HHS Public Access

Author manuscript

Int J Neuropsychopharmacol. Author manuscript; available in PMC 2015 August 01.

Published in final edited form as:

Int J Neuropsychopharmacol. 2014 August ; 17(8): 1177–1191. doi:10.1017/S1461145714000674.

The effects of methylphenidate on resting-state striatal., thalamic and global functional connectivity in healthy adults

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Abstract

By blocking dopamine and norepinephrine transporters, methylphenidate affects cognitive performance and regional brain activation in healthy individuals as well as those with neuropsychiatric disorders. Resting-state connectivity evaluates the functional integrity of a network of brain regions. Here, we examined how methylphenidate effects resting-state functional connectivity of the dorsal striatum and thalamus, areas each with dense dopaminergic and noradrenergic innervations, as well as global cerebral connectivity. We administered a single, oral dose (45 mg) to 24 healthy adults and compared resting-state connectivity to 24 demographically matched adults who did not receive any medication. The results showed that methylphenidate alters seed-based and global connectivity between the thalamus/dorsal striatum with primary motor cortex, amygdala/hippocampus and frontal executive areas ($p<0.05$, corrected). Specifically, while methylphenidate at this dosage enhances connectivity to the motor cortex and memory circuits, it dampens prefrontal cortical connectivity perhaps by increasing catecholaminergic signalling past the 'optimal' level. These findings advance our understanding of a critical aspect of the multifaceted effects of methylphenidate on brain functions. The results may also facilitate future studies of the aetiology and treatment of neurological and psychiatric disorders that implicate catecholaminergic dysfunction.

Keywords

fMRI; Functional connectivity; methylphenidate; thalamus; striatum

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Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145714000674.

Statement of Interest

None

Introduction

By blocking norepinephrine and dopamine transporters, methylphenidate increases the availability of catecholamines, which play a critical role in cognitive functioning (Berridge et al., 2006, 2012; Devilbiss and Berridge, 2006; Spencer et al., 2012). Methylphenidate is a common treatment and improves cognitive performance in people with attention-deficit hyperactivity disorder (Tannock et al., 1989; Aron et al., 2003; Scheres et al., 2003; Broyd et al., 2005; Jonkman et al., 2007). For instance, methyl-phenidate improves the stop signal reaction time in the stop signal task (Aron et al., 2003), and reduces response errors on the go/no-go task (Broyd et al., 2005). Methylphenidate increases medial prefrontal cortical activation and restores the Stroop effect, where the reaction time for interference trials is prolonged compared to noninterference trials (Zang et al., 2005). Methylphenidate also improves cognitive performance in patients with other neurological conditions, including traumatic brain injury (Kim et al., 2006) and Parkinson's disease (Auriel et al., 2006; Devos et al., 2007; Pollak et al., 2007), suggesting that its cognition enhancing effects could help clinical populations beyond ADHD.

Connectivity analysis of resting-state functional magnetic resonance imaging (fMRI) data characterizes functional integrity of brain networks (Passingham et al., 2002). Specifically, low frequency blood oxygenation level dependent (BOLD) signal fluctuations reflect connectivity between functionally related brain regions (Biswal et al., 1995; Fair et al., 2007; Fox and Raichle, 2007). Studies of this 'spontaneous' activity have provided insight into the intrinsic functional architecture of the brain (Fox and Raichle, 2007). For instance, based on the findings that regions with similar functionality tend to correlate in spontaneous BOLD activity, we described functional subdivisions of the medial superior frontal cortex (Zhang and Li, 2012b) and precuneus (Zhang and Li, 2012a) recently. Few studies have examined how catecho-laminergic agents influence cerebral functional connectivity during resting state. In children with ADHD, methylphenidate increased and decreased regional homogeneity, a measure of functional connectivity of local in contrast to surrounding voxels, each in bilateral ventral prefrontal cortex/cerebellar vermis and right parietal/visual cortices (An et al., 2013). Methylphenidate also increased regional homogeneity (Zhu et al., 2013) but has otherwise not been studied for its effects on resting-state functional connectivity in healthy adults.

Midbrain dopaminergic neurons project to the basal ganglia, including the caudate, putamen, pallidum and throughout the cerebral cortex (Bentivoglio and Morelli, 2005). Noradrenergic neurons of the locus coeruleus heavily innervate the thalamus and cerebral cortex (Descarries and Saucier, 1972; O'Donnell et al., 2012). A number of cognitive processes including inhibitory control and behavioural adjustment are mediated by the cortico-striato-thalamic circuitry (Wagner et al., 2006; Diamond and Ahissar, 2007; Urbain and Deschenes, 2007). In an earlier work, we demonstrated a critical role of the thalamus and epithalamus in orchestrating error-related cognitive control (Hendrick et al., 2010; Ide and Li, 2011a, b). Because these cortico-subcortical circuits are regulated by catecholaminergic signalling (Graybiel, 1990; Crawford et al., 1998; Bymaster et al., 2002; Grillner et al., 2005; Andrews and Lavin, 2006; Monchi et al., 2006), we hypothesized that pharmacological manipulation of catecholamine availability would likely result in changes in functional connectivity.

In this exploratory study, we used resting-state fMRI to examine whether and how methylphenidate alters functional connectivity between the striatum and thalamus with the rest of the brain in healthy adults. We also performed an analysis of global connectivity, as an additional measure, to identify the effects of methylphenidate on network functional changes.

Method

Participants

The study was performed under a protocol approved by the Yale Human Investigation and Magnetic Resonance Imaging Safety Committees. Participants were recruited from the greater New Haven area by advertisement, word of mouth and referrals. Written informed consent was obtained from all participants after a full explanation of study procedures. Twenty-five healthy adults (17 females; age 25±6 years; all right-handed) were recruited and compensated for their participation in the study. All participants were admitted as outpatients to the Yale New Haven Hospital, and were without medical, neurological or psychiatric conditions. All denied history of head injury and current use of prescription medications or illicit substances. One subject was eliminated from the study because of a lesion found on the structural brain image. The resulting 24 participants comprised 16 females, with a mean age of 24±4 years – the methylphenidate (MPH) group. Data of a cohort of 24 matched healthy participants (16 females; age 24±4 years) scanned under identical imaging protocols except without being given methylphenidate were used for comparison – the no-MPH group.

