

Modafinil enhances alerting-related brain activity in attention networks

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Abstract

Rationale Modafinil is a wake-promoting agent and has been reported to be effective in improving attention in patients with attentional disturbance. However, neural substrates underlying the modafinil effects on attention are not fully understood. **Objectives** We employed a functional magnetic resonance imaging (fMRI) study with the attention network test (ANT) task in healthy adults and examined which networks of attention are mainly affected by modafinil and which neural substrates are responsible for the drug effects.

Methods We used a randomized placebo-controlled within-subjects cross-over design. Twenty-three healthy adults participated in two series of an fMRI study, taking either a placebo or modafinil. The participants performed the ANT task, which is designed to measure three distinct attentional networks, alerting, orienting, and executive control, during the fMRI scanning. The effects of modafinil on behavioral performance and regional brain activity were analyzed.

Results We found that modafinil enhanced alerting performance and showed greater alerting network activity in the left

middle and inferior occipital gyri as compared with the placebo. The brain activations in the occipital regions were positively correlated with alerting performance.

Conclusions Modafinil enhanced alerting performance and increased activation in the occipital lobe in the alerting network possibly relevant to noradrenergic activity during the ANT task. The present study may provide a rationale for the treatment of patients with distinct symptoms of impaired attention.

Keywords Modafinil · Attention network test · Alerting · fMRI

Introduction

Attention is an essential cognitive function for almost all aspects of behaviors. Through the “top-down” and “bottom-up” processes of attention, we detect targets with alerting features, select relevant inputs, ignore irrelevant inputs, and maintain appropriate task sets (Sarter et al. 2001). Posner and Petersen (1990) have proposed that the attention system can be divided into three networks: alerting, orienting, and executive control. These three networks have been theorized to be functionally and anatomically segregated (Fan et al. 2002; Posner and Rothbart 2007). In addition, pharmacological studies have revealed that each network is preferentially affected by a specific neurotransmitter system. Noradrenaline controls the efficiency of alerting, whereas acetylcholine and dopamine affect orienting and executive control, respectively (Green et al. 2008). To simultaneously study these three networks, the attention network test (ANT) has been developed (Fan et al. 2002). Through ANT, attentional functions have been studied during drug treatments (Conen et al. 2013; Ikeda et al. 2012; Thienel et al. 2009). Dysfunctions of attentional networks

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have also been reported in patients with attention deficit hyperactivity disorder (ADHD) (Johnson et al. 2008) and schizophrenia (Backes et al. 2011).

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is a wake-promoting agent that is structurally distinct from central nervous stimulants such as amphetamine and methylphenidate (Rugino 2007), and is prescribed worldwide for the treatment of excessive daytime sleepiness associated with narcolepsy (Minzenberg and Carter 2008). In addition, modafinil has also been prescribed for off-label uses in a variety of conditions including neuropsychiatric disorders (Peñaloza et al. 2013). Of note, modafinil has been reported to be effective in improving attention in patients with attentional disturbance, including ADHD (Turner 2006) and schizophrenia (Turner et al. 2004) for off-label uses. The mechanism of action of modafinil is unique and complex, and is distinct from that of traditional psychostimulants such as amphetamine (Mereu et al. 2013; Minzenberg and Carter 2008). Modafinil acts on dopaminergic and noradrenergic systems in the brain. Modafinil increases extracellular levels of dopamine in rodents (Murillo-Rodríguez et al. 2007) and humans (Volkow et al. 2009) possibly through binding to and inhibiting dopamine transporter (DAT) (Kim et al. 2014; Madras et al. 2006; Volkow et al. 2009). Modafinil also binds to norepinephrine transporter (NET) in monkey thalamus (Madras et al. 2006). Animal studies have suggested roles of D₁ and D₂ dopaminergic (Qu et al. 2008) and α and β adrenergic receptors (Lin et al. 1992) in the effects of modafinil. In addition to the dopaminergic and noradrenergic systems, modafinil affects other neurotransmitter systems including glutamate, γ -aminobutyric acid (GABA), serotonin, and histamine (Ferraro et al. 1999, 2000; Ishizuka et al. 2010). Therefore, modafinil is suggested to exert its effects via multiple neurotransmitter systems in the brain, although the exact action mechanism has not yet been clearly identified.

As expected from its wide range of action mechanisms, modafinil has been shown to enhance many cognitive functions (Minzenberg and Carter 2008). Interestingly, modafinil improves attention in healthy individuals (Caviola and Faber 2015) as well as in patients with cognitive dysfunctions. Modafinil has been reported to enhance sustained attention (Randall et al. 2005), attention switching (Marchant et al. 2009), and divided attention (Hart et al. 2006) in healthy individuals. On the other hand, other reports have shown no significant effects of modafinil on divided attention (Theunissen et al. 2009) and sustained attention (Randall et al. 2003). Thus, the reported effects of modafinil on attention remain inconsistent in spite of its clinical use for patients with attentional deficits.

