Published in final edited form as:

Psychiatry Res. 2013 November 30; 214(2): . doi:10.1016/j.psychres.2013.06.009.

Methylphenidate remediates error-preceding activation of the default mode brain regions in cocaine addicted individuals

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Abstract

Many previous studies suggest the potential of psychostimulants in improving cognitive functioning. Our earlier pharmacological brain imaging study showed that intravenous methylphenidate (MPH) improves inhibitory control by altering cortico-striato-thalamic activations in cocaine dependent (CD) individuals. Here we provide additional evidence for the effects of MPH in restoring cerebral activations during cognitive performance. Ten CD individuals performed a stop signal task (SST) during functional magnetic resonance imaging (fMRI) in two sessions, in which either MPH (0.5 mg/Kg BW) or saline was administered intravenously. In the SST, a frequent go signal instructs participants to make a speeded response and a less frequent stop signal instructs them to withhold the response. Our previous work described increased activation of the precuneus/posterior cingulate cortex and ventromedial prefrontal cortex – regions of the default mode network (DMN) – before participants committed a stop error in healthy control but not CD individuals (Bednarski et al., 2011). The current results showed that, compared to saline, MPH restored error-preceding activations of DMN regions in CD individuals. The extent of the changes in precuneus activity was correlated with MPH-elicited increase in systolic blood pressure. These findings suggest that the influence of MPH on cerebral activations may extend beyond cognitive control and provide additional evidence warranting future studies to investigate the neural mechanisms and physiological markers of the efficacy of agonist therapy in cocaine dependence.

Keywords

stimulants; catecholamine; cognitive control; default mode network; fMRI

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1. Introduction

Deficits in self-control have frequently been implicated and represent a potential therapeutic target in cocaine dependence (Goldstein and Volkow, 2002; Garavan and Hester, 2007; Everitt et al., 2008; Li and Sinha, 2008; de Wit, 2009). One such method to test self-control, a stop signal task (SST), has demonstrated altered cerebral activations during inhibitory control and error processing in patients with cocaine and other stimulant misuse (Fillmore and Rush, 2002; Monterosso et al., 2005; Li et al., 2006; Colzato et al., 2007; Li et al., 2008; 2010a; Li and Sinha, 2008). In particular, we showed in a previous pharmacological fMRI study that intravenous administration of methylphenidate (MPH) improves inhibitory control concomitant with changes in prefrontal and striato-thalamic activations in non-treatment seeking cocaine using individuals (Li et al., 2010b). These latter findings provide support for the efficacy of psychostimulants in remediating self-control in cocaine addicts (Kosten et al., 2002; Castells et al., 2007; Moeller et al., 2008; Vansickel et al., 2008; Sofuoglu, 2010).

In the current study, we intend to provide additional evidence that MPH could restore cerebral activations in cognitive functioning. Using a new analysis of previously published fMRI data (Li et al., 2010b), we examined error-preceding regional activations in the SST of non-treatment seeking cocaine using individuals. In the SST, a frequent “go” signal instructs participants to make a response while a less frequent stop signal instructs them to refrain from making the response. Lapses in sustained attention will lead to unmonitored responses and stop errors, as were demonstrated in other behavioral paradigms (Weissman et al., 2006). Such attentional lapses are reported to involve increased activation of brain regions from the default mode network (DMN), an array of functionally connected cortical regions that respond more to resting or non-goal directed conditions than to environmental stimuli or task based conditions (Raichle and Snyder, 2007; Fox et al., 2009).

For instance, a previous fMRI study showed that in healthy individuals the precuneus/posterior cingulate cortex and ventromedial prefrontal cortex – key structures of the DMN – increased in activation during the “go” trials preceding stop errors, as compared to those preceding stop successes (Li et al., 2007), suggesting that DMN activation predicts performance errors. Furthermore, these error-preceding activities were diminished in cocaine dependent individuals and the extent of this altered error-preceding activation was linearly correlated with years of cocaine use (Bednarski et al., 2011). It is not known whether this dysfunction of the DMN can be remediated with pharmacologic treatment in cocaine-addicted individuals. The current study addresses this question by examining whether, in contrast to saline placebo, MPH can restore these error-preceding cerebral activations in the DMN of this population.

