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ORIGINAL INVESTIGATION

Moral decision making under modafinil: a randomized placebo-controlled double-blind crossover fMRI study

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Abstract

Rationale Modafinil is increasingly used by healthy humans as a neuroenhancer in order to improve cognitive functioning. Research on the effects of modafinil on cognition yielded most consistent findings for complex tasks relying on the prefrontal cortex (PFC).

Objectives The present randomized placebo-controlled double-blind crossover study aimed to investigate the effect of a single dose of modafinil (200 mg) on everyday moral decision making and its neural correlates, which have been linked to the ventro- and dorsomedial PFC.

Methods Healthy male study participants were presented with short stories describing everyday moral or neutral dilemmas. Each moral dilemma required a decision between a personal desire and a moral standard, while the neutral dilemmas required decisions between two personal desires. The participants underwent this task twice, once under the influence of modafinil and once under placebo. Brain activity associated with the processing of the dilemmas was assessed by means of functional magnetic resonance imaging.

Results For the processing of moral vs. neutral dilemmas, activations were found in a network of brain regions linked to social cognitive processes including, among others, the bilateral medial PFC, the insula, and the precuneus. Modafinil was found to increase the number of moral decisions and had no effect on brain activity associated with dilemma processing. Exploratory analyses revealed reduced response-locked activity in the dorsomedial PFC for moral compared to neutral dilemmas under modafinil, but not under placebo.

Conclusions The results are discussed in terms of altered predictions of others' emotional states under modafinil, possibly due to higher processing efficiency.

Keywords Moral reasoning · Decision making · Modafinil · Prefrontal cortex · fMRI

Introduction

The drug modafinil is used to treat daytime sleepiness in different sleep disorders such as shift work disorder, obstructive sleep apnea, or narcolepsy (Akintomide and Rickards 2011; Murillo-Rodríguez et al. 2018; Battleday and Brem 2015). For patients suffering from narcolepsy, for example, it has also been shown to have positive effects on cognitive functions (e.g., Becker et al. 2004). Modafinil is also one of the drugs that are increasingly used as potential neuroenhancers, that is, psychoactive substances with the capability to increase cognitive functioning in healthy humans, as revealed by recent surveys (Dietz et al. 2013; Franke et al. 2013; Franke et al. 2014; Teter et al. 2006). It belongs to the prescription drugs, which are less frequently used than the freely available over-the-counter drugs such as caffeine tablets or *Ginkgo biloba*, but still reach lifetime prevalence rates of up to 20% for a single non-medical use (Franke et al. 2014). However, the prevalence rates for the non-medical use of prescription drugs vary considerably, depending on the studied population and the

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assessment technique. For example, Franke et al. (2011) reported a rate of 1.29% in German high school and university students, whereas the rates in a sample of German surgeons (8.9%) and in a large international sample of academics (20%) were much higher (Franke et al. 2013; Maher 2008), with modafinil being the second most popular drug following methylphenidate in the latter study.

Systematic investigations of the effects of a single dose of modafinil on healthy human subjects' performance in cognitive tasks revealed inconsistent findings, however, and reliable positive effects emerged only in some cognitive domains. Repantis et al. (2010) performed a meta-analysis on modafinil effects, distinguishing between sleep-deprived and non-sleep-deprived participants, and they found that only attention was enhanced in non-sleep-deprived individuals. In a recent review, a distinction between simple and complex tasks was suggested (Battleday and Brem 2015). In simple tasks, mostly focusing on one cognitive domain and consisting of neuropsychological standard tests, no consistent modafinil-induced improvements were seen for attention or memory function (Marchant et al. 2009; Müller et al. 2004; Müller et al. 2013; Randall et al. 2003; Randall et al. 2004; Randall et al. 2005a; Randall et al. 2005b; Turner et al. 2003; Winder-Rhodes et al. 2010). The pattern was mixed for executive functions, with no clear effects on working memory and set shifting (Franke et al. 2014; Müller et al. 2004; Müller et al. 2013; Turner et al. 2003), but an enhancement of performance in tasks requiring inhibition (Fernández et al. 2015; Kulendran et al. 2017). Consistent improvements following modafinil administration were found for complex tasks, which are based on a combination of simple functions (Esposito et al. 2013; Marchant et al. 2009; Müller et al. 2013; Turner et al. 2003).

As outlined by Battleday and Brem (2015), the tasks for which positive modafinil effects were found appear to have two things in common. They are ecologically valid, resembling everyday tasks, and recruit (parts of) the prefrontal cortex (PFC), either because they require the orchestration of different cognitive processes, or because the tested function itself is linked to the PFC such as inhibitory control. This suggests that PFC function is the main target of modafinil effects. Indeed, the few studies that have directly investigated the effects of modafinil on brain activity revealed altered task-related PFC as well as anterior cingulate cortex (ACC) activity compared to placebo (Minzenberg et al. 2008; Rasetti et al. 2010). Minzenberg et al. (2011) further observed stronger task-induced deactivation of brain activity in the ventromedial prefrontal cortex (vmPFC), which is part of the default mode network. Modafinil effects on PFC function are also in line with its pharmacological effects, because it particularly increases the extracellular levels of dopamine (DA) and noradrenaline, although also other neurotransmitter systems are affected indirectly (Kim et al. 2014; Madras et al. 2006; Qu et al. 2008; Volkow et al. 2009). In mice, DA has been shown to underlie the wakefulness-promoting effect of modafinil. In humans, modafinil modulates reward processing and reward-based learning (Bellebaum et al. 2017; Funayama et al. 2014), which are closely linked to the DA system (Schultz 2016). DA, in turn, modulates information processing related to cognitive control in the prefrontal cortex via striato-cortical circuits (Ott and Nieder 2019; Vogelsang and D'Esposito 2018).

