Effects of Methylphenidate on Resting-State Functional Connectivity of the Mesocorticolimbic Dopamine Pathways in Cocaine Addiction

Anna B. Konova, MA; Scott J. Moeller, PhD; Dardo Tomasi, PhD; Nora D. Volkow, MD; Rita Z. Goldstein, PhD

**IMPORTANCE** Cocaine addiction is associated with altered resting-state functional connectivity among regions of the mesocorticolimbic dopamine pathways. Methylphenidate hydrochloride, an indirect dopamine agonist, normalizes task-related regional brain activity and associated behavior in cocaine users; however, the neural systems-level effects of methylphenidate in this population have not yet been described.

**OBJECTIVE** To use resting-state functional magnetic resonance imaging to examine changes in mesocorticolimbic connectivity with methylphenidate and how connectivity of affected pathways relates to severity of cocaine addiction.

**DESIGN** Randomized, placebo-controlled, before-after, crossover study.

**SETTING** Clinical research center.

**PARTICIPANTS** Eighteen nonabstaining individuals with cocaine use disorders.

**INTERVENTIONS** Single doses of oral methylphenidate (20 mg) or placebo were administered at each of 2 study sessions. At each session, resting scans were acquired twice: immediately after drug administration (before the onset of effects [baseline]) and 120 minutes later (within the window of peak effects).

**MAIN OUTCOMES AND MEASURES** Functional connectivity strength was evaluated using a seed voxel correlation approach. Changes in this measure were examined to characterize the neural systems-level effects of methylphenidate; severity of cocaine addiction was assessed by interview and questionnaire.

**RESULTS** Short-term methylphenidate administration reduced an abnormally strong connectivity of the ventral striatum with the dorsal striatum (putamen/globus pallidus), and lower connectivity between these regions during placebo administration uniquely correlated with less severe addiction. In contrast, methylphenidate strengthened several corticolimbic and corticocortical connections.

**CONCLUSIONS AND RELEVANCE** These findings help elucidate the neural systems-level effects of methylphenidate and suggest that short-term methylphenidate can, at least transiently, remodel abnormal circuitry relevant to the pathophysiologic characteristics of cocaine addiction. In particular, the effects of methylphenidate within striatal and cortical pathways constitute a potentially viable mechanism by which methylphenidate could facilitate control of behavior in cocaine addiction.

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Resting-state functional connectivity is a noninvasive and replicable method for assessing neural circuitry function in neuropsychiatric disorders. This method captures the synchronicity of low-frequency, spontaneous fluctuations in blood oxygen level–dependent signals that reflect fluctuations in neuronal activity between brain regions in the absence of external stimulation. These synchronous fluctuations are confined to gray matter and can be observed for monosynaptic or polysynaptic anatomic connections. More important, resting-state connectivity is linked to task-related functioning of discrete brain regions comprising the same circuits and to corresponding behavior. Thus, resting-state connectivity can be useful for advancing neural systems–level understanding of the functional and behavioral abnormalities that characterize neuropsychiatric disorders such as addiction, with the potential to also serve as a target for therapeutic interventions.

Perturbations in resting-state connectivity within and between functional brain networks that subserve attentional, emotional, and inhibitory control processes have been observed in individuals addicted to nicotine, opioids, and cocaine. Specifically, individuals with cocaine use disorders (CUDs) exhibit reduced connectivity of the dorsal frontoparietal attention network; in addition, and especially pertinent to the current study, cocaine users exhibit reduced connectivity of the mesocorticlimbic dopamine pathways. However, thus far it has not been shown whether this abnormal connectivity could be modified in individuals with chronic, severe CUD.

Methylphenidate hydrochloride is a psychostimulant widely used to treat attention-deficit/hyperactivity disorder. Like cocaine, methylphenidate competitively blocks dopamine and norepinephrine transporters, thereby increasing extracellular concentration of these neuromodulatory neurotransmitters. However, unlike cocaine, the rate of clearance of orally administered methylphenidate from the brain is substantially slower (90-minute half-life compared with 20-minute half-life for cocaine), contributing to its lower abuse potential and possible viability as a therapeutic agent in treating cocaine addiction. Methylphenidate improves task-related regional brain activation in the dopamine-innervated ventral medial prefrontal and dorsal anterior cingulate cortices and corresponding stop signal reaction times in CUD. Oral methylphenidate also has been shown to attenuate changes in glucose metabolism in the lateral orbitofrontal and inferior frontal cortices, hippocampus, and nucleus accumbens when cocaine users are exposed to drug cues.