On the day of fMRI, participants rested in a recovery room for at least 10 min, during which baseline heart rate, blood pressure and anxiety measurements were taken. An hour prior to fMRI scans a physician examined participants before approving administration of a single 45 mg oral dose of methylphenidate. All participants in the MPH group received methylphenidate, although participants did not know whether they would be receiving methylphenidate or a placebo, according to the protocol and consent. From this time until the beginning of the structural MRI scans (approximately 40 min), heart rate and blood pressure as well as anxiety were monitored every 5 min. These measures were taken approximately every 10 min between sessions during fMRI. At each vital sign reading, participants also marked how anxious they felt on a visual analogue scale from one (not anxious at all) to ten (extremely anxious). Compared to baseline, MPH increased heart rate, systolic blood pressure and anxiety rating, as we reported recently (Farr et al., 2013).

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=4 mm 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 repetition time=2000 ms, echo time=25 ms, bandwidth=2004 Hz/ pixel, flip angle=85°, field of view=220×220 mm, matrix =64×64, 32 slices with slice thickness=4 mm and no gap. Three hundred images were acquired in the resting state run, following four other BOLD runs during which participants performed a stop signal task (Farr et al., 2013). In the resting state scans, participants were instructed to close their eyes but stay awake.

Imaging data pre-processing

Brain imaging data were pre-processed using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging Neuroscience, University College London, UK), as described in our previous work (Zhang et al., 2012). Briefly, images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per each run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation (Friston et al., 1995; Ashburner and Friston, 1999). The normalization parameters determined for the structural volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at full width at half maximum.

Additional pre-processing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Rombouts et al., 2003; Fox et al., 2006; Fair et al., 2007; Fox and Raichle, 2007). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, the white matter and the whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.

Cordes and colleagues suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (Cordes et al., 2001). The majority of resting state studies low-pass filtered BOLD signal at a cut-off of 0.08 or 0.1 Hz (Fox and Raichle, 2007). Thus, we applied a temporal band-pass filter (0.009 Hz$<f<$0.08 Hz) to the time course in order to obtain low-frequency fluctuations (Fox et al., 2006; Fair et al., 2007; Fox and Raichle, 2007).

Seed-based functional connectivity: linear correlations

We used the templates from the Anatomical Automatic Labelling (AAL) atlas for each region of interest- caudate, putamen, pallidum and thalamus (Tzourio-Mazoyer et al., 2002). The BOLD time courses were averaged spatially across all voxels each for the four seed regions. We computed the correlation coefficient between the averaged time course of each mask and the time courses of individual voxels of the brain for individual subjects. To assess and compare the resting state ‘correlograms,’ we converted these image maps, which were not normally distributed, to z score maps by Fisher’s z transform (Jenkins and Watts, 1968; Berry and Mielke, 2000): $z=0.5 \log_e[(1+r)/(1-r)]$. The z maps were used in group random

effect analyses (Penny et al., 2004) with a two-sample *t*-test to compare MPH and no-MPH groups.

Global connectivity

Global connectivity was computed as the averaged voxel-to-voxel connectivity across the whole brain (Cole et al., 2010b). Here, we examined the connectivity of individual voxels to the 116 anatomical masks from the AAL atlas (Tzourio-Mazoyer et al., 2002); not to voxels of the whole brain), in order to manage computational load. The BOLD time courses were averaged spatially across the voxels within each of the 116 masks for correlation with the time course of each grey matter voxel, for each individual subject. Because positive and negative connectivities would cancel each other out, global connectivity was computed for positive and negative connectivities separately. Otherwise, for instance, an area with equally strong positive and negative connectivity would exhibit no significant connectivity. We also weighted by the number of voxels of each mask to account for seed size after *z* transformation. Thus, each correlation coefficient (Pearson's *r*) was Fisher's *z* transformed and then the weighted averaged *z* map was obtained for each of the positive and negative connectivity and for each subject. Voxels connected to more of the 116 masks positively or negatively would be more connected globally.

Because individual positive/negative global connectivity maps contain only positive/negative values, all grey matter voxels would show significant connectivity with one sample *t*-test. We thus applied the 'top percentage' threshold (Cole et al., 2010b) to identify voxels with the highest global connectivity and to quantify the connectivity for each group. Thresholds were determined by reducing the *p* value (i.e. applying a higher threshold) until the desired percentage (e.g. 5%) of the total grey matter voxels remained for each group's one sample *t*-test. This analysis identified brain regions that are most connected and allowed us to examine changes in global connectivity as a result of methylphenidate, complementing findings from the seed-based analyses.

For both seed-based and global connectivity, we used two sample *t*-tests to compare MPH and no-MPH groups and identified voxels that were significant at a corrected threshold. Investigators have argued that the corrected voxel peak threshold of $p<0.05$, based on the Gaussian random field theory, may be too restrictive and suggested the use of a cluster threshold (Poline et al., 1997; Hayasaka and Nichols, 2003). Thus, we present results that satisfy either peak voxel FWE $p<0.05$ or a combined threshold of voxel $p<0.001$, uncorrected and cluster FWE $p<0.05$.

Results

Seed-based functional connectivity

We first examined the right and left caudate, putamen, pallidum and thalamic seed regions separately and found no hemispheric differences in functional connectivity ($p<0.001$ uncorrected). We thus elected to show and discuss the results from the bilateral seeds for each area of interest. Figure 1 shows the results of one-sample *t*-tests each for the methylphenidate (MPH) and no-MPH group. The results of two sample *t*-tests are shown in

Fig. 2 and summarized in Table 1. Supplementary Figure S1 shows the effect sizes of each group for all seed-based connectivities that differed between MPH and no-MPH. In the following, we describe structures that share significant connectivity with each seed region in both no-MPH and MPH groups (one-sample *t* tests) and those that demonstrate significant differences in connectivity (two-sample *t* test). In the latter case, we highlight whether the differences result from a change in the strength of connectivity or a reversal in the sign of connectivity.