The consumption of neuroenhancers typically aims at improving functioning at school, university, or work, so that the modafinil effects on complex everyday tasks that are mediated by the PFC appear to be of particular importance. The PFC is also implicated in a variety of social cognitive processes (Shamay-Tsoory 2011; Bzdok et al. 2012), which critically affect functioning in everyday life. One of the most complex social cognitive processes recruiting the PFC is moral reasoning and decision making, as it requires not only theory of mind and empathy (i.e., insight into other person's thoughts and feelings) but also the integration of this information with the estimated effects of own actions on other persons (Greene et al. 2001; Greene et al. 2004; Greene 2007). Alterations of moral reasoning and related functions can have implications for complex decisions in multiple situations, e.g., within a professional environment, and it seems thus important to study these functions in order to judge the potential of modafinil as a neuroenhancer. In the present study we therefore asked whether moral decision making is affected by modafinil, focusing on everyday moral dilemmas (Sommer et al. 2010).

Most previous studies on moral reasoning focused on dead-or-alive-dilemmas, in which a moral conflict is induced in healthy participants by asking if, for example, they would decide to sacrifice the life of one person in order to save the life of five others (Garrigan et al. 2016; Greene et al. 2001; Greene et al. 2004; Tobler et al. 2008). According to dual-process theory, the imagination of actions that harm people elicits intuitive emotional reactions, represented in the vmPFC. If, at the same time, this action can be beneficial for other people, healthy humans engage in a utilitarian cost-benefit analysis, which is considered the second process and is supported by the dorsolateral prefrontal cortex (dlPFC). If there is a conflict between these processes, the ACC as a region underlying cognitive control is activated (Greene et al. 2001; Greene et al. 2004). Moll and de Oliveira-Souza (2007) suggested instead a more general role of the vmPFC related to the integration of information concerning effects of specific actions on the self and on others, thereby generally serving social cognitive processes. In accordance with this notion, recent meta-analytic evidence shows that neural networks involved in moral reasoning partially overlap with those for theory of mind and empathy. The greatest overlap, however, was seen in the dorsomedial PFC (dmPFC; Bzdok et al. 2012) and not the vmPFC. The dmPFC and adjacent regions have also been linked to processes of inhibition and

uncertainty (Aron 2007; Bhanji et al. 2010), which may also play a role for moral reasoning and especially decision making (Sommer et al. 2010). Apart from other brain regions such as the temporal cortex, the temporoparietal junction (TPJ), and the posterior cingulate cortex, the vmPFC and dmPFC are also involved in the processing of everyday moral dilemmas which require a decision between a moral standard and a personal desire in an everyday situation (Sommer et al. 2010).

Given the prominent role of the PFC in moral reasoning, and the findings on altered PFC function under modafinil, we hypothesized that a single dose of modafinil would affect the processing related to everyday moral decision making in the PFC via effects on two potential target regions. First, altered processing in the vmPFC could indicate modafinil-induced changes in the integration processes required in moral decision making, especially for emotional information. Second, modafinil could affect processes mediated by the dmPFC related to social cognition (theory of mind and empathy), inhibition, or uncertainty that are important for moral decision making. While we hypothesized to find reduced brain activity in these regions under the influence of modafinil, in accordance with the notion of increased processing efficiency (see Rasetti et al. 2010), the presence and direction of behavioral effects on moral decision making could not be predicted.

Methods

Participants

Eighteen right-handed, male participants with a mean age of 27.4 years (SD = 6.3 years, range 20 to 41 years) took part in the experiment. All participants were German native speakers and had normal or corrected-to-normal vision. Criteria for exclusion were history of neurological or psychiatric disorder, any medication consumption within the last 4 weeks, regular nicotine consumption, and history of substance abuse. Furthermore, shortly before the acquisition session, participants were screened for current drug consumption by means of a urine test covering cannabinoids, benzodiazepines, opiates, cocaine, and amphetamines. Participants were asked not to consume any caffeine 6 h before the experiment started. The experiment complies with the Helsinki Declaration. It was approved by the ethics committee of the Medical Faculty at Ruhr-University Bochum, Germany. Before the experiment started, written informed consent was obtained from all participants.

Stimuli and task

As in the study by Sommer et al. (2010), moral or neutral (i.e., nonmoral) dilemmas were presented to the participants during the experimental trials, and the participants were asked to decide for one particular behavioral option. As two parallel versions of the experimental task were needed (see below), a total of 100 short stories were used, including (i) a description of a dilemma, always ending with the question "What should I do?", and (ii) two possible behavioral alternatives. Fifty stories described moral dilemmas from a first-person narrative point of view (e.g., "I am standing at the counter in a supermarket and want to pay my shopping, which costs 8 €. I give the cashier a 10 € note. Accidentally, the cashier passes back 4 € instead of 2 €. What should I do?"). Moral dilemmas were characterized by a decision between a personal desire and a moral standard (e.g., wanting to get money vs. having to return money that is owned by someone else). The decision was reflected in two behavioral alternatives which were also formulated from the first-person narrative point of view and presented to the participant (e.g., "I keep the money" vs. "I return the money"), who could choose one of them by pressing a corresponding button. For each moral dilemma, the moral standard was defined as the behavioral option that was in accordance with a universally accepted moral rule such as helping other people or being honest (see Sommer et al. 2010). The remaining 50 stories described neutral dilemmas (e.g., "Today I am on holiday and I would like to read a new book. The TV magazine says that there is an interesting movie. What should I do?"). Neutral dilemmas were characterized by a decision between two alternative personal desires, which were again presented as behavioral alternatives from a first-person perspective (e.g., "I read the book" or "I watch the movie"). From the total of 100 dilemmas, 56 (28 moral and 28 neutral dilemmas) were taken from the study by Sommer et al. (2010), whereas the other 44 (22 moral and 22 neutral) were developed for the purpose of the present study.