2. Methods

2.1 Subjects and informed consent

Ten non-treatment seeking volunteers (8 men; 39.9 ± 5.5 years of age) with cocaine dependence (CD) participated in the study. CD volunteers met criteria for current cocaine dependence (Diagnostic and Statistical Manual or DSM-IV, American Psychiatric Association, 1994). The sample had an average of 18.3 ± 7.9 years of cocaine use, with 9 predominantly smoking and 1 preferring intranasal use of cocaine. All subjects were cigarette smokers and all except one used alcohol with the amount ranging from 1-2 drinks per week to 2-3 drinks per day (none meeting DSM-IV criteria for dependence). Recent cocaine use was confirmed by urine toxicology screens upon admission. Participants were drug-free for a minimum of 5 days and an average of 7.6 days while staying in an inpatient unit prior to the current fMRI study. All subjects were right handed and physically healthy with no major medical illnesses or current use of prescription medications. All subjects

denied a history of head injury or neurological illness. Other exclusion criteria included dependence on another psychoactive substance (except nicotine) or past history of any substance abuse/dependence (except nicotine) and current or past history of psychotic disorders. Individuals with current depressive or anxiety symptoms requiring treatment or currently being treated for these symptoms were excluded as well. The Human Investigation committee at Yale University School of Medicine approved all study procedures, and all subjects signed an informed consent prior to study participation.

2.2 Procedures of physiological assessments and fMRI

Each subject participated in two sessions, in which either saline (placebo) or MPH (0.5 mg/kg of body weight) was injected intravenously, approximately 45 minutes prior to fMRI. The two sessions were scheduled 48 hours apart, the order of which was counter-balanced across subjects, with 5 subjects participating in the placebo session first. On the day of fMRI, a research nurse confirmed study consent of the patient before setting up an intravenous line and electronic monitoring of heart rate and blood pressure. Heart rate and blood pressure recording continued every five minutes for 30 minutes after the injection and, after the patients were transported to the scanner, every ten minutes until approximately 30 minutes after completion of imaging. Patients continued to be closely monitored for six hours after they returned to the inpatient unit. No adverse events occurred throughout the entire study.

2.3 Behavioral task

We employed a simple reaction time task in this stop-signal paradigm (Figure 1; Chao et al., 2009; Li et al., 2009; Logan et al., 1984). There were two trial types: “go” and “stop,” randomly (not pseudo-randomly) intermixed. Thus, a stop trial could appear after a stop trial or any intervening number of go trials. A small dot appeared on the screen to engage attention at the beginning of a go trial. After a randomized time interval (fore-period) ranging between 1 and 5 s (Li et al., 2005), the dot turned into a circle (the “go” signal), prompting the subjects to quickly press a button. The circle vanished at a button press or after 1 s had elapsed, whichever came first, and the trial terminated. A premature button press prior to the appearance of the circle also terminated the trial. Approximately three quarters of all trials were go trials. The remaining one quarter were stop trials. In a stop trial, an additional “X,” the “stop” signal, replaced the go signal and prompted the subjects to withhold the button press. Likewise, a trial terminated at button press or when 1 s had elapsed since the appearance of the stop signal. The stop signal delay (SSD) – the time interval between the go and stop signal – started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing or decreasing by 64 ms each after a stop success or stop failure (Levitt, 1971). There was an inter-trial-interval of 2 s. Figure 2 shows the distribution of the inter-onset times of the stop trials. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up in a small number of trials. Prior to the fMRI study each subject had a practice session outside the scanner. In the scanner each subject completed four 10-min runs of the task. Depending on the actual stimulus timing (trials varied in fore-period duration) and speed of response, the total number of trials varied slightly across subjects in an experiment. With the staircase procedure we anticipated that the subjects would succeed in withholding their response in approximately half of the stop trials. For each individual subject, we computed a critical SSD – the time delay required for one to succeed in half of the stop trials – and estimated the stop signal reaction time (SSRT) as an index of the capacity of response inhibition, on the basis of the race model (Logan et al., 1984). The SST is used extensively to study the component processes of cognitive control both in health and disease in our earlier work (Farr et al., 2012; Hendrick et al., 2010; Hu and Li, 2012; Hu et al., 2012; Ide and Li, 2011a;

2011b; Ide et al., 2013; Li et al., 2006; Li et al., 2009; Luo et al., 2013; Winkler et al., 2013; Zhang and Li, 2012).

2.4 Imaging protocol

Conventional T₁-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC-PC line with TR = 300 ms, TE = 2.5 ms, bandwidth = 300 Hz/pixel, flip angle = 60°, field of view = 220 × 220 mm, matrix = 256 × 256, 32 slices with slice thickness = 4mm and no gap. Functional, blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient echo echo-planar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with TR = 2,000 ms, TE = 25 ms, bandwidth = 2004 Hz/pixel, flip angle = 85°, field of view = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4mm and no gap. Three hundred images were acquired in each run for a total of 4 runs.