Caudate—Both groups showed positive connectivity of the caudate nucleus with the medial frontal cortex including supplementary motor area (SMA) and pre-SMA, and anterior cingulate cortex, as well as the middle frontal cortex, orbitofrontal cortex, thalamus and basal ganglia. Both groups showed negative connectivity of the caudate with the precuneus, occipital cortices, hippocampus, parahippocampal gyri and cerebellum.

Methylphenidate reversed the negative connectivity between the caudate and left primary motor cortex (PMC) and positive connectivity between the caudate and frontal polar cortex as well as superior/middle temporal gyri, as observed for the no-MPH group (Fig. 2*a*; Table 1).

Pallidum—Both groups showed positive connectivity of the pallidum with the medial frontal cortex including supplementary motor area (SMA) and pre-SMA, and anterior cingulate cortex, as well as middle frontal cortex, thalamus, basal ganglia and insula. Both groups showed negative connectivity of the pallidum with the precuneus, occipital cortices and the posterior cingulate cortex.

Methylphenidate reversed the negative connectivity between the pallidum and left pre-central and post-central cortices, as observed in the no-MPH group. Methylphenidate reversed the positive connectivity between the pallidum and anterior and posterior cingulate cortices, cerebellum and medial prefrontal cortex. Methylphenidate also decreased negative connectivity of the pallidum with the occipital cortices (Fig. 2*b*; Table 1).

Putamen—Both groups showed positive connectivity of the putamen with the medial frontal cortex including supplementary motor area (SMA) and pre-SMA, and anterior cingulated cortex, as well as middle/inferior frontal cortices, thalamus, basal ganglia, superior temporal cortex and insula. Both groups showed negative connectivity of the putamen with the precuneus, occipital cortices, parahippocampal gyri and the posterior cingulate cortex.

Methylphenidate reversed the positive connectivity between the putamen and mid/posterior cingulate cortex and right supramarginal gyrus. Methylphenidate also decreased positive connectivity of the putamen to cerebellum (Fig. 2*c*; Table 1).

Thalamus—Both groups showed positive connectivity of the thalamus with the medial frontal cortex including supplementary motor area (SMA) and pre-SMA, and anterior cingulate cortex, as well as thalamus and basal ganglia. Both groups showed negative connectivity of the thalamus with the occipital and inferior temporal cortex.

Methylphenidate reversed the negative connectivity between the thalamus and a wide array of brain regions, including bilateral pre-central, post-central, and occipital cortices, as well as the superior temporal gyri, parahippocampal gyri and precuneus, as observed for the no-MPH group. Methylphenidate also reversed the positive connectivity between the thalamus and cerebellum, superior/middle frontal gyri and the inferior parietal cortex (Fig. 2*d*; Table 1).

Global connectivity

The results of one-sample *t* tests for global connectivity are shown in Fig. 3. For both groups, we observed voxels with more positive connectivity in the dorsolateral prefrontal cortex, putamen, visual cortices, precuneus, cuneus and insula, and more negative connectivity with the supplementary motor area, midbrain, temporal cortices, insula, parietal cortices and occipital cortices. This aligns with previous findings of the inferior parietal cortex, inferior frontal cortex and cuneus as being the most connected across a large number of participants (Tomasi and Volkow, 2010).

In two-sample *t* tests, the negative global connectivity of primary motor cortex and supplementary motor cortex decreased in MPH compared to no-MPH group (Fig. 4; Table 2). In contrast, medial prefrontal and parietal cortices showed more negative global connectivity in the MPH as compared to no-MPH group. We did not observe any significant differences in positive global connectivity between the two groups.

Gender differences in connectivity and correlation with physiological variables

For both seed-based and global connectivity, we performed a full factorial analysis to include gender (32 females, 16 males) as a covariate, in order to examine gender main effects as well as group (MPH vs. no-MPH) by gender interactions. The results showed that, as expected, the group main effects were identical to what we reported. In addition, there were no significant regional brain activations for the gender main effects, at voxel $p<0.001$, uncorrected and cluster $p<0.05$ FWE corrected. For the group by gender interaction, there is a single cluster in the area of right superior temporal cortex, secondary somatosensory cortex and insula ($x=48$, $y=-4$, $z=10$, $z = 3.93$, cluster size=3132 mm^3), which showed greater negative global connectivity in men than women with administration of methylphenidate (i.e. [MPH_Men – noMPH_Men]>[MPH_Women – noMPH_Women]).

We also explored correlations between the effect sizes of seed-based as well as global connectivity and percentage changes in SBP, HR and anxiety rating. As shown in Supplementary Table S1, there were few significant correlations at $p<0.05$, and none of these correlations were significant at a corrected $p=0.05/90=0.00055$ (with a total of 90 tests).

Discussion

Methylphenidate and thalamic/striatal connectivity to the primary motor cortex

With the exception of putamen, the thalamus/dorsal striatum showed negative resting state functional connectivity with the motor and somatosensory cortices, as observed in the no-

MPH group and many previous studies of healthy participants (Baird et al., 2013; Erpelding et al., 2013; Nasrallah et al., 2013; Posner et al., 2013; Werner et al., 2013; Zhou et al., 2013). Methylphenidate alters the functional connectivity from negative to positive between the thalamus/dorsal striatum and somatomotor cortices. Methylphenidate also decreases negative global connectivities of the motor cortex and paracentral lobules. Thus, overall, methylphenidate enhances somatomotor functional connectivity to the thalamus and striatum, in accord with previous studies where levodopa and haloperidol each increased and decreased resting-state and task-related functional connectivity between the motor cortex and striatum in healthy participants (Tost et al., 2010; Cole et al., 2013).

These findings are also consistent with reported effects of methylphenidate and other catecholaminergic agents on motor performance. For instance, methylphenidate increased locomotor activity in mice (Penner et al., 2001). A single dose of methylphenidate improved motor coordination in children with developmental coordination disorder and ADHD (Bart et al., 2013), perhaps compensating for impaired integrity of the white matter connecting the thalamus with primary motor cortex and hippocampus (Xia et al., 2012).

