Methylphenidate Effects on Neural Activity During Response Inhibition in Healthy Humans

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Methylphenidate (MPH) is a catecholamine transporter blocker, with dopamine agonist effects in the basal ganglia. Response inhibition, error detection, and its mediating frontostriatal brain activation are improved by MPH in patients with attention-deficit/hyperactivity disorder. However, little is known about the effects of MPH on response inhibition and error processing or its underlying brain function in healthy individuals. Therefore, this study employed functional magnetic resonance imaging (fMRI) and 2 response inhibition tasks in 52 healthy males. Subjects underwent fMRI during a go/no-go task and a tracking stop-signal task after administration of 40 mg MPH and placebo in a double-blind, placebo-controlled, repeated-measures design. Results revealed task- and condition-specific neural effects of MPH: it increased activation in the putamen only during inhibition errors but not during successful inhibition and only in the go/no-go task. We speculate that task specificity of the effect might be due to differences in the degree of error saliency in the 2 task designs, whereas errors were few in the go/no-go task and thus had high saliency and the stop-signal task was designed to elicit 50% of errors in all subjects, diminishing the error saliency effect. The findings suggest that neural MPH effects interact with the saliency of the behavior under investigation.

Keywords: dopamine, fMRI, human, methylphenidate, response inhibition

Introduction

Methylphenidate is a catecholamine reuptake inhibitor that predominantly blocks dopamine transporters in the basal ganglia, leading to enhanced striatal dopamine availability. In frontal regions, methylphenidate blocks both dopamine and noradrenaline transporters, leading to enhanced availability of both catecholamines (Arnsten 2006a; Volkow et al. 2009). Methylphenidate is the treatment of choice for attention-deficit/hyperactivity disorder (ADHD) (Greenhill et al. 1999; Müller 2008). The therapeutic effects of methylphenidate are thought to be due to its increasing extracellular levels of noradrenaline and dopamine in the brain, particularly of striatal dopamine (Volkow et al. 2001), a neurotransmitter linked in cognition (Nieoullon 2002), reward, and motivation (Schultz 2002), as well as motor response inhibition (Hershey et al. 2004).

Motor response inhibition is the ability to inhibit reflexive or inappropriate motor actions (Mostofsky and Simmonds 2008). Poor motor response inhibition is observed in ADHD on the go/no-go and stop-signal tasks (Willcutt et al. 2005; Alderson et al. 2007; Rubia, Smith, Taylor, Brammer 2007). Evidence for impairment in other inhibitory tasks such as interference inhibition is less consistent (van Mourik et al. 2005; Lansbergen et al. 2007).

The go/no-go and stop-signal tasks share the requirement to suppress a contextually inappropriate prepotent motor response and activate frontostriatal neural circuitry (Rubia et al. 2001; Rubia, Smith et al. 2003; Rubia et al. 2006; Rubia, Smith, Taylor, Brammer 2007; Garavan et al. 2002). However, there are also factors on which the tasks differ. The go/no-go task requires responding on frequent go trials and inhibiting this response on infrequent no-go trials. The go or no-go signal is always presented at the beginning of the trial, indicating immediately whether a response or nonresponse is required. The task thus measures selective inhibition in the context of response selection. In contrast, the stop-signal task requires inhibiting responses to a stop signal presented unexpectedly shortly after some of the go stimuli. Therefore, the subject does not know at the beginning of the trial whether the go signal is a “true” go signal and needs to be responded to or is converted into a “no response” signal by the subsequent stop signal. The stop-signal task, therefore, measures a later, more challenging inhibitory process, that is, the retraction of a motor response that is triggered by the go signal and already on its way to execution (Rubia et al. 2001).

There is also likely a difference in error-processing mechanisms between the tasks due to differences in error frequency. In the tracking version of the stop-signal task (Verbruggen and Logan 2009), the delay at which the stop signal appears after the go signal is individually adjusted so as to achieve a 50% rate of successful inhibition. Therefore, response errors cannot be avoided in about half the stop trials and consequently occur relatively frequently. In comparison, response suppression in the go/no-go task is entirely under the control of the subject; in healthy samples, the task typically yields a relatively low error rate, meaning that errors are highly salient. Errors represent violation of reward prediction. When a reward is smaller than predicted or fails to occur, activity in dopamine neurons is inhibited (Schultz et al. 1997), and the inhibitory dopamine signaling suppresses future actions that result in punishment (Bromberg-Martin et al. 2010). Therefore, although a similar and domain-independent error detection mechanism may be active in both tasks, there are likely to be differences in the dopaminergic error-processing mechanisms between the 2 tasks due to differences in the saliency of errors and the level of control the subject has over them.

