

Comparative effects of methylphenidate, modafinil and MDMA on response inhibition neural networks in healthy subjects

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Abstract

Background: Psychostimulants such as methylphenidate (MPH) and modafinil are increasingly used by healthy people for cognitive enhancement purposes, whereas the acute effect of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) on cognitive functioning in healthy subjects remains unclear. This study directly compared the acute effects of MPH, modafinil and MDMA on the neural mechanisms underlying response inhibition in healthy subjects.

Methods: Using a double-blind within-subject placebo-controlled cross-over design, MPH, modafinil and MDMA were administered to 21 healthy subjects, while performing a Go/No-Go event-related functional magnetic resonance imaging task to assess brain activation during motor response inhibition.

Results: Relative to placebo, MPH and modafinil but not MDMA improved inhibitory performance. MPH significantly increased activation in the right middle frontal gyrus, middle/superior temporal gyrus, inferior parietal lobule, presupplementary motor area and anterior cingulate cortex compared with placebo. MPH also induced significant higher activation in the anterior cingulate cortex and presupplementary motor area and relative to modafinil. Relative to placebo, modafinil significantly increased activation in the right middle frontal gyrus and superior/inferior parietal lobule, while MDMA significantly increased activation in the right middle/inferior frontal gyrus and superior parietal lobule.

Conclusions: Direct comparison of MPH, modafinil and MDMA revealed broad recruitment of fronto-parietal regions but specific effects of MPH on middle/superior temporal gyrus, anterior cingulate cortex and presupplementary motor area activation, suggesting dissociable modulations of response inhibition networks and potentially the superiority of MPH in the enhancement of cognitive performance in healthy subjects.

Keywords: cognitive control, response inhibition, methylphenidate, modafinil, MDMA, fMRI

Significance Statement

- Methylphenidate (MPH) and modafinil are being increasingly used by healthy people for cognitive enhancement purposes, whereas the acute effect of the party drug MDMA (ecstasy) on cognitive functioning in healthy subjects remains still unclear.
- This study directly compared the acute effects of MPH, modafinil and MDMA on the behavioural and neural correlates of response inhibition in healthy subjects.
- Our findings reveal that MPH and modafinil but not MDMA improved inhibitory performance.
- MPH, modafinil and MDMA revealed broad recruitment of fronto-parietal regions but specific effects of MPH on middle/superior temporal gyrus, anterior cingulate cortex and presupplementary motor area activation.
- The additional recruitment of fronto-temporal regions might reflect the superiority of MPH for enhancing cognitive performance in healthy subjects.

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Introduction

Successful response inhibition is essential to process and integrate incoming perceptual information in a flexible fashion (Bari and Robbins, 2013). Such a trial-by-trial adjustment of information processing is important for adapting ongoing behaviour according to prevailing conditions in the respective environment. The inability to inhibit responses has been linked to several prevalent disorders, including obsessive-compulsive disorder, autism, and attention-deficit/hyperactivity disorder (ADHD). Response inhibition - as often operationalized by the Go/No-Go task (Bari and Robbins, 2013) - has been associated with significant activation in a widespread network of brain regions including the superior, middle and inferior frontal gyrus (SFG, MFG, IFG), inferior parietal lobule, striato-thalamic regions and the presupplementary motor area (pre-SMA) / anterior cingulate cortex (ACC) (Simmonds et al., 2008; Swick et al., 2011). Although a complex neural circuit is involved in response inhibition, it is the activation in the right IFG that allows the inhibition of a pre-potent motor response, a conclusion that is corroborated by connectivity and causality studies (Aron et al., 2014). Hence the assessment of IFG activation help to study the neuropharmacological mechanisms of response inhibition and to test the efficacy of potentially novel medications for disorders associated with impaired response inhibition.

A previous meta-analysis of stop-signal and Go-NoGo tasks showed that ADHD patients reveal reduced activation in the right IFG, SMA and ACC, as well as striato-thalamic areas during response inhibition (Hart et al., 2013). It has been shown that MPH, the most frequently prescribed drug for the treatment of ADHD (Briars and Todd, 2016), normalized fronto-temporal activation (including right IFG) during response inhibition in ADHD patients during the stop-signal (Rubia et al., 2014). The therapeutic effect of MPH is likely mediated through increases in extracellular levels of norepinephrine (NE) and dopamine (DA) in prefronto-striatal brain regions (Hannestad et al., 2010), both neurotransmitters critically involved in response inhibition (Bari and Robbins, 2013). Acute MPH administration also

improved response inhibition during the stop-signal task (Nandam et al., 2011) and increased activation in the ACC, right IFG, superior temporal gyrus, caudate and left MFG and left angular gyrus during the Go/No-Go task in healthy subjects (Nandam et al., 2014). In contrast, however, it has also been shown that MPH reduced activation in the right IFG / insula to infrequent stimuli associated with successful inhibition, failed inhibition and attentional capture during stop-signal tasks in healthy subjects (Pauls et al., 2012). Interestingly, another study found that MPH increased activation in the putamen only during inhibition errors but not during successful inhibition and only in the Go/No-Go but not stop-signal task (Costa et al., 2013).