In the present study, we used a placebo-controlled, before-after, crossover experimental design to examine the effects of short-term methylphenidate administration on resting-state connectivity in active cocaine users. To our knowledge, the only study that assessed drug-induced changes in resting-state connectivity in individuals with CUD included a small sample size, used intravenous cocaine, and focused on the sensorimotor cortices. We examined mesocorticlimbic connectivity using a seed correlation approach based on a more recent study reporting that cocaine addiction was associated with reduced connectivity in several pathways involved in emotion processing. Given the normalizing effects of methylphenidate on task-related activation and behavior in CUD, we hypothesized that methylphenidate would strengthen connectivity of the medial frontal cortex in pathways underlying emotion regulation (eg, with amygdala and hippocampus) and inhibitory control (eg, with dorsal and lateral prefrontal cortex). In addition, because methylphenidate attenuated brain metabolism following exposure to cocaine cues, we expected reduced connectivity between regions underlying cue-induced craving (eg, orbitofrontal cortex, ventral and dorsal striatum, and amygdala). Finally, to examine whether methylphenidate modified connectivity in pathways directly associated with addictive behavior, we inspected correlations between connectivity strength and severity of cocaine addiction.

### Methods

**Participants**

Participants were 18 nontreatment-seeking individuals with CUD, recruited from advertisements in local newspapers and by word of mouth. All participants were right-handed and native English speakers and provided their written consent to participate in the study in accordance with the Stony Brook University institutional review board. Participants were otherwise healthy and not taking any medications, as ascertained during a full physical and neurologic examination by a neurologist and a diagnostic interview by a clinical psychologist. This latter interview included the Structured Clinical Interview for DSM-IV Axis I disorders (research version) and the Addiction Severity Index. All participants were currently using cocaine and identified cocaine as their primary drug of choice, meeting criteria for current cocaine dependence (n = 17) or abuse (n = 1) (see Appendix in the Supplement). Current comorbidities included heroin dependence (n = 1), marijuana abuse (n = 1), alcohol abuse (n = 1), and nicotine dependence (n = 14). Exclusion criteria were (1) history of head trauma or loss of consciousness (>30 minutes) or other neurologic disease, (2) abnormal vital signs at the time of screening, (3) history of major medical conditions, (4) history of major psychiatric disorder (other than substance abuse or dependence), (5) pregnancy as confirmed with a urine test in all women, (6) contraindications to the magnetic resonance imaging (MRI) environment, (7) history of glaucoma, and (8) except for cocaine, positive urine screen results for psychoactive drugs or their metabolites (amphetamine or methamphetamine, phencyclidine, benzodiazepines, cannabis, opiates, barbiturates, and inhalants). Nine participants tested positive for cocaine on methylphenidate day and 8 tested positive for cocaine on placebo day (see the eAppendix in the Supplement for additional information). Demographic information is reported in Table 1.

Cocaine withdrawal symptoms were assessed prior to medication administration at each study day with the Cocaine Selective Severity Assessment scale; participants also completed the Cocaine Craving Questionnaire and the Severity of Dependence Scale, which captures perceived con-
control over drug-taking and difficulty with stopping drug use during the past year. For each participant, the severity of addiction was quantified as a composite score (average Z value) of the severity of withdrawal, craving, and dependence as assessed on placebo day and the frequency of use of cocaine in the past 30 days as assessed during the clinical interview. The severity of withdrawal and dependence did not differ significantly between the study days (P > .11); however, participants reported more recent use of cocaine and more severe craving on methylphenidate day than on placebo day (Table 2).

Study Sessions
At each of the 2 study sessions (conducted at mean [SD], 8.9 [4.0] days apart), participants were randomized to receive a single oral dose of methylphenidate (20 mg) or placebo (lactose). This methylphenidate dose has been shown to affect task-related brain activation and behavior in CUD.

Image Acquisition
Functional MRI was performed (4-T Varian/Siemens MRI scanner) using a coronal T2*-weighted single-shot gradient-echo planar imaging sequence (echo time/repetition time, 20/1600 milliseconds; 3.125 × 3.125 mm² in-plane resolution; 4-mm slice thickness; 1-mm gap; 33 coronal slices; 20-cm field of view; 64 × 64 matrix size; 90°-flip angle; and 200-kHz bandwidth with ramp sampling). Padding was used to minimize motion, and earplugs and headphones were used to minimize the influence of scanner noise on brain activation. Participants were instructed to keep their eyes open, lie as still as possible, and remain awake during the resting scans. No video corroboration that participants adhered to the instructions could be obtained. Each resting scan was approximately 8 minutes in duration (representing 311 consecutive data points after the first 10 data points were removed to account for signal stabilization). This length is comparable to that in previous studies of this type and within the recommended range for optimal assessment of seed-based connectivity. Of 21 participants initially scanned, 3 were excluded because of missing data (n = 2) or signal dropout (n = 1) on at least 1 of the 4 scans.

