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Abnormal response to methylphenidate across multiple fMRI procedures in cocaine use disorder: Feasibility study

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Abstract

Rationale—The indirect dopamine agonist methylphenidate remediates cognitive deficits in psychopathology, but the individual characteristics that determine its effects on the brain are not known.

Objectives—We aimed to determine whether targeted dopaminergically-modulated traits and individual differences could predict neural response to methylphenidate across multiple functional magnetic resonance imaging (fMRI) procedures.

Methods—We combined neural measures from three separate procedures (two inhibitory control tasks differing in their degree of emotional salience, and resting-state functional connectivity) during methylphenidate (20 mg oral, versus randomized and counterbalanced placebo) and correlated these aggregated responses with cocaine use disorder diagnosis (22 cocaine abusers, 21 controls), symptoms of attention deficit hyperactivity disorder, and working memory capacity.

Results—Cocaine abusers, relative to controls, had a lower response in the dorsolateral prefrontal cortex to methylphenidate across all three procedures, driven by responses to the two inhibitory control tasks; reduced methylphenidate fMRI response in this region further correlated with more frequent cocaine use.

Conclusions—Cocaine abuse (and its frequency), associated with lower tonic dopamine levels, correlated with a reduction in activation to methylphenidate (versus placebo). These initial results provide feasibility to the idea that multimodal fMRI tasks can be meaningfully aggregated, and these aggregated procedures show a common disruption in addiction, in a highly anticipated region relevant to cognitive control. Results also suggest that drug use frequency may represent an

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Disclosure/Conflict of Interest

None declared.

important modulatory variable in interpreting the efficacy of pharmacologically-enhanced cognitive interventions in addiction.

INTRODUCTION

The mesocorticolimbic dopamine system is perturbed across many psychopathologies, including drug addiction and attention deficit hyperactivity disorder (ADHD), highlighting dopamine's role in supporting numerous functions that bear on these diseases [e.g., reward prediction (Schultz 2010), incentive salience (Berridge 2007), arousal (Horvitz 2000), and novelty (Zald et al. 2008)]. The indirect dopamine and norepinephrine agonist methylphenidate (MPH) increases extracellular dopamine by blocking both transporters (Kuczenski and Segal 1997), and is thought to enhance attention and executive functioning by decreasing the energy requirements needed to perform cognitive tasks [i.e., by enhancing signal-to-noise ratio of neuronal activity (Swanson et al. 2011) and/or by modulating brain regions relevant to optimal task performance (Tomasi et al. 2011)]. Yet, the factors that predict an individual's response to MPH (e.g., as measured by modulation of activity in dopaminergic brain regions) are currently unknown. Uncovering the individual factors associated with MPH responsiveness, particularly when assessed across multiple functional magnetic resonance imaging (fMRI) tasks and procedures conducted in the same participants, could inform which individuals might benefit most from a pharmacologically-enhanced cognitive intervention and, more broadly, can clarify if dopamine agonists exert consistent effects on brain function in health and disease across multiple contexts.

In the present study, we aggregated fMRI data collected during a MPH challenge targeting select dopaminergically-innervated, anatomically-defined cortical and subcortical brain regions of interest (ROIs) [orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), thalamus, hippocampus, midbrain, and striatum] across three different fMRI procedures: (A) a classical color-word Stroop task (Leung et al. 2000)]; (B) an emotional (drug) word variant of this Stroop task (Goldstein et al. 2009)]; and (C) resting-state global functional connectivity density, which captures the overall number of functional connections to a given brain region (Konova et al. 2015; Tomasi and Volkow 2011). We then tested associations of responses in these regions with targeted, dopaminergically-relevant individual difference variables that could predict an aggregated MPH-related response. Our primary interest was in (A) *cocaine use disorder* (CUD), as MPH modulated neural response (in ways suggesting a beneficial response) during tasks and during the resting state in prefrontal cortical regions (Goldstein et al. 2010; Li et al. 2010; Matuskey et al. 2013; Moeller et al. 2014a) and subcortical regions (Konova et al. 2013; Moeller et al. 2012a). Moreover, CUD is classically associated with multiple neurocognitive deficits, including in inhibitory control (Luijten et al. 2014), which is a function indexed by the current drug-word and Stroop tasks. Secondly, we examined (B) *ADHD symptoms*, as MPH modified neural responses during executive function to a greater extent in these individuals than healthy controls (Rubia et al. 2011a; Rubia et al. 2011b); and (C) *working memory capacity*, as MPH has been shown to modulate task performance based on an individual's baseline ability (Mehta et al. 2000; van der Schaaf et al. 2013).

METHODS

Participants

Twenty-two CUD (20 males) and 21 healthy controls (20 males), recruited through advertisements in local newspapers and by word-of-mouth, participated in this research; all provided written informed consent in accordance with the Stony Brook University Institutional Review Board. All participants were medically healthy and not currently taking any medications. Based on a comprehensive diagnostic interview (Supplement), CUD were classified as either meeting diagnostic criteria for current cocaine dependence (N=21) or abuse (N=1) (see Table 1 for cocaine-related clinical information and the Supplement for additional clinical information, including CUD comorbidities). Exclusion criteria were: (A) history of head trauma or loss of consciousness (> 30 min) or other neurological disease of central origin (including seizures); (B) abnormal vital signs at time of screening; (C) history of major medical conditions, encompassing cardiovascular (high blood pressure, cardiac arrhythmias apart from sinus bradycardia, or an abnormal electrocardiography at screening), endocrinological (including metabolic), oncological, or autoimmune diseases; (D) history of major psychiatric disorder (other than substance abuse or dependence for CUD; healthy controls needed to be free of all psychiatric diagnoses, with the exception of nicotine dependence); (E) pregnancy (based on a urine test); (F) contraindications to MRI; (G) history of glaucoma; and (H) except for cocaine in CUD, positive urine screens for psychoactive drugs or their metabolites.

Methylphenidate Administration

Participants were randomized to receive 20 mg oral MPH or placebo (lactose) on two study days, separated by approximately one to two weeks (CUD: 9.2 ± 4.3 days; control: 12.9 ± 11.6 days; $p > 0.1$). Oral MPH or placebo was given 60 minutes prior to testing, within the window of peak effects (60–120 minutes), first single-blind (N=31) and then transitioned to double-blind (N=12) (see Supplement for additional detail). Methylphenidate plasma concentrations were collected via venous blood draws before MPH, and at 45 and 120 min post-MPH, and were analyzed using capillary Gas Chromatography-Mass Spectroscopy (Srinivas et al. 1991).