The pool of stories was split into two sets, each including 25 moral dilemmas and 25 neutral dilemmas, which were used in the two testing sessions per participant (see below). In order to match the two sets of moral and neutral dilemmas, respectively, and to compare the moral and neutral dilemmas on important variables, a behavioral test and rating was performed in an extra sample of nine subjects before the study started. These subjects decided for one behavioral option for each of the 100 moral and neutral dilemmas, with the decision for moral dilemmas being between a moral standard and a personal desire. Then, for each dilemma, the subjects rated on five-point Likert scales (1 = "not at all" to 5 = "very much") how realistic they considered the dilemma to be, how difficult it was for them to decide for one behavioral option, how sure they were about their decision, and how strong the moral implications of the described dilemma were. In addition, the reading time was assessed for each dilemma by asking subjects to press a response button as soon as they had finished reading the dilemma. The two sets for moral and neutral dilemmas, referred to as versions A and B in the following, were then created by minimizing the differences between sets for the mentioned variables.

After the sets had been created, statistical analyses were performed to compare the two versions on the variables assessed. A paired *t* test revealed that the percentage of dilemmas for which a response in accordance with a moral standard was chosen did not differ between versions A and B (59%, SD = 20%, vs. 61%, SD = 21%; $P = 0.447$). Then analyses of variance (ANOVAs) were performed on the mean ratings of the dilemmas and the reading time, with the factors Content (moral vs. neutral) and Version (A vs. B). As expected, the moral implications were rated as being stronger for the moral (mean rating = 3.7, SD = 0.6) than for the neutral dilemmas (mean rating = 1.3, SD = 0.4, $P < 0.001$). The versions A and B did not differ and there was no interaction between Content and Version (both $P > 0.870$). For the question how sure subjects were about their decision, no main effects of Content or Version and no interaction between the factors occurred (all $P > 0.640$). However, moral dilemmas were rated as slightly, but significantly less realistic (mean rating neutral dilemmas = 4.0, SD = 0.5; mean rating moral dilemmas = 3.7, SD = 0.5; $P = 0.015$). The decision for one behavioral option was rated as more difficult for moral (mean rating = 2.5, SD = 0.6) than for neutral dilemmas (mean rating = 2.2, SD = 0.5; $P = 0.001$). The effects of Version and the Version by Content interactions were not significant for these two ratings (all $P > 0.850$). Finally, the reading times were not significantly different between moral and neutral dilemmas, although they were descriptively lower for moral (mean = 7371 ms; SD = 1466 ms) than for neutral dilemmas (mean = 7942 ms; SD = 1550 ms), which yielded a statistical trend for the factor Content in the analysis ($P = 0.064$). The effect of the factor Version and the interaction Content by Version did not reach or approach significance (both $P > 0.880$). Based on the assessment of the reading time, the duration of the presentation of the dilemmas was set to 13 s for the fMRI experiment (see below); as for all dilemmas, the reading time was clearly below this duration.

Procedure

Participants underwent two fMRI acquisition sessions, conducted on different days. In one session, participants were treated with a single oral dose of modafinil (200 mg), while in the other session they received placebo. Modafinil or placebo was administered as tablet at least 2 h before the start of the session, as the maximum plasma concentration of modafinil is normally reached in the time between 2 and 4 h after intake. Neither the participant, nor the experimenter was informed about the type of treatment for a particular session. The tablets, modafinil or placebo, were administered by a physician (P.R.). While he was aware of the drug that was administered, he was neither involved in the assessment, nor in the analysis of the experimental data. As the two tablets were not identical, they were administered in a glass of orange juice.

Directly before the administration of modafinil or placebo (time point T0), 120 (T120) and 210 (T210) minutes after the treatment (i.e., before and after the fMRI acquisition), the systolic and diastolic blood pressure and the heart rate were assessed as physiological measures. In addition, visual analogue scales (VAS; Bond and Lader 1974) were used to obtain subjective measures of wakefulness ("not at all awake" to "fully awake") and mood ("very bad" to "very good") at T0, T120, and T210.

The order of the treatments was counterbalanced between participants, as was the assignment of the two versions of the experiment, A and B, to both the treatments and the testing session. In one fMRI acquisition session, participants were presented with one set of 50 dilemmas, whereas in the other fMRI session they were presented with the other set, with each set including 25 moral and 25 neutral dilemmas. All researchers involved in data acquisition and analysis remained blind to the treatment of individual subjects in each testing session until treatment information was required for inferential analyses on the group level.

In each fMRI acquisition session, the stories were presented in an event-related experimental design by using Presentation software (Neurobehavioral Systems Inc. Albany, CA). Participants wore goggles, on which the computer screen was projected at a resolution of 800 × 600 pixels. The experimental trial structure was similar to the one described in Sommer et al. (2010). Specifically, each trial started with the presentation of a fixation cross in the middle of the screen (duration 8, 10, or 12 s), followed by the simultaneous presentation of the dilemma story and the question "What should I do?" (duration = 13 s). Then, the two possible alternatives were presented (duration = 5 s), one on the right and one on the left side of the screen. For moral dilemmas, the assignment of the type of response (according to the moral standard or the personal desire) to the screen side was counterbalanced. During this interval, participants were instructed to think about their decision. Finally, the letters "A" and "B" appeared above the left and the right response alternative, respectively (duration = 2 s). During this interval, participants were instructed to decide and indicate their choice by pressing the left button of an MR compatible response pad with the index finger of their right hand for option "A" or the right button with the middle finger of their right hand for option "B." All stimuli were written in black (font, Arial 24) and presented on a white background. Each fMRI acquisition session consisted of two consecutive acquisition runs including both moral and neutral dilemmas in random order and lasted about 30 min. As outlined above, the overall number of dilemmas was 50 (25 moral and 25 neutral) for each fMRI acquisition session. Each run thus contained 25 dilemmas, with the exact number of moral and neutral dilemmas varying between runs.

At the beginning of the acquisition session, participants were presented with standardized instructions followed by a brief training session consisting of three dilemmas, which were neither used in the experimental runs nor included in the data analysis. After the experiment, participants were informed that they were not allowed to drive a car or use any dangerous machines for the next 24 h due to potential effects of the treatment. Participants received 200 € for participation in the experiment.

Data acquisition

Participants were scanned with a 3-Tesla Philips Achieva MR scanner equipped with a 32-channel head coil. For each participant, a structural image (220 slices, time of repetition (TR) = 8.2 ms, time of echo (TE) = 3.7 ms, slice thickness = 1 mm, in-plane resolution = 1 × 1 mm) was recorded in the first session of data acquisition.