Table 1. Demographic and Clinical Characteristics of 18 Individuals With Cocaine Use Disorders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No.</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>Race, No.</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>15</td>
</tr>
<tr>
<td>Othera</td>
<td>3</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>45.6 (7.3)</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>12.9 (1.8)</td>
</tr>
<tr>
<td>Verbal IQ, mean (SD)b</td>
<td>91.8 (9.2)</td>
</tr>
<tr>
<td>Nonverbal IQ, mean (SD)c</td>
<td>9.3 (3.1)</td>
</tr>
<tr>
<td>Socioeconomic status: Hollingshead Index, mean (SD)</td>
<td>35.8 (8.4)</td>
</tr>
<tr>
<td>Drug use history</td>
<td></td>
</tr>
<tr>
<td>Cigarette smokers, No.</td>
<td></td>
</tr>
<tr>
<td>Current or past</td>
<td>14</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>4</td>
</tr>
<tr>
<td>Cigarettes per day, mean (SD), No.</td>
<td>8.0 (4.2)</td>
</tr>
<tr>
<td>(12 current smokers only)</td>
<td></td>
</tr>
<tr>
<td>Age of onset of cocaine use, mean (SD), y</td>
<td>26.9 (6.3)</td>
</tr>
<tr>
<td>Duration of cocaine use, mean (SD), y</td>
<td>15.3 (7.5)</td>
</tr>
<tr>
<td>Preferred route of cocaine administration,a No.</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>14</td>
</tr>
<tr>
<td>Intranasal</td>
<td>1</td>
</tr>
<tr>
<td>Intravenous</td>
<td>1</td>
</tr>
<tr>
<td>Days of cocaine use per week, mean (SD), No. in past 30 d</td>
<td>2.7 (2.1)</td>
</tr>
</tbody>
</table>

Abbreviation: WASI, Wechsler Abbreviated Scale of Intelligence.

* White, Hispanic, or Asian.

b Determined with the Wide Range Achievement Test III–Reading Scale.

c Determined with the WASI–Matrix Reasoning Scale.

d Variables used to compute the addiction severity composite score.

e Determined with the Beck Depression Inventory II (score range, 0-63).

f Determined with the 5-item Craving Questionnaire (score range, 0-25).

g Determined with the Severity of Dependence Scale (score range, 0-126).

Table 2. Daily Baseline Assessment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methylphenidate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine urine status, No.</td>
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<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Negative</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Current cocaine abstinence, mean (SD), d since last usea</td>
<td>5.4 (6.5)</td>
<td>7.8 (9.5)</td>
</tr>
<tr>
<td>Depression score, mean (SD)b</td>
<td>6.9 (5.5)</td>
<td>6.1 (4.8)</td>
</tr>
<tr>
<td>Withdrawal symptomsc,d</td>
<td>15.9 (10.6)</td>
<td>12.2 (7.8)</td>
</tr>
<tr>
<td>Severity of Dependence Scalee,f,g</td>
<td>7.4 (2.5)</td>
<td>7.3 (2.6)</td>
</tr>
<tr>
<td>Cocaine cravingf,g</td>
<td>22.0 (13.4)</td>
<td>17.4 (12.7)</td>
</tr>
</tbody>
</table>

* P < .05.

d Determined with the Beck Depression Inventory II (score range, 0-63).

c Determined with the 18-item Cocaine Selective Severity Assessment (score range, 0-126).

d Variables used to compute the addiction severity composite score.

e Determined with the Severity of Dependence Scale (score range, 0-126).

f Determined with the 5-item Craving Questionnaire (score range, 0-25).

g Determined with the 5-item Craving Questionnaire (score range, 0-25).

R P < .01.
Image Processing and Construction of the Functional Connectivity Maps

Image processing and analyses were performed in SPM8 (Welcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The data were first realigned, slice time–corrected, and spatially normalized to a standard Montreal Neurological Institute (MNI) frame, resulting in a final voxel size of $3 \times 3 \times 3$ mm. Other preprocessing steps were carried out in Interactive Data Language (Exelis Visual Information Solutions; http://www.exelisvis.com/ProductsServices/IDL.aspx) and included motion correction using the 6 time-varying realignment parameters (3 translations and 3 rotations), global signal normalization, and band pass filtering (0.01-0.10 Hz) to remove magnetic field drifts of the scanner and minimize physiologic noise of high-frequency components. Because a recent study showed that movement at a finer time scale can increase the variability of functional connectivity measures, we additionally computed the mean absolute displacement of the brain from every time frame to the next. Displacement was in the minimal range for all 4 resting scans (0.14-0.21 mm); however, displacement was higher overall on placebo day than on methylphenidate day ($F_{1,17} = 5.56, P = .03$; for all other effects, $P > .68$ (eAppendix in the Supplement).