To further characterize the effects of modafinil on attention, we therefore employed a functional magnetic resonance imaging (fMRI) study while healthy adults performed the ANT task. We attempted to reveal the networks of attention that are

mainly affected by modafinil as well as the neural substrates that are responsible for the drug effects. Further, through the results from the present study, we also tried to provide a rationale for the choice of drug for the treatment of patients with attention deficits or dysfunction.

Materials and methods

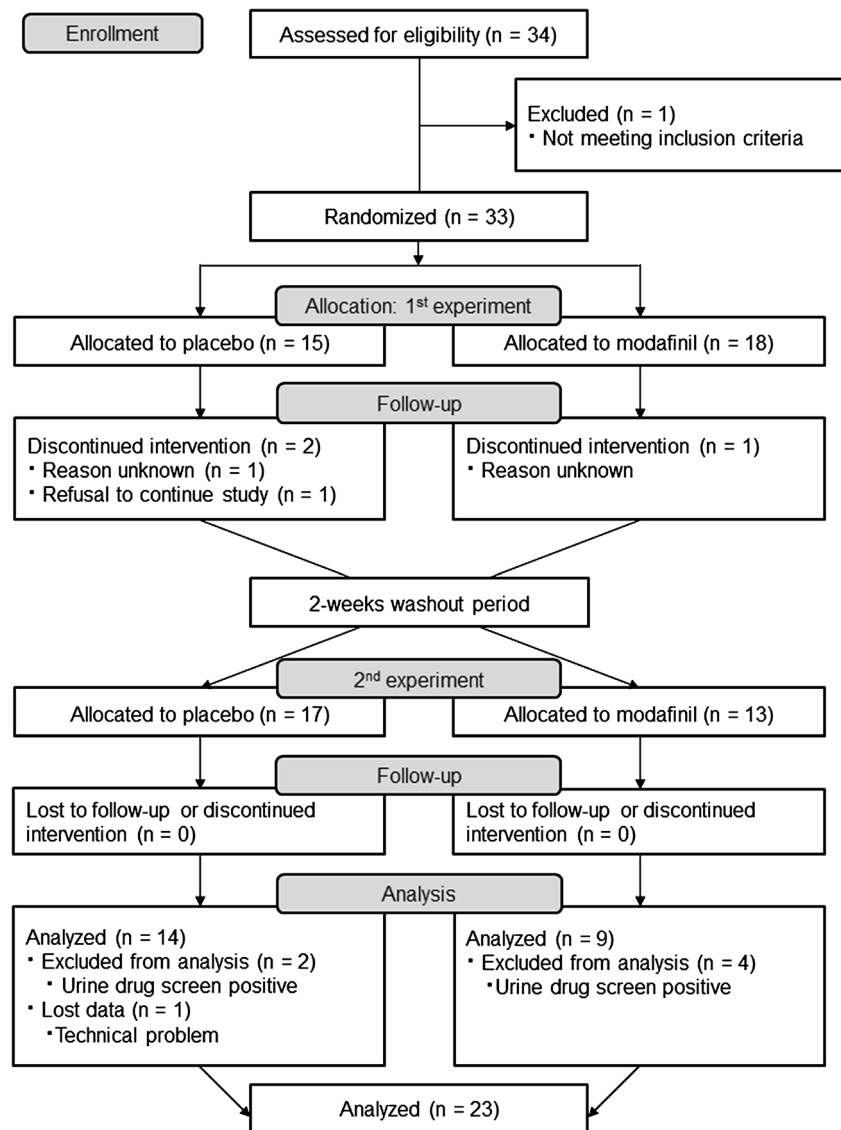
Participants

Thirty-four healthy volunteers participated in the study, and the data of 23 subjects with normal weight were analyzed (Fig. 1). All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971). As for the excluded subjects, those with a medical history of psychiatric disorders, cardiac disorders, epilepsy, or allergy to modafinil; those with any diseases such as hypertension, hepatic dysfunction, or renal dysfunction; those who had taken any drugs for at least 2 weeks prior to the experiment; those with any contraindications to fMRI; and those with excessive consumption of alcohol or caffeine, smokers, and pregnant women were ruled out. In addition, the baseline mood and subjective states of the participants were assessed, and those with Beck Depression Inventory (BDI) score ≥ 11 , Epworth Sleepiness Scale (ESS) score ≥ 10 , State-Trait Anxiety Inventory (STAI)-state ≥ 42 , and STAI-trait ≥ 45 were also excluded. BDI is widely used to quantify the severity