2.5 Data analysis and statistics

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Images from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between RF pulsing and relaxation. Images of each individual subject were realigned (motion-corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject for each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image, based on a mutual information criterion, and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation (Friston et al., 1995a; Ashburner and Friston, 1999). Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum. These procedures are described in detail in the SPM8 manual (Ashburner and the FIL Methods Group, 2013).

Four main types of trial outcome were first distinguished: go success (G), go error (F), stop success (SS), and stop error (SE) trial (Figure 1). G trials were further divided into those that preceded a G (preG), SS (preSS), or SE (preSE) trial. A statistical analytical design was constructed for each individual subject, using the general linear model (GLM) with the onsets of go signal in each of these trial types convolved with a canonical hemodynamic response function (HRF) and with the temporal derivative of the canonical HRF and entered as regressors in the model (Friston et al., 1995b). Additional regressors with the go trial reaction time and stop trial SSD were included for parametric modulation. The inclusion of temporal derivative of the HRF and the parametric modulators improved fit of the GLM. The GLM estimates the component of variance explained by each of the regressors, with the coefficient of each regressor constituting a beta image. The beta image reflects the height of average activation across trials for a particular event, while the beta image of the parametric modulator regressor informs how well the residual fluctuations in the BOLD signal co-vary with the parametric modulator for the event (Glascher, 2009). We employed stringent head restraint during fMR scanning. The average head motion was 0.297 mm during placebo and 0.279 mm during the MPH session (translation) and 0.138° during placebo and 0.181° during the MPH session (rotation). No subjects showed a translational motion greater than 0.9 mm in any dimension or rotational motion greater than 0.7° around any axis and subjects did not show differences in head movement between the two sessions either in translation ($p=0.68$, paired-sample t test) or in rotation ($p=0.29$). Nonetheless, realignment parameters in all 6 dimensions were also entered in the model. The data were high-pass filtered (1/128

Hz cutoff) to remove low-frequency signal drifts. Serial autocorrelation was corrected by a first-degree autoregressive or AR (1) model.

We constructed for each individual subject a contrast $\text{preSE} > \text{preSS}$ to assess regional processes that preceded errors. In group-level, random effects analyses, regional brain activations of $\text{preSE} > \text{preSS}$ were evaluated with one-sample *t* test separately for the placebo and MPH session. The effects of MPH versus saline placebo were examined using a flexible factorial with the order of MPH administration entered as a factor. In addition to the whole brain voxelwise analysis, we also examined the significance of the regional brain activations using small volume correction for two masks obtained from our previous study of a large sample of subjects (Li et al., 2007): spheres with 15 mm in radius centered on posterior cingulate cortex/precuneus ($x=-16$, $y=-60$, $z=32$) and ventromedial prefrontal cortex ($x=4$, $y=32$, $z=4$).

We used MarsBaR (a toolbox available for SPM8; Brett et al., 2002) to compute for each individual subject the effect size of activity change for the regions of interest derived from group analyses. The effect size rather than mean difference in brain activity was derived for correlation with behavioral and clinical measures in order to account for individual differences in the variance of the mean. The effect size measures of regional brain activation were correlated across subjects with the difference in the changes (from baseline) in heart rate, systolic, and diastolic blood pressure.

3. Results

3.1 Methylphenidate elicited changes in heart rate and blood pressure

In the MPH as compared to saline placebo session, CD volunteers showed an increase in heart rate ($Z=2.803$, $p=0.005$ during the first 30 minutes after injection; and $Z=2.803$, $p=0.005$ during fMRI; two-tailed paired-sample Wilcoxon signed rank test), systolic blood pressure ($Z=2.803$, $p=0.005$; and $Z=2.703$, $p=0.007$), and diastolic blood pressure ($Z=2.701$, $p=0.007$; and $Z=2.293$, $p=0.022$), as described in our previous work (Li et al., 2010b).

3.2 Behavioral performance and regional brain activations

The results of behavioral performance were described in detail earlier (Li et al., 2010b). Briefly, compared to saline placebo, MPH decreased the SSRT (i.e., improved response inhibition; 182 ± 38 vs. 238 ± 41 ms, $p<0.0025$, two-tailed paired sample *t* test) but not any other aspects of stop signal performance.