Patients with Parkinson's disease (PD) demonstrate altered cortical and subcortical activation and functional connectivity (Eidelberg et al., 1994; Huang et al., 2007; Ma and Eidelberg, 2007). Low doses of methylphenidate improved gait and voluntary movement (Auriel et al., 2006; Devos et al., 2007; Kwak et al., 2010), and along with levodopa improved performance on complex hand movements (Nutt et al., 2004) in patients with PD. In an earlier study, adding methylphenidate to levodopa treatment increased peak hand tapping speed in patients with PD compared to levodopa alone (Camicioli et al., 2001). Pridopidine, a dopamine-stabilizing compound, improved motor performance in patients with Huntington's disease (Investigators, 2013), who showed decreased white matter integrity of the caudate, putamen and primary motor cortex in progression with their motor symptoms (Bohanna et al., 2011). Together, these studies suggested that patients with clinical conditions that implicate catecholaminergic dysfunction show altered motor cortical connectivity and performance that can be ameliorated by methylphenidate.

Methylphenidate and thalamic/striatal connectivity to the hippocampus and amygdala

Methylphenidate increased connectivity between the thalamus and hippocampus, amygdala and visual areas, in addition to the primary motor cortex. The thalamus, amygdala and hippocampus all receive direct noradrenergic projections from the locus coeruleus (Ishikawa and Tanaka, 1977; Talley et al., 1996; Glass et al., 2001), a circuitry known to promote wakefulness and arousal (McBride and Sutin, 1976; McCormick et al., 1991). The thalamus plays a critical role in the detection of, filtering and reorientation to salient stimuli (Petersen et al., 1985; Robinson and Petersen, 1992; Saalmann et al., 2012), and, through projections to the hippocampus, facilitates learning and memory of salient information (Grieve et al., 2000; Casanova et al., 2001).

Methylphenidate increased metabolism/activity in thalamus and hippocampus (Glavin, 1985), and improved working memory (Ramasubbu et al., 2012) as well as decision-making (Schlosser et al., 2009) in healthy adults and/or children with ADHD (Bedard et al., 2007; Bedard and Tannock, 2008; Strand et al., 2012). In rodents, methylphenidate increased

noradrenergic metabolism in the thalamus and amygdala (Glavin, 1985) and facilitated spatial memory (Guo et al., 2012) and cue-reward learning (Ferry et al., 1999; Tye et al., 2010). Thalamus showed stronger resting-state connectivity to the amygdala in association with increased autonomic activity and physiological arousal in healthy men (Hermans et al., 2011; Chang et al., 2013). Norepinephrine, which surges during arousal, promotes long-term potentiation at thalamo-amygdalar synapses (Tully et al., 2007), and influences affective (Li and Kirouac, 2008), reward and saliency processing (Baxter and Murray, 2002; Etkin et al., 2006; Murray, 2007; Haber and Knutson, 2010; Linke et al., 2010). Thus, the current findings may provide a neural basis in evaluating this earlier body of work.

Methylphenidate and thalamic/striatal connectivity to regions of executive control

In resting state, the thalamus/dorsal striatum showed positive functional connectivity with many brain regions instrumental to executive control, such as the superior/ middle frontal cortex and medial prefrontal cortex including the SMA, pre-SMA and dorsal anterior cingulate cortex and inferior parietal cortex, as observed in the no-MPH group and many previous studies of healthy participants (Baird et al., 2013; Erpelding et al., 2013; Nasrallah et al., 2013; Posner et al., 2013; Werner et al., 2013; Zhou et al., 2013). In contrast to its effects on motor cortical connectivity, methylphenidate decreases the positive thalamic/ striatal connectivity to the frontopolar cortex and some fronto-parietal control regions or alters the connectivity from positive to negative with these brain regions. This is consistent with an earlier work where sulpiride, a dopamine antagonist, enhanced striato-thalamic activity to the dorsolateral prefrontal cortex, while methylphenidate appeared to produce the opposite effects (Honey et al., 2003). Furthermore, methylphenidate increased negative global connectivity of the fronto-parietal cortices. These findings in healthy adults are in contrast with many previous studies of clinical populations, where methylphenidate increased regional activations and connectivities in association with executive functioning (Scheres et al., 2003; Kim et al., 2006; Jonkman et al., 2007; Pollak et al., 2007; Li et al., 2010; Tye et al., 2010; Nandam et al., 2011; Tomasi et al., 2011). For instance, methylphenidate improved working memory and visuospatial attention in patients with traumatic brain injury (Kim et al., 2006), and increased prefrontal activations for cognitive control in cocaine-addicted adults (Li et al., 2010). Although speculative, this contrasting pattern of the effects of methylphe-nidate may reflect the inverted U relationship between level of catecholaminergic signalling and cognitive performance, as postulated earlier (Birnbaum et al., 1999; Arnsten, 2009; Berridge et al., 2012; Rajala et al., 2012). That is, while methylphenidate facilitates cognitive performance in clinical populations who are compromised in catecholaminergic neurotransmission, it dampens performance in healthy adults by increasing catecholamines past the optimal level, as has been observed in dosaging studies of methylphenidate in rodents, non-human primates and humans (Sagvolden et al., 1988; Tannock et al., 1989; Elliott et al., 1997; Rajala et al., 2012).

Conclusions and limitations of the study

To summarize, methylphenidate enhances resting-state functional connectivity of the striatum/thalamus with primary motor cortex and increases negative connectivity with frontal executive regions. Augmented motor cortical connectivity is consistent with the effects of methylphenidate and other catecholaminergic agents in improving motor functions

in healthy participants and various clinical populations. Methylphenidate also increases thalamic/striatal connectivity to the hippocampus and amygdala, which may speak to its alerting and memory-enhancing effects. We also speculate that the findings of methylphenidate-elicited decrease in striatal/ thalamic connectivity to prefrontal regions may have to do with individual variation in catecholaminergic signals for optimal cognitive functioning. Together, the influences of methylphenidate on cerebral functioning are multifaceted, an issue that deserves consideration in studies of its use and misuse.