In each fMRI session, whole brain functional images were acquired using a T2*-weighted gradient-echo, EPI pulse sequence, using BOLD contrast (TR = 2000 ms, TE = 30 ms, flip angle = 90°). Each functional image comprised 28 slices acquired in ascending order (slice thickness = 3 mm, gap = 1 mm, field of view = 224 mm × 240 mm). In each acquisition session, participants underwent two consecutive fMRI scanning runs, each comprising 385 scans, plus five initial dummy scans, which were discarded prior to data analysis.

Data analysis

Physiological data, VAS ratings, and behavioral data from the moral dilemmas

Heart rate, diastolic and systolic blood pressure, and the VAS ratings for mood and wakefulness (in %, with 100% meaning "very good" mood and "fully awake," respectively) were analyzed by means of ANOVA with the factors Treatment (modafinil vs. placebo) and Time (T0 vs. T120 vs. T210).

Concerning the behavioral data from the moral dilemmas, a moral index was calculated as the percentage of the number of moral decisions (i.e., decisions in accordance with the moral standard) for each participant, separately for the two fMRI sessions in the two treatment conditions (modafinil, placebo). To test the effect of treatment, the moral index values were then compared by means of a paired *t* test.

For all analyses described above, the level of significance was set to $P < 0.05$. Whenever the sphericity assumption was violated in the ANOVAs, the Greenhouse-Geisser correction was applied. If this was the case, epsilon-corrected *P* values and uncorrected degrees of freedom are reported. Partial eta-squared values are reported as estimates of effect sizes for significant effects in the ANOVAs, while Cohen's *d* is reported for *t* tests.

fMRI data

Preprocessing The functional imaging data of the 18 participants were preprocessed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm), including slice time correction, realignment, and normalization to the Montreal Neurological Institute (MNI) space. Normalization was performed by applying the New segment procedure as implemented in SPM8 and by using the subject-specific segmented versions of the anatomical image as customized segmentation priors (for a similar procedure, see Ghio et al. 2016). Functional images were smoothed with a 6-mm FWHM Gaussian kernel.

Before the statistical analysis was conducted (see below), the functional imaging data of each participant were reviewed both by considering the realignment parameters and by applying the tsdiffana utility (http://sourceforge.net/projects/spmtools) in order to explore the amount of head motion of the participants. This procedure revealed that nearly half of our participants exhibited large head movements during one or both acquisition sessions, which could be sources for artifacts during data analysis. To account for motion-related effects, we thus applied a scrubbing procedure for the functional imaging data (Power et al. 2012; Siegel et al. 2014). By using the formula reported in Power et al. (2012) and Siegel et al. (2014), we first computed the frame displacement (FD) as a metric of data quality, which combines the six motion parameters that were calculated for each volume during the realignment procedure. All volumes whose FD exceeded the threshold of 0.90 mm were flagged as volumes of suspect quality. Additionally, we flagged the volume 1 back and 1 forward from any volume of suspect quality (Power et al. 2012; Siegel et al. 2014). All the flagged volumes were censored by modeling them in the first-level general linear model as regressors of no interest (see below).

General linear model statistical analysis We applied a two-stage random-effects statistical analysis, restricted to an explicit mask including only the voxels with gray matter tissue probability > 0.1. The mask was based on the re-sampled and smoothed, segmented structural image of each participant.

At the first level, the time series of each participant were high-pass filtered at 128 s and pre-whitened by means of an autoregressive model AR(1). Global normalization was applied. For each participant, we modeled two runs for the modafinil treatment session, and two runs for the placebo treatment session (see also above). Each run included four regressors for the moral dilemmas and four regressors for the neutral dilemmas. The first regressor for each type of dilemma modeled the time interval during which the dilemma and the question "What should I do?" were presented on the screen (duration = 13 s); the second regressor modeled the time interval during which the two response alternatives were

shown on the screen, and participants were asked to think about their decision (duration = 5 s); the third regressor modeled the time interval during which the letters "A" and "B" were shown above the two options, and participants were asked to take their decision by pressing a button (duration = 2 s); the fourth regressor modeled the time point of the response. Additional regressors modeled the six head movement realignment parameters and those volumes classified as of suspect quality (see above). Specifically, for each flagged volume we modeled a separate regressor, which included all zeros except for a value of one for the flagged volume. Importantly, if the onset (plus the duration) of any event of interest occurred concomitantly with a flagged volume, the event was removed from the corresponding experimental regressor, and modeled in an additional confound regressor. As the main interest of the present study was to investigate modafinil effects on the processing of moral dilemmas, subjects were included in the following group analyses if there were at least 10 (out of 25) events in each of the four experimental conditions of interest (i.e., moral and neutral dilemma presentation in, respectively, the modafinil and the placebo condition, see below). Based on this criterion, two participants were excluded from the group analyses. For the remaining 16 participants, the mean number of events that were considered in the dilemma processing analysis (see below) in the different conditions amounted to 23.1 (moral dilemmas under modafinil), 22.4 (neutral modafinil), 22.1 (moral placebo), and 21.1 (neutral placebo).

After estimating the first-level general linear model, we defined a set of first-level Student's t test contrasts for each subject. For a comparison with the work by Sommer et al. (2010), we focused the analysis on the time interval during which the dilemma (either moral or neutral) and the question were presented, as modeled by the first regressor of interest (see above). Therefore, we specified the following contrasts modeling: (i) the effect of the Type of dilemma, with a weight of + 1 and − 1 for the regressors modeling the moral and the neutral dilemmas, respectively; (ii) the effect of Treatment, with a weight of + 1 and − 1 for the regressors modeling the dilemmas in the modafinil and the placebo condition, respectively; (iii) the interaction between Type of dilemma and Treatment, with a weight of + 1 for the regressors modeling the moral dilemmas in the modafinil condition, a weight of − 1 for the regressors modeling the neutral dilemmas in the modafinil condition, a weight of − 1 for the regressors modeling the moral dilemmas in the placebo condition, and a weight of + 1 for the regressors modeling the neutral dilemmas in the placebo condition. A weight of zero was defined for all the other regressors not specified above.