The present study investigated the effects of methylphenidate on motor response inhibition and the neural networks underlying inhibition as well as error processing. Methylphenidate improves motor response inhibition (Trommer et al.
ADHD (Epstein et al. 2007; Lee et al. 2009) as well as error processing and performance monitoring (Krusch et al. 1996; Groen et al. 2009) in the go/no-go and stop-signal tasks in ADHD. Functional magnetic resonance imaging (fMRI) studies have shown that these improvements are associated with upregulation of inferior frontostriatal inhibitory (Vaidya et al. 1998; Epstein et al. 2007; Rubia, Halari, Cubillo et al. 2011) as well as with striatal error-processing networks (Rubia, Halari, Mohammad et al. 2011).

However, despite this evidence from ADHD and the widespread use of response inhibition paradigms in cognitive and clinical neuroscience (Aron and Poldrack 2005; Aron 2007; Eagle et al. 2008), only few studies have investigated methylphenidate effects on motor response inhibition in healthy subjects (Turner et al. 2003; Nandam et al. 2011) and only one study has investigated methylphenidate effects on the neural correlates of motor response inhibition in healthy children (Vaidya et al. 1998), which, however, does not easily extrapolate to adults, given developmental influences on both inhibitory control (Durston et al. 2002) and dopamine signaling (Seeman et al. 1987). No study has investigated the neural mechanisms of methylphenidate effects on motor response inhibition and response error processing in healthy adults. Such a study would be important not only to better understand this clinically relevant compound but also to further our understanding of the neurotransmitter mechanisms underlying cognitive control. Although patient studies are useful in this regard, factors such as clinical heterogeneity, comorbidity, interfering symptoms, and long-term medication may confound experimental effects; these can be circumvented in studies of healthy subjects (Berto et al. 2000; Koren 2003).

Therefore, we used fMRI and the stop-signal and go/no-go tasks to investigate methylphenidate effects on the neural networks of successful and erroneous motor response inhibition in healthy males. We hypothesized that the neural effect of methylphenidate would be primarily in the striatum, where the largest amount of dopamine transporters is located (Arnsten 2006b), with additional effects in frontal regions. Additionally, we hypothesized that methylphenidate would improve performance as previously shown in individuals with ADHD (Epstein et al. 2007; Lee et al. 2009) and healthy subjects (Nandam et al. 2011).

Materials and Methods

Subjects
Subjects were recruited through advertisements placed around the community and universities. The recruitment criteria were male gender, between 18 and 45 years old, nonsmokers, right-handed, of European origin, good command of the German language, and physically, neurologically, and psychiatrically healthy. All potential subjects were first prescreened by telephone. If they fulfilled the general study criteria, they were invited to participate in the baseline screening session that included an electroencephalogram, an electrocardiogram, a blood test, and a detailed interview to exclude any psychiatric, neurological, and medical illness, including alcohol and drug abuse. Other exclusion criteria were current consumption of prescription or over-the-counter medication, current or recent (within the last 12 months) use of drugs, metallic implants, and claustrophobia. They were asked to refrain from alcohol 24 h prior to each study appointment. Additionally, subjects had to also refrain from consuming caffeine before the appointment on the days when they were scanned. The study was approved by the local Ethics Committee, and all subjects provided written informed consent and received monetary compensation for their participation.

Study Design and Procedure
A randomized, double-blind, placebo-controlled design was used. Each subject was scanned twice, approximately 1 week between the 2 sessions. During each test session, 2 capsules containing either an oral dose of 40 mg of methylphenidate or placebo (lactose) was administered to the subject. The chosen dose is comparable to doses reported in previous studies investigating methylphenidate effects in healthy subjects (Mehta et al. 2000; Volkow et al. 2001; Dodds et al. 2008; Clatworthy et al. 2009; Schlosser et al. 2009; Finke et al. 2010). Furthermore, according to NICE guidelines (www.nice.org.uk), methylphenidate medication for adults is typically titrated for each subject’s responsiveness and side effects from a minimum of 15 mg to a maximum of 100 mg. Therefore, 40 mg is within the typical clinical range of drug administration. After capsule administration, the subjects relaxed in a waiting room, where they were allowed to do activities such as read, listen to music, or work on their laptop. Subjects were not allowed to eat or drink, with the exception of water, during the waiting period. The fMRI scan started 60 min after capsule administration. Before scanning, on each session, subjects had to carry out a practice test of both tasks outside the scanner. Subjects also had to fill out visual analog rating scales (VARSs) at 3 time points (before capsule administration, immediately before scan, and immediately after scan) during each session. A blood sample (one 7.5 mL tube) for methylphenidate plasma level analysis was taken by venepuncture at the end of each session.