There are a few important limitations to this study. First and most significantly, we did not have a placebo control for the individuals who received methylphenidate. The placebo effect is thus a potential confound for the differences that we observed between the methylphenidate and no-methylphenidate group. Additionally, we did not collect blood samples and assay plasma levels of methylphenidate to control for individual differences in pharmacokinetics. Secondly, methylphenidate influences both dopaminergic and noradrenergic neurotransmission. While there is heavy dopaminergic innervation of the basal ganglia circuitry, the cortical mantle receives both dopaminergic and noradrenergic inputs. Thus, it remains to be determined whether and how blockade of dopaminergic and/or noradrenergic transporters by methylphenidate accounts for the current findings. Furthermore, although the seed regions do not overlap spatially, they are functionally connected. It remains to be examined in future studies whether and how shared and distinct thalamic and striatal connectivities relate to cognitive and affective functions, as influenced by methylphenidate. It is also to be noted that we evaluated global connectivity to the 116 AAL masks and a voxel-wise analysis may reveal a finer pattern of connectivities as influenced by methylphenidate. Similarly, a top percentage threshold limits our analysis to those brain regions that are most connected. It remains to be evaluated whether and how other brain regions are altered in global connectivity. Third, our participants are not assessed for cognitive or motor performance; thus, the functional implications of the current findings need to be re-considered in future work. Fourth, this study involved only healthy adult participants. Thus, the implications of the current results cannot be generalized to patient populations or older adults (Hu et al., 2012, 2013). Fifth, stimulants can potentially influence fMRI blood oxygenation level-dependent (BOLD) signals, which depend on the haemodynamic 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., 1998; Rao et al., 2000), and that haemodynamic responses were faithfully followed by neuronal responses after their peak effects (at 6 min after administration) on blood flow and volume (Devonshire et al., 2004). Heart rate also had no effect on BOLD signals in one of these studies (Rao et al., 2000) and neither changes in heart rate or blood pressure was correlated to changes in functional connectivities (Supplementary Table 1). Nevertheless, we acknowledge that these physiological variables could potentially confound imaging findings and need to be considered in future experiments that properly quantify these changes in a placebo-controlled setting. Finally, we wish to consider a methodological issue regarding the findings on negative functional connectivity, which has been reported since the very beginning of the resting-state fMRI studies (Biswal et al., 1995). Negative functional connectivity, or anti-correlation, represents negative cross-correlation in spontaneous BOLD

signal between two brain regions. It was suggested that global signal regression, a common step of data pre-processing in seed-based connectivity analyses, is a likely cause of anti-correlated functional networks (Murphy et al., 2009; Weissenbacher et al., 2009). However, recent investigations demonstrated that the negative correlations are not an artifact but have biological origins (Fox et al., 2009; Chen et al., 2011; Chai et al., 2012). For instance, negative functional connectivity is associated predominantly with long-range connections and correlates with the shortest path length in the human brain network (Scholvinck et al., 2010; Chen et al., 2011; Schwarz and McGonigle, 2011). Indeed, the negative correlations between brain regions with presumably opposing functional roles have been observed in many different studies (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005; Kelly et al., 2008; Uddin et al., 2009; Chen et al., 2011), including those using independent component analysis, which does not involve global signal regression (Cole et al., 2010a; Zuo et al., 2010; Zhang and Li, 2012c). Furthermore, the existence of negative functional connectivity was also suggested by computational simulations of cerebral network activities in both monkeys and humans (Honey et al., 2007; Izhikevich and Edelman, 2008; Deco et al., 2009) and supported by simultaneous recording of unit activity and local field potentials from task-positive and task-negative (default mode) networks in cats (Popa et al., 2009). Together, these earlier studies suggest functional significance of negative functional connectivity. On the other hand, future work that combines BOLD signal acquisition and electrophysiological recording of neuronal activities is needed to fully understand the effects of the methylphenidate on positive vs. negative functional connectivities (Goense and Logothetis, 2008).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was part of Olivia Farr's thesis work for the Interdepartmental Neuroscience Program at Yale University and was supported by NIH grants T32 NS07224 (Crair), R01DA023248 (Li), R21AA018004 (Li), K02DA026990 (Li), R01AA021449 (Li), K24 DA017899 (Malison), P20DA027844 (Potenza) and a NARSAD Young Investigator Award (Li). We also thank the staff at the Connecticut Mental Health Center for assistance in medical evaluation of the participants and the Connecticut Department of Mental Health and Addiction Services (DMHAS) for their support. We thank Dr Amy Arnsten for her input to this work. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Drug Abuse, National Center for Research Resources or the National Institutes of Health.