At the second level, we specified three second-level, random-effects, one-sample t tests to examine the effect of the Type of dilemma and Treatment, and their interaction, respectively.

In order to correct for multiple comparisons, we applied the Gaussian random field theory as implemented in SPM8 to obtain clusters satisfying $P < 0.05$ family-wise error (FWE) corrected at a cluster-defining threshold of $P < 0.001$ (uncorrected).

Results

Physiological data and VAS ratings

Table 1 lists mean values and SDs for physiological measures (heart rate and blood pressure) and the VAS ratings (mood and wakefulness) in the two Treatment conditions and for three time points for those participants whose data were considered for the fMRI analysis. Note that for the physiological measures, data of one participant are missing, and for the VAS ratings data of two participants are missing. As these measures mainly served to assess if and in how far the treatment caused unspecific changes in physiological measures and subjective well-being, only effects involving the factor Treatment will be reported. For the heart rate, the main effect of Treatment and the Time by Treatment interaction were both not significant (both $P > 0.05$). Likewise, no significant Treatment effects were found for the diastolic blood pressure (both $P > 0.71$). The systolic blood pressure was generally enhanced in the modafinil session (main effect Treatment, $F(1, 14) = 7.222$, $P = 0.018$, $\eta^2_p = 0.340$), while the Treatment by Time interaction was not significant ($P > 0.29$). For the mood and the wakefulness VAS ratings, the main effects of Treatment and the interaction did not reach significance (all $P > 0.10$).

Behavioral results from the moral dilemmas

Concerning the decisions in the moral dilemmas, there was a significant effect of Treatment for the 16 participants that were included in the fMRI analysis. Under modafinil, the participants responded according to the moral standard in 53% of the dilemmas on average (SD = 16%), whereas under placebo the percentage of moral responses was significantly lower (M = 45%, SD = 17%, $t(15) = 2.773$, $P = 0.014$, $d = 0.40$). When the sample of participants was divided into two groups according to the assignment of experiment versions A and B to the respective treatment conditions of modafinil and placebo (n = 8 for each combination), it was found that the percentage of "moral" responses was comparably elevated irrespective of the experiment versions ($P = 0.861$ for the interaction of Treatment and Assignment group).

fMRI results

We first evaluated the effect of the Type of dilemma to examine the network of brain regions involved in processing

Table 1 Means and SDs for physiological measures and VAS ratings at different time points from modafinil and placebo administration

	Modafinil			Placebo		
	T0	T120	T210	T0	T120	T210
Physiological measures[a]						
Heart rate (BPM)	80 ± 11	74 ± 10	75 ± 11	79 ± 9	69 ± 9	72 ± 14
Diastolic blood pressure (mmHg)	70 ± 7	74 ± 10	78 ± 8	70 ± 7	71 ± 8	78 ± 16
Systolic blood pressure (mmHg)	129 ± 13	130 ± 9	133 ± 7	126 ± 14	121 ± 16	130 ± 14
VAS ratings[b]						
Mood (%)	59 ± 21	68 ± 23	63 ± 24	63 ± 19	66 ± 18	67 ± 21
Wakefulness (%)	61 ± 17	76 ± 18	61 ± 23	66 ± 18	64 ± 19	58 ± 18

Note. T0 = before the treatment administration; T120 and T210 = 120 and 210 min after the treatment administration

[a] Based on the data of 15 participants

[b] Based on the data of 14 participants

everyday moral dilemmas compared to neutral dilemmas, which also allowed a comparison with the findings by Sommer et al. (2010). We found stronger activations for processing moral versus neutral dilemmas in two frontal clusters, one involving the dmPFC including the bilateral superior medial frontal gyrus and extending into the bilateral anterior cingulate cortex and the medial orbital gyrus, and one in the bilateral inferior frontal gyrus, extending into the insula. Additional activations were found in the right hemisphere, including one cluster in the middle temporal gyrus and one cluster involving the supramarginal gyrus, the angular gyrus, and extending into the superior and middle temporal gyrus. Similarly, in the left hemisphere we found one cluster of activation involving the supramarginal gyrus, the angular gyrus, the inferior parietal lobule, and extending into the middle temporal gyrus. Bilateral activations were found in the precuneus and the middle cingulate cortex (see Table 2 for a list of coordinates, and Fig. 1; with a cluster-defining threshold of $P = 0.001$, the $P = 0.05$ FWE-corrected critical cluster size was 70 voxels).

The analysis of the effect of Treatment did not reveal any significant difference in the brain activations between the modafinil and the placebo condition. Also the analysis of the Type of dilemma by Treatment interaction did not yield any significant result. For both these effects, no significant results were found even by adopting a liberal threshold of $P < 0.001$ uncorrected (extent cluster threshold = 10 voxels).

Given that we observed a behavioral effect of modafinil, we then conducted further exploratory analyses on a potential effect of Treatment on brain activity (Treatment main effect and Treatment by Type of dilemma interaction) by considering the other phases of our decision making paradigm, namely the time interval during which the participants were asked to think about their decision (thinking phase), the time interval during which the participants were asked to take their decision (decision phase), and the time of the response (see also the Methods section for information about how these phases were modeled at the single-subject level). Neither significant effects of Treatment, nor significant Treatment by Type of dilemma interactions were found for any of the analyzed phases with the threshold that we applied (see Methods section).