Modafinil, licensed for the treatment of narcolepsy, shift-work disorder and obstructive sleep apnea (Erman et al., 2007; Sheng et al., 2013), has also emerged as a possible agent to improve cognition. Both MPH and modafinil are being increasingly used as cognitive enhancers for non-medical reasons (Sahakian et al., 2015). Modafinil produced cognitive enhancing effects and decreased stop-signal reaction time in healthy adults (Turner et al., 2003) and improved cognitive functioning in people with ADHD (Turner et al., 2004). Acute administration of modafinil to healthy subjects improved task performance during the stop-signal task but did not modulate brain activation (Schmaal et al., 2013). Modafinil is a weak inhibitor of DA and NE transporter and has additional effects on the brain GABA, glutamate, and orexin systems (Minzenberg and Carter, 2008), although the precise neuropharmacological mode of action of modafinil remains unclear.

Response inhibition is also strongly associated with integrity of the serotonergic (5-HT) system in humans and animals (Eagle et al., 2007). A reduction of 5-HT has been linked to impulsive, suicidal and aggressive behaviour, whereas high levels of 5-HT have been shown to decrease impulsive behaviour (Pattij and Vanderschuren, 2008; Fitzgerald, 2011). A

previous study demonstrated improved response inhibition in a stop-signal task after acute administration of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) in healthy subjects compared to placebo (Ramaekers and Kuypers, 2006). Given that MDMA acts primarily by releasing 5-HT from presynaptic terminals (Liechti and Vollenweider, 2000; Hysek et al., 2011; Hysek et al., 2012), the authors suggested a possible link with 5-HT neurotransmission for this effect (Ramaekers and Kuypers, 2006). However, this MDMA-induced improvement in response inhibition is in contrast to another study reporting increased reaction times in a stop-signal task after MDMA administration to healthy controls (van Wel et al., 2012).

The present study directly compares for the first time the acute effects of MPH, modafinil, and MDMA on the behavioural and neural correlates of response inhibition in healthy controls. It thereby sought to elucidate the neural mechanisms underlying MPH’s and modafinil’s cognitive enhancing effect and to provide further insights into the neuropharmacological base of response inhibition. Using a within-subject placebo-controlled cross-over design, MPH, modafinil, and MDMA were administered to healthy subjects while performing a fMRI Go/No-Go task. Our a priori hypothesis was that MPH and modafinil but not MDMA would improve inhibitory performance during the Go/No-Go task compared to placebo. We further predicted that MPH and modafinil but not MDMA would increase brain activation (in particular IFG activation) during response inhibition.

Method

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the local Ethics Committee and Swiss Agency for Therapeutic Products (Swissmedic). The administration of MDMA to healthy subjects was authorized by the Swiss Federal Office for Public Health, Bern, Switzerland. The study was registered at ClinicalTrials.gov (NCT01951508). After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion.

Participants and study design

We recruited a group of 24 healthy subjects by word of mouth or an advertisement placed on the web market platform of the University of Basel. Subjects were excluded due to the following reasons: a) chronic or acute medical condition including clinically relevant abnormality in physical exam, laboratory values, or ECG. In particular: seizures or a cardiac or neurological disorder; b) current or previous psychotic or major affective disorder; c) prior illicit drug use more than 5 times (except occasional use of THC-containing products) or any time within the previous 2 months; d) pregnant or nursing women; e) participation in another clinical trial (currently or within the last 30 days); f) use of medications that are contraindicated or otherwise interfere with the effects of the study medications (monoamine oxidase inhibitors, antidepressants, sedatives etc.) and g) tobacco smoking (regularly > 10 cigarettes /day). Previous drug use is reported in the Supplementary Table S1. Subjects were asked to abstain from any illicit drug use including cannabis during the study and drug tests were performed during screening and randomly before test-sessions. There were no positive urine tests for stimulants, opioids, THC, or hallucinogens and therefore no exclusions from the study. Subjects were also asked to abstain from excessive alcohol consumption between test sessions and in particular to limit their use to one glass on the day

before the test sessions.

Using a double-blind placebo-controlled randomized within-subject design, participants received methylphenidate (60 mg), modafinil (600 mg), MDMA (125 mg) and placebo in a counter-balanced order. The wash-out period between sessions was at least 7 days. Three participants did not complete all four Go/No-Go sessions, resulting in a final sample of 21 subjects (10 men, 11 women; mean age: 23.6 ± 2.8 , range: 21-30).