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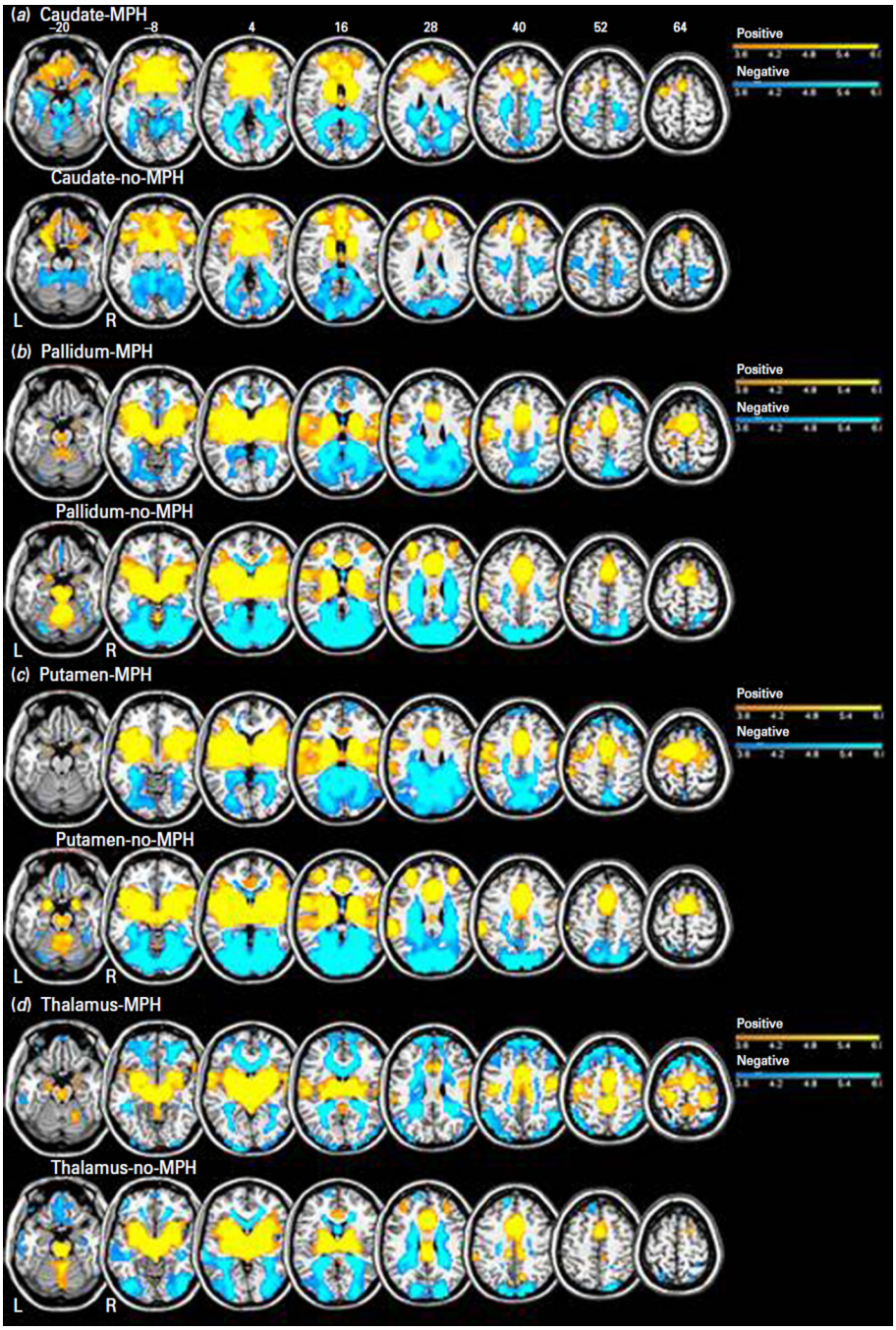

Fig. 1.

One sample *t*-tests for resting-state functional connectivity with bilateral caudate (a); pallidum (b); putamen (c); or thalamus (d) as the seed region ($p<0.001$, uncorrected). Warm and cool colour shows positive and negative connectivity. BOLD contrasts are superimposed on a T1 structural image in axial sections from $z=-20$ to $z=64$, in neurological orientation. The adjacent sections are 12 mm apart. The colour bar represents voxel *T* value.

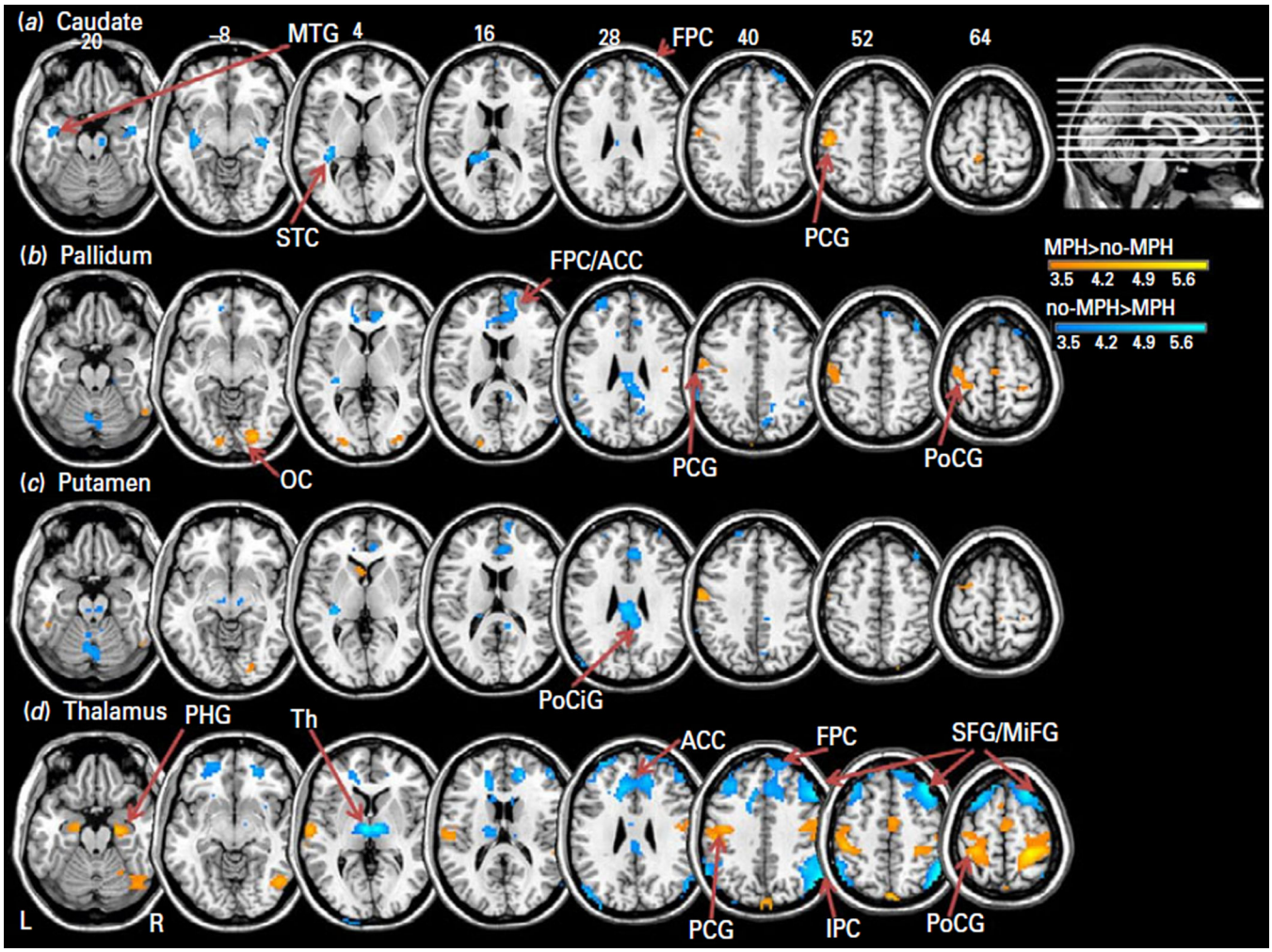

Fig. 2.