Finally, a small volume correction procedure was applied concerning the activation in the vmPFC and dmPFC, for which we predicted modulatory effects of modafinil. The small search volumes were based on the ALE meta-analysis of moral cognition by Bzdok et al. (2012) and consisted in 6 mm spheres centered at the following coordinates: x = 4, y = 58, z = − 8 (right vmPFC); x = − 10, y = 42, z = − 18 (left vmPFC); x = 0, y = 54, z = 36 (bilateral dmPFC). The small volume correction procedure was applied to test the main effect of Treatment and the interaction between Treatment and Type of dilemma for each phase of the task (i.e., dilemma processing, thinking, decision, and response). The only significant effect emerged for the analysis of response-locked activity, where we found a significant Treatment by Type of dilemma interaction in the dmPFC (x = 0, y = 50, z = 36; *z*-value = 3.44, $P = 0.013$). Analysis of the percent signal change at this coordinate revealed the underlying pattern for the interaction: Under modafinil, the response in the moral dilemmas was associated with lower activation ($M = -3.19$, SD = 8.38) compared with the response in neutral dilemmas ($M = 10.63$, SD = 18.56, $P = 0.012$), while similar activations were observed for responses in both types of dilemmas in the placebo condition (moral dilemmas: $M = 5.67$, SD = 11.87; neutral dilemmas: $M = 5.24$, SD = 19.38, $P = 0.935$).

Discussion

The aim of the present study was to examine the effect of acute modafinil administration on the processing of moral dilemmas and on moral decision making. The participants of the present

Table 2 Moral dilemmas > neutral dilemmas

Hemisphere and region (cytoarchitectonic probability[a])	Cluster p (FWE corr)	Cluster size (voxels)	Peak MNI coordinates			*z*-values
			x	y	z	
R superior medial frontal gyrus	< 0.001	550	6	50	28	5.78
L superior medial frontal gyrus	„	„	− 6	56	16	4.70
R anterior cingulate cortex	„	„	8	52	12	4.26
L anterior cingulate cortex	„	„	− 8	42	16	3.89
R medial orbital gyrus	„	„	4	64	− 8	3.41
L medial orbital gyrus	„	„	− 2	60	− 12	3.99
R rectal gyrus	„	„	4	58	− 16	3.33
R Insula	< 0.001	185	34	18	− 16	5.22
R temporal pole	„	„	42	20	− 20	5.09
R inferior frontal gyrus (p. Orbitalis)	„	„	42	28	− 12	4.35
R inferior frontal gyrus (p. Triangularis)	„	„	48	28	4	3.63
L Insula	0.002	70	− 28	16	− 12	4.14
L inferior frontal gyrus (p. Orbitalis)	„	„	− 38	16	− 16	4.08
R middle temporal gyrus	< 0.001	211	54	− 6	− 20	4.99
R supramarginal gyrus	< 0.001	420	62	− 50	28	4.92
R angular gyrus	„	„	52	− 48	24	4.56
R superior temporal gyrus	„	„	60	− 54	20	4.48
R middle temporal gyrus	„	„	42	− 56	20	3.73
L supramarginal gyrus	< 0.001	378	− 58	− 52	28	4.67
L angular gyrus	„	„	− 46	− 56	24	3.75
L inferior parietal lobule	„	„	− 58	− 52	40	3.87
L middle temporal gyrus	„	„	− 56	− 50	20	4.76
R precuneus	< 0.001	597	4	− 56	36	5.57
L precuneus	„	„	− 10	− 56	44	4.48
L middle cingulate cortex	„	„	− 4	− 44	48	3.37

Note. The significance threshold for the reported activations was set to cluster-level $P < 0.05$, FWE corrected, FWE-corrected critical cluster size = 70. R = right; L = left

[a] According to www.fz-juelich.de/ime/spm_anatomy_toolbox

study were tested twice with parallel task versions and received either modafinil or placebo before they engaged in a moral decision making task. Concerning the behavior in the moral dilemmas, we found that modafinil slightly but significantly enhanced the proportion of responses in accordance with a moral standard. With respect to the neural correlates of moral reasoning (compared to reasoning on neutral dilemmas) across treatments, our results revealed activation clusters in the bilateral dmPFC extending into the anterior cingulate cortex, the bilateral inferior frontal gyrus extending into the insula, the right middle temporal gyrus, the bilateral supramarginal gyrus and angular gyrus extending into the middle temporal gyrus, and the bilateral precuneus extending into the middle cingulate cortex. No effects of treatment on brain activity associated with moral dilemma processing were found, neither as a main effect, nor in interaction with the type of dilemma (moral vs. neutral). However, an exploratory analysis of the different phases of moral decision making in predefined regions of interest revealed reduced response-locked activity in the dmPFC for moral compared to neutral dilemmas under modafinil, but not placebo.

The activation pattern found for moral reasoning is consistent with previous work on both dead-or-alive dilemmas requiring active decisions (Bzdok et al. 2012; Garrigan et al. 2016; Sevinc and Spreng 2014), as well as with the study by Sommer et al. (2010) on everyday moral dilemmas in suggesting that there is no "moral brain." Instead, specific activations for moral reasoning were found in regions that are involved in social cognitive processes in general (Bzdok et al. 2012). For example, the bilateral dmPFC, the middle temporal gyrus, and the supramarginal/angular gyrus (consistent with reports of activity in the temporoparietal junction in the literature) have been shown to also support theory of mind and/or empathy (Bzdok et al. 2012), suggesting that access to the thoughts and feelings of other persons is critical for moral reasoning. In accordance with this notion, the dmPFC is recruited during