Go/No-Go Task
The go/no-go task was implemented in an event-related design similar to that used by Chikazoe et al. (2009). Three types of trials were used: 200 go trials (77%), 30 oddball trials (11.5%), and 30 no-go trials (11.5%). Each trial consisted of a colored circle presented for 500 ms on a black background in the middle of the screen, followed by an average interstimulus interval of 1500 ms (jittered between 1100 and 1500 ms) where only the black background was shown. Go trials were indicated by a gray circle, and no-go and oddball trials were indicated by yellow or blue circles. The circle color for the no/go and oddball trials was counterbalanced across subjects.

The purpose of the oddball trials was to allow the investigation of the inhibition process independent of the confounds of the visuospatial attentional “oddball effect” of the processing of low frequency no-go relative to the high frequency go trials. The order of the trials was quasi-randomized with at least 3 go trials between no-go and oddball trials and between no-go trials. Subjects had to press a button with their right index finger on go trials and oddball trials, but had to withhold the button press on no-go trials. The whole task lasted 7 min 59 s. The dependent variables were the percentage of incorrect no-go, go, and oddball trials and the mean reaction times (MRTs) and the intra-individual coefficient of variation (ICV) of RTs during incorrect no-go, correct go, and correct oddball trials. The ICV was calculated using the following formula: ICV = standard deviation (SD) go RT/RT.

Stop-Signal Task
The stop-signal task was implemented in an event-related design as described previously (Rubia, Smith et al. 2003b). There were 234 go trials and 60 no-go trials in total. Each trial consisted of a white arrow pointing right or left presented for 500 ms on a black background in the middle of the screen, followed by an average interstimulus interval of 1500 ms (jittered between 1100 and 1500 ms). The basic task was a choice RT task in which subjects had to press a left or right button with the index or middle finger, respectively, of the right hand corresponding to the direction of the arrow (go trials). In 20% of the trials, pseudorandomly interspersed, the go signals are followed unpredictably (about 250 ms later) by arrows pointing upwards (stop
signals). Subjects had to inhibit their motor responses on these trials. The initial interval between go and stop stimulus was 250 ms. A tracking algorithm then adapted this time interval according to each subject's performance by recalculating the percentage of correct stop trials after each stop trial. The time interval between go and stop signal (stop-signal delay) increased by 50 ms when the subjects' overall inhibition was higher than 50%, making the task more difficult, or decreased by 50 ms when the percentage of inhibition was lower than 50%, making the task easier for the subject. The algorithm elicited about 50% successful and 50% failed stop trials for each subject. 

All performance variables from the go/no-go and stop-signal tasks were calculated using the effect size estimator partial η². Effect sizes for the repeated-measures ANOVA were calculated using the effect size estimator partial η² (before capsule administration, before scan, and after scan) as within-subject factors. Effect sizes for the repeated-measures ANOVA were calculated using the effect size estimator partial η².

**Behavioral Data Analysis**

All performance variables from the go/no-go and stop-signal tasks were analyzed with paired 2-tailed t-tests to compare performance between drug and placebo. Effect sizes for the t-tests were calculated using Cohen's d. Each item on the VARS was analyzed with a within-subject 2 × 3 (Drug × Time) repeated-measures analysis of variance (ANOVA), with Drug (methylphenidate and placebo) and Time (before capsule administration, before scan, and after scan) as within-subject factors. Effect sizes for the repeated-measures ANOVA were calculated using the effect size estimator partial η².

**fMRI Data Acquisition and Analysis**

T2*-weighted whole-brain MR echo planar images of the blood oxygenation level-dependent (BOLD) response were collected on a Siemens Verio scanner at 3 T field strength. About 264 and 298 functional images were acquired for the go/no-go and stop-signal tasks, respectively, with a repetition time (TR) of 1.8 s on each task. The first 4 volumes were discarded to allow for establishment of steady-state longitudinal magnetization. Each image volume compromised 28 axial slices, each 4 mm thick with an interslice gap of 0.8 mm and an in-plane resolution of 3 × 3 mm. For each sequence, the flip angle was 80° and echo time (TE) was 30 ms. Slices were acquired in the ascending sequence (inferior to superior) parallel to the AC-PC line.