Two-sample *t*-tests showed differences in resting-state functional connectivity with bilateral caudate (a); pallidum (b); putamen (c); or thalamus (d) as the seed region, at $p<0.001$ uncorrected. MPH>no-MPH (warm colours) and no-MPH>MPH (cool colours). Clusters that met cluster $p<0.05$, FWE corrected are listed in Table 1 and some of them are labelled here: FPC: fronto-polar cortex; ACC: anterior cingulate cortex; PCG: pre-central gyrus; PoCG: post-central gyrus; OC: occipital cortex; MTG: middle temporal gyrus; STC: superior temporal cortex; PoCiG: posterior cingulate gyrus; PHG: parahippocampal gyrus; Th: thalamus; MFG: medial frontal gyrus; SFG/MiFG: superior frontal gyrus/middle frontal gyrus; IPC: inferior parietal cortex. BOLD contrasts are superimposed on a T1 structural image in axial sections from $z=-20$ to $z=64$, in neurological orientation. The adjacent sections are 12 mm apart. The colour bar represents voxel *T* value.

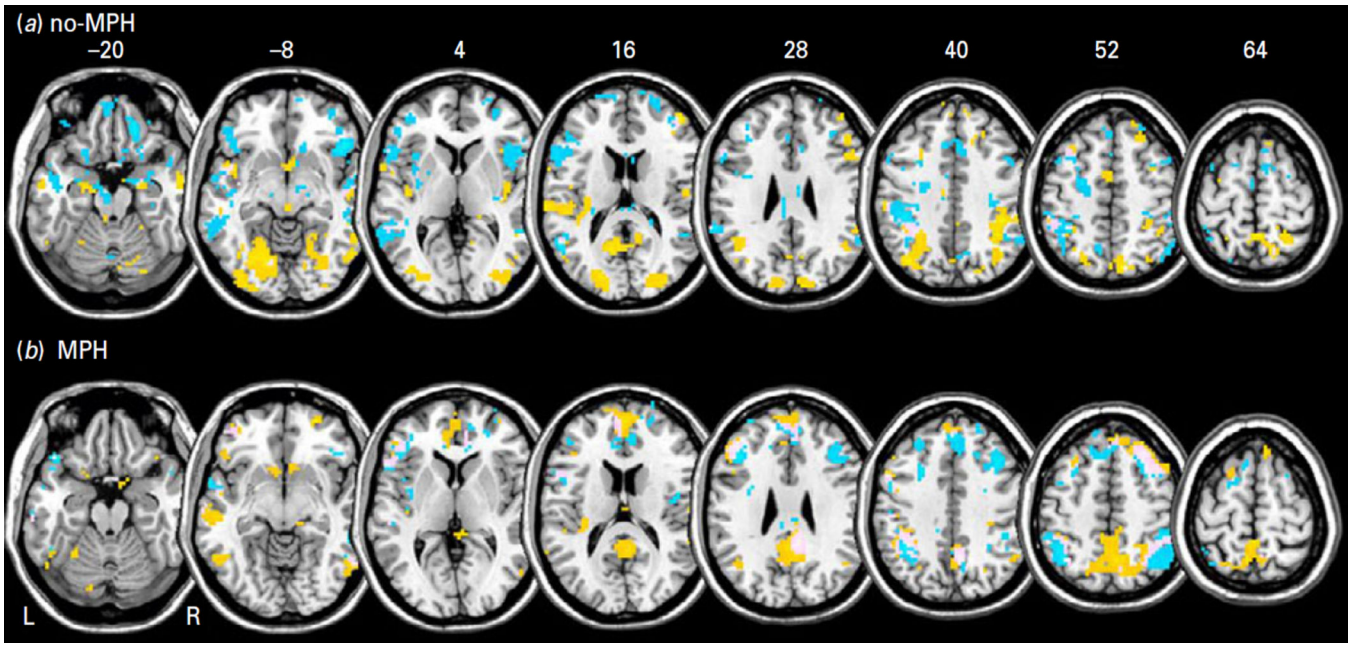

Fig. 3.

One sample *t*-tests for global resting-state functional connectivity for (a) no-MPH and (b) MPH group showing the top 5% of voxels. Warm and cool colour shows positive and negative connectivity. BOLD contrasts are superimposed on a T1 structural image in axial sections from $z=-20$ to $z=64$, in neurological orientation. The adjacent sections are 12 mm apart.

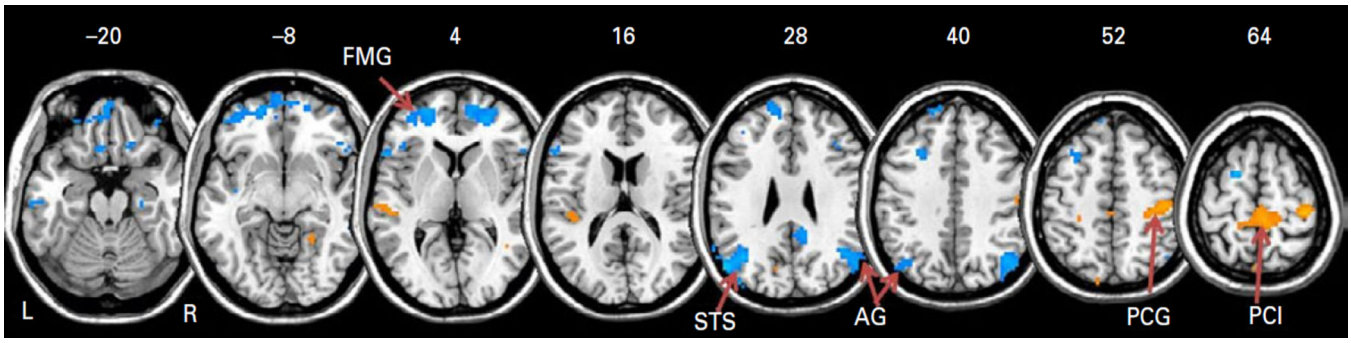

Fig. 4.