MDMA was administered in a single absolute dose of 125 mg corresponding to a relatively high dose of (mean \pm SD) 1.9 ± 0.3 mg/kg body weight. This dose of MDMA is in the high range of the doses typically used in clinical research (Kirkpatrick et al., 2014; Kirkpatrick et al., 2015; Kuypers et al., 2017) and is within the dose range that is used recreationally (Brunt et al., 2012). MPH was administered in a single relatively high dose of 60 mg as done in previous studies (Martin et al., 1971; Korostenskaja et al., 2008). The subjective and cardiostimulant effects of this dose have previously been assessed on the same tests (Hysek et al., 2014) and have also been statistically compared with a lower dose of 40 mg (Schmid et al., 2014). The doses of MDMA and MPH were expected to be equivalent regarding their cardiovascular stimulant effects (Hysek et al., 2014). The therapeutic starting dose of modafinil is 100 mg and common doses are 400 mg/day. In this study, modafinil was administered in a single high dose of 600 mg. The goal was to use high single doses of all substances to maximize the subjective drug effects and reach responses close to E_{\max} .

Drug administration

Each of the four test sessions lasted 7 hours. Subjects arrived at the laboratory at 8:45 AM. MPH, modafinil, MDMA, or placebo was administered orally at 9:45 AM. fMRI scanning was performed between 11:15 AM and 12:15 PM during the expected drug peak effects (Wong et al., 1998; Hysek et al., 2014; Schmid et al., 2014). The sessions ended at 3:45 PM.

Psychometric Assessment

The Adjective Mood Rating Scale (AMRS) (Janke, 1978) was used to assess subjective drug effects directly before (75 minutes post-treatment) and after (150 minutes post-treatment) the fMRI scanning took place. We averaged the values of the 75 and 150 min post-treatment assessments to best relate the subjective drug effects to the Go/No-Go task. In this study, we focussed on the AMRS subscales related to cognitive control functioning such as activation, concentration and performance-related activation. Performance-related activation is the sum of activation and concentration ratings.

The Go/No-Go task

Ninety minutes after drug administration, all patients underwent an event-related Go/No-Go fMRI paradigm that was conducted with jittered inter-stimulus intervals (ISIs) and incorporated infrequently presented oddball stimuli to optimize statistical efficiency, i.e., the accuracy with which the hemodynamic response to different stimuli can be estimated for a given amount of imaging time (Dale, 1999). The task is a well-validated paradigm used in previous fMRI studies (Rubia et al., 2006; Schmitz et al., 2006; Smith et al., 2006; Borgwardt et al., 2008; Lawrence et al., 2009; Atakan et al., 2013; Schmidt et al., 2013; Bhattacharyya et al., 2014; Daly et al., 2014; Bhattacharyya et al., 2015), requiring either the execution or the inhibition of a motor response, depending on the visual presentation of the stimuli. The basic Go task is a choice reaction time paradigm, in which arrows point either to the left or to the right side for 500 ms, with a mean ISI of 1800 ms (jitter range: 1600–2000 ms). During Go trials, subjects were instructed to press a left or right response button according to the direction of the arrow. In 11% of the trials, arrows pointing upward appeared. During these so-called 'No-Go' trials, participants were required to inhibit their motor response. During another 11% of the trials, arrows pointing left or right at a 23° angle were presented, and

subjects were told to respond to these in the same way as for Go stimuli (even though they pointed obliquely). These 'oddball' stimuli were used to control for novelty effects associated with the low frequency and different orientation of the No-Go relative to the Go trials (stimulus-driven attention allocation). In total, there were 24 No-Go, 160 Go, and 24 oddball trials, with task duration of approximately 6 min.

Analyses of inhibitory performance and subjective feelings of cognitive controls

Behavioural task performance was evaluated by the probability of inhibition, correct number of Go trials and reaction time to Go trials. Treatment differences in task performance and the four AMRS items were examined using a repeated measures analysis of variance (ANOVA) with treatment as within-subject factor. Where the ANOVA null hypothesis of equal means was rejected, we used post hoc tests (Bonferroni).

fMRI image acquisition and analysis

Scanning was performed on a 3T scanner (Siemens Magnetom Verio; Siemens Healthcare, Erlangen, Germany), using an interleaved T2*-weighted echo planar imaging (EPI) sequence with 2.5 s repetition time, 28 ms echo time, a matrix size of 76 x 76, and 38 slices with 0.5-mm interslice gap, providing a resolution of 3 x 3 x 3 mm³ and a field of view of 228 x 228 cm². In total, 160 volumes were acquired.

EPIs were analysed using an event-related design with SPM12 (www.fil.ion.ucl.ac.uk/spm). During preprocessing, images were realigned to the first image in the series, spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with a Gaussian kernel of 8 mm full half-width maximum (FWHM). All images underwent visual inspection and participants with a high number of severely corrupted images and/or gross

artefacts were excluded (none). Additionally, all images were checked for movement artefacts, and all scans with more than 3 mm deviation from the previous scan in any dimension, resulting in corrupted volumes, were excluded and replaced with the average of the neighbouring volumes (4 volumes were replaced in total, all after MDMA administration). Subjects with more than 10% corrupted volumes were excluded (none). There were no movement differences across treatment in any dimension (Supplementary Table S2).

Voxel-wise maximum likelihood parameter estimates were calculated during the first level analysis using the general linear model. Our design matrix included an autoregressive AR(1) model of serial correlations and a high-pass filter with a cutoff of 128 s. Onset times for Go, No-Go, and oddball trials across all four treatments were convolved with a canonical hemodynamic response function and motion parameters acquired during the realignment procedure were added to the individual design matrix as multiple regressors. Five subject-specific contrast images were generated per participant: four images representing response inhibition controlled for the attentional oddball effect due to the low frequency occurrence of No-Go trials (No-Go vs. Oddball trials) for each treatment (placebo, MPH, modafinil, MDMA); and one average image for response inhibition over all treatments (to compute the effect of task). A 1-sample t test was performed to examine whole brain activation during response inhibition across all treatments (effect of task). Treatment differences were examined using a within-subject ANOVA design. To control for drug order effects, we included drug order as regressor of no interest into the ANOVA analysis. According to recent recommendations on cluster-extent based thresholding in fMRI analyses (Woo et al., 2014), significance was assessed at a cluster-level threshold of $p < 0.05$ family-wise error (FWE) corrected across the whole brain, using an uncorrected cluster-forming threshold of $p < 0.001$ with an extent threshold of 20 voxels.

Result

Subjective feelings of cognitive performance

All stimulants overall significantly increased scores on activation as revealed by a significant main effect of treatment ($F_{3,18} = 3.622, p=0.033$). Post hoc testing showed a significantly enhanced activation following MPH administration relative to placebo ($p=0.018$), while no other differences between drugs were found (Figure 1). We found no main effect of treatment for concentration ($F_{3,18} = 1.953, p=0.157$; Figure 1). Furthermore, there was a main effect of treatment for performance-related activation ($F(3, 18) = 3.323, p=0.043$). Bonferroni post hoc testing yielded that this effect was driven by a significant enhancement of performance-related activation after MPH intake relative to placebo ($p=0.022$) (Figure 1).

Insert Figure 1 about here

Behavioural task performance

We found a significant treatment effect for probability of inhibition ($F(3, 18) = 4.24, p = 0.020$), indicating a generally improved inhibitory performance after stimulant exposures. Post hoc analysis revealed that MPH ($p = 0.012$) and modafinil ($p = 0.038$), but not MDMA improved inhibitory performance relative to placebo (Figure 2A).

Stimulants significantly increased the responses to Go trials ($F(3, 18) = 7.30, p = 0.002$).

The number of correct Go trials was higher following MPH ($p = 0.003$) and modafinil ($p = 0.005$) but not MDMA administration compared with placebo (Figure 2B). There was also a significant treatment effect for reaction times ($F(3, 18) = 6.19, p = 0.004$), indicating faster reactions in response to Go trials after stimulant intake. Relative to placebo, reaction times were significantly lower after MPH exposure ($p = 0.003$, Figure 2C).

Insert Figure 2 about here

Brain activation during response Inhibition

Effect of Task

Combined treatment maps revealed significant activation in frontal, parietal, temporal, striato-thalamic and cerebellar brain regions during response inhibition (Supplementary Table S3).

Treatment effects during response inhibition

Brain activation during response inhibition significantly differed across treatments in the right MFG, superior/inferior parietal lobule and supramarginal gyrus and pre-SMA (Supplementary Figure 1 and Supplementary Table S4).

Post hoc testing revealed that MPH increased brain activation relative to placebo in the right MFG, inferior parietal lobule, supramarginal gyrus, middle/superior temporal gyrus, as well as in the right ACC and pre-SMA (Figure 3A, Supplementary Table S5). Compared with placebo, modafinil increased activation in the right MFG and superior and inferior parietal lobule, whereas MDMA increased activation in the right MFG (extending to the IFG), superior parietal lobule and angular gyrus (Figure 3B and 3C, Supplementary Table S5). Finally, ACC and pre-SMA activation was significantly higher after MPH compared to modafinil administration (Figure 3D, Supplementary Table S5).

Insert Figure 3 about here

Discussion

To the best of our knowledge, this is the first within-subject study directly comparing the acute effects of MPH, modafinil and MDMA on the behavioural and neural correlates of response inhibition in healthy controls. We found that both MPH and modafinil enhanced inhibitory performance with a concomitant increase in fronto-parietal activation. In addition, MPH was dissociable from modafinil and placebo in terms of its modulation of ACC and pre-SMA activation. Finally, MDMA did not alter inhibitory performance, but was associated with alteration in fronto-parietal activation relative to placebo.

Besides their use for treating symptoms in ADHD patients (Briars and Todd, 2016), psychostimulants such as MPH and modafinil are being increasingly used by healthy people for cognitive enhancement purposes mainly to produce alertness and to enhance professional performance (Sahakian et al., 2015). In the present study, both MPH and modafinil improved inhibitory performance in healthy people during the Go/No-Go task relative to placebo, supporting the view of beneficial effect of MPH and modafinil on cognitive performance in healthy people (Sahakian and Morein-Zamir, 2015). These findings are in line with other studies in healthy subjects demonstrating improved response inhibition (stop-signal reaction time) after acute MPH (Nandam et al., 2011) and modafinil (Turner et al., 2003; Schmaal et al., 2013).