Imaging data were preprocessed and analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB R2008a (The MathWorks Inc.). All images were aligned to the first image in the time series, normalized to the Montreal Neurological Institute (MNI) template, and spatially smoothed using an 8 mm full-width half-maximum Gaussian filter. The data were high-pass filtered (128 s), and the onsets of the stimuli were modeled as events. For the go/no-go task, the conditions (1) successful no-go trials, (2) unsuccessful no-go trials, (3) correct oddball trials, (4) incorrect oddball trials, and (5) incorrect go trials were modeled using a synthetic canonical hemodynamic response function. The data for the stop-signal task were similarly modeled for the conditions (1) successful stop trials, (2) unsuccessful stop trials, and (3) incorrect go trials. For all conditions, we modeled the onsets of the trials and not the responses, if any occurred. Go trials on both tasks were not included in the model and served as a baseline (see e.g. Chamberlain et al. 2009; Chikazoe et al. 2009). Individual realignment parameters were included in the model as multiple regressors.

For each task, we focussed on the BOLD data underlying successful and unsuccessful inhibition. The analysis of these data used a within-subject 2 × 2 full factorial model with Drug (methylphenidate and placebo) and Condition (successful inhibition and unsuccessful inhibition) as factors, separately for each task. Incorrect oddball or go trials on the go/no-go task were not analyzed at the second level due to the small number of responses made. Results involving correct oddball trials on the go/no-go task are shown in Supplementary Material.

For all analyses, the threshold for statistical significance was set at P < 0.05 and family-wise error (FWE) corrected at the voxel level across the whole brain. An additional minimum cluster size criterion of 20 voxels was applied. Conversion from MNI to Talairach coordinates of peak voxels within a cluster was performed using a nonlinear transformation (Brett et al. 2002), and identification of anatomic areas was determined using the stereotactic atlas by Talairach and Tournoux (1988).

**Results**

Fifty-four subjects (mean ± SD: 23.65 ± 2.97 years; range: 18–30 years; all right-handed, male nonsmokers) completed the study. However, 1 subject failed to comply with the exclusion criteria. One subject showed excessive motion artifacts during fMRI (>5 mm), and 2 subjects performed no errors on the go/no-go task. Due to technical problems, data of 11 subjects could not be obtained for the stop-signal task and methylphenidate plasma levels could not be obtained for 1 subject. Therefore, the final sample consisted of 50 subjects for the VARS and the go/no-go task, 42 subjects for the stop-signal task, and 49 subjects for the plasma analysis.

**Behavioral Data, VARS, and Plasma Levels**

There was an effect of methylphenidate on the ICV of correct go trials on the go/no-go task [t(49) = −1.99, P = 0.05, d = −0.40]. A trend-level effect was also observed on the intra-individual SD of RT of go trials on the go/no-go task.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics of behavioral variables on the go/no-go and stop-signal tasks during methylphenidate and placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go/no-go variables</td>
<td>Methylphenidate (N = 50)</td>
</tr>
<tr>
<td>Percentage of incorrect no-go</td>
<td>17.13</td>
</tr>
<tr>
<td>Percentage of incorrect Go</td>
<td>0.60</td>
</tr>
<tr>
<td>Percentage of incorrect oddball</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean RT correct go</td>
<td>321.50</td>
</tr>
<tr>
<td>Mean RT incorrect no-go</td>
<td>393.75</td>
</tr>
<tr>
<td>Mean RT correct oddball</td>
<td>378.21</td>
</tr>
<tr>
<td>Mean RT incorrect oddball</td>
<td>62.56</td>
</tr>
<tr>
<td>SD RT correct go</td>
<td>152.84</td>
</tr>
<tr>
<td>SD RT incorrect no-go</td>
<td>86.81</td>
</tr>
<tr>
<td>SD RT correct oddball</td>
<td>0.19</td>
</tr>
<tr>
<td>SD RT incorrect oddball</td>
<td>0.30</td>
</tr>
<tr>
<td>ICV correct go</td>
<td>0.23</td>
</tr>
<tr>
<td>ICV correct oddball</td>
<td>0.22</td>
</tr>
<tr>
<td>Percentage of incorrect no-go*</td>
<td>17.13</td>
</tr>
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<td>0.22</td>
</tr>
</tbody>
</table>

Note: N, number of subjects.

*Due to the low number of errors of some subjects, their SD values could not be calculated.