Study Procedures

We aggregated and re-analyzed data from several of our previously published studies (Goldstein et al. 2010; Konova et al. 2015; Konova et al. 2013; Moeller et al. 2014a; Moeller et al. 2012a). Task procedures encompassed a salient drug-word task, a color-word Stroop task, and a resting-state scan, all described below and completed in this fixed order. Forty participants (21 CUD, 19 controls) completed the drug-word task, 37 (20 CUD, 17 controls) completed the color-word Stroop task, and 33 (18 CUD, 15 controls) completed resting-state scans (16 CUD and 11 controls completed all three study procedures). Reasons for noncompletion were generally incidental (e.g., time constraints), and completers of all three procedures were demographically and clinically similar to noncompleters; the only (non-Bonferroni corrected) differences in Table 1 variables were in non-verbal IQ (higher in noncompleters; $p=0.040$) and pre-MPH cocaine craving (higher in completers on the MPH day; $p=0.013$).

Salient Drug Word Task—Participants were instructed to press for the ink color of drug words or neutral words while ignoring the emotional salience of the drug words (e.g., Goldstein et al. 2009; Konova et al. 2016; Konova et al. 2012; Moeller et al. 2013; Moeller et al. 2012b). In brief, the task consisted of six 3.4 min task repetitions (three drug and three neutral), each containing two blocks of 20 drug or neutral words, interleaved with a 20 s fixation window. Participants performed each word sequence under one of three counterbalanced monetary reward amounts (50¢, 25¢, or 0¢), gained for correct performance for up to \$75 of real money; participants could not lose money on the task. Each trial consisted of a 500 ms fixation, a 2000 ms word presentation (for word reading), a 500 ms response window, and a 500 ms feedback displaying the amount of money earned for a correct response or an “X” for an incorrect response. Word color order was pseudorandomized across all task runs.

Color-Word Stroop Task—Participants performed three runs of this event-related task, with instructions to press for the ink color of color-words (red, blue, yellow, green) printed in their congruent (e.g., ‘blue’ in blue ink; 94% of trials) or incongruent (e.g., ‘blue’ in red ink; 6% of trials) fonts (Leung et al. 2000; Moeller et al. 2015; Moeller et al. 2014a; Moeller et al. 2014b; Moeller et al. 2012a). Because of our implicit task baseline of correct events (see fMRI analysis below), the task did not contain a jittered intertrial interval. No word or color of an incongruent stimulus mirrored the preceding congruent color-word; otherwise, stimuli were presented randomly. Each word was presented for 1300 ms (intertrial interval=350 ms). Remuneration for task completion was fixed at \$25.

Resting-State Scan—Participants were instructed to keep their eyes open, lie as still as possible, and remain awake. Resting scan time was approximately 10 min in duration. This resting scan allowed us to determine global functional connectivity density, which is a data-driven connectivity-based approach that provides a metric of the total number of functional connections to a given region as previously described (Konova et al. 2015; Tomasi and Volkow 2011).

Individual Difference Variables

Diagnosis (CUD versus Control)—Diagnosis constituted the individual difference variable of primary interest in this study, given the current addicted sample, with attendant dopaminergic compromises (Goldstein and Volkow 2011), and given prior work by us and others indicating that MPH normalized behavior and brain function in this psychopathology (Goldstein et al. 2010; Konova et al. 2013; Li et al. 2010; Matuskey et al. 2013; Moeller et al. 2014a; Moeller et al. 2012a).

Symptoms of ADHD—Because the majority of the literature on MPH comes from ADHD, we examined participant responses on the Conners Adult ADHD Rating Scale (CAARS) (Conners et al. 1999). The CAARS, which was completed without MPH on board and outside of fMRI, provides self-assessment of severity of ADHD symptoms on a four-point scale (0=Not at All to 3=Very Much).

Working Memory—Digit span (backwards) (Wechsler 1997), which measures attentional capacity and verbal working memory, was assessed as part of a comprehensive neuropsychological battery described elsewhere (Woicik et al. 2009). Similarly to CAARS, participants completed this measure without MPH on board and outside of fMRI, and thus this measure reflects a general, dopaminergically-relevant individual difference in working memory capacity. The contributions of dopamine to working memory are well-characterized (D'Esposito and Postle 2015). Of relevance for the current study, digit span (backwards) is sensitive to dopamine neurotransmission, evidenced by a study in Parkinson's patients where performance on this measure was rescued by dopamine-enhancing medications (Cools et al. 2010).

Data Analysis

Data analysis proceeded in four phases. First, we defined and extracted average values of the fMRI blood-oxygenation-level-dependent (BOLD) signals in 10 select ROIs for each of the three fMRI procedures, which were subsequently converted to z-scores to standardize measurements across procedures. Second, we averaged each participant's z-scored MPH minus placebo response across the three fMRI procedures in these 10 brain regions. Third, we tested for associations between these averaged MPH relative to placebo (MPH>placebo) signals and the dopamine-relevant individual difference variables. Fourth, we conducted supplementary analyses to help buttress interpretations for any significant differences revealed as part of the third phase. These four phases are described in further detail below (and in the Supplement).

Identification of Brain Regions Potentially Targeted by MPH—*A priori* unbiased, anatomical ROIs, created in PickAtlas, were defined in key brain regions relevant to dopaminergic neurotransmission that support a range of cognitive and emotional functions, and that were engaged by MPH in our prior pharmacological fMRI studies using these same fMRI tasks, contrasts, and procedures (Goldstein et al. 2010; Konova et al. 2015; Konova et al. 2013; Moeller et al. 2014a; Moeller et al. 2012a); importantly, however, the current ROIs were independent from these prior studies' peak activations. These ROIs encompassed (A) five cortical regions: ACC [comprising portions of Brodmann Areas (BAs) 24, 32, and 25], dorsal ACC/midcingulate (comprising portions of BAs 32 and 23), DLPFC (encompassing BAs 9 and 46), lateral OFC (comprising BA 11 and 47) and medial OFC (comprising portions of BA 11 and the gyrus rectus that were distinct from the lateral OFC ROI); and (B) five subcortical regions: thalamus, caudate, putamen, hippocampus, and midbrain [note that the caudate and putamen, considered together, encompass the dorsal striatum and most of the ventral striatum including the nucleus accumbens (i.e., where the head of the caudate fuses with the putamen)]. Figure 1 displays coverage of all ROIs. Note that we used bilateral ROIs to restrict the number of analyses and reduce the potential of Type I errors. Moreover, several of our regions of interest were medially located (e.g., ACC, midcingulate, medial OFC), meaning that laterality effects, if they occurred, would have been ambiguous to interpret. In all three fMRI procedures, 2nd Level functional maps were computed for each medication condition and for each participant according to the particular 1st Level analysis strategy (see fMRI procedures, below). MARSBAR was then used to

extract the BOLD signals during the fMRI tasks or the degree of connectivity during the resting-state scans from each anatomical ROI for each participant.