Consistent with another Go/No-Go study in healthy subjects (Nandam et al., 2014), we found that MPH increased activation in right MFG, superior temporal gyrus and ACC compared with placebo. MPH also increased activation in the right supramarginal gyrus, inferior parietal lobule, middle temporal gyrus and pre-SMA in this study. Although MPH also increases DA levels in prefrontal regions, the here observed increase in prefrontal activation is likely mediated via NE neurotransmission (Chamberlain and Sahakian, 2007), given that in frontal

regions MPH increases NE more than DA via reuptake inhibition of NE transporter (Hannestad et al., 2010). This corresponds with a previous fMRI Go/No-Go study, which showed that atomoxetine, a selective NE reuptake inhibitor increased fronto-temporal brain activation in healthy people (Chamberlain et al., 2009).

In the present study, acute modafinil administration also increased activation in the right MFG and superior / inferior parietal lobule compared with placebo. Modafinil is a non-amphetamine psychostimulant that elevates synaptic NE and DA levels in prefrontal regions (de Saint Hilaire et al., 2001). Many of modafinil's cognitive and behavioural effects are mediated by adrenergic receptors (Minzenberg and Carter, 2008). A previous fMRI study in healthy humans reported that modafinil increased activation in the locus coeruleus and prefrontal cortex and the functional coupling between these regions during a cognitive control task (Minzenberg et al., 2008). Another study in rats demonstrated that response inhibition in the stop-signal paradigm improved after modafinil and MPH administration, and these effects were not blocked by concurrent DA receptor antagonism, nor was response inhibition affected by DA receptor antagonism per se (Eagle et al., 2007). Furthermore, direct infusion of the alpha-2 adrenoceptor antagonist yohimbine into the prefrontal cortex of non-human primates impaired inhibitory control on a Go/No-Go paradigm, and was associated with increased locomotor hyperactivity (Ma et al., 2005). Together, these findings suggest that increased prefrontal activation after modafinil and MPH administration is more likely mediated by increased levels of NE than DA. Such an interpretation resonances with previous works suggesting a key role for prefrontal NE neurotransmission in the inhibition of an already initiated response, whereas DA appears to modulate motor readiness for both inhibition and activation, potentially at the level of the striatum (Chamberlain and Sahakian, 2007; Bari and Robbins, 2013).

Party drugs such as MDMA are consumed recreationally for their acute mood- and socially-enhancing effects. It has been shown that the acute psychological and physiological effects

of MDMA in humans are mediated via an increase in 5-HT (Liechti et al., 2000; Liechti and Vollenweider, 2000; Liechti et al., 2001). Acute MDMA administration has been shown to increase impulse control when 5-HT levels are high (Ramaekers and Kuypers, 2006). In the present study, acute MDMA administration did not affect inhibitory performance relative to placebo during the Go/No-Go task. This finding supports previous evidence that pharmacological manipulations of the 5-HT system has no detectable behavioural effects on response inhibition (Chamberlain and Sahakian, 2007). Although behavioural NoGo effects of 5-HT interventions are often mild or absent in humans, neuroimaging has revealed altered activation in frontal regions. For instance, reduced IFG activation during the Go/No-Go task has been found after acute tryptophan depletion in healthy volunteers (Rubia et al., 2005), while the selective 5-HT reuptake inhibitor escitalopram increased activation in the ACC, middle frontal and temporal gyrus during successful inhibition during a stop-change paradigm (extension of stop-signal task) (Drueke et al., 2013). Along this line, citalopram also increased activation in the right dorsolateral prefrontal cortex and middle frontal gyrus in healthy subjects during the Go/No-Go task (Del-Ben et al., 2005). Consistent with these findings, we found increased activation in the right MFG / IFG after MDMA administration compared with placebo, and also in the superior parietal lobule and angular gyrus. However, we cannot be certain whether this effect is mediated directly via a MDMA-induced increase in 5-HT (34) or rather NE (Hysek et al., 2012). This interpretation fits with findings from a recent study showing that the psychotropic effects of MDMA are not only mediated through 5-HT but also NE release (Hysek et al., 2011; Hysek et al., 2012). However, although there were indications of improvements in all behavioural measures after MDMA intake in this study, the MDMA-induced increase in right IFG /MFG and inferior parietal lobule activation may not have been sufficient to improve inhibitory performance. The lack of effect on inhibitory performance following MDMA administration despite neural changes is intriguing. It supports previous studies using acute tryptophan depletion in healthy controls that failed to find effects on inhibitory control during the Go/No-Go task in healthy subjects (Rubia et al., 2005; Lamar et al., 2009). We can speculate that potential noradrenergic MDMA effects on inhibitory

performance are offset by its serotonergic effects.