Six functional seed regions were defined by centering bilateral 9-mm cubes (27 voxels) at the coordinates shown in Figure 1. The size of the seed regions was chosen on the basis of our previous studies and was kept constant across anatomic regions to minimize systematic bias in averaging signals across larger vs smaller volumes. After conversion to MNI space, these seeds were identical to those used by Gu et al (ventral tegmental area, nucleus accumbens, amygdala, hippocampus, thalamus, and rostral anterior cingulate). Control seeds were also placed in the primary motor (coordinates in MNI space: $x = \pm 44, y = -10, z = 10$), auditory ($x = \pm 44, y = -36, z = 13$), and visual ($x = \pm 10, y = -91, z = 1$) cortices to determine the specificity of effects to mesocorticilimbic regions. Whole-brain cross-correlation maps were calculated separately for each seed and for each participant for each of the 4 scans (methylphenidate peak effects, placebo peak effects [ie, after the parallel time has elapsed, reflecting an active baseline], methylphenidate baseline [ie, before the expected onset of medication effects], and placebo baseline), reflecting correlations over time between average blood oxygen level–dependent signal fluctuations in the respective seed region (averaged time series across all voxels in the seed) and those in all other voxels of the brain. These cross-correlation coefficient maps were converted to Z-score maps using the Fisher Z transform and smoothed with an 8-mm full-width at half-maximum gaussian kernel prior to group-level analyses in SPM8.

Functional Connectivity Analysis

A 2 (medication: methylphenidate, placebo) × 2 (time: baseline, peak drug effects at 120 minutes) repeated-measures analysis of covariance in SPM8 was used to analyze differences in the strength of each seed’s connectivity as a function of methylphenidate administration. In these analyses, to control for differences between the methylphenidate and placebo days in abstinence, craving, the potential influence of the medication administration paradigm, and micromotion, we included as covariates days since last cocaine use, the Craving Questionnaire scores, a dummy regressor indicating whether participants received single- or double-blind medication administration, and mean absolute head displacement.

The primary analysis involved a comparison of methylphenidate peak effects vs placebo peak effects. Two strategies were used. First, using region of interest analyses, we tested for restored connectivity with methylphenidate of regions previously reported to exhibit reduced connectivity with our seed regions in CUD. The following anatomic regions were created in PickAtlas (ANSIR Laboratory; http://fmri.wfubmc.edu/software/PickAtlas): (1) bilateral thalamus (for analyses with the ventral tegmental area seed); (2) Brodmann areas (BAs) 10, 9, and 24 in the medial prefrontal cortex (for analyses with the amygdala seeds); (2) bilateral putamen (for analyses with the thalamus seeds); (4) BAs 6, 8, and 9 in the superior and lateral frontal cortex (for analyses with the hippocampus seeds); (4) BAs 41 and 13 in the temporal gyrus/insula (for analyses with the rostral anterior cingulate seeds); and (5) right parahippocampal gyrus, hippocampus, and amygdala (for analyses with the rostral anterior cingulate seeds) (eFigure 1 in the Supplement). These region of interest analyses were thresholded at $P < .05$ familywise error (FWE)-corrected at the voxel level. Sec-
and, we explored whole-brain changes in connectivity using a cluster-level $P < .05$ FWE-corrected threshold (see eAppendix in the Supplement). Here, we selected a priori a minimum height ($P < .005$ uncorrected) and cluster extent (20 adjacent voxels) threshold. We then applied the FWE correction (at the cluster level) as implemented in SPM8 to determine the probability of obtaining a given cluster size assuming a random gaussian field distribution. Significant regions from the methylenidate vs placebo peak contrast were extracted as 3-mm radius spheres, chosen according to the image smoothness (i.e., the volume of the resolution elements$^{47}$), using the EasyROI toolbox (http://www.sbirc.ed.ac.uk/LCL/LCL_M1.html). The extracted average signal in these regions was used for visual representation of the data, comparison with healthy controls, and multiple regression analysis with addiction severity, described below. Anatomic specificity was determined with the Anatomy toolbox.$^{48}$

Secondary (control) analyses compared methylenidate peak effects vs same-day baseline and methylenidate same-day baseline vs placebo same-day baseline, both used to rule out ancillary factors particular to each study session (e.g., premedication administration cocaine craving and days since last cocaine use) (Table 2). Results from the control analyses were masked by the methylenidate peak effects vs placebo peak effects contrast ($P < .05$ uncorrected) and are reported at $P < .005$ uncorrected with a minimum cluster extent of 20 adjacent voxels.

Finally, we sought to determine whether methylenidate modified connectivity in participants with CUD to a level that no longer significantly differs from that of healthy individuals. For this purpose, we compared connectivity strength during placebo and, separately, during methylenidate with that of an independent sample of 16 healthy control participants for whom we acquired resting-state data under placebo conditions (see eAppendix in the Supplement for additional information).