fMRI Analysis—For all procedures, scanning was performed on a 4T whole-body Varian/Siemens MRI scanner. Data analyses were performed with Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London UK), running on Matlab version 7.7 (Mathworks Inc., Natick, MA). Acquisition and pre-processing procedures can be found in our prior reports (Goldstein et al. 2010; Konova et al. 2015; Konova et al. 2013; Moeller et al. 2014a; Moeller et al. 2012a), and are also provided in the Supplement for further reference.

To calculate individual BOLD-fMRI maps for the drug-word monetary reward task, which has a blocked design comprising 128 time points, we used a box-car design convolved with a canonical hemodynamic response function and high-pass filter (cut-off frequency: 1/520 sec). Contrast maps reflecting the average percent signal change from the fixation baseline across all task conditions (0¢, 25¢, and 50¢ blocks, for both drug and neutral word blocks) were calculated for each participant. We analyzed this combined contrast to ensure maximum sample size for our analyses, and because our previous results showed that the effects of MPH on this task generally did not vary by money or word conditions (Goldstein et al. 2010). Indeed, in the current study, a 2 (medication: MPH, placebo) $\times$ 3 (money: 0¢, 25¢, 50¢) $\times$ 2 (word: drug, neutral) $\times$ 2 (group: CUD, control) ANOVA on the behavioral data revealed no main effects or interactions with medication condition (all $p > 0.108$).

To calculate individual BOLD-fMRI maps for the color-word Stroop task, which has an event-related design comprising 207 time points, we used a general linear model with six motion regressors (3 translation and 3 rotation) convolved with a canonical hemodynamic response function and a high-pass (cut-off frequency: 1/90 s) filter. We computed a design matrix that specifically modeled all error events – given that our prior results with this task showed MPH effects for (all) error processing but not Stroop conflict processing (Moeller et al. 2014a; Moeller et al. 2012a). This design matrix included one regressor collapsed across both error trials (Congruent Incorrect and Incongruent Incorrect), leaving both correct trials (Congruent Correct and Incongruent Correct) to serve as the active, implicit baseline, and was defined as (Incongruent Error + Congruent Error) – (Incongruent Correct + Congruent Correct). The number of errors on each study day and by study condition was as follows: 24.5 ± 17.4 for MPH congruent trials, 12.2 ± 8.1 for MPH incongruent trials, 42.6 ± 35.3 for placebo congruent trials, and 14.0 ± 8.5 for placebo incongruent trials. A 2 (medication: MPH, placebo) $\times$ 2 (condition: congruent, incongruent) $\times$ 2 (group: CUD, control) ANOVA on task errors revealed no effects of group but did reveal that all participants committed more errors during placebo than MPH [medication main effect: $F(1,40)=10.68$, $p=0.002$], especially during congruent trials (i.e., the more frequent task condition) [medication $\times$ condition interaction: $F(1,40)=12.07$, $p=0.001$]. Thus, we modeled all errors, not just incongruent errors, to maximize statistical power.

Connectivity analysis was based on our prior work (Tomasi and Volkow 2011), used to identify functional hubs in the human brain as determined by the density, or estimated number, of functional connections for a given brain region. Voxels with signal-to-noise as a

function of time < 50 were first eliminated to minimize unwanted effects from susceptibility-related signal-loss artifacts. The remaining preprocessed data then underwent global functional connectivity density mapping, where we computed the total number of functional connections of every voxel in the brain. The Pearson correlation was used to assess the strength of the functional connectivity of each voxel with each other voxel, and a correlation threshold of 0.6 was used to compute the binary undirected connectivity coefficient, a_{ij} . This correlation threshold ensures significant correlations between time-varying signal fluctuations at $p < 0.001$ (family-wise error). The global functional connectivity density at every voxel was calculated from the $N \times (N - 1)/2$ binary matrices ($N = 57,713$ voxels) as $k_i = \sum a_{ij}$, using a C-algorithm and parallel computing (Konova et al. 2015; Tomasi and Volkow 2011).

Statistical Analyses

Associations with Individual Difference Variables: We computed 10 generalized linear models (GZLMs) with robust estimation, to account for violations of normality in some of the variables. The outcome variable in each model was the extracted MPH>placebo fMRI signal, averaged across all three fMRI procedures, in each brain ROI. Because activation in each brain region was averaged across the three procedures, participants were still included in the analyses even if they were missing data from a given procedure(s) (see Table 2 for sample sizes of each analysis); this more liberal inclusion was instituted to maximize sample size in this feasibility study. The predictor variables in these models were specified as either factors (diagnosis: CUD, control) or continuous covariates (CAARS and digit span). We also included a fourth (continuous) covariate in these models (MPH plasma level) because MPH permeability, which can be indexed by plasma levels, may also modulate MPH-related brain response (Muller et al. 2005). To minimize Type I error, we adopted a highly conservative $p < 0.001$ significance level for these analyses.

Supplementary Analyses: Additional analyses were conducted to help interpret, and provide functional relevance to, our main analyses above. First, in cases where a significant effect was observed across the three fMRI procedures, we conducted analyses separately for each fMRI procedure to examine whether a particular procedure(s) drove the aggregated effect (i.e., to explain the source of the effect in the averaged variables). Second, in cases where Diagnosis (i.e., CUD, control) was the modulating variable, we examined associations with frequency of recent cocaine use (days per week, last 30 days) (Table 1). Additional analyses, described in the Supplement, examined the respective influences of noncompletion of all three fMRI tasks, laterality (among the already significant regions), and covariates that differed between the groups (age, depression, cigarette smoking history, and history of substance use comorbidities); and examined associations of brain data with task data. In all supplementary analyses, effects were considered significant at the more traditional $p < 0.05$ threshold (i.e., since the primary brain effect needed to have been already observed at the conservative $p < 0.001$ threshold).