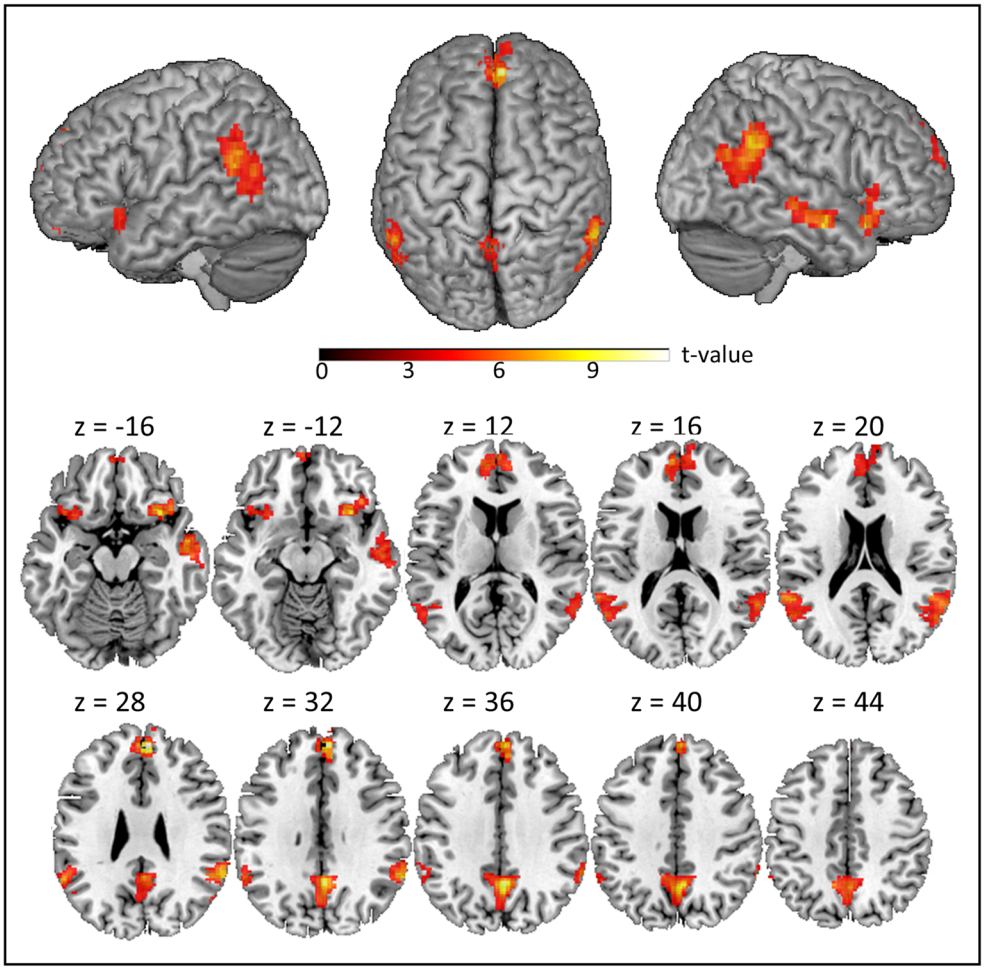

Fig. 1 Significant activations specific to Moral dilemmas > Neutral dilemmas (cluster-defining threshold $P < 0.001$ uncorrected, cluster-level $P < 0.05$, FWE-corrected; FWE-critical cluster size = 70 voxels). All effects are displayed on cortical renderings and on axial (z coordinate levels in mm) slices of the anatomical template image (ch2better template image in MRICron; Rorden, C., and Brett, M. (2000). Stereotactic display of brain lesions. Behav. Neurol. 12, 191–200. doi: https://doi.org/10.1155/2000/421719)

the formation of impressions of other persons (Mitchell et al. 2004, 2006; van Overwalle 2009) and plays a role for cognitive aspects of empathy (Shamay-Tsoory 2011). The TPJ has consistently been linked to theory of mind processes (Shamay-Tsoory 2011), but, compared to the dmPFC, it seems to be especially involved when others' current goals or intentions have to be extracted (van Overwalle 2009), and in processes of self-other distinction (Decety and Lamm 2007). The superior temporal sulcus (STS), located adjacent to the middle temporal cortex, processes and integrates social stimuli in different modalities (Ethofer et al. 2013; Pelphrey et al. 2003; Watson et al. 2014). Finally, the precuneus, which is part of the default mode network and has been associated with self-referential processing (Raichle et al. 2001; Raichle 2015), was activated for the processing of moral dilemmas in the present study. It plays a role, for example, during self-ascription of positive and negative sentences describing socially relevant everyday-life situations (Cabanis et al. 2013), suggesting that reference to the self is an important process in moral decision making (Reniers et al. 2012).

Compared to the study by Sommer et al. (2010), the activation pattern for moral vs. neutral dilemmas in the present study also showed some differences. First, the activations we observed in the regions described above were overall less pronounced and widespread, and no clusters of activation were seen in the left middle temporal gyrus and the vmPFC. These differences are unlikely to be related to the sample size, as there were more participants in our study (16 vs. 12) and our participants were exposed to more experimental trials because they underwent two fMRI acquisitions. Especially the lack of vmPFC involvement in the present study appears to be surprising, because this region has been ascribed a key role in moral reasoning (Bzdok et al. 2012; Greene et al. 2004; Greene 2007; Moll and de Oliveira-Souza 2007). Yet, as it has been pointed out in a recent meta-analysis, the dmPFC, but not the vmPFC, is typically activated in moral reasoning paradigms in which participants are asked to choose between different response alternatives, as was also the case in the present study (Garrigan et al. 2016). The vmPFC instead is more involved in general moral evaluation tasks. A second difference between the present findings and the results by Sommer et al. (2010) is the increased activation that we found in the bilateral inferior frontal cortex for moral dilemmas, extending into the insula. This area, especially the insula, is

associated with representations of emotions, both when they are self-experienced and observed in others. Together with the ACC, the (anterior) insula has been ascribed a critical role in predicting other persons' states or feelings and in linking these to own actions (see Bernhardt and Singer 2012). Consequently, inferior frontal gyrus and anterior insula activations have been observed consistently in moral dilemmas that required an "active" judgment or response (Schaich Borg et al. 2011; Sevinc and Spreng 2014).

While we could largely corroborate the results by Sommer et al. (2010) on the neural correlates of everyday moral decision making, the main focus of our study was on the effects of modafinil on moral reasoning and decision making, which are less clear in our data. On the one hand, we observed a behavioral effect of modafinil, which led to an increase in the number of responses in accordance with a moral standard. On the other hand, we did not find strong effects of modafinil on brain activation. For most phases of our decision making paradigm, and in particular for the processing of the dilemmas, there was neither a general effect of modafinil, nor a specific effect on moral processing. However, also in previous studies addressing modafinil effects on cognition and brain activity, dissociations between the two dependent measures were described. For example, Rasetti et al. (2010) reported decreased PFC and ACC activity for working memory and attention tasks under modafinil in the absence of behavioral changes and attributed this pattern of findings to an increase of processing efficiency induced by modafinil. Potential target regions of modafinil in the present study were the vmPFC and dmPFC, as both are implicated in moral reasoning and decision making (Bzdok et al. 2012; Garrigan et al. 2016), and modafinil has been shown to affect task-related activity in the medial PFC (Minzenberg et al. 2011; Rasetti et al. 2010). Enhanced processing efficiency in these regions, for example in the integration of different types of information for reaching a decision, might thus have led to the enhanced number of moral responses under modafinil, even in the absence of clear activation changes.