### Association of Connectivity Strength With Severity of Cocaine Addiction

To determine whether methylenidate modified connectivity between regions that, under baseline conditions (i.e., placebo peak effects), were directly associated with severity of cocaine addiction, we used the composite addiction severity score (Table 2) as the dependent variable in a multiple regression analysis in SPSS 18.0 (SPSS, Inc) restricting the predictors to include connectivity measures in regions that both changed after methylenidate and differed significantly from healthy controls (either in the present study [eTable 2 in the Supplement] or as reported by Gu et al$^{15}$) (6 total predictors).

### Results

#### Effects of Methylphenidate on Cardiovascular Reactivity and Subjective Mood

Except for diastolic blood pressure (which was higher after methylphenidate than after placebo), changes in cardiovascular reactivity and mood did not differ significantly between the methylphenidate and placebo study sessions (eTable 1 in the Supplement). Consistent with prior studies using 20 mg of oral methylphenidate,$^{17,19}$ self-reports of cocaine wanting also did not differ significantly (eAppendix in the Supplement).

#### Effects of Methylphenidate on Connectivity Strength

### Primary Analyses: Methylphenidate vs Placebo Peak Effects

The region of interest analyses indicated that methylphenidate modified 2 corticolimbic connections that were previously reported to be disrupted in CUD$^{12}$: compared with placebo, methylphenidate increased the connectivity of (1) the right and left hippocampus with the left postcentral gyrus (BAs 4, 6) (peak coordinate in MNI space: $x = −60, y = −3, z = 33$, $Z = 4.39, FWE-corrected P = .008$; and $x = −63, y = 3, z = 30$, $Z = 4.05, FWE-corrected P = .03$, respectively) (Figure 2) and (2) the left rostral anterior cingulate with the right parahippocampal gyrus ($x = 15, y = −36$, and $z = −9$, $Z = 3.57, FWE-corrected P = .02$) (Figure 3A and B).

Whole-brain analyses revealed additional effects of methylenidate in connections relevant to self-control and craving (Table 3 and eFigure 2 in the Supplement). Specifically, compared with placebo, methylphenidate increased the connectivity of (1) the right rostral anterior cingulate with the left ventral striatum (eFigure 3 in the Supplement), (2) the right thalamus with the medial orbitofrontal cortex, and (3) the right nucleus accumbens with the medial orbitofrontal cortex and right superior temporal gyrus extending to the postcentral gyrus and rolandic operculum (Figure 4A and C). Methylphenidate also reduced the connectivity of (1) the ventral tegmental area with the right caudate and putamen; (2) the left hippocampus with the left insula, thalamus, and putamen; (3) the right thalamus with the bilateral putamen; and (4) the right nucleus accumbens with the left putamen/globus pallidus (Figure 4A and D). Other methylphenidate-induced changes included reduced connectivity of the ventral tegmental area, right hippocampus, and left rostral anterior cingulate with the cerebral peduncle and reduced connectivity of the left rostral anterior cingulate (Figure 4C), right hippocampus, and right nucleus accumbens with the inferior parietal cortex extending to the angular gyrus and precuneus. No significant changes in connectivity strength were observed for the bilateral amygdala, left thalamus, or left nucleus accumbens seeds in either the region of interest or the whole-brain analyses.

### Control Analyses

Supporting the idea that these changes in connectivity were due to the pharmacologic effects of methylphenidate (and not differences between the study days or the participants’ expectation to receive methylphenidate), baseline connectivity did not differ significantly between the 2 study days for any of the seeds (as inspected with the methylphenidate baseline vs placebo baseline contrast, masked by the methylphenidate peak > placebo peak or methylphenidate peak < placebo peak contrasts reported above). The methylphenidate peak effect vs same-day baseline contrast was similarly examined and, in contrast, revealed significant results in most brain regions identified by the methylphenidate peak vs placebo peak contrast (regions identified in both analyses are indicated in Table 3).

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Notably, methylphenidate generally did not modify connectivity with our control seeds, with the exception of an increase in connectivity between the primary motor cortex and the cerebellum. This exception is a well-established motor pathway that also depends on dopamine (eAppendix in the Supplement).