Therefore, N = 48 and 47 for the ICV incorrect no-go during methylphenidate and placebo, respectively.


\[ (t(49) = -1.82, P = 0.075, d = -0.27). \] There were no other significant behavioral effects of methylphenidate on the go/no-go or stop-signal tasks (all \( P > 0.46 \)). Descriptive statistics of the variables of both tasks can be seen in Table 1.

For VARSs, significant interactions between Drug and Time were observed for the items my thoughts are racing (\( F_{2,98} = 11.53, P < 0.001 \), partial \( \eta^2 = 0.19 \)), energetic (\( F_{2,98} = 7.40, P = 0.001 \), partial \( \eta^2 = 0.13 \)), attentive (\( F_{2,98} = 3.42, P = 0.04 \), partial \( \eta^2 = 0.07 \)), restless (\( F_{2,98} = 18.47, P < 0.001 \), partial \( \eta^2 = 0.28 \)), and tired (\( F_{2,98} = 5.43, P = 0.006 \), partial \( \eta^2 = 0.10 \)). Methylphenidate increased ratings in these variables more strongly than placebo, with the exception of tired, where ratings increased with placebo but decreased with methylphenidate. Further statistical analysis of VARS items can be found in Supplementary Material.

The mean and SD of plasma levels were \( 14.39 \pm 5.63 \) ng/mL following drug administration and 0 following placebo administration.

**fMRI Data**

**Task Main Effects**

As described earlier, the threshold for statistical significance of fMRI results was set at \( P < 0.05 \) and FWE-corrected at the voxel level across the whole brain.

The within-subject ANOVA revealed significant task-related activation on both tasks. During successful inhibition in the go/no-go task (no-go trials) compared with baseline, extensive activation in widespread cortical and subcortical networks included the bilateral inferior frontal cortex, middle and superior frontal cortex, superior temporal cortex, posterior cingulate, occipital regions, thalamus, putamen, and cerebellum (Fig. 1A). The activation during unsuccessful inhibition compared with baseline on the go/no-go task included the bilateral inferior and superior frontal cortex, inferior parietal cortex, insula, middle temporal cortex, middle frontal cortex, superior temporal cortex, anterior cingulate, thalamus, precentral gyrus, and precuneus (Fig. 1B).

Similarly on the stop-signal task during successful inhibition compared with baseline, significant and extensive activation was seen in widespread networks, including the bilateral middle frontal cortex, right middle and superior temporal cortex and left inferior and middle temporal cortex, left postcentral, precentral, and occipital regions (Fig. 2A). During unsuccessful inhibition compared with baseline, activation was seen in the bilateral superior temporal cortex, right middle temporal cortex, left inferior and middle frontal cortex, right superior frontal cortex, anterior cingulate, left insula, and precentral gyrus (Fig. 2B).

We then directly compared successful with unsuccessful inhibition trials. In the go/no-go task, there was significantly stronger activation in the putamen bilaterally and in the right middle occipital gyrus during successful inhibition when compared with unsuccessful inhibition (Fig. 3A and Table 2). The inverse contrast (unsuccessful inhibition > successful inhibition) on the go/no-go task yielded significant clusters in the anterior cingulate cortex, bilateral inferior frontal gyrus, left putamen, left inferior parietal lobe, and head of the right caudate (Fig. 3B and Table 2). In the stop-signal task, greater activation was seen during successful inhibition when compared with unsuccessful inhibition in the bilateral putamen, as well as in the bilateral middle frontal gyrus, bilateral middle occipital gyrus, right inferior frontal gyrus, and cerebellar regions (Fig. 4A and Table 2). The inverse contrast showed greater activation during unsuccessful inhibition than during successful inhibition in the left insula (Fig. 4B and Table 2).

**Drug Effects**

For the go/no-go task, there were no main effects of Drug for any contrast. However, there was a significant interaction between Drug and Condition in a cluster in the right putamen (\( x = 26, y = -2, z = -3, Z = 5.79, \) cluster size = 72 voxels), which is located closely within the putamen cluster of the contrast successful > unsuccessful (Fig. 3A). In order to explore whether the effect was in fact lateralized to the right putamen, we changed the statistical correction to \( P < 0.05 \) false discovery rate; this analysis also revealed an interaction effect in a cluster in the left putamen (\( x = -26, y = -2, z = 6, Z = 4.77, \) cluster size = 182 voxels), which showed the same pattern as in the right hemisphere.