RESULTS

MPH Effects on Aggregated fMRI Response

Table 2 displays all GZLM coefficients and significance levels. Diagnosis membership (CUD versus control) was associated with averaged MPH>placebo response in the DLPFC; that is, CUD had reduced aggregate DLPFC response to MPH, whereas controls had increased aggregate DLPFC response to MPH (Figure 2A) [also note a similar, albeit nonsignificant, direction of correlations in most other cortical regions (Table 2)]. This DLPFC effect was independent of the amount of MPH in plasma, a variable that correlated with midbrain MPH>placebo response (the higher the plasma MPH, the greater the MPH>placebo response in midbrain) (Table 2). No other associations reached significance at the conservative $p<0.001$ threshold.

Supplementary Analyses

When examining each fMRI procedure separately, the CUD participants had reduced DLPFC response as measured with the drug-word task ($p=0.006$) and the color-word Stroop task ($p=0.005$); a similar, albeit not significant, pattern was observed for resting-state functional connectivity ($p=0.408$) (Figure 2A). These supplemental analyses suggest that MPH exerts a common signature in the DLPFC that is modulated by Diagnosis, although this signature may be more prominent during the performance of inhibitory control tasks than during rest.

Given the association between Diagnosis and DLPFC, we tested, within CUD only, whether the amount of DLPFC modulation (combined measure across the three procedures) by MPH was associated with current frequency of cocaine use (last 30 days). Results showed that DLPFC modulation by MPH was negatively associated with recent drug use (i.e., the more MPH decreased fMRI response in the DLPFC, the greater the current drug use) (Figure 2B). This correlation was also significant for each of the three fMRI procedures when considered separately (drug-word task: $p=0.032$; color-word Stroop task: $p=0.035$; resting-state connectivity: $p=0.021$). Thus, MPH may have exerted the greatest benefit in individuals who needed it most (i.e., CUD with the most frequent current drug use).

Additional analyses, described more comprehensively in the Supplement, indicated that these DLPFC results were not attributable to: demographic or clinical (including drug use comorbidities) differences between groups, noncompletion of all three fMRI procedures, or laterality effects. Moreover, there were interesting, though nonsignificant, trends toward decreased MPH>placebo DLPFC correlating with better MPH>placebo task performance.

DISCUSSION

In this study, we aggregated individuals' response to MPH in 10 cortical and subcortical brain regions across three different fMRI procedures, encompassing a salient drug word task, a color-word Stroop task, and hub-based resting-state functional connectivity. We then correlated this combined MPH (relative to placebo) response with dopaminergically-relevant individual differences variables related to clinical phenotypes. To our knowledge, this is the

first study to examine the individual characteristics, including a substance use disorder, that associate with multimodal fMRI responsiveness to MPH.

Across the three fMRI procedures, compared with healthy controls, individuals with CUD showed a reduction in DLPFC activity/connectivity with MPH. Modulation of the DLPFC by MPH may be associated with the modulation of executive functions needed to perform the current inhibitory control tasks, potentially including non-emotional conflict resolution, the implementation of cognitive control (Egner et al. 2008; Kerns et al. 2004; Luijten et al. 2014), and/or working memory (Brunoni and Vanderhasselt 2014; Owen et al. 2005) (although note that working memory itself was not associated with MPH response in this region). Additional studies are needed to evaluate MPH effects on DLPFC connectivity, which in the current study showed a similar, albeit nonsignificant, pattern of effects as the task data. Indeed, little work has examined the effects of MPH on DLPFC connectivity during resting-state, though one study in healthy controls reported that thalamic-DLPFC connectivity was reduced with MPH (Farr et al. 2014), which is the pattern we observed here for CUD. Importantly, the combined DLPFC modulation by MPH (i.e., tasks and resting state) was further correlated with the frequency of recent cocaine use. Given this correlation, it is reasonable to attribute the DLPFC effect to active cocaine use, rather than simply to CUD diagnosis (that may contain attendant potential confounds, such as issues with incomplete group matching and/or comorbid drug use including cigarette smoking). Although the neurochemical mechanism of the current effects remains to be determined, one possibility is that, in the individuals for whom dopamine signaling is perturbed (i.e., CUD) (Volkow et al. 2014) – and perhaps especially in CUD with the most frequent drug use – MPH produced a pattern of more efficient brain responses (Swanson et al. 2011). Although it was somewhat surprising that similar effects did not emerge for CAARS (ADHD index), null effects could be attributable to the very conservative significance threshold, and by the current sample that was not selected *a priori* to exhibit ADHD symptoms.

Our results are consistent with other studies finding that MPH reduces neural activity/connectivity across multiple psychopathologies. In ADHD, MPH reduced prefrontal cortex fMRI response and regional cerebral blood flow (Liddle et al. 2011; Peterson et al. 2009; Schweitzer et al. 2003; Schweitzer et al. 2004), and improvements in ADHD symptoms following a therapeutic course of MPH were associated with reduced activity in several prefrontal regions including the left ACC/supplementary motor area (Schulz et al. 2012). A meta-analysis of fMRI studies in ADHD showed that MPH decreased activation during response inhibition and error processing in the dorsal ACC/supplementary motor area (although other regions, such as the inferior frontal gyrus and insula, showed an opposite direction of effects) (Rubia et al. 2014). In traumatic brain injury, MPH reduced global gray matter cerebral blood flow (Kim et al. 2012) and decreased fMRI activation (in ACC, thalamus, and other regions) during performance of a working memory (N-back) task (Newsome et al. 2009). In methamphetamine-addicted individuals, MPH (relative to placebo) decreased activation in parietal and occipital regions during color-word Stroop incongruent trials (Jan et al. 2014). In CUD, MPH reduced an abnormally high (i.e., normalized, such that differences from healthy controls were attenuated) functional connectivity in an important striatal habit formation pathway (Konova et al. 2013). Of greater importance for the current study, MPH also decreased BOLD-fMRI response in the

DLPFC during the color-word Stroop (i.e., such that CUD resembled controls during placebo) (Moeller et al. 2014a) – although here we showed that this response was not only driven by the color-word Stroop task, but also by the drug-word task and by a similar pattern also during rest. In other research, reduced DLPFC fMRI response predicted better clinical outcome (treatment retention) in CUD (Brewer et al. 2008).

