temporal pole** (middle and **superior parts**)
300	2	−84	4	Bilateral **calcarine** gyrus, cuneus, lingual gyrus, cerebellum, vermis
217	44	18	−14	Right inferior frontal gyrus (orbital, opercula, and triangular parts), insula, putamen, **temporal pole** (**superior part**)
177	46	−44	56	Right **parietal gyrus** (**inferior** and superior parts), supramarginal gyrus, angular gyrus
121	10	−74	38	Right precuneus, **cuneus**, parietal gyrus (superior part)
104	2	−20	−4	Bilateral thalamus
92	−4	−42	−40	Bilateral cerebellum, vermis
Regions Deactivated by Perseverative Errors				
1195	−4	−2	18	Bilateral inferior frontal gyrus (orbital part), olfactory tubercle, caudate, left middle frontal gyrus (orbital part), insula, hippocampus, cuneus, precuneus, thalamus, right gyrus rectus
474	12	−14	24	Right hippocampus, caudate, thalamus, posterior cingulate
424	0	−62	24	bilateral cingulum (medial and posterior parts), **preuneus**, paracentral lobue, right supplementary motor area, left cuneus
207	−44	−74	34	Left angular gyrus, parietal gyrus (inferior part), **middle occipital gyrus**, temporal gyrus (middle part)
161	52	−68	20	Right **temporal gyrus** (**middle** and superior parts), angular gyrus, occipital gyrus (middle part)
105	52	−66	6	**Right temporal gyrus** (inferior and middle parts), occipital gyrus (inferior and middle parts)
81	−2	−42	−30	Left cerebellum, vermis
64	30	−94	4	Right **occipital** gyrus (**middle** part), calcarine
54	−34	−54	10	Left temporal gyrus (middle part), occipital gyrus (middle part)

The regions in bold refer to the peak of the cluster. The cluster sizes result from an initial thresholding of $p = .05$ (uncorrected), which were then tested by permutation inference at a statistical threshold corrected for multiple comparisons such the expected number of false positive tests was less than 1 (i.e., $p < .00057$).

AAL, automated anatomical labeling.

[a]Coordinates are given in Montreal Neurological Institute space.

response to pramipexole in terms of attentional bias for drug words (5) but not in terms of neutral stimuli in a reversal learning task. Whereas the SDIs were actively using stimulants at the time of testing, the majority of the OCD patients were being treated with SSRIs, which are known to affect dopamine neurotransmission in their own right; either of these drug classes may have obscured any additional effects of pramipexole. Reversal learning performance, however, has shown to be unaffected by SSRI treatment in either medicated or unmedicated OCD patients (21,22).

Response perseveration on other tests, such as the Wisconsin Card Sort Test, is predictive of poor treatment retention in cocaine-dependent individuals (61,62). Combined with our finding that pramipexole abolished perseverative deficits in SDI individuals, these results support the use of pramipexole in the treatment of substance dependence. However, previous studies suggest that dopamine agonist treatment is only of limited efficacy in the treatment of SDIs (63,64). To judge whether pramipexole has a potential for use in the treatment of stimulant dependence, further research is needed using multiple doses and chronic treatment regimes. Finally, it should also be noted that the SDI group's poor performance was not limited to perseveration. The drug users also demonstrated difficulties with the learning of the reinforcement contingencies, making more spontaneous errors and requiring more trials on each reversal sequence to reach criterion. Critically, however, this deficit does not confound the interpretation of the perseverative error data because 1) in both the behavioral and fMRI analyses, perseverative responding was only examined on reversal sequences in which participants did reach criterion and 2) the effects of drug and the drug-by-group interaction were nonsignificant for these other measures. Nonetheless, these deficits suggest that stimulant dependence is associated with other cognitive abnormalities that may pose a barrier to rehabilitation and warrant further investigation (Table 3).

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Supplementary material cited in this article is available online.

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