To clarify the origin of this interaction, we carried out post hoc \( t \)-tests in SPM5 using criteria for significance as described earlier. It was found that with placebo, there was significantly greater BOLD signal in the putamen bilaterally (\( x = 28, y = 0, z = -3, Z = 7.54, \) cluster size = 492 voxels; \( x = -26, y = -4, z = 8, Z = 7.00, \) cluster size = 364 voxels) and the right middle occipital gyrus (\( x = 32, y = -84, z = 21, Z = 4.92, \) cluster size = 24 voxels).

**Figure 1.** Neural effects of successful and unsuccessful inhibition in the go/no-go task. (A and B) Activation of the contrast successful > baseline (\( P < 0.05, \text{FWE} \)) and unsuccessful > baseline, respectively, on the go/no-go task (\( P < 0.05, \text{FWE} \)).
during successful inhibition when compared with unsuccessful inhibition; however, no such difference was seen with methylphenidate. Post hoc t-tests also showed that methylphenidate significantly increased activation during the unsuccessful inhibition condition in the right putamen compared with placebo ($x=30$, $y=-4$, $z=-1$, cluster size = 22 voxels), but not during the successful inhibition condition (not significant). Together, these findings suggest that methylphenidate increased the BOLD signal in the putamen during incorrect no-go trials to the levels observed during correct no-go trials. Figure 5 illustrates this pattern for the cluster, which showed the significant Drug by Condition interaction in the ANOVA model.

For the stop-signal task, there were no significant main effects of Drug and there was no significant interaction between Drug and Condition. In an attempt to explore whether a similar effect as on the go/no-go task might exist in the data, we changed the correction to $P<0.05$ false discovery rate; again, no main effect of drug or interaction effect was found. t-tests, analogous to those carried out on the go/no-go task, showed significantly stronger BOLD signal in right ($x=26$, $y=8$, $z=7$, cluster size = 874) and left ($x=-24$, $y=10$, $z=-3$, cluster size = 738) putamen during correct than incorrect trials during placebo. This effect remained significant with methylphenidate in the left ($x=-24$, $y=8$, $z=-2$, cluster size = 363 voxels) and right ($x=24$, $y=9$, $z=-7$, cluster size = 363 voxels) putamen, suggesting that unlike in the go/no-go task, methylphenidate did not alter striatal BOLD during error trials on the stop-signal task.

In order to further confirm the specificity of the methylphenidate effect on the go/no-go but not the stop-signal task, the parameter estimates were extracted from the cluster in the right putamen that showed a significant interaction effect in the go/no-go task (peak coordinate: $x=26$, $y=-2$, $z=-3$). Data for this cluster were extracted for both the go/no-go and stop-signal tasks using the MarsBar toolbox (Brett et al. 2002; see http://marsbar.sourceforge.net/). A 2 (methylphenidate and placebo) × 2 (go/no-go and stop signal) × 2 (successful inhibition and unsuccessful inhibition) repeated-measures ANOVA was carried out on these data in PASW Statistics, release version 19.0 (SPSS Inc. 2010). A significant 3-way interaction was found ($F_{1,40}=11.88$, $P<0.001$, partial $\eta^2=0.23$), confirming that the effect of methylphenidate on BOLD signal in the right putamen is task-dependent, that is, specific to the go/no-go task.
We also reran the analysis of the go/no-go data excluding subjects who committed less than 2 (N = 5) or less than 3 errors (N = 15) (not including the subjects already excluded from the main analysis). There were no major changes in the results when these subjects were excluded.

Finally, in order to explore whether drug effects at behavioral and neural levels were correlated, we carried out Pearson’s correlations between magnitude of change (methylphenidate-placebo/methylphenidate) in the BOLD signal in the putamen and magnitude of change in no-go error trials as well as stop-signal RT. None of these correlations were significant (all $P > 0.47$).

Discussion

This study used fMRI and the go/no-go and tracking stop-signal tasks to investigate neural and behavioral effects of methylphenidate on motor response inhibition and error monitoring in healthy adults. At the behavioral level, methylphenidate decreased intra-individual response time variability on the go/no-go task without affecting response inhibition performance on either task. Methylphenidate also increased self-ratings of perceived activity levels. At the neural level, methylphenidate administration led to an increase in the BOLD signal in the putamen during response inhibition errors on the go/no-go but not the stop-signal task.

fMRI Task Main Effects

On both tasks, extensive activation was seen during successful inhibition compared with baseline in cortical and subcortical areas, in line with previous findings in healthy adults (Garavan et al. 2002; Rubia, Smith et al. 2003; Rubia, Smith, Taylor, Brammer 2007; Aron et al. 2007). Furthermore, greater activation was found in the putamen during successful inhibition compared with unsuccessful inhibition on both tasks, supporting previous findings on the involvement of the putamen in both healthy subjects and patients with ADHD during motor inhibition in the go/no-go task (Garavan et al. 2002; Durston et al. 2003; Bedard et al. 2010) as well as in the stop-signal task (Vink et al. 2005; Rubia, Smith, Taylor, Brammer 2007; Zandbelt and Vink 2010). In the stop-signal task, there was additional right inferior frontal as well as middle frontal activation in this contrast, consistent with previous evidence (Aron et al. 2003b; Rubia, Smith et al. 2003; Rubia, Smith, Taylor, Brammer 2007; Verbruggen and Logan 2008; Chambers et al. 2009).