The primary limitation of this study is the sample composition. Given that the primary consideration throughout all analyses of this feasibility study was to maximize sample size, we included participants with incomplete data; consequently, we did not conduct stringent group matching (e.g., on age or comorbid drug use including cigarette smoking history) nor did we precisely interrogate task condition effects. Prioritizing these other considerations would have compromised power, either by reducing the number of participants and/or by reducing the number of task trials available for analysis. Thus, although covariation analyses indicated that these respective factors did not drive our findings (Results and Supplement), future studies are needed with larger samples. Larger samples will enable: analyses to be restricted to individuals with complete data, better group matching, study conditions to be appropriately isolated (e.g., money versus word effects in the drug-word task; congruency versus error effects in the color-word Stroop task), and laterality to be examined in greater depth. For the latter, however, even for regions showing laterality effects during Stroop-like tasks, the difference between the functions subserved by left and right hemispheres appears nuanced. For example, the left DLPFC may be particularly active during conflict (i.e., to adjust the previous task strategy), whereas the right DLPFC may be particularly active after conflict (i.e., to maintain the new task strategy) (Vanderhasselt et al. 2009); in this feasibility study, we could not conduct such fine-grained analyses, and indeed we did not find evidence of laterality effects in this DLPFC region (Supplement). A second limitation is that conclusions are constrained by the fMRI procedures/contrasts and brain regions we selected. Different tasks and/or fMRI contrasts may have yielded different results, potentially helping to explain an opposite (increased) pattern of MPH effects in other studies [e.g., ADHD (Bush et al. 2008; Cubillo et al. 2014a; Cubillo et al. 2014b; Rubia et al. 2014; Wong and Stevens 2012); traumatic brain injury (Kim et al. 2009); CUD (Camchong et al. 2011; Goldstein et al. 2010)]. Thus, future studies aiming to integrate brain function across multiple experimental procedures may wish to incorporate tasks that have similar baseline conditions and similar structural designs (e.g., all event-related). For the latter, however, it is important to note that studies comparing block designs versus event-related designs of the same experimental paradigm, whether emotionally neutral or emotionally salient, have largely reported highly overlapping fMRI activations (Buhler et al. 2008; Chee et al. 2003); accordingly, it is unlikely that the use of both blocked and event-related designs substantially modified any of our interpretations. Nevertheless, interpretative issues with fMRI tasks underscore the importance in the current study of including functional connectivity density, which is not constrained by task idiosyncrasies. A final limitation is that MPH also blocks the norepinephrine transporter (Hannestad et al. 2010). Even so, the mechanism of optimization could still be dopaminergic because norepinephrine transporters also have affinity for dopamine (Hannestad et al. 2010), especially in prefrontal regions (where norepinephrine transporters outnumber dopamine transporters).

In summary, individual differences related to dopamine signaling (e.g., a cocaine use disorder) predict MPH response across multiple, disparate fMRI procedures. Our data favor the interpretation that a reduced (potentially more efficient) DLPFC response to MPH versus placebo characterizes individuals with CUD across a range of contexts. Furthermore, this effect may be accentuated in those using cocaine at a higher frequency – a possibility not previously examined in clinical trials of MPH in substance users that may have contributed to mixed findings (Gawin et al. 1985; Grabowski et al. 1997). More broadly, combining multiple fMRI measures inclusive of cognitive tasks and resting state can provide new insights into the mechanisms underlying the effects of dopamine agonists on brain function in health and disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Beck, AT.; Steer, RA.; Brown, GK. Beck Depression Inventory Manual. 2. The Psychological Corporation; San Antonio: 1996.
- Berridge KC. The debate over dopamine's role in reward: The case for incentive salience. *Psychopharmacology*. 2007; 191:391–431. [PubMed: 17072591]
- Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. *Biol Psychiatry*. 2008; 64:998–1004. [PubMed: 18635157]
- Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain and cognition*. 2014; 86:1–9. [PubMed: 24514153]
- Buhler M, Vollstadt-Klein S, Klemen J, Smolka MN. Does erotic stimulus presentation design affect brain activation patterns? Event-related vs. blocked fMRI designs. *Behav Brain Funct*. 2008; 4:30. [PubMed: 18647397]
- Bush G, Spencer TJ, Holmes J, Shin LM, Valera EM, Seidman LJ, Makris N, Surman C, Aleardi M, Mick E, Biederman J. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Arch Gen Psychiatry*. 2008; 65:102–14. [PubMed: 18180434]
- Camchong J, MacDonald AW 3rd, Nelson B, Bell C, Mueller BA, Specker S, Lim KO. Frontal hyperconnectivity related to discounting and reversal learning in cocaine subjects. *Biol Psychiatry*. 2011; 69:1117–23. [PubMed: 21371689]
- Chee MW, Venkatraman V, Westphal C, Siong SC. Comparison of block and event-related fMRI designs in evaluating the word-frequency effect. *Hum Brain Mapp*. 2003; 18:186–93. [PubMed: 12599276]
- Conners, CK.; Erhardt, D.; Sparrow, EP. Conners' Adult ADHD Rating Scales (CAARS): Technical manual. Multi-Health; North Tonawanda, NY: 1999.
- Cools R, Miyakawa A, Sheridan M, D'Esposito M. Enhanced frontal function in Parkinson's disease. *Brain*. 2010; 133:225–33. [PubMed: 19995871]