Comparison With Health
Within these connections, relative to healthy controls who were studied during active baseline (ie, during placebo peak effects), individuals with CUD showed reduced connectivity of (1) the bilateral hippocampus with the left postcentral gyrus (corroborating findings by Gu et al12) and (2) the right nucleus.
Table 3. Whole-Brain Changes in Resting-State Functional Connectivity With Methylphenidate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BA</th>
<th>Side</th>
<th>Cluster Size, mm³</th>
<th>Peak Z Value</th>
<th>P Value, Corrected</th>
<th>MNI Coordinates</th>
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</thead>
<tbody>
<tr>
<td><strong>Seed: VTA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate/putamen</td>
<td></td>
<td>R</td>
<td>385</td>
<td>-4.3</td>
<td>.03</td>
<td>15</td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td>L</td>
<td>540</td>
<td>-3.7</td>
<td>.008</td>
<td>-6</td>
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<tr>
<td><strong>Seed: R hippocampus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebellum</td>
<td></td>
<td>R</td>
<td>943</td>
<td>-4.3</td>
<td>&lt;.001</td>
<td>3</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td></td>
<td>R</td>
<td>397</td>
<td>-3.9</td>
<td>.04</td>
<td>15</td>
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<tr>
<td>Middle occipital/angular gyrus/precuneus</td>
<td></td>
<td>L</td>
<td>436</td>
<td>-3.5</td>
<td>.03</td>
<td>-9</td>
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<tr>
<td><strong>Seed: L hippocampus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal gyrus/postcentral gyrus</td>
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<td>R</td>
<td>417</td>
<td>+3.6</td>
<td>.03</td>
<td>60</td>
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<tr>
<td>Insula/thalamus/putamen</td>
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<td>L</td>
<td>702</td>
<td>-4.0</td>
<td>.003</td>
<td>-33</td>
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<tr>
<td><strong>Seed: R MDN thalamus</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Medial orbitofrontal cortex gyrus rectus</td>
<td></td>
<td>L</td>
<td>408</td>
<td>+4.6</td>
<td>.04</td>
<td>18</td>
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<tr>
<td>Putamen/thalamus</td>
<td></td>
<td>L</td>
<td>1148</td>
<td>-4.1</td>
<td>&lt;.001</td>
<td>-30</td>
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<tr>
<td><strong>Seed: R rostral ACC (BA 24)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dorsal ACC</td>
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<td>L</td>
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<td>+4.0</td>
<td>.058</td>
<td>-3</td>
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<td><strong>Seed: L rostral ACC (BA 24)</strong></td>
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<tr>
<td>Cerebellum</td>
<td></td>
<td>R</td>
<td>593</td>
<td>-4.3</td>
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<td>12</td>
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<tr>
<td>Inferior parietal/supramarginal gyrus</td>
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<td>L</td>
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<td>-3.7</td>
<td>.016</td>
<td>-33</td>
</tr>
<tr>
<td><strong>Seed: R NAcc</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal gyrus/postcentral gyrus/rolandic operculum</td>
<td></td>
<td>R</td>
<td>1292</td>
<td>+4.7</td>
<td>&lt;.001</td>
<td>57</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex gyrus rectus</td>
<td></td>
<td>R</td>
<td>823</td>
<td>+4.5</td>
<td>.001</td>
<td>6</td>
</tr>
<tr>
<td>Inferior parietal/angular gyrus</td>
<td></td>
<td>R</td>
<td>841</td>
<td>-5.2</td>
<td>&lt;.001</td>
<td>-54</td>
</tr>
<tr>
<td>Putamen/globus pallidus/thalamus</td>
<td></td>
<td>L</td>
<td>2671</td>
<td>-5.0</td>
<td>&lt;.001</td>
<td>-27</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; L, left; MDN, mediodorsal nucleus; MNI, Montreal Neurological Institute; NAcc, nucleus accumbens; R, right; VTA, ventral tegmental area.

*Analysis of covariance (covariates: medication administration paradigm, baseline craving, days since last cocaine use, and micromotion).
*Positive Z score indicates increased connectivity strength with methylphenidate hydrochloride (methylphenidate > placebo peak effects). Negative Z score indicates decreased connectivity strength with methylphenidate (methylphenidate < placebo peak effects).
*Statistical threshold: cluster-level $P < .05$ familywise error-corrected with a voxel-level $P < .005$ corrected height threshold and $k = 20$ voxels ($T = 2.65$). No significant effects of methylphenidate were observed for the bilateral amygdala, left thalamus, or left NAcc seeds at the set significance threshold.

Region also showing effects for the methylphenidate peak effects vs same-day baseline contrast (voxel-level $P < .005$ uncorrected and $k = 20$ voxels within a methylphenidate vs placebo peak effects $P < .05$ uncorrected inclusive mask). In all regions, no differences were observed for the methylphenidate same-day baseline vs placebo same-day baseline contrast using the same statistical threshold and masking procedure.
*Region significantly different from healthy controls during placebo peak effects (eTable 1 in eAppendix in the Supplement).
accumbens with the right superior temporal gyrus, extending to the postcentral gyrus and rolandic operculum, and increased connectivity of (1) the left rostral anterior cingulate with the left inferior parietal cortex and (2) the right nucleus accumbens with the left putamen/globus pallidus (eTable 2 in the Supplement). More important, after methylphenidate administration, group differences in all of these connections were no longer significant, suggesting that methylphenidate normalized connectivity strength between these regions.

