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.