Exploratory analyses of brain activity in the other phases of the decision making task in predefined regions revealed, however, that modafinil may have exerted an effect on response-locked activity in the dmPFC. Here we found that activity was reduced for responses in the moral compared to the neutral dilemmas, but only under modafinil. While the dmPFC is consistently reported to be involved in moral reasoning, its exact role is still a matter of debate. At the same time, the region is not clearly defined, and in many studies widespread activations were found in the medial prefrontal cortex, which also extended into other brain regions (Bzdok et al. 2012; Garrigan et al. 2016; Sevinc and Spreng 2014). Accordingly, dmPFC activations in the context of moral reasoning have been linked to different cognitive processes that are directly or indirectly relevant for moral decision making such as inhibition and uncertainty processing (Sommer et al. 2010) and represented in several regions in the PFC (Aron 2007; Bhanji et al. 2010). However, the localization of the effect that we identified by means of small volume correction seems to be more compatible with an interpretation in terms of social cognitive processes. According to the meta-analysis by Bzdok et al. (2012), the dmPFC is part of a network underlying theory of mind and empathy, thereby also contributing to moral reasoning. As already pointed out above, access to feelings and thoughts of others is a prerequisite for the evaluation of the moral dilemmas in the present study, as the dilemma stories always involved another person. Importantly, the core of the conflicts in these stories was in the behavioral options between which the participant could choose, and one criterion for the decision was probably the expected effect of the own behavior on the other person. As described above, the dmPFC seems to be particularly relevant for moral reasoning when a decision has to be made between different options (Garrigan et al. 2016). It may thus not be surprising that we found a modafinil-induced modulation of dmPFC activation time-locked to the response, possibly underlying the behavioral effect of more moral responses under modafinil. In order to explain the potential role of the dmPFC for the decision process in the present study, a reference to the neural networks underlying empathy-related processes might provide important insights. According to the model by Bernhardt and Singer (2012), the (anterior) insula and the ACC, which both show activity related to moral reasoning in the present study, closely interact during the process of empathizing with others. While the insula is seen as an input region integrating information from various sources to represent "feeling states" for the self and others, the ACC and adjacent medial PFC represent the output stage, using this information for action selection. The close link between feeling states and actions can then be used to understand and predict emotions and actions of others. Although the modafinil effect on neural processing was found outside of the ACC in the present study, the ACC and the dmPFC seem to belong to one functional activation cluster for moral vs. neutral dilemma processing. One interpretation is that the reduced dmPFC activity for moral vs. neutral dilemmas under modafinil at the time point of the response represents altered processing related to information integration for the decision. This seems unlikely, as the decision itself was probably already made in the experimental phases before the actual response was performed, in accordance with the instruction. An alternative interpretation is that modafinil modulated the prediction of the (emotional) consequences of the chosen behavior for the other person in the dilemma. Reduced activity might then indicate that the prediction requires less processing effort, again in line with the assumption of increased efficiency of information processing induced by modafinil (Rasetti et al. 2010). In any case, the results

concerning modafinil effects on brain activity related to moral decision making have to be interpreted with caution, as they were obtained only by applying a small volume correction in selective brain regions. Thus, future studies are needed to corroborate and extend these findings.

The most obvious limitation of our study is the small size of the sample that we examined. It cannot be excluded that with a larger sample of participants differences between the modafinil and placebo conditions concerning the neural processing of moral dilemmas would have been more pronounced. Still, the sample size can be considered as acceptable given the placebo-controlled crossover-design of the present study. Functional imaging studies with a similar design and involving pharmacological treatment have often investigated even smaller samples (e.g., Shiner et al. 2012; Sommer et al. 2010).

Another limitation is that we did not systematical assess participants' insight into treatment, that is, whether they had received modafinil or placebo at a given testing session. Insight into treatment might have an impact on subjective beliefs and evaluations and thus on behavior. But we assessed changes in self-reported mood and wakefulness from the time point of treatment to the time points of the beginning and the end of the fMRI acquisition. Although the wakefulness measure before the start of the experiment was descriptively enhanced in the modafinil condition, we did not find significant effects of modafinil on both measures, suggesting that modafinil did at least not generally enhance subjective well-being and vigilance. It is possible, however, that with other, more specific measures changes in mood or related states could have been detected.

Finally, physiological measures were also taken to control for potential modafinil effects on cardiovascular functions. Here, no significant effects of treatment were found on heart rate and diastolic blood pressure, but systolic blood pressure was enhanced under modafinil. The latter effect is difficult to interpret, because for a specific modafinil effect an interaction between Time and Treatment would be expected, with no significant differences at time point 0. Although thus only one out of three cardiovascular measures was affected by the type of treatment, it cannot be excluded that direct vascular effects of modafinil had an impact on the result pattern of the present study. In this context, it has to be mentioned as another limitation of the study that we did not measure cardiovascular functions during the experiment which is strongly recommended for future studies on modafinil effects on brain activity.

To conclude, our study yielded a small behavioral effect towards more moral responses under the influence of modafinil. Concerning the neural processing, modafinil did not alter brain activity related to moral reasoning in general, but exploratory analyses yielded that brain activity time-locked to the response in moral dilemmas was reduced under modafinil. One possible interpretation might be in terms of altered prediction processes for the emotional state of other persons involved in the moral dilemma and enhanced processing efficiency induced by modafinil. While the findings need to be replicated before firm conclusions can be reached, we consider it unlikely that modafinil specifically affects moral reasoning and decision making. Rather, it might support complex cognitive processes that also underlie moral behavior.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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