Relationship to Severity of Cocaine Addiction

To determine whether connectivity modified by methylphenidate was directly associated with cocaine addiction severity, we conducted a multiple regression analysis in SPSS with addiction severity as the dependent variable. The predictors (ie, the extracted average connectivity measures during placebo peak effects) in this analysis included the 6 connectivity pathways that significantly differed from those of healthy controls during placebo administration in the present study or as reported by Gu et al.12 and that were normalized in strength with methylphenidate (regions in bold in eTable 2 in the Supplement). More important, after methylphenidate administration, group differences in all of these connections were no longer significant, suggesting that methylphenidate normalized connectivity strength between these regions.

Increased right (R) NAcc (A) (seed shown in white) with R superior temporal gyrus (STG) extending to the postcentral gyrus and rolandic operculum connectivity (C) and decreased R NAcc with left (L) putamen/globus pallidus (GP) connectivity (D) following a single dose of oral methylphenidate hydrochloride, 20 mg. Color map (A) shows increased (orange) or decreased (cyan) connectivity strength with methylphenidate vs placebo in a T-score window from ±3.0 to ±7.0. Bar plots (C and D) show the Fisher Z values for placebo peak effects (light gray) and methylphenidate peak effects (dark gray) plotted from values of healthy control participants scanned during placebo conditions. Error bars represent SEM. The connectivity strength between the R NAcc and L putamen/GP during placebo (C) was uniquely positively correlated with the severity of cocaine addiction composite scores (B). *P < .005. †P < .05.

Discussion

Using short-term oral administration of methylphenidate, the present study showed that mesocorticolimbic connectivity is susceptible to dopaminergic manipulation in CUD. Taking into account differences in baseline connectivity from healthy individuals and correlations between these measures and severity of addiction, the direction of change in connectivity strength with methylphenidate is consistent with a beneficial response to the drug, extending its previously reported efficacy in normalizing task-related brain activation and behavior in this population.17,18 Moreover, our study design enabled us to show that connectivity with our seed regions was stable such that the observed changes in connectivity were due to the
effects of methylphenidate and not ancillary factors particular to each study session.

Using predefined regions of interest, we found that methylphenidate strengthened connectivity of the bilateral hippocampus with the postcentral gyrus and of the rostral anterior cingulate with the parahippocampal gyrus—corticobasal connections suggested to underlie successful emotion regulation that were reported to be disrupted in cocaine addiction. In particular, the postcentral gyrus is involved in craving suppression, and both the postcentral gyrus and the hippocampus fail to normally activate when cocaine users are exposed to stress, abnormalities that could underlie stress-related vulnerability to cocaine relapse. Strengthened connectivity in emotion processing and memory formation pathways with methylphenidate may contribute to enhanced retention of emotional associative learning (as has been shown in rodents) and better control over emotional disturbances and emotional memories (e.g., when combined with exposure therapy), particularly those associated with withdrawal symptoms and conditioned responses that frequently lead to relapse in addiction.

In addition to strengthened corticobasal connectivity, methylphenidate strengthened connectivity of the rostral anterior cingulate with the dorsal cingulate. These cingulate regions have differential anatomic connections with emotion and cognitive control networks, and reduced correlations have been observed between these regions during processing of salient cues in cocaine users. Therefore, strengthened frontal cortical connectivity with methylphenidate may point to the mechanism that contributes to the methylphenidate-induced improvements in behavioral and neural measures of self-control on both neutral and salient tasks of executive function in CUD. This finding is also important in view of tractography studies in CUD, in which higher fractional anisotropy in regions of the frontal cortex and the rostral corpus callosum linking these regions predicts longer abstinence. Although methylphenidate increased connectivity of the rostral with dorsal cingulate, an executive control and attention network region, methylphenidate reduced connectivity of the rostral cingulate with the inferior parietal cortex/supramarginal gyrus, a “default mode” region, which may play a role in methylphenidate’s attention-enhancing properties.

Most notably, methylphenidate reduced the connectivity of several subcortical regions, including the ventral tegmental area, hippocampus, thalamus, and nucleus accumbens, with the dorsal striatum. In particular, connectivity within striatal circuits, possibly instantiated via the spinothalamic projections to the midbrain that link the nucleus accumbens with the dorsal striatum or via other nodes of the cortico-thalamic-striatal loops, is strongly implicated in drug-seeking. Because the progression of cocaine addiction involves a shift in striatal circuits from ventral to dorsal, the strength of connectivity between these regions may be marking individual differences in disease severity. Indeed, higher baseline connectivity of the nucleus accumbens with the putamen/globus pallidus uniquely correlated with more severe addiction. The finding that short-term methylphenidate can modify this connection may be clinically relevant given that blocking striato-midbrain-striatal serial connectivity selectively decreased drug-seeking in rats trained to habitually self-administer cocaine. Future longer-term intervention studies should test whether systematic, prolonged weakening of this connection helps restore control over drug-seeking behavior in humans. Other effects of methylphenidate may also contribute to increased control over craving and drug-seeking, including methylphenidate-strengthened connectivity of the nucleus accumbens with a region encompassing the superior temporal and postcentral gyri and the rolandic operculum. Indeed, cognitive control of craving is associated with inverse coupling between these cortical regions and the nucleus accumbens in addicted individuals using different strategies to resist craving.