- Cubillo A, Smith AB, Barrett N, Giampietro V, Brammer M, Simmons A, Rubia K. Drug-specific laterality effects on frontal lobe activation of atomoxetine and methylphenidate in attention deficit hyperactivity disorder boys during working memory. *Psychol Med*. 2014a; 44:633–46. [PubMed: 23597077]
- Cubillo A, Smith AB, Barrett N, Giampietro V, Brammer MJ, Simmons A, Rubia K. Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naïve ADHD boys. *Cereb Cortex*. 2014b; 24:174–85. [PubMed: 23048018]
- D’Esposito M, Postle BR. The cognitive neuroscience of working memory. *Annu Rev Psychol*. 2015; 66:115–42. [PubMed: 25251486]
- Egner T, Etkin A, Gale S, Hirsch J. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. *Cereb Cortex*. 2008; 18:1475–84. [PubMed: 17940084]
- Farr OM, Zhang S, Hu S, Matuskey D, Abdelghany O, Malison RT, Li CS. The effects of methylphenidate on resting-state striatal, thalamic and global functional connectivity in healthy adults. *Int J Neuropsychopharmacol*. 2014; 17:1177–91. [PubMed: 24825078]
- Gawin F, Riordan C, Kleber H. Methylphenidate treatment of cocaine abusers without attention deficit disorder: a negative report. *Am J Drug Alcohol Abuse*. 1985; 11:193–7. [PubMed: 4091158]
- Goldstein RZ, Alia-Klein N, Tomasi D, Honorio Carrillo J, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proc Natl Acad Sci USA*. 2009; 106:9453–9458. [PubMed: 19478067]
- Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci*. 2011; 12:652–69. [PubMed: 22011681]
- Goldstein RZ, Woicik PA, Maloney T, Tomasi D, Alia-Klein N, Shan J, Honorio J, Samaras D, Wang R, Telang F, Wang GJ, Volkow ND. Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. *Proc Natl Acad Sci U S A*. 2010; 107:16667–72. [PubMed: 20823246]
- Grabowski J, Roache JD, Schmitz JM, Rhoades H, Creson D, Korszun A. Replacement medication for cocaine dependence: methylphenidate. *J Clin Psychopharmacol*. 1997; 17:485–8. [PubMed: 9408812]
- Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, Malison RT, Carson RE, Ding YS. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. *Biol Psychiatry*. 2010; 68:854–60. [PubMed: 20691429]
- Horvitz JC. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. *Neuroscience*. 2000; 96:651–6. [PubMed: 10727783]
- Jan RK, Lin JC, McLaren DG, Kirk IJ, Kydd RR, Russell BR. The effects of methylphenidate on cognitive control in active methamphetamine dependence using functional magnetic resonance imaging. *Frontiers in psychiatry / Frontiers Research Foundation*. 2014; 5:20.
- Kerns JG, Cohen JD, MacDonald AW 3rd, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. *Science*. 2004; 303:1023–6. [PubMed: 14963333]
- Kim J, Whyte J, Patel S, Europa E, Wang J, Coslett HB, Detre JA. Methylphenidate modulates sustained attention and cortical activation in survivors of traumatic brain injury: a perfusion fMRI study. *Psychopharmacology (Berl)*. 2012; 222:47–57. [PubMed: 22203319]
- Kim YW, Shin JC, An YS. Effects of methylphenidate on cerebral glucose metabolism in patients with impaired consciousness after acquired brain injury. *Clinical neuropharmacology*. 2009; 32:335–9. [PubMed: 19667974]
- Konova AB, Moeller SJ, Parvaz MA, Frobose MI, Alia-Klein N, Goldstein RZ. Converging effects of cocaine addiction and sex on neural responses to monetary rewards. *Psychiatry Res*. 2016; 248:110–8. [PubMed: 26809268]
- Konova AB, Moeller SJ, Tomasi D, Goldstein RZ. Effects of chronic and acute stimulants on brain functional connectivity hubs. *Brain Res*. 2015; 1628:147–56. [PubMed: 25721787]
- Konova AB, Moeller SJ, Tomasi D, Parvaz MA, Alia-Klein N, Volkow ND, Goldstein RZ. Structural and behavioral correlates of abnormal encoding of money value in the sensorimotor striatum in cocaine addiction. *Eur J Neurosci*. 2012; 36:2979–88. [PubMed: 22775285]

- Konova AB, Moeller SJ, Tomasi D, Volkow ND, Goldstein RZ. Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction. *JAMA Psychiatry*. 2013; 70:857–68. [PubMed: 23803700]
- Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem*. 1997; 68:2032–7. [PubMed: 9109529]
- Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the stroop color word interference task. *Cereb Cortex*. 2000; 10:552–60. [PubMed: 10859133]
- Li CS, Morgan PT, Matuskey D, Abdelghany O, Luo X, Chang JL, Rounsaville BJ, Ding YS, Malison RT. Biological markers of the effects of intravenous methylphenidate on improving inhibitory control in cocaine-dependent patients. *Proc Natl Acad Sci U S A*. 2010; 107:14455–9. [PubMed: 20660731]
- Liddle EB, Hollis C, Batty MJ, Groom MJ, Totman JJ, Liotti M, Scerif G, Liddle PF. Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. *J Child Psychol Psychiatry*. 2011; 52:761–71. [PubMed: 21073458]
- Luijten M, Machielsen MW, Veltman DJ, Hester R, de Haan L, Franken IH. Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *Journal of psychiatry & neuroscience : JPN*. 2014; 39:149–69. [PubMed: 24359877]
- Matuskey D, Luo X, Zhang S, Morgan PT, Abdelghany O, Malison RT, Li CS. Methylphenidate remediates error-preceding activation of the default mode brain regions in cocaine-addicted individuals. *Psychiatry Res*. 2013; 214:116–21. [PubMed: 23973363]
- Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci*. 2000; 20:RC65. [PubMed: 10704519]
- Moeller SJ, Beebe-Wang N, Schneider KE, Konova AB, Parvaz MA, Alia-Klein N, Hurd YL, Goldstein RZ. Effects of an opioid (proenkephalin) polymorphism on neural response to errors in health and cocaine use disorder. *Behav Brain Res*. 2015; 293:18–26. [PubMed: 26164485]
- Moeller SJ, Honorio J, Tomasi D, Parvaz MA, Woicik PA, Volkow ND, Goldstein RZ. Methylphenidate enhances executive function and optimizes prefrontal function in both health and cocaine addiction. *Cereb Cortex*. 2014a; 24:643–53. [PubMed: 23162047]
- Moeller SJ, Konova AB, Parvaz MA, Tomasi D, Lane RD, Fort C, Goldstein RZ. Functional, structural, and emotional correlates of impaired insight in cocaine addiction. *JAMA Psychiatry*. 2014b; 71:61–70. [PubMed: 24258223]
- Moeller SJ, Parvaz MA, Shumay E, Beebe-Wang N, Konova AB, Alia-Klein N, Volkow ND, Goldstein RZ. Gene x Abstinence Effects on Drug Cue Reactivity in Addiction: Multimodal Evidence. *J Neurosci*. 2013; 33:10027–36. [PubMed: 23761898]
- Moeller SJ, Tomasi D, Honorio J, Volkow ND, Goldstein RZ. Dopaminergic involvement during mental fatigue in health and cocaine addiction. *Transl Psychiatry*. 2012a; 2:e176. [PubMed: 23092980]
- Moeller SJ, Tomasi D, Woicik PA, Maloney T, Alia-Klein N, Honorio J, Telang F, Wang GJ, Wang R, Sinha R, Carise D, Astone-Twerell J, Bolger J, Volkow ND, Goldstein RZ. Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. *Addict Biol*. 2012b; 17:1013–25. [PubMed: 22458423]
- Muller U, Suckling J, Zelaya F, Honey G, Faessel H, Williams SC, Routledge C, Brown J, Robbins TW, Bullmore ET. Plasma level-dependent effects of methylphenidate on task-related functional magnetic resonance imaging signal changes. *Psychopharmacology (Berl)*. 2005; 180:624–33. [PubMed: 15830222]
- Newsome MR, Scheibel RS, Seignourel PJ, Steinberg JL, Troyanskaya M, Li X, Levin HS. Effects of methylphenidate on working memory in traumatic brain injury: a preliminary fMRI investigation. *Brain imaging and behavior*. 2009; 3:298–305. [PubMed: 22005992]
- Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*. 2005; 25:46–59. [PubMed: 15846822]

- Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, Plessen KJ, Yu S. An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *Am J Psychiatry*. 2009; 166:1286–94. [PubMed: 19755575]
- Rubia K, Alegria AA, Cubillo AI, Smith AB, Brammer MJ, Radua J. Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Biol Psychiatry*. 2014; 76:616–28. [PubMed: 24314347]
- Rubia K, Halari R, Cubillo A, Smith AB, Mohammad AM, Brammer M, Taylor E. Methylphenidate Normalizes Fronto-Striatal Underactivation During Interference Inhibition in Medication-Naïve Boys with Attention-Deficit Hyperactivity Disorder. *Neuropsychopharmacology*. 2011a; 36:1575–1586. [PubMed: 21451498]
- Rubia K, Halari R, Mohammad AM, Taylor E, Brammer M. Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2011b; 70:255–62. [PubMed: 21664605]
- Schultz W. Dopamine signals for reward value and risk: basic and recent data. *Behav Brain Funct*. 2010; 6:24. [PubMed: 20416052]
- Schulz KP, Fan J, Bedard AC, Clerkin SM, Ivanov I, Tang CY, Halperin JM, Newcorn JH. Common and unique therapeutic mechanisms of stimulant and nonstimulant treatments for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 2012; 69:952–61. [PubMed: 22945622]
- Schweitzer JB, Lee DO, Hanford RB, Tagamets MA, Hoffman JM, Grafton ST, Kilts CD. A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology*. 2003; 28:967–73. [PubMed: 12700698]
- Schweitzer JB, Lee DO, Hanford RB, Zink CF, Ely TD, Tagamets MA, Hoffman JM, Grafton ST, Kilts CD. Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. *Biol Psychiatry*. 2004; 56:597–606. [PubMed: 15476690]
- Srinivas NR, Hubbard JW, Quinn D, Korchinski ED, Midha KK. Extensive and enantioselective presystemic metabolism of dl-threo-methylphenidate in humans. *Progress in neuro-psychopharmacology & biological psychiatry*. 1991; 15:213–20. [PubMed: 1871323]
- Swanson J, Baler RD, Volkow ND. Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology*. 2011; 36:207–26. [PubMed: 20881946]
- Tomasi D, Volkow ND. Functional connectivity hubs in the human brain. *Neuroimage*. 2011; 57:908–17. [PubMed: 21609769]
- Tomasi D, Volkow ND, Wang GJ, Wang R, Telang F, Caparelli EC, Wong C, Jayne M, Fowler JS. Methylphenidate enhances brain activation and deactivation responses to visual attention and working memory tasks in healthy controls. *Neuroimage*. 2011; 54:3101–10. [PubMed: 21029780]
- van der Schaaf ME, Fallon SJ, Ter Huurne N, Buitelaar J, Cools R. Working memory capacity predicts effects of methylphenidate on reversal learning. *Neuropsychopharmacology*. 2013; 38:2011–8. [PubMed: 23612436]
- Vanderhasselt MA, De Raedt R, Baeken C. Dorsolateral prefrontal cortex and Stroop performance: tackling the lateralization. *Psychon Bull Rev*. 2009; 16:609–12. [PubMed: 19451392]
- Volkow ND, Tomasi D, Wang GJ, Logan J, Alexoff DL, Jayne M, Fowler JS, Wong C, Yin P, Du C. Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers. *Mol Psychiatry*. 2014; 19:1037–43. [PubMed: 24912491]
- Wechsler, D. Wechsler Adult Intelligence Scale. 3. Psychological Corporation; San Antonio, TX: 1997.
- Wechsler, D. Wechsler abbreviated scale of intelligence. San Antonio, TX: Psychological Corporation; 1999.
- Wilkinson, G. The Wide-Range Achievement Test 3- Administration Manual. Wide Range Inc; Wilmington, DE: 1993.
- Woicik PA, Moeller SJ, Alia-Klein N, Maloney T, Lukasik TM, Yeliosof O, Wang GJ, Volkow ND, Goldstein RZ. The neuropsychology of cocaine addiction: Recent cocaine use masks impairment. *Neuropsychopharmacology*. 2009; 34:1112–1122. [PubMed: 18496524]

- Wong CG, Stevens MC. The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2012; 71:458–66. [PubMed: 22209640]
- Zald DH, Cowan RL, Riccardi P, Baldwin RM, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. *J Neurosci*. 2008; 28:14372–8. [PubMed: 19118170]

Figure 1. Regions of interest (A–J). Abbreviations: ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex.

Figure 2.

