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


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...
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 D2/3 receptor agonist and a D2/3 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 D2/3 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 unequivocal life-limiting illnesses. 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 (D2/3 receptor antagonist), 0.5 mg pramipexole (D2/3 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 contingencies...
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 perseverative 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 x 64, within-plane voxel dimensions = 3.0 x 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

<table>
<thead>
<tr>
<th>Performance Measures</th>
<th>Healthy Volunteers</th>
<th>Stimulant Users</th>
<th>OCD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Trials per Sequence</td>
<td>15.3 (±1.0)</td>
<td>17.7 (±3.4)</td>
<td>15.8 (±1.3)</td>
</tr>
<tr>
<td>Number of Perseverative Errors</td>
<td>20.1 (±6.1)</td>
<td>17.7 (±6.5)</td>
<td>16.2 (±6.2)</td>
</tr>
<tr>
<td>Number of Sequences on Which Criterion for Perseveration Was Met⁴</td>
<td>15.2 (±3.3)</td>
<td>11.8 (±4.7)</td>
<td>12.4 (±4.9)</td>
</tr>
<tr>
<td>Perseverative Error Rate⁴</td>
<td>1.3 (±3)</td>
<td>1.6 (±6)</td>
<td>1.4 (±3)</td>
</tr>
<tr>
<td>Number of Spontaneous Errors</td>
<td>5.5 (±3.7)</td>
<td>15.8 (±10.3)</td>
<td>9.0 (±10.2)</td>
</tr>
<tr>
<td>Number of Probabilistic Switches</td>
<td>3.5 (±5.0)</td>
<td>5.7 (±5.1)</td>
<td>8.6 (±7.0)</td>
</tr>
</tbody>
</table>

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.

⁴The 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.

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 (31) 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) = 160, 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].
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 \([t(16) = 2.42, p = .02]\) but did not affect performance in the other two groups \([t(17) = -1.39, p = .183; OCD: t(17) = -1.17, p = .260]\). 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 \([OCD: r = -.06, p > .1]\). However, this drug effect was qualified by a highly significant drug-by-group interaction \[F(2,49) = 3.63, p = .034\] 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 \([t(16) = 2.42, p = .02]\) but did not affect performance in the other two groups \([t(17) = -1.39, p = .183; OCD: t(17) = -1.17, p = .260]\). 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 \[F(2,42) = .20, p = .822\].

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**Brain Responses Associated with Perseverative Errors**

The brain regions activated by perseverative responding (controlling for negative feedback) included bilateral inferior, medial,
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and superior frontal lobe structures and anterior and middle cingu-
late cortex, insular, caudate, thalamus, parietal, and occipital lobe
structures (see Figure 2 and Table 2 for anatomical details), as pre-
viously 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 persevera-
tion.

The regional mean activation statistics for each of these four
behaviorally relevant regions were then estimated for each individ-
ual 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 signifi-
cant 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 = .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 com-
pared 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 underacti-
vated the caudate on placebo relative to control volunteers [t(33) =
2.89, p = .007], but there was no difference on pramipexole [t(33) =
−4.1, 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 persevera-
tion 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 follow-
ing pramipexole was associated with reduced perseverative re-
sponding in SDIs.

Discussion

We report that compulsive behavior in stimulant dependen-
tce, as reflected by response perseveration and associated
brain activation during reversal learning, can be normalized by
a single dose of the D2/3 agonist pramipexole. Thus, under pla-
cego, the stimulant-drug-dependent group exhibited greater
difficulty in adjusting their behavior following a rule change
compared with healthy volunteers and patients with OCD (Fig-
ure 2B), a finding that is consistent with previous research in
both humans and experimental animals (8,9). However, the D2/3
receptor agonist pramipexole reversed this perseverative be-
avior in the SDI group (Figure 2B), as well as normalizing an
associated reduction of brain functional activation in the cau-
date nucleus in this group (Figure 2D).

Our finding that pramipexole reduced perseveration in SDIs to
levels seen in healthy volunteers is consistent with previous evi-
dence that the ability to detect changes in reinforcement contin-
gencies, and to adjust behavior accordingly, is modulated by dopa-
minergic neurotransmission in the ventral striatum (19,40).
Research in both animals and humans indicates that dopamine
challenges modulate reversal learning, and these modulatory ef-
ccts can be localized to the striatum (41). Caudate activation dur-
ing 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 asso-
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 as-
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 acti-
vation in the ventral striatum (19), but the beneficial effects of
dopamine agonist treatment on reversal-learning performance de-
depend on baseline levels of dopamine D2/3 receptor availability in
the caudate (41). Pramipexole has high affinity for dopamine D2
receptors (45), which are abundant in the ventral striatum (46),
raising the possibility that this dopamine agonist pharmacologi-
cally compensated for pathologically reduced dopamine transmis-
sion in the midbrain in SDIs (47). This result is thus consistent with
previous findings of reduced D2/3 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 D2/3
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 insuffi-
cient to cause impairment.

Both SDIs and OCD patients reported high subjective levels of
compulsivity, but we were unable to find any evidence for perse-
veration 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 persevera-
tion 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 me-
sostriatal dopamine transmission in stimulant dependence associ-
ated with an apparent downregulation of D2/3 receptors (54). Our
data confirm that such a downregulation may be associated with
increasing perseverative behavior, which can be ameliorated by

treatment with a D2/3 receptor agonist. Several studies have shown
that SDIs perform significantly better on cognitive tests under the
treatment with a D2/3 receptor agonist. Several studies have shown
that SDIs perform significantly better on cognitive tests under the

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 dopamine agonist treatment is only of limited efficacy 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.