Finally, we found that acute MPH administration increased ACC and pre-SMA activation compared with modafinil. It has been proposed that the ACC is functionally interconnected with the basal ganglia and prefrontal cortex to form a key node of the response inhibition network (Aron et al., 2014). Whilst the prefrontal cortex maintains goals and the basal ganglia suppress irrelevant motor responses, the ACC may detect response conflict (Aron et al., 2014). Therefore ACC activation during response inhibition might reflect the conflict that occurs when two incompatible responses, such as whether to go or stop, are both compelling (MacDonald et al., 2000). Consistent with such an interpretation, a previous work showed that MPH acutely increased activation in the ACC and superior frontal gyrus for failed inhibitions during a stop-signal task, but only after controlling for attentional capture (Pauls et al., 2012). Furthermore, MPH also increased activation in the putamen during inhibition errors in the Go/No-Go task (Costa et al., 2013). Based on these findings and having in mind that we also controlled our imaging results for effects of stimulus-driven attention allocation, our finding suggests that MPH induced higher ACC activation in response to failed inhibitions than modafinil. ACC functioning has been associated with DA (Jocham and Ullsperger, 2009; Ko et al., 2009) and NE signalling (Aston-Jones et al., 2000; Aston-Jones and Cohen, 2005). Therefore, the MPH effect on ACC activation relative to modafinil is perhaps caused by differential modulation of DA pathways that project from the ventral tegmental (Williams and Goldman-Rakic, 1998) and of NE projections from the locus coeruleus (Aston-Jones et al., 2000). We might speculate that increased prefrontal activation after MPH is due to a higher blockade of DA and NE transporter relative to modafinil, leading to increased levels of DA and NE. In other words, the MPH-induced increase in prefrontal activation relative to modafinil is probably mediated through differential dynamic effects of MPH and modafinil on DA and NE in the prefrontal cortex (Rowley et al., 2014).

Some limitations of our study merit comment. Although we used a well-established paradigm from previous fMRI studies (Rubia et al., 2006; Schmitz et al., 2006; Borgwardt et al., 2008; Lawrence et al., 2009; Schmidt et al., 2013; Bhattacharyya et al., 2014; Daly et al., 2014; Bhattacharyya et al., 2015), we were not able to disentangle neural activation in response to successful versus failed inhibitions in the present study due to the modest number of NoGo trials. The small number of inhibition trials (i.e., NoGo trials) also limits the functional relevance of our behavioral results, albeit MPH and modafinil significantly increased the probability of inhibition. In this regard, it is also possible that the modest number of inhibition trials may explain the lack of alteration after MDMA administration. Future studies with a higher number of NoGo trials are required to address these points. Furthermore, we cannot exclude effects on cerebral vasoactivity induced by the drugs (Honey and Bullmore, 2004), which might have confounded our fMRI results. For instance, it is possible that the effect of modafinil and MPH on MFG, ACC and pre-SMA activation might be driven by their effects on regional cerebral blood flow in the same regions (Udo de Haes et al., 2007; Joo et al., 2008).

In conclusion, this study shows a common recruitment of fronto-parietal regions after MPH, modafinil and MDMA but specific effects of MPH on middle/superior temporal gyrus, anterior cingulate cortex and presupplementary motor area activation, suggesting dissociable modulations of response inhibition networks and potentially the superiority of MPH in the enhancement of cognitive performance in healthy subjects. These effects are likely mediated via increased extracellular concentrations of NE, which may have reached the highest levels after MPH administration.

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Conflict of Interest

The authors have nothing to declare.