With administration of saline placebo, CD individuals showed increased activation of the right inferior insula ($x=45$, $y=2$, $z=-14$, $Z=4.11$, 64 voxels; Figure 2, top panel) at $p<0.001$, uncorrected. With MPH, CD individuals showed increased activation of the ventromedial prefrontal cortex (in the area of the subgenual anterior cingulate, $x=-3$, $y=17$, $z=-8$, $Z=4.44$, 75 voxels) and precuneus ($x=0$, $y=-64$, $z=28$, $Z=3.82$; 433 voxels, Figure 2, middle panel). A flexible factorial analysis was performed to examine the main effect of MPH vs. placebo with session order as a covariate. In this analysis there was greater activation in the precuneus ($x=0$, $y=-64$, $z=31$, $Z=3.35$, 68 voxels) and ventromedial prefrontal cortex ($x=3$, $y=17$, $z=-11$, $Z=3.45$, 37 voxels) during the MPH as compared to saline session (Figure 2, bottom panel). This precuneus cluster survived $p<0.05$, corrected for family-wise error of multiple comparisons in a small volume correction analysis using a mask obtained from our earlier study (Li et al., 2007; see Methods). There was no correlation between the changes in precuneus activations and the changes in SSRT ($p=0.168$, Pearson regression).

3.3 Correlation between changes in regional brain activations and cardiovascular measures elicited by MPH

In linear regressions, the change in activation during preSE>preSS of the precuneus was positively correlated with the change in systolic blood pressure ($p=0.013$, $R=0.746$, Pearson regression), but not diastolic pressure ($p=0.225$) or heart rate ($p=0.809$), across subjects.

4. Discussion

The current study showed that MPH restored error-preceding activations of the default mode network in the cerebral cortex of CD individuals. These activations were found for go trials at a time before stop errors were committed on the SST and included the precuneus and ventromedial prefrontal cortex (in the area of the subgenual anterior cingulate cortex). These areas have previously been shown to fail to increase in activity preceding stop errors, with the extent of altered activity correlated with years of cocaine use, in CD individuals, when compared to healthy individuals (Bednarski et al., 2012). These findings are consistent with previous work that found task-based hypoactivations in the ventromedial prefrontal cortex of CD individuals that were independent of performance in an emotional saliency task (Goldstein et al., 2009) and were partially corrected following oral MPH (Goldstein et al., 2010). Altogether, these effects of MPH may signal a normalization of neural processes in multiple cognitive domains in CD individuals.

In our previous study, we reported that, as compared to saline placebo, MPH elicited ventromedial prefrontal activation during stop success in contrast to stop error trials, which were inversely correlated with the changes in systolic blood pressure and SSRT (Li et al., 2010b). These latter results contrast with the current findings of greater MPH-elicited error-preceding activations of the ventromedial prefrontal cortex. This seeming discrepancy speaks to the importance of distinguishing the psychological constructs and model contrasts that underlie these regional activities. The current findings derived from a comparison between pre-stop error and pre-stop success go trials and the previous results were between stop success and error trials. These contrasts involved distinct events and, therefore, psychological constructs. The contrast between stop success and stop error trials (the previous study) involved attentional monitoring and response inhibition and the major finding that MPH-elicited activations of the ventromedial prefrontal cortex negatively correlated with SSRT suggested that decreased activation of this DMN region is associated with greater self control and improved SSRT. The current study, however, used a contrast between pre-stop error and pre-stop success go trials that examined the cognitive state prior to the occurrence of an error. The greater activation of this DMN region suggested less attention to the environmental event, a process that may lead to the occurrence of errors. Thus, the processes highlighted in these papers are distinct but share the commonality of understanding MPH activation on prefrontal cortical activity across the stop signal task in CD individuals.

MPH influences catecholaminergic neurotransmission by binding to the dopamine and norepinephrine transporters. While little is known about noradrenergic effects on the DMN, one possible mechanism of the modulatory effects of MPH on the DMN is through the dopaminergic pathways (Kelly et al., 2009; Tomasi et al., 2009; Sambataro et al., 2011). Studies in healthy people have documented dopaminergic modulation of DMN activity through apomorphine (Nagano-Saito et al., 2009), L-DOPA (Kelly et al., 2009), MPH (Tomasi et al., 2011), and transient dopamine depletion (Nagano-Saito et al., 2008). For instance, oral MPH increased activation in the dorsal attentional network and deactivation in the posterior cingulate cortex in healthy men performing working memory and visual attention tasks (Tomasi et al., 2011). Additionally, recent studies of genetic variations in DA transporter binding (Tomasi et al., 2009), catechol-*O*-methyl transferase (Liu et al., 2010)

and dopamine D2 receptor (Sambataro et al., 2011) have provided convergent evidence for functional effects of dopamine on the DMN circuit.