Although not hypothesized a priori or identified as abnormal relative to healthy controls, connectivity in other pathways modified by methylphenidate also may be relevant to addiction; further research is needed to clarify the precise mechanisms and consequences of these changes. For example, because the locus ceruleus, which is in close proximity to our ventral tegmental area seed, is the main source of noradrenergic innervation to the cerebellum, connectivity reductions in this pathway could be the result of differential effects of methylphenidate on norepinephrine. Other effects may also have noradrenergic underpinnings, including methylphenidate-strengthened connectivity of the thalamus with the medial orbitofrontal cortex, potentially signaling normalization of noradrenergic deficits in this region in cocaine abusers.

Several caveats should be considered when interpreting the current results. First, like most stimulants, methylphenidate produce cardiovascular changes that differed from those with placebo. However, because blood oxygen level-dependent fluctuations correlating with heart rate and respiration are global, these changes are not likely to significantly influence our results. At the neurochemical level, a second concern is that the effects of methylphenidate are not specific to dopamine because methylphenidate also blocks the norepinephrine transporter (and may account for some of its effects, as discussed above). Nevertheless, even if effects are the result of norepinephrine transporter blockade, the underlying mechanism could still be dopaminergic, since dopamine also has high affinity for norepinephrine transporters—particularly in regions where norepinephrine transporters are more abundant than dopamine transporters, such as the frontal cortex. Third, similar to prior studies, we detected a number of negative relationships with our seed regions. One concern that arises is the possible contribution of analytical procedures (e.g., global signal normalization). However, prior work suggests that negative relationships cannot simply be attributed to correction for the global signal and that removing global signal from the data, which is primarily localized to gray matter, can actually improve neuroanatomic specificity of positive relationships. Nevertheless, because our contrast of interest was a within-subject change in connectivity, this issue is unlikely to modify our conclusions. Fourth, although seed-based methods for connectivity are one
of the most commonly used approaches, in part because these methods are reliable\textsuperscript{25} and especially appropriate when researchers have specific a priori hypotheses,\textsuperscript{26} they are limited by (1) the univariate nature of the analysis, which limits the scope of network-level conclusions that can be drawn,\textsuperscript{26} and (2) susceptibility to biases related to variations in seed positioning.\textsuperscript{26,27} We addressed this latter limitation by using seeds identical to those used in previous research.\textsuperscript{22} Future studies could also apply complementary methods (eg, those based on graph theory\textsuperscript{42} or independent component analysis) to capture the effects of methylphenidate on brain networks. Last, we cannot at present speak to whether methylphenidate-induced modulation of connectivity is a viable target for treatment approaches in CUD. Future studies would need to examine the effects of methylphenidate using dose-dependent and/or prolonged administration (ie, occurring over days or weeks). In addition, because methylphenidate as a stand-alone treatment may be insufficient to achieve a positive clinical outcome in cocaine addiction,\textsuperscript{78,79} except for in instances of comorbidity with attention-deficit/hyperactivity disorder,\textsuperscript{80} the therapeutic effects of methylphenidate should be explored in conjunction with behavioral interventions targeted toward increasing emotion regulation and self-control and decreasing conditioned associations.

In summary, our findings provide novel evidence that mesocorticolimbic connectivity is susceptible to modification by pharmacologic agents targeting dopamine in individuals with chronic, severe CUD. Methylphenidate primarily strengthened connections between regions underlying emotion regulation and cognitive control and reduced connections between regions underlying habits, including compulsive drug-seeking and craving. Although the precise mechanism of these effects remains to be determined, our data suggest that methylphenidate may transiently, and independently of task demands, modify striatal and cortical synchronous activity with connected brain regions. These changes could serve to facilitate behavior or make cortical processing underlying behavior more efficient\textsuperscript{77,81-83} or less difficult to override.\textsuperscript{84} By highlighting effects in mesocorticolimbic pathways in CUD, our results extend prior work that has shown pharmacologic modulation of default mode and executive control network circuitry in nicotine dependence (via nicotine patch\textsuperscript{79}) and limbic circuitry in depression (via the antidepressant sertraline). A better understanding of the potentially therapeutic effects of methylphenidate on neural circuitry function in CUD (eg, with future studies evaluating the clinical efficacy of methylphenidate) may promote the development of improved treatment options for stimulant addictions.

**REFERENCES**


Effects of Methylphenidate in Cocaine Addiction

Original Investigation Research


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