Associations with individual characteristics relevant to dopaminergic signaling. (A) Cocaine use disorder is associated with decreased response to methylphenidate (MPH) versus placebo in the dorsolateral prefrontal cortex (DLPFC) (Brodmann Areas 9 and 46) across all three procedures [and specifically in the drug-word (DW) task and the color-word (CW) Stroop task], but less so for resting-state functional connectivity (RSFC) density] (asterisks indicate a significant difference between groups); and (B) the greater the decrease in DLPFC MPH>placebo signal across the three fMRI procedures, the more frequently cocaine was used in the last 30 days.

Table 1

Demographics, individual difference variables, and drug use of study participants.

	Test (Between)	Cocaine N = 22	Control N = 21
Gender: Male / Female	$\chi^2=0.3$	20/2	20/1
Race: African-American / Caucasian / Other	$\chi^2=2.3$	18/4/0	15/4/2
Age (years)	$t=3.6^{**}$	46.4 ± 7.0	39.0 ± 6.5
Education (years)	$t=1.6$	13.2 ± 1.9	14.0 ± 1.5
Verbal IQ: Wide Range Achievement Test III – Scaled Score (Wilkinson 1993)	$t=1.5$	93.1 ± 9.5	98.4 ± 13.8
Non-Verbal IQ: WASI - Matrix Reasoning Scale (Wechsler 1999)	$t=0.5$	9.7 ± 2.9	10.1 ± 3.5
Depression: Beck Depression Inventory II (Beck et al. 1996)	$Z=-3.7^{***}$	7.1 ± 5.3	1.9 ± 3.6
Socioeconomic Status: Hollingshead Index	$t=0.1$	37.6 ± 9.0	37.2 ± 11.0
CAARS Total Score	$t=1.4$	9.3 ± 5.4	7.2 ± 7.4
Digit Span (Backwards)	$t=1.3$	4.5 ± 1.3	5.1 ± 1.7
Methylphenidate Plasma Levels	$t=1.7$	3.6 ± 2.0	2.7 ± 1.5
Cigarette Smokers (current or past / nonsmokers) ¹	$\chi^2=14.9^{***}$	16/6	2/18
Daily cigarettes (current smokers: N = 12 / 0)	--	8.8 ± 3.9	--
Cocaine age of onset (years)	--	26.5 ± 6.5	--
Cocaine duration of use (years)	--	16.4 ± 7.3	--
Cocaine past month use: days/week	--	3.0 ± 2.3	--
Cocaine current abstinence (min – max, median)	--	0–25, 2	--
Cocaine urine status (yes/no): Methylphenidate Placebo	--	11/11 10/12	--
Severity of Dependence Scale (0–15): Methylphenidate Placebo	--	7.1 ± 2.4 6.9 ± 2.8	--
Withdrawal symptoms: 18-item CSSA (0–126): Methylphenidate Placebo	--	17.2 ± 9.9 14.9 ± 9.1	--
Cocaine Craving: 5-item Questionnaire (0–45) : Methylphenidate Placebo ²	--	23.2 ± 12.5 20.1 ± 12.8	--

Note. All demographic information was obtained before or after all methylphenidate procedures, therefore not reflective of any methylphenidate effects;

^{**}
 $p<0.01$;

^{***}
 $p<0.001$;

¹ smoking history missing for one control participant;

² significantly different ($p<0.05$) between methylphenidate and placebo sessions;

WASI = Wechsler Abbreviated Scale of Intelligence; CAARS = Conners Adult ADHD Rating Scale; CSSA = Cocaine Selective Severity Assessment Scale; values are frequencies or means ± standard deviation.

Table 2

Generalized linear model results.

	Diagnosis (Cocaine)		CAARS ADHD Index (Continuous)		Digit Span Backwards (Continuous)		Control Variable: Methylphenidate Plasma (Continuous)	
	b (SE)	P	b (SE)	P	b (SE)	P	b (SE)	P
Regions of Interest (Participant Ns)								
1. ACC (20 CUD, 19 HC)	-0.21 (0.22)	0.35	-0.00 (0.01)	0.85	0.05 (0.06)	0.38	0.04 (0.06)	0.49
2. Midcingulate (20 CUD, 19 HC)	-0.37 (0.24)	0.14	0.01 (0.02)	0.75	-0.04 (0.08)	0.58	0.06 (0.08)	0.43
3. DLPFC (20 CUD, 19 HC)	-0.63 (0.17)	<0.001*	0.01 (0.03)	0.67	-0.03 (0.05)	0.55	-0.07 (0.06)	0.23
4. Medial OFC (20 CUD, 19 HC)	-0.06 (0.21)	0.77	-0.03 (0.01)	0.048+	0.01 (0.05)	0.85	0.15 (0.07)	0.023+
5. Lateral OFC (20 CUD, 19 HC)	0.08 (0.22)	0.73	-0.02 (0.02)	0.27	-0.01 (0.07)	0.87	-0.00 (0.05)	0.96
6. Thalamus (20 CUD, 19 HC)	0.01 (0.24)	0.97	0.01 (0.05)	0.86	-0.05 (0.07)	0.47	-0.01 (0.05)	0.86
7. Midbrain (20 CUD, 19 HC)	0.48 (0.19)	0.010+	-0.02 (0.01)	0.24	0.05 (0.06)	0.40	-0.23 (0.05)	<0.001*
8. Caudate (20 CUD, 18 HC)	0.21 (0.23)	0.37	0.00 (0.01)	0.99	-0.05 (0.08)	0.56	-0.04 (0.07)	0.60
9. Putamen (20 CUD, 19 HC)	0.02 (0.26)	0.93	-0.02 (0.02)	0.22	-0.08 (0.06)	0.24	-0.06 (0.07)	0.36
10. Hippocampus (20 CUD, 19 HC)	-0.01 (0.29)	0.97	-0.01 (0.02)	0.65	0.01 (0.08)	0.90	-0.07 (0.07)	0.31

Note. Numbers represent unstandardized regression coefficients (*b*), with associated standard errors (*SE*); for diagnosis, healthy controls are the reference group [i.e., a negative slope indicates decreased methylphenidate (versus placebo) response in cocaine participants]; for the continuous variables, negative slopes indicate that methylphenidate (versus placebo) response is associated with less ADHD symptomatology, less working memory, and less methylphenidate plasma levels, respectively;

* $p < 0.001$,

+ $p < 0.05$ (possible interesting effects to follow up on in future studies);

CUD = individuals with cocaine use disorder; HC = healthy control; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex.