

REGULAR RESEARCH ARTICLE

Acute Effects of Methylphenidate, Modafinil, and MDMA on Negative Emotion Processing

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Abstract

Background: Stimulants such as methylphenidate and modafinil are frequently used as cognitive enhancers in healthy people, whereas 3,4-methylenedioxymethamphetamine (ecstasy) is proposed to enhance mood and empathy in healthy subjects. However, comparative data on the effects of methylphenidate and modafinil on negative emotions in healthy subjects have been partially missing. The aim of this study was to compare the acute effects of methylphenidate and modafinil on the neural correlates of fearful face processing using 3,4-methylenedioxymethamphetamine as a positive control.

Methods: Using a double-blind, within-subject, placebo-controlled, cross-over design, 60 mg methylphenidate, 600 mg modafinil, and 125 mg 3,4-methylenedioxymethamphetamine were administered to 22 healthy subjects while performing an event-related fMRI task to assess brain activation in response to fearful faces. Negative mood states were assessed with the State-Trait Anxiety Inventory and subjective ratings.

Results: Relative to placebo, modafinil, but not methylphenidate or 3,4-methylenedioxymethamphetamine, increased brain activation within a limbic-cortical-striatal-pallidal-thalamic circuit during fearful face processing. Modafinil but not methylphenidate also increased amygdala responses to fearful faces compared with 3,4-methylenedioxymethamphetamine. Furthermore, activation in the middle and inferior frontal gyrus in response to fearful faces correlated positively with subjective feelings of fearfulness and depressiveness after modafinil administration.

Conclusions: Despite the cognitive enhancement effects of 600 mg modafinil in healthy people, potential adverse effects on emotion processing should be considered.

Keywords: methylphenidate, modafinil, MDMA, fearful faces, fMRI, amygdala, negative emotions, adverse effects

Introduction

Methylphenidate (MPH) and modafinil are stimulants used in the treatment of attention deficit hyperactivity disorder and narcolepsy, respectively, but also frequently used as cognitive enhancers in healthy people (Repantis et al., 2010; Sahakian and Morein-Zamir, 2015). Despite their cognitive enhancing potential

in healthy subjects (Sahakian et al., 2015), their effects on negative emotions are still poorly understood. Exploring the effect of MPH and modafinil on negative emotion processing in healthy people is helpful to detect potential adverse effects despite their potential to improve cognitive performance. In this study,

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Significance Statement

Methylphenidate (MPH) and modafinil are increasingly used by healthy people for cognitive enhancement purposes. However, comparative data how they modulate negative emotion processing in healthy people are widely missing. This study directly compared the acute effects of MPH and modafinil on neural responses during fearful face processing and whether these effects were related to negative mood states. We used 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) as a positive control given its mood enhancing and prosocial effects in healthy people. We found that modafinil but not MPH increased activation in brain regions responsible for fear processing such as the amygdala and the prefrontal cortex compared with placebo and MDMA. Some of these effects were associated with subjective feelings of fear and depressiveness. Our findings suggest that potential adverse side effects should be considered when using 600 mg modafinil for cognitive enhancement purposes in healthy people.

we compared the acute effects of MPH and modafinil on neural responses to fearful faces and whether these effects were related to negative mood states. 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) was used as a positive control given its mood-enhancing and prosocial effect in healthy people (Hysek et al., 2014b; Kirkpatrick et al., 2014, 2015; Kuypers et al., 2017).

Recognition of the feelings of other people from their facial expression is fundamental to social interaction and behavior (Becker et al., 2012). Emotional faces, especially negative expressions, increase neuronal activity relative to neutral faces in specific brain areas, including the amygdala (Morris et al., 1996, 1998), whereas its volume is positively correlated with that of social networks (Bickart et al., 2011). Studies have consistently reported a positive relation between amygdala response to attended and unattended fearful faces and state-anxiety (for review, see Calder et al., 2011). Accordingly, the negative emotional processing bias in depressed individuals is characterized by amygdala hyperactivity in response to fearful faces (Peluso et al., 2009), which is more apparent with an implicit rather than explicit processing task (Monk et al., 2008). It has been shown that amygdala activation during implicit processing of fearful faces can be attenuated with acute administration of cannabidiol (Fusar-Poli et al., 2009a) and LSD (Mueller et al., 2017) in healthy people and after heroin administration in addicted patients (Schmidt et al., 2014). Notably, other cognitive enhancers such as amphetamine induce fear and anxiety (Ellinwood et al., 1973; Hall et al., 1988) along with exaggerated amygdala responses to fearful facial expressions in healthy subjects (Hariri et al., 2002). Therefore, it is instructive to compare the effects of MPH and modafinil on brain activation during fearful processing and the relationship to subjective mood states such as state-anxiety.

Studies investigating the cognitive enhancement effects of MPH in healthy people typically use dosages between 5 and 60 mg (Repantis et al., 2010; Linssen et al., 2014). In our previous study, we could show that a relatively high dose of 60 mg MPH improved behavioral and neural responses during cognitive control in healthy subjects (Schmidt et al., 2017). However, the same dose also increased state-anxiety in relation to placebo, increased misclassification of emotions as angry (Dolder et al., 2017), and enhanced the recognition of fearful faces in healthy people (Hysek et al., 2014a). Given the positive relationship between state-anxiety and amygdala activation during fearful face processing (Calder et al., 2011), these findings of these studies (Hysek et al., 2014a; Dolder et al., 2017) suggest that 60 mg MPH would increase amygdala activation in response to fearful faces despite its cognitive enhancement effect in healthy subjects.

Comparable with the effect of 60 mg MPH, it has been shown that 600 mg modafinil also improved behavioral (Makris et al., 2007) and neural responses during cognitive processing (Schmidt

et al., 2017), even though 200 mg is typically used for cognitive enhancing purposes in healthy subjects (Minzenberg and Carter, 2008) and related to task enjoyment (Müller et al., 2013). In our previous study, 600 mg modafinil had no effect on state-anxiety but also increased misclassification of emotion as angry, similar as 60 mg MPH (Dolder et al., 2017). Furthermore, 600 mg modafinil produced significant adverse effects that lasted up to 24 hours (mostly insomnia, headache, and lack of appetite) (Dolder et al., 2017). This is in line with a previous study showing a dose-response relationship in the incidence of adverse events after modafinil administration in healthy people (Wong et al., 1999a). In particular, this study reported that 50%, 83%, 100%, and 100% of subjects in the 200-, 400-, 600-, and 800-mg-dose groups reporting at least one adverse event such as insomnia, anxiety, and palpitations (Wong et al., 1999a). Together, these results suggest that even though 600 mg modafinil improves cognitive performance in healthy subjects, it may also increase amygdala activation in response to fearful faces due to its side effects.

In contrast to 60 mg MPH and 600 mg modafinil, 125 mg MDMA did not improve cognitive control in healthy subjects (Schmidt et al., 2017). But in accordance with other studies in healthy people using 1.5 mg/kg MDMA (Bedi et al., 2010), we previously found that 125 mg MDMA impaired the recognition of fearful faces (Hysek et al., 2014a, 2014b; Dolder et al., 2017). The same dose also biased mind-reading towards positive and away from negative emotions (Hysek et al., 2012a) and led to misclassification of emotions as happy (Dolder et al., 2017). Furthermore, 125 mg MDMA also increased levels of oxytocin in healthy subjects (Hysek et al., 2014b; Dolder et al., 2017), which has been associated with prosocial behavior (Hysek et al., 2014b). However, while 1.5 mg/kg MDMA did attenuate amygdala responses to angry facial expressions stimuli in healthy volunteers, it did not affect amygdala response to fearful expressions relative to placebo in healthy subjects (Bedi et al., 2009).

Using a within-subject, placebo-controlled, cross-over design, this study directly compared the acute effects of a single dose of 60 mg MPH and 600 mg modafinil on neural responses and in particular amygdala responses to fearful faces using 125 mg MDMA as positive control. We hypothesized that 60 mg MPH and 600 mg modafinil would increase amygdala responses to fearful faces compared with 125 mg MDMA and placebo and that these effects would be related to negative mood states.

Methods

Participants

Twenty-four healthy subjects (12 men, 12 women) with a mean \pm SD age of 22.6 ± 3.0 years (range, 19–29 years) were recruited via advertisement and word of mouth. Inclusion

criteria were age 18 to 45 years and body mass index 18 to 27 kg/m². Subjects with a personal or first-degree-relative history of psychiatric disorders or chronic or acute physical illness were excluded. Additional exclusion criteria were tobacco smoking (>10 cigarettes/d) and a lifetime history of using illicit drugs more than 5 times, with the exception of occasional cannabis use in the past. Drug use histories are shown in [supplementary Table 1](#). Subjects who used any illicit drugs within the past 2 months or during the study period were excluded. We performed drug tests at screening and before each test session using TRIAGE 8 (Biosite). All female subjects used oral contraceptives and were investigated during the follicular phase of their menstrual cycle (day 2–14 after the start of the menstruation according to self-report) to account for cyclic changes in reactivity, which has been demonstrated to modulate amphetamine effects ([White et al., 2002](#)).

Study Design and Drug Administration

We used a double-blind, placebo-controlled, randomized, cross-over design with 4 experimental sessions (125 mg MDMA, 60 mg MPH, 600 mg modafinil, and placebo). The order of the 4 experimental sessions was counterbalanced. The washout periods between sessions were at least 7 days. All 24 participants completed all 4 sessions of the study as previously reported ([Dolder et al., 2017](#)).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee northwest/central Switzerland and the Swiss Agency for Therapeutic Products (Swissmedic). All the subjects provided written consent before participating in the study and received reimbursement for their participation. The study (including the a priori defined focus on amygdala activation) was registered at ClinicalTrials.gov (NCT01951508).

MDMA was administered in a single absolute dose of 125 mg corresponding to a relatively high dose of (mean ± 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 with respect to its prosocial and mood-enhancing effect ([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](#)). Even though there is no recommended dose for MPH to enhance cognition in healthy people, studies investigating this population typically use single doses between 5 and 60 mg ([Repantis et al., 2010](#); [Linszen et al., 2014](#)). In this study MPH was administered in a single, relatively high dose of 60 mg as done in previous studies ([Volkow et al., 1998](#); [Dodds et al., 2008](#); [Clatworthy et al., 2009](#)). We recently showed that 60 mg MPH improved behavioral and neural responses during cognitive control in healthy subjects ([Schmidt et al., 2017](#)), and the same dose was shown to be efficient and safe in patients with attention deficit hyperactivity disorder ([Muniz et al., 2008](#)). Furthermore, the subjective and cardiostimulant effects of this dose were previously assessed on the same tests as used in the present study ([Hysek et al., 2014a](#)) and have also been statistically compared with a lower dose of 40 mg ([Schmid et al., 2014](#)). With the overarching goal to achieve comparable cardiostimulant effects ([Hysek et al., 2014a](#)) and maximize the subjective drug effects, we also administered a single high dose of 600 mg modafinil, even though 200 mg is the typical dose used for cognitive enhancing purposes in healthy subjects ([Minzenberg and Carter, 2008](#)). Comparable with the effect of 60 mg MPH, 600 mg modafinil also improved behavioral ([Makris et al., 2007](#)) and neural responses during cognitive processing ([Schmidt et al., 2017](#)) and is generally well tolerated in

healthy volunteers ([Wong et al., 1999b](#)). All administered doses were well tolerated by the participants, and no severe adverse events have been reported ([Dolder et al., 2017](#)).

Each of the 4 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., 2014a](#); [Schmid et al., 2014](#)). The sessions ended at 3:45 PM. Additional study findings are reported elsewhere ([Dolder et al., 2017](#); [Schmidt et al., 2017](#)).

Assessment of Negative Emotional States

Negative emotional states were assessed directly before and after the fMRI took place (75 and 150 minutes posttreatment, respectively). We averaged the values of the 75- and 150-minute posttreatment assessments to best relate the subjective drug effects to brain activation during fMRI task. Negative emotions were assessed with the State-Trait anxiety inventory ([Spielberger et al., 1970](#)) and the Adjective Mood Rating Scale ([Janke and Debus, 1978](#)). For the latter, we focused on subjectively experienced feelings of fearfulness and depressiveness.

Facial Emotion Recognition Task (FERT)

We used the FERT to assess drug effects on facial emotion recognition ([Hysek et al., 2014a](#); [Schmid et al., 2014](#)). The FERT included 10 neutral faces and 160 faces that expressed 1 of 4 basic emotions (i.e., happiness, sadness, anger, and fear) with pictures morphed between 0% (neutral) and 100% in 10% steps. Two female and 2 male pictures were used for each of the 4 emotions. The stimuli were presented in random order for 500 milliseconds and then were replaced by the rating screen where participants had to indicate the correct emotion. The main outcome measure was accuracy (proportion of correct answers). The FERT was performed 150 minutes after drug administration. Results on the FERT have already been published ([Dolder et al., 2017](#)). In line with the fearful > neutral contrast used for the fMRI analysis, here we report the accuracy for the recognition performance of fearful relative to neutral faces.

Statistical Analyses of Negative Emotional States and the FERT

Treatment differences in negative emotional states and FERT performance were examined using a repeated-measures ANOVA with treatment as within-subject factor. Where the ANOVA null hypothesis of equal means was rejected, we used posthoc tests (Bonferroni).

Fearful Face Processing

fMRI scanning took place between 11:15 AM and 12:15 PM during the drug peak effects ([Dolder et al., 2017](#)). During this time, study subjects participated in a well-established, 6-minute experiment with event-related fMRI where they were presented with 10 different facial identities, each expressing 50% or 100% intensities of fear or a neutral expression ([Fusar-Poli et al., 2009a](#); [Fusar-Poli et al., 2010](#); [Schmidt et al., 2014, 2015](#); [Mueller et al., 2017](#)). There were thus 30 different facial stimuli in total; each face was presented twice for 2 seconds. Individuals therefore viewed 60 stimuli in total. The order of facial identities and expression type was pseudo-randomized such that there was no successive presentation of the same identity or facial expression type.

During the interstimulus interval, the duration of which was varied from 3 to 8 sec according to a Poisson distribution with an average interval of 5.9 sec, individuals viewed a fixation cross (Surguladze et al., 2005). To ensure a maximal degree of attention on the presented faces, subjects were requested to decide on the gender of face stimuli via button-press. We previously demonstrated that amygdala activity and connectivity during implicit fearful face processing in this task is related to subjective anxiety ratings (Schmidt et al., 2014, 2015).

Image Acquisition and Analysis

Scanning was performed on a 3-T scanner (Siemens Magnetom Verio; Siemens Healthcare) with an echo planar sequence with 2.5-second repetition time, 28-millisecond echo time, a matrix size of 76x76, and 38 slices with .5-mm inter-slice gap, providing a resolution of 3x3x3 mm³ and a field of view of 228x228 mm². In total, 152 volumes were acquired. Data analysis was performed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). All volumes were realigned to the first volume, normalized into a standard stereotaxic space (Montreal Neurological Institute), and smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel.

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 >3 mm deviation from the previous scan in any dimension, resulting in corrupted volumes, were excluded and replaced with the average of the neighboring volumes (6 volumes were replaced in total, all after MDMA administration). Subjects with >10% corrupted volumes were excluded ($n=2$; final sample of 22 subjects). There were no movement differences across treatment in any dimension (supplementary Table 2).

During first-level model specification, onset times for each trial of neutral, 50%, and 100% fearful faces across all 4 treatments were convolved with a canonical hemodynamic response function. Serial correlations were removed with a first-order autoregressive model, and a high-pass filter (128 seconds) was applied to remove low-frequency noise. Six movement parameters were also entered as nuisance covariates. Each trial for 50% and 100% fearful faces was then contrasted against neutral faces, producing a subject-specific contrast image propagated to the second-level analysis. To extract the highest potential impact of fearful expressions, we specifically focused on the “100% fearful vs neutral face” contrast. To compute the effect of task, we also generated one average image for the “100% fearful vs neutral face” across all 4 treatments.

A 1-sample t test was performed to examine whole brain activation during fearful face processing across all treatments (effect of task). Treatment differences were examined using a within-subject ANOVA design using drug order as regressor of no interest. Significance was assessed at a cluster-level threshold of $P < .05$ family-wise error (FWE) corrected across the whole brain, using an uncorrected cluster-forming threshold of $P < .001$ according to recent recommendations (Woo et al., 2014). For completeness, all results surviving a cluster threshold of $k=20$ are reported, but only those results surviving cluster-correction are discussed in the text. We also focused our analysis on the amygdala, as this was part of our primary hypothesis, using a voxel-level approach. The amygdala region of interest was defined using coordinates taken from a previous meta-analysis of fearful face processing (Fusar-Poli et al., 2009b): right ($x=20$; $y=-4$; $z=-14$) and left ($x=-22$; $y=-4$; $z=-10$). Small volume correction was applied for this analysis using 8-mm spheres around these coordinates (Vuilleumier et al., 2001), and a voxel-level threshold of $P < .05$ FWE corrected was considered significant.

Relationship between Brain Activation and Negative Emotional States

Based on significant treatment effects on brain activation, relationships between neural responses to fearful faces and negative emotions were identified by including measures of fearfulness, depressiveness, and state-anxiety as covariates in second-level models.

Results

Negative Emotional States

There was a trend for a main effect of treatment for state-anxiety ($F=2.592$, $P=.083$) (Figure 1A), indicating a trend for higher values after MPH than MDMA treatment ($P=.073$). No significant treatment effects were found for fearfulness ($F=1.259$, $P=.317$) (Figure 1B) and depressiveness ($F=1.129$, $P=.362$) (Figure 1C).

FERT

A main effect of treatment was found for the recognition of fearful relative to neutral faces ($F=3.679$, $P=.030$). Posthoc testing revealed a significantly improved recognition of fearful relative to neutral faces after modafinil than MDMA administration ($P=.039$) (Figure 1D). There was no significant relationship between the recognition of fearful faces and negative emotional states after modafinil administration.

Brain Activation during Fearful Face Processing

Effect of Task

Averaged across all treatments, fearful relative to neutral faces induced significant activation in widespread regions including the amygdala, fusiform gyrus, anterior cingulate and orbito-frontal cortex, calcarine sulcus, dorsal striatum, and insula and inferior frontal gyrus (all results are cluster-level FWE-corrected across the whole brain) (supplementary Table 3).

Treatment Effects during Fearful Face Processing

Brain activation during fearful face processing significantly differed across treatments in the left amygdala (small volume peak-level FWE-corrected), right amygdala, right putamen and left pallidum, and thalamus (cluster-level FWE-corrected across the whole brain) (supplementary Table 4).

Subsequent treatment comparison revealed that modafinil increased brain activation relative to placebo in the bilateral amygdala (small volume peak-level FWE-corrected) and anterior cingulate cortex, right putamen, pallidum and supplementary motor area, and left pallidum, caudate nucleus, and thalamus (cluster-level FWE-corrected across the whole brain) (Figure 2A; supplementary Table 5).

Furthermore, modafinil also increased brain activation compared with MDMA in the right amygdala (small volume peak-level FWE-corrected) (Figure 2B; supplementary Table 5).

Relationship between Brain Activation and Negative Emotional States

Based on the modafinil effects on brain activation, we further tested the relationship between neural activation and negative emotional states after modafinil exposure. There was a significant positive relationship between activation in the right middle and inferior frontal gyrus and subjectively

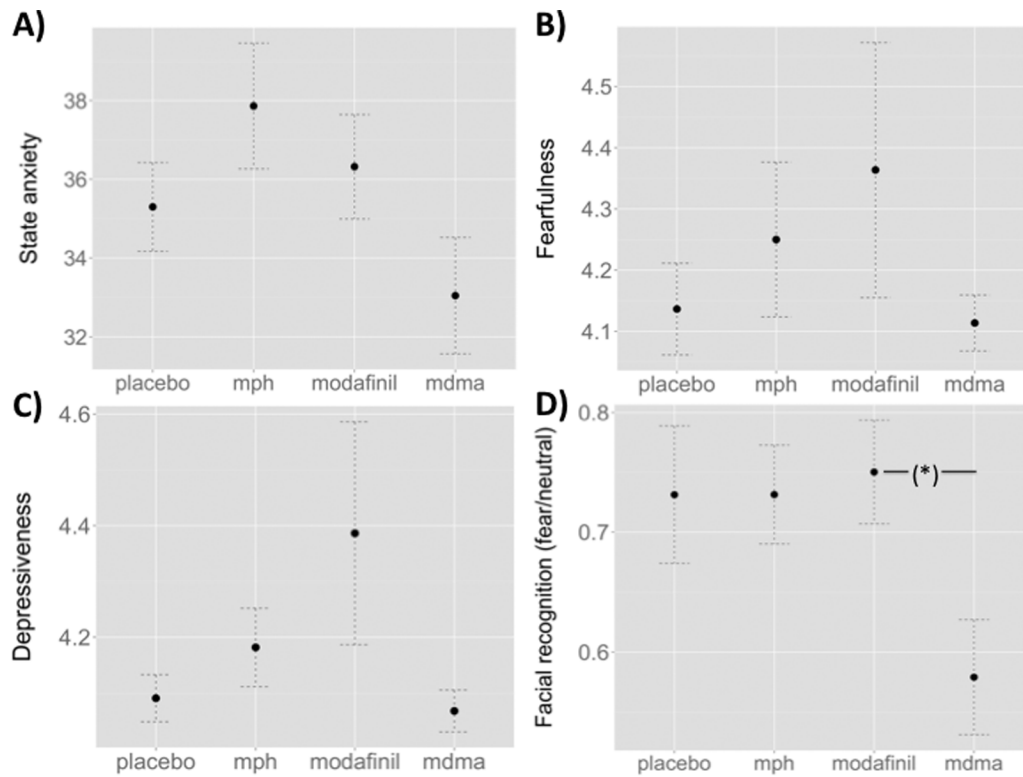


Figure 1. Acute effects of 3,4-methylenedioxyamphetamine (MDMA), modafinil, methylphenidate (MPH), and placebo administration on (A) state anxiety, (B) fearfulness, (C) depressiveness, and (D) facial recognition. *Indicates significant between-treatment effects.

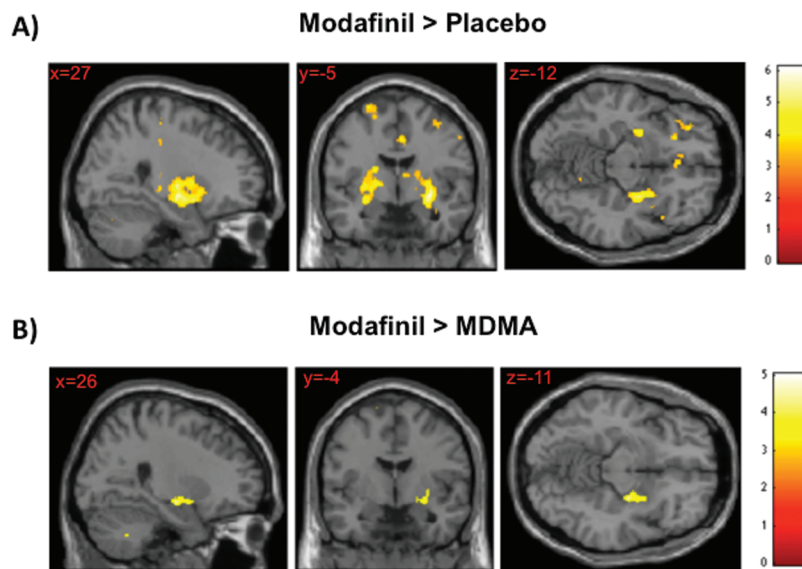


Figure 2. Significantly increased brain activation after acute modafinil relative to (A) placebo and (B) 3,4-methylenedioxyamphetamine (MDMA) administration during fearful face processing. Results are illustrated using a cluster-forming threshold $P < .001$ uncorrected, with an extent threshold of 20 voxels.

experienced fearfulness after modafinil intake (Figure 3A-B; supplementary Table 6).

Furthermore, self-reported feelings of depressiveness also correlated positively with activation in the bilateral middle and inferior frontal gyrus after modafinil intake (Figure 4A-B; supplementary Table 7). There was no significant relationship between state-anxiety and brain activation during fearful face processing following modafinil administration.

Discussion

This study provides 3 major results: firstly, modafinil increases brain activation in response to fearful faces within the limbic-cortical-striatal-pallidal-thalamic circuit relative to placebo. Secondly, modafinil also increases amygdala responses to fearful faces compared with MDMA. Finally, fear-induced activation in the middle and inferior frontal gyrus correlated positively with

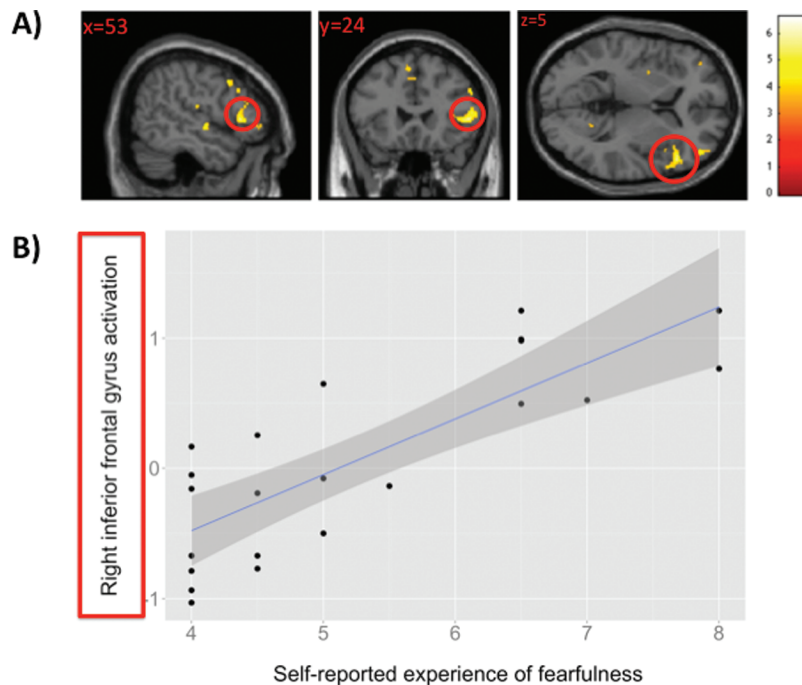


Figure 3. (A) Significant positive relationship between brain activation during fearful face processing and subjective feelings of fearfulness after modafinil administration. Results are illustrated using a cluster-forming threshold $P < .001$ uncorrected, with an extent threshold of 20 voxels. (B) Scatterplots showing the positive relationship between right inferior frontal gyrus activation and feelings of fearfulness after modafinil administration ($r = 0.804$).

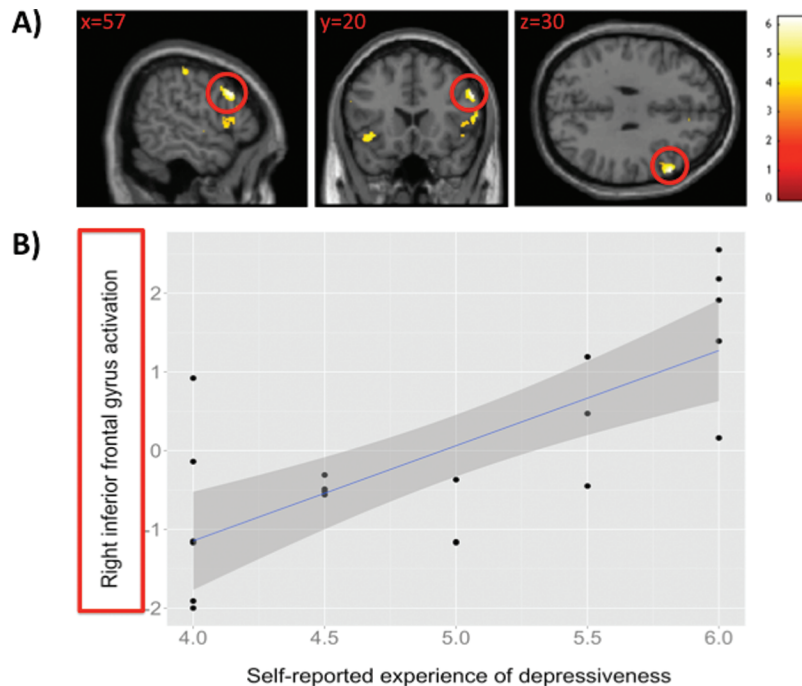


Figure 4. (A) Significant positive relationship between brain activation during fearful face processing and subjective feelings of depressiveness after modafinil administration. Results are illustrated using a cluster-forming threshold $P < .001$ uncorrected, with an extent threshold of 20 voxels. (B) Scatterplots showing the positive relationship between right inferior frontal gyrus activation and feelings of depressiveness after modafinil administration ($r = 0.771$).

subjectively experienced feelings of fearfulness and depressiveness after modafinil administration.

We found that relative to placebo, modafinil increased activation in the limbic-cortical-striatal-pallidal-thalamic circuitry including the amygdala during fearful face processing, the core of the neural system that has been implicated in

negative emotional states and mood disorders (Drevets et al., 2008; Price and Drevets, 2010). A previous study showed that 400 mg modafinil also increased regional cerebral blood flow in arousal- and emotion-related brain regions such as the orbito-frontal, superior frontal, middle frontal gyri, short insular gyri, left cingulate gyrus, left middle/inferior temporal gyri, left

parahippocampal gyrus, and left pons (Joo et al., 2008). However, our finding partially contrasts with a previous study showing that repeated administration of 100 mg modafinil for 1 week diminished amygdala activation in response to fearful faces (Rasetti et al., 2010). This discrepancy may reflect the influence of different doses and dosing schedules used across studies.

Although we did not find that 600 mg modafinil increased state-anxiety or other negative mood states, significant adverse effects (mostly insomnia, headache, and lack of appetite) that lasted up to 24 hour were observed (Dolder et al., 2017). This is in line with a previous study showing a progressive increase of adverse effects such as insomnia, anxiety, and palpitations after 200, 400, 600, and 800 mg modafinil administration in healthy subjects (Wong et al., 1999a). Such physical symptoms of anxiety have also been reported after 100 mg modafinil intake in healthy people (Randall et al., 2003), and another study showed that 400 mg modafinil increased tension-anxiety in narcoleptic patients (Broughton et al., 1997). Thus, we can speculate that the increase in activation of fear-associated brain regions after 600 mg modafinil might be driven by significant sympathomimetic and adverse effects as previously described (Dolder et al., 2017).

Modafinil is a weak inhibitor of the DA and NE transporter and has additional effects on the brain GABA, glutamate, and orexin system (Minzenberg and Carter, 2008), although the precise neuropharmacological mode of action of modafinil remains unclear. It has been proposed that the modafinil-induced adverse effects ("somatic anxiety") are probably mediated via reduced GABAergic neurotransmission (Randall et al., 2003). Supportive for such an interpretation, it has been demonstrated that the neuropeptide oxytocin, which decreases anxiety and stress and facilitates social behavior (Bartz and Hollander, 2006), reduces amygdala responses to fearful faces in patients with generalized social anxiety disorder (Labuschagne et al., 2010) probably by activating GABAergic interneurons in the amygdala (Huber et al., 2005). These GABAergic interneurons are thought to integrate the output activity of the central nucleus of the amygdala (Cassell et al., 1999). Given that modafinil also decreases levels of GABA in the cortex (Tanganelli et al., 1995), striatum, globus pallidus (Ferraro et al., 1998), and thalamus (Ferraro et al., 1997), we can speculate that the modafinil-induced increase of activation within the limbic-cortical-striatal-pallidal-thalamic circuitry relative to placebo is due to reduced GABA function.

In contrast to the modafinil-induced increase in neural activation, we did not find a significant MPH (60 mg) effect on brain activation during fearful face processing compared with placebo, which corresponds with a previous study using 35 mg of MPH (Bottelier et al., 2015). Having in mind that both MPH and modafinil enhance DA and NE neurotransmission (Madras et al., 2006; Qu et al., 2008; Hannestad et al., 2010; Schmeichel and Berridge, 2013; Simmler et al., 2014) and that modafinil has additional effects on GABAergic neurotransmission (Minzenberg and Carter, 2008), the lack of effect after MPH administration suggests on one hand that its modulation on the DA and NE system did not affect neural responses to fearful faces and on the other hand that modafinil's effect is indeed mediated via GABA function. However, other factors either alone or together with modulation of the GABA system might be responsible for these effects.