Two sample *t*-test shows differences in global resting-state functional connectivity at $p<0.001$, uncorrected: MPH>no-MPH (warm colours) and no-MPH>MPH (cool colours). BOLD contrasts are superimposed on a T1 structural image in axial sections from $z=-20$ to $z=64$, in neurological orientation. The adjacent sections are 12 mm apart. Clusters that met cluster $p<0.05$, FWE corrected are listed in Table 2 and labelled here: AG: angular gyrus; FMG: frontal marginal gyrus; PCG: pre-central gyrus; PCL: paracentral lobule; STS: superior temporal sulcus.

Table 1

Brain regions showing significant differences in seed-based functional connectivity between participants who received methylphenidate (MPH) and those who did not (no-MPH); two-sample *t* test, at voxel $p<0.001$ uncorrected and cluster-level $p<0.05$, FWE corrected or voxel $p<0.05$ FWE corrected

						MNI coordinates (mm)				
Seed ROI	**Contrast**	**MPH**	**no-MPH**	**Cluster size (mm^3)**	***z*-score**	***X***	***Y***	***Z***	**Side**	**Identified region**
Caudate	MPH>no-MPH	+	_^	2970	4.42	−45	−19	55	L	Pre-central G
	no-MPH>MPH	_^	++^	4023	4.49	30	53	34	R	Fronto-polar C
		_^	+^	4725	4.46	−36	−31	1	L	Superior Temporal G
		_^	+^	4752	3.99	45	2	−41	R	Middle Temporal G
Pallidum	MPH>no-MPH	_^	_^	4617*	4.8	24	−85	−11	R	Inferior Occipital G
		_^	_^		3.86	36	−85	−2	R	Middle Occipital G
		++^	−	3780	4.54	−54	−10	46	L	Pre-central G
		++^	−		3.53	−48	−25	49	L	Post-central G
		+	_^	2538	3.86	−30	−31	67	L	Pre-central G
	no-MPH>MPH	−	++^	36612*	5.05	−15	−49	−41	L	Cerebellum
		_^	+	4131	4.15	6	−40	25	R/L	Cingulate G
		_^	++^	4752	1.07	12	59	13	R	Medial frontal G
		_^	++^		3.77	9	38	10	R/L	Anterior cingulate G
Putamen	MPH>no-MPH			None significant						
	no-MPH>MPH	−	+	6426*	4.59	6	−40	22	R/L	Posterior cingulate G
		_^	+		4.41	0	−25	28	R/L	Mid-cingulate G
		+^	++^	34911	4.5	−12	−46	−35	L	Cerebellum
		−	++^	1782**	4.9	66	−46	34	R	Supramarginal G
Thalamus	MPH>no-MPH	++^	_^	21600*	5.31	27	−37	61	R	Post-central G
		++^	_^		4.32	45	−7	34	R	Pre-central G
		++^	_^		4.19	63	−7	7	R	Superior Temporal G
		+^	_^	6453*	4.81	39	−70	−14	R	Middle Occipital G

Seed ROI	Contrast	MPH	no-MPH	Cluster size (mm^3)	z-score	MNI coordinates (mm) X	Y	Z	Side	Identified region
		+^	–^		3.94	24	−58	−17	R	Cerebellum
		+^	–^		3.83	33	−64	−17	R	Inferior Occipital G
		++^	–	3456*	4.77	−63	−16	10	L	Post-central G
		++^	–	15471	4.48	−45	−10	46	L	Pre-central G
		++^	–		4.3	−54	−19	46	L	Post-central G
		++^	+^	3213	3.75	3	−7	61	R/L	Medial Frontal G
		+^	–^	2592**	4.81	0	−88	46	R/L	Precuneus
		++^	–	2133**	4.69	−21	−7	−26	L	Parahippocampal G
	no-MPH>MPH	–^	+^	54837*	6.17	12	−85	−32	R	Cerebellum
		–^	+^	67068*	5.77	39	29	55	R	Middle Frontal G
		–^	+^		5.3	21	26	58	R	Superior Frontal G
		–^	+^		5.22	51	23	43	R	Middle Frontal G
		–^	+	16740*	5.74	57	−58	46	R	Inferior Parietal G
		+^	++^	7695*	5.36	−6	−13	4	R/L	Thalamus
		–^	–	7749*	5.1	−60	−58	43	L	Inferior Parietal G

*Also significant at peak $p<0.05$, FWE corrected

**Only significant at peak $p<0.05$, FWE corrected; R- right, L- left; G- gyrus; +/++ positively/more positively connected and −/− negatively/more negatively connected by one-sample *t*-test, with the sign and magnitude of connectivity determined by the effect size of each cluster.

^A superscript on +/− indicates significant at $p<0.05$ for one sample *t*-test of the effect size for the cluster.

Table 2

Summary of significant negative global connectivity differences between participants who received methylphenidate (MPH) and those who did not (no-MPH) at a combined threshold of voxel $p<0.001$ uncorrected and cluster-level $p<0.05$, FWE corrected

					MNI coordinates (mm)				
Contrast	**MPH**	**no-MPH**	**Cluster size (mm^3)**	***z*-score**	***X***	***Y***	***Z***	**Side**	**Identified region**
MPH>no-MPH	–	–	11124	4.4	39	−28	61	R	Pre-central G
	–	–		4.24	9	−25	76	R	Paracentral lobule
no-MPH>MPH	–	–	6210	4.53	−57	−67	22	L	Superior temporal S
	–	–		4.39	−54	−73	31	L	Angular G
	–	–	9990	4.33	−21	53	−2	L	Frontal marginal G
	–	–		3.96	24	47	4	R	Middle frontal/anterior cingulate G
	–	–	5940	4	42	−61	31	R	Angular G
	–	–		3.96	42	−67	40	R	Inferior parietal G
	–	–		3.89	54	−70	25	R	Middle temporal G

R- right, L- left; G- gyrus; S- sulcus; −/− indicates significance of the negative connectivity.