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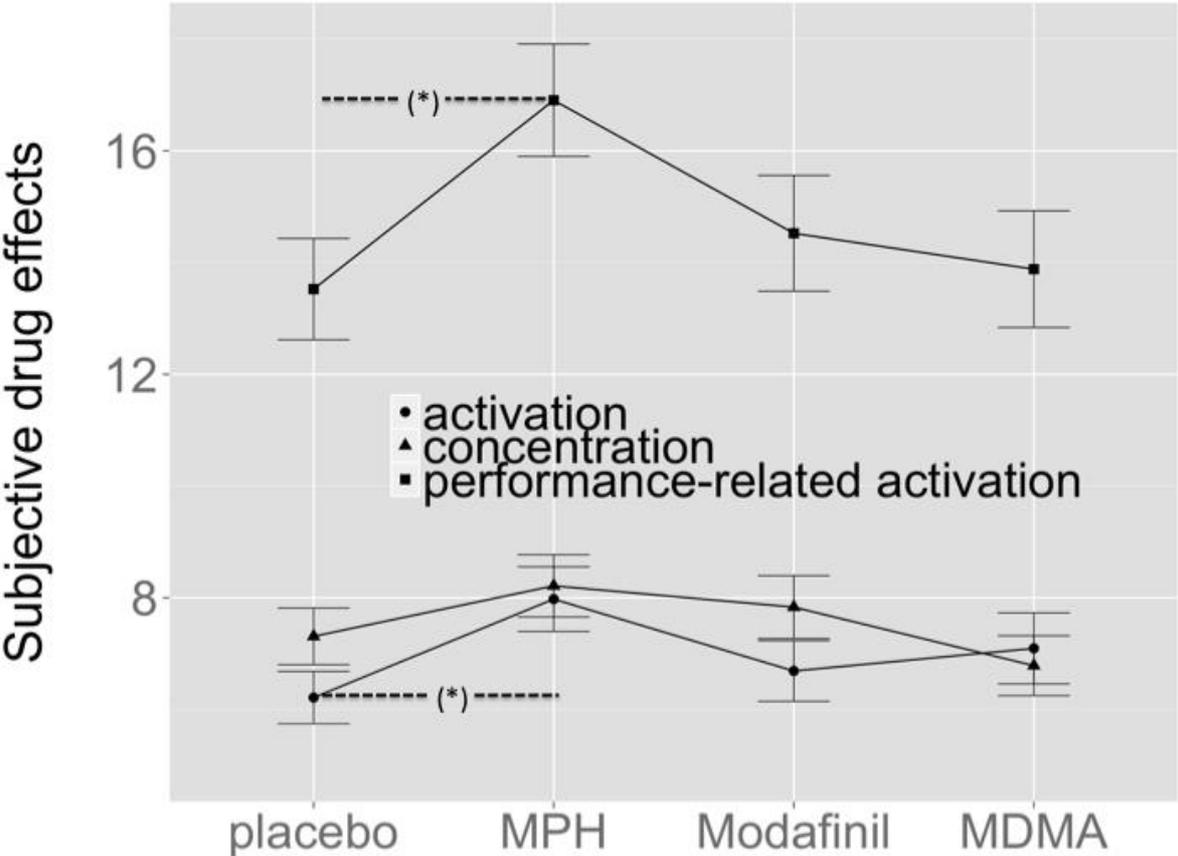
Figure legends

Figure 1. Subjective ratings of cognitive control (activation, concentration, and performance-related activation) after substance administration. (*) reflects significant differences compared to placebo. Error bars represent standard errors.

Figure 2. Task performance expressed as **A)** probability of inhibition, **B)** number of correct responses to Go trials and **C)** reaction times to Go trials after substance administration. (*) significant differences in task performance between substances. Error bars represent standard errors.

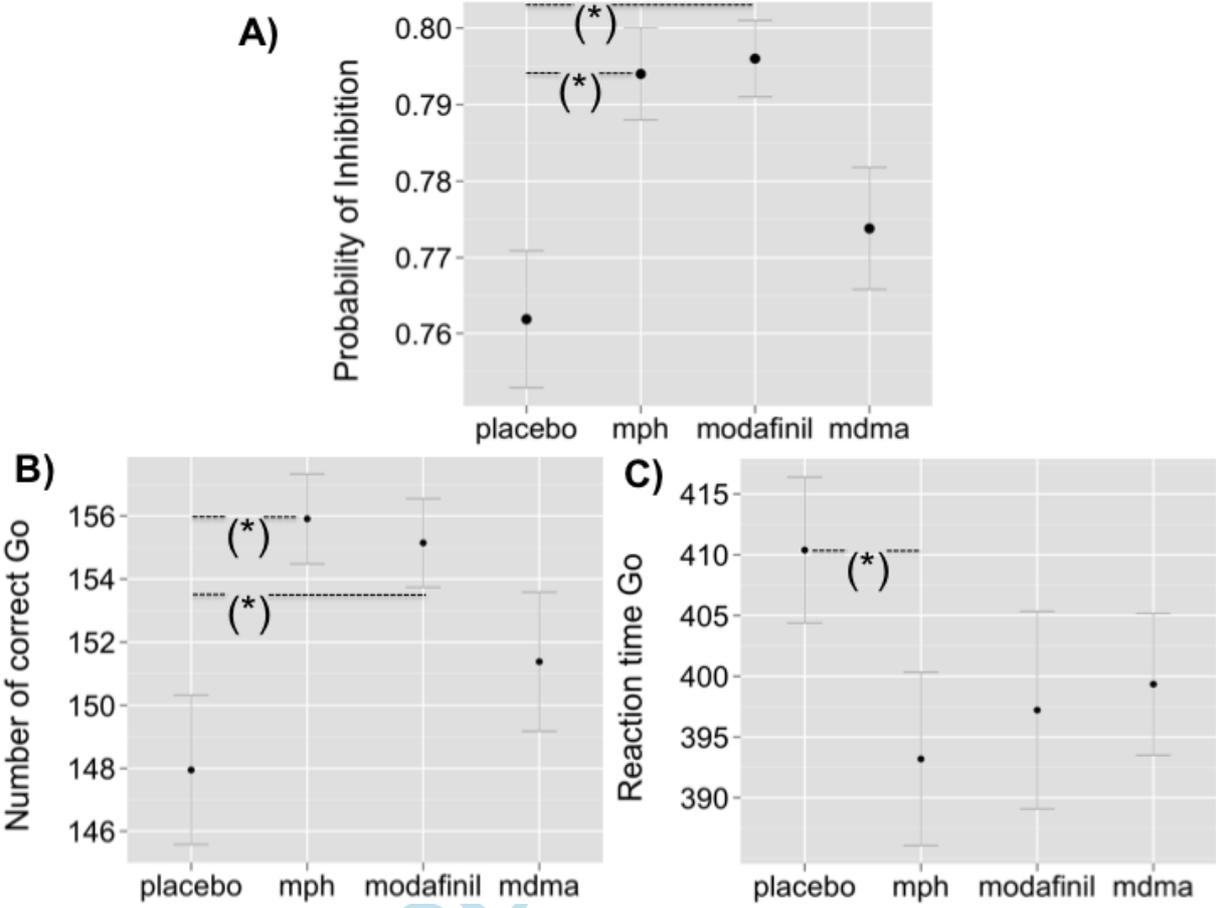
Figure 3. Significant differences in brain activation during response inhibition between **A)** MPH and placebo, **B)** modafinil and placebo, **C)** MDMA and placebo and **D)** MPH and modafinil. Image is displayed at a cluster-forming threshold of $p < 0.001$ uncorrected, with an extent threshold of 20 voxels. The colour bar indicates t-values.