In a previous study with the same sample, acute administration of 125 mg MDMA elicited increased well-being, happiness, trust, feelings of closeness to others, wanting to be with others, wanting to hug someone, and also reduced state anxiety compared with MPH and modafinil (Dolder et al., 2017). Compared

with placebo (Bedi et al., 2010; Hysek et al., 2014b), MPH and/or modafinil (Hysek et al., 2014a; Schmid et al., 2014; Dolder et al., 2017), MDMA administration also significantly impaired the recognition of fearful faces. Furthermore, MDMA also enhanced emotional empathy and prosociality relative to placebo (Hysek et al., 2014b; Kuypers et al., 2017). In line with other evidence (Wardle et al., 2014; Kirkpatrick and de Wit, 2015; Bershad et al., 2016), these findings underpin the socially enhancing effects of MDMA. In contrast to our hypothesis, however, we did not find diminished brain (amygdala) activation during fearful face processing after 125 mg MDMA administration relative to placebo. This lack of effect is consistent with a previous study, which revealed attenuated amygdala response to angry but not fearful faces in healthy subjects after using a comparable dose of MDMA (1.5 mg/kg) (Bedi et al., 2009), suggesting that acute administration of representative recreational or clinical doses of 100 to 125 mg MDMA does not affect the neural correlates of fearful face processing in healthy subjects compared with placebo. However, we did find that subjects revealed decreased amygdala responses to fearful faces after MDMA compared with modafinil. This coincides with our finding that people under MDMA exposure had more problems to recognize fearful faces (relative to neutral faces) than after modafinil administration. The decreased amygdala activation after MDMA relative to modafinil but not placebo and MPH could be explained again by reduced GABA release after modafinil administration. Furthermore, given that there was no significant difference between MPH and modafinil on amygdala activation, the difference in amygdala activation between MDMA and modafinil is perhaps mediated via reduced GABA and increased 5-HT release.

Finally, we found that brain activation in the middle and inferior frontal gyrus under modafinil exposure correlated positively with subjective feelings of fearfulness and depressiveness following modafinil administration. Together with the amygdala, the inferior frontal gyrus is part of the extended system for face perception (Haxby et al., 2002; Ishai et al., 2005), where semantic aspects (emotion evaluation) of faces are processed (Leveroni et al., 2000). Surgical resection of the right prefrontal cortex in a patient with epilepsy resulted in a severe deficit in the recognition of emotional facial expressions, especially fear (Marinkovic et al., 2000). It has further been shown that threat-induced anxiety increased the functional connectivity between the right amygdala and bilateral inferior frontal gyrus in healthy adults (Gold et al., 2015) and that cortical-amygdala connectivity correlated with social anxiety symptom severity in patients with social anxiety disorder (Cremers et al., 2015). Our finding suggests that the modafinil-induced adverse effects contribute to a higher emotional evaluation of fearful faces as reflected by increased activation in the middle and inferior frontal gyrus.

Some limitations of our study merit comment. The high number of drugs included in the present analysis might have dampened the statistical power to find treatment effects on negative mood states. Future studies on this topic should also use validated scales such as the Positive and Negative Affect Schedule or Profile of Mood States questionnaire to assess negative mood states. The demanding study design has further prevented examination of dose-response curves. The observed differences between drugs were seen at the doses used in this study but may not be present at different doses. However, dose-effect relationships show E_{\max} curve characteristics (Hysek et al., 2012c), and we used single but relatively high doses of all drugs expected to result in subjective drug effects close to E_{\max} based on previous studies (Hysek et al., 2012b, 2012c; Dolder et al., 2017). Another point of contention is the use of self-reports to

ascertain the phase of menstrual cycle. Although the assessment of the menstrual cycle phase is a strength of this study, the validity of self-reports should be considered with caution (Small et al., 2007). Finally, we cannot exclude effects on neurovascular coupling induced by the drugs (Honey and Bullmore, 2004), which might have confounded our fMRI results. For instance, it has been shown that modafinil increased regional cerebral blood in the arousal-related systems and in brain areas related to emotion and executive function (Joo et al., 2008).

In summary, our findings show that acute administration of a relatively high single dose of 600 mg modafinil, a dose previously reported to enhance cognitive performance in healthy subjects (Makris et al., 2007; Schmidt et al., 2017), increased neural activation in widespread brain regions implicated in fear processing and that some of the effects were related to negative mood states. Although 600 mg modafinil improves cognitive performance in healthy people (Schmidt et al., 2017), potential adverse side effects on emotion processing should be considered.

Supplementary Material

Supplementary data are available at International Journal of Neuropsychopharmacology online.

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Statement of Interest

None.

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