The results of the comparison of unsuccessful inhibition with baseline were similar in both tasks, showing greater activation during inhibition errors in the anterior cingulate, temporal and parietal areas, and inferior and superior frontal cortices with stronger bilateral frontal activation in the go/no-go task (Liddle et al. 2001; Menon et al. 2001; Rubia, Smith et al. 2003; Rubia, Smith, Taylor, Brammer 2007b). However, activation during unsuccessful compared with successful inhibition was stronger for the go/no-go task than the stop-signal task: in the stop-signal task, only a cluster in the left insula was activated, whereas in the go/no-go task, there was activation in the anterior cingulate, frontal, and parietal cortex. The stronger activation in the go/no-go task for this contrast could have been due to the greater saliency of errors in this task: as the error rate in the go/no-go task was smaller than that of the stop-signal task, it can be inferred that go/no-go errors had a higher saliency than stop-signal errors.

Neural Effects of Methylphenidate

Methylphenidate increased the BOLD signal in the putamen during unsuccessful go/no-go inhibition trials, but did not affect the BOLD signal during successful inhibition trials. These findings may be reconciled with methylphenidate effects in ADHD, in which methylphenidate has been found to increase activation in the caudate and putamen during motor inhibition in the go/no-go task (Garavan et al. 2002; Durston et al. 2003; Bedard et al. 2010) as well as in the stop-signal task (Vink et al. 2005; Rubia, Smith, Taylor, Brammer 2007; Zandbelt and Vink 2010). In the stop-signal task, there was additional right inferior frontal as well as middle frontal activation in this contrast, consistent with previous evidence (Aron et al. 2003b; Rubia, Smith et al. 2003; Rubia, Smith, Taylor, Brammer 2007; Verbruggen and Logan 2008; Chambers et al. 2009).

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Evidence from our study together with prior studies thus suggests that methylphenidate may have a stronger effect on striatal-mediated performance monitoring than on inhibitory...
networks (Cubillo et al. 2011) and that the neural effects of methylphenidate of upregulating basal ganglia activation are not only present in patients with ADHD, but also in healthy adults. Together, these findings also provide support for hypotheses concerning a modulating role of dopamine in error processing related to executive function (Braver and Cohen 2000; Hazy et al. 2007).

However, our findings also suggest that the neural effects of methylphenidate may differ between healthy individuals and ADHD patients in frontal areas. In ADHD, methylphenidate has been shown to upregulate frontal activation during motor response inhibition (Vaidya et al. 1998; Epstein et al. 2007; Prehn-Kristensen et al. 2011; Rubia, Halari, Cubillo et al. 2011; Rubia, Halari, Mohammad et al. 2011) and other cognitive functions (Bush et al. 2008; Rubia, Halari, Christakou et al. 2009; Rubia, Halari, Cubillo 2009; Lee et al. 2010), although there have also been negative findings (Shafritz et al. 2004; Kobel et al. 2009; Peterson et al. 2009). In contrast, in healthy subjects, methylphenidate effects on frontal regions appear to be more inconsistent and more strongly task-dependent. For example, methylphenidate reduced frontal activation during a working memory task (Mehta et al. 2000) but enhanced frontal activation during a rewarding working memory task (Marquand et al. 2011). Methylphenidate has also been shown to modulate striatal activation during response reversal, but to modulate prefrontal activation during simple repetitive executive processes (Dodds et al. 2008).

A noteworthy finding of the present study is that the neural effects of methylphenidate were anatomically highly specific to the putamen. This localization is compatible with methylphenidate’s mechanism of action of blocking about 60–70% of striatal dopamine transporters (Volkow et al. 1998) and increasing extracellular levels of dopamine in the human striatum (Volkow et al. 2001).

Another important finding of the present study is that the result in the putamen was task-specific, which is observed on the go/no-go but not the stop-signal task. A number of differences between the 2 tasks may be invoked to explain this pattern.