Figure 1



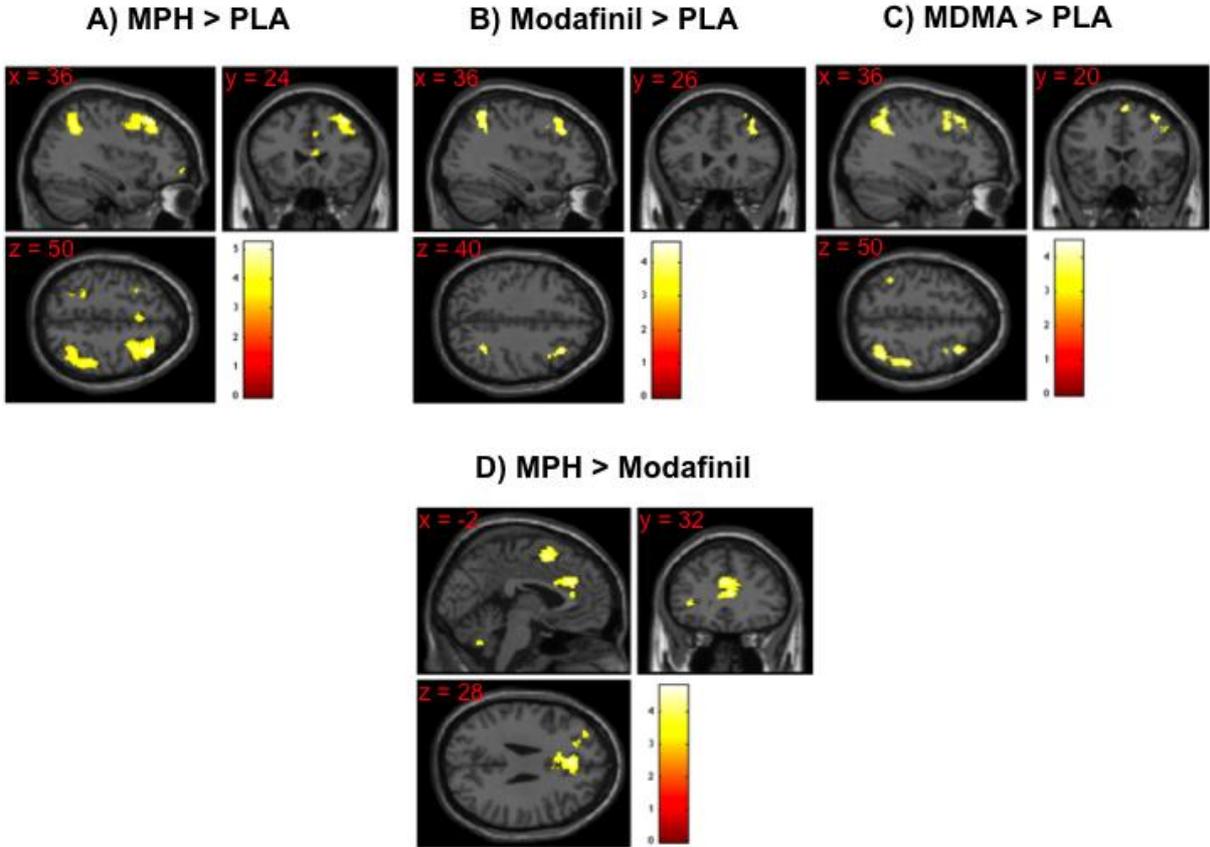
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Figure 2



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Figure 3



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