Clinical conditions that have dopamine dysfunction as one of their cardinal features offer another venue to examine the role of dopaminergic signaling in the DMN. In Parkinson's disease, patients have less central activating dopamine and most studies have shown a less deactivated DMN, or even a reversal of the activation/deactivation pattern in the DMN during executive functions (Van Eimeren et al., 2009). L-Dopa administration has been found to partially restore the DMN activity in patients with Parkinson's disease (Delaveau et al., 2010). Similarly, in attention deficient hyperactivity disorder, lapses of attention are associated with attenuated deactivation of DMN, which is normalized by MPH or task-related motivational incentives (Peterson et al., 2009; Liddle et al., 2011).

Taken as a whole, these studies highlight the critical importance of dopamine in regulating DMN activity. The current study supports these findings and expands the effects of dopamine related DMN activity to include CD individuals.

An additional finding was an increase in systolic blood pressure that correlated with change in precuneus activity as elicited by MPH. This results is consistent with a role for the central nervous system (CNS) in mediating the cardiovascular effects of stimulants (Vongpatanasin et al., 1999; Tuncel et al., 2002) as well as neuroimaging findings of a correlation between CNS (e.g., stimulant-induced dopamine release as measured by positron emission tomography) and cardiovascular measures (e.g., stimulant-induced increases in systolic blood pressure) as a result of stimulant administration (Volkow et al., 1993). This finding is of potential interest as it suggests changes in systolic blood pressure as a biomarker for MPH response, as described earlier (Li et al., 2010b).

A number of limitations need to be considered for the study. The small sample size and the use of uncorrected threshold indicated that the current results need to be replicated. Second, MPH blocks both dopamine and norepinephrine transporters. Therefore, we cannot rule out a role of noradrenergic neurotransmission in the effects of MPH. Furthermore, while the dopamine hypothesis discussed remains a plausible explanation for these findings, these are descriptive results with the mechanistic link remaining to be firmly established. Third, stimulants can potentially influence fMRI blood oxygenation level-dependent (BOLD) signals, which depend on the hemodynamic coupling of neuronal activities and local changes in blood flow and oxygenation. However, a number of earlier studies have suggested that stimulants decreased cortical cerebral blood flow but did not obscure BOLD signals (Gollub et al., 2008; Rao et al., 2000), and that hemodynamic responses were faithfully followed by neuronal responses after their peak effects (at 6 minutes after administration) on blood flow and volume (Davonshire et al., 2004). Heart rate also had no effect on BOLD signals in one of these studies (Rao et al., 2000); nevertheless, factors such as this could potentially confound some of the current results. Finally, it was not within the scope of this paper to examine whether these findings have clinical relevance for CD. Additional research is needed by investigating whether this normalized pattern of brain activations can be sustained after a longer period of oral treatment with stimulant mediations and related to clinical outcome measures (e.g. craving, length of abstinence and impulsivity) in a longitudinal study.

Acknowledgments

This study was supported by NIH grants R03DA022395 (Li), K02DA026990 (Li), T32 MH019961 (Matuskey/Malison), K24-DA017899 (Malison) and CTSA Grant UL1 RR024139 (Robert Sherwin) from the National Center for Research Resources (NCRR) and NIH Roadmap for Medical Research. The study also receives partial support from the State of Connecticut. The content is solely the responsibility of the authors and does not necessarily

represent the official views of the National Institute of Drug Abuse, NCRR or the National Institutes of Health. We thank Andreas Rodrigues and Nikkia Moss for their assistance in patient recruitment and staff at the Clinical Neuroscience Research Unit, Connecticut Mental Health Center, Connecticut Department of Mental Health and Addiction Services for their inpatient care. We are also grateful to Bill Hoffman and Anne O'Connor of the Yale Clinical Center of Investigation and staff at the Hospital Research Unit for their coordination and nursing support.

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Figure 1.

(a) stop signal paradigm. In “go” trials (~75%) observers responded to the go signal (a circle) and in “stop” trials (~25%) they had to withhold the response when they saw the stop signal (an X). In both trials the go signal appeared after a randomized time interval between 1 to 5 seconds (the fore-period or FP, uniform distribution) following the appearance of the fixation point. The stop signal followed the go signal by a time delay – the stop signal delay (SSD). The SSD was updated according to a staircase procedure, whereby it increased and decreased by 64 ms following a stop success and stop error trial, respectively. We distinguished go success, go error, stop success and stop trials during the task. (b) Go successes were further distinguished by their subsequent trial; thus G trials followed by a G, SS, and SE trial were indicated by pre-G, pre-SS, and pre-SE trials, respectively.

Figure 2.

Regional brain activations prior to errors (pre-stop error go trials > pre-stop success go trials) during placebo (top panel) and methylphenidate (MPH, middle panel) administration. A flexible factorial analysis showed the difference between MPH and placebo sessions (bottom panel). Color bar represents voxel T value.