A first explanation concerns the type of response inhibition required in the 2 tasks. Schachar et al. (2007) distinguished between action restraint and action cancellation. Action restraint is the inhibition of the motor response before it has started, which describes the form of inhibition on the go/no-go task. Action cancellation refers to inhibition during the execution of the motor response, which describes the form of inhibition on the stop-signal task. The 2 forms of inhibition differ in the way they assess the amount of time required to inhibit a motor response. The processing of the no-go stimulus during action restraint takes place before motor execution, and therefore, the time taken to process the no-go stimulus includes both response inhibition and decision making or response selection (Rubia et al. 2001). However, during action cancellation, each trial begins as a go trial and the subject has to inhibit the motor response as soon as the stop stimulus appears, thereby demanding the withdrawal of a response that is already on its way to execution, without implicating selective attention or decision making at the stimulus onset (Rubia et al. 2001). Studies on the neurotransmitter substrates of these processes suggest that action restraint may be...
related to serotonin (Anderson et al. 2002; Evers et al. 2006; Eagle et al. 2008), whereas action cancellation may be associated with noradrenaline (Eagle et al. 2008).

The observed task specificity of methylphenidate effects may also be explained by differences in error processing between the 2 tasks. As outlined earlier, errors on the go/no-go task were fully avoidable, less frequent, and therefore likely more salient than errors on the stop-signal task. A relevant study by Volkow et al. (2004) found that methylphenidate increased dopamine levels during a rewarded mathematical task but not during a neutral task. They proposed that methylphenidate-induced dopamine enhances the saliency only of the task that is already salient to the subjects. Subjects in our study were aware that they had no control over the overall rate of errors on the stop-signal task; this might have led to a state of loss of control similar to what has been described in the literature on learned helplessness (Maier and Seligman 1976; Bauer et al. 2003). As a result, stop-signal errors may not have been as salient as go/no-go errors. Furthermore, error trials in the go/no-go task were less frequent than those in the stop-signal task, further adding to a saliency effect. Considering that dopamine release is enhanced by salient stimuli (Braver and Cohen 2000) and the striatal effects of methylphenidate are associated with blockade of dopamine transporters and dopamine signaling, the upregulation effects of methylphenidate on performance monitoring in the stop-signal task may not have been observed in healthy adults due to relatively lower saliency of stop errors of this task, which may only have reached the necessary saliency threshold in the go/no-go task.

While methylphenidate has been shown to enhance striatal saliency processing in the stop-signal task in patients with ADHD (Rubia, Halari, Cubillo et al. 2011), it is possible that higher saliency is needed to interact with methylphenidate to elicit a neural effect in healthy subjects. In medication-naive ADHD patients, lower levels of dopamine and striatal dopamine transporters have been reported in comparison to healthy subjects. The neurofunctional striatal upregulation effects observed in ADHD patients with methylphenidate are, therefore, likely to take place at a lower threshold of saliency (Volkow et al. 2007) in line with the conclusions of Volkow et al. (2004).

Behavioral Effects of Methylphenidate

Methylphenidate had a stimulating effect at the level of subjective self-ratings, leading to increases (compared with placebo) in perceived levels of activation and attentiveness but also in restlessness.

Methylphenidate furthermore reduced intra-individual RT variability, but did not affect inhibitory performance. RT variability in a number of tasks is increased in ADHD (Klein et al. 2006; Evers et al. 2006; Taylor 2007) and found to be associated with overall performance levels (e.g. Ettinger and Corr 2001; Flehmig et al. 2007).

Limitations

A limitation of the study was that the sample consisted of healthy young volunteers drawn from a university population. While such a screened sample is of course highly suitable for pharmacological challenge studies, their high level of performance on the tasks might have contributed to a ceiling effect.

Secondly, the sample consisted of only males. Some (Sonuga-Barke et al. 2007) but not all studies (Gray and Kagan 2000; Owens et al. 2003) have reported gender differences in methylphenidate response in ADHD. Therefore, generalizability of the present findings to the general population may be limited.

A final limitation is that there were relatively few error trials on the go/no-go task, which may have resulted in low statistical power. However, exclusion of subjects with very few inhibition errors on the go/no-go task did not affect the methylphenidate effects reported here.

Conclusions

In summary, neural effects of methylphenidate during motor response inhibition tasks in healthy adults are observed in the putamen, where the drug modulates neural activity only during errors and specifically in the go/no-go task, but not in the stop-signal task. This task specificity may be due to differences in error saliency between the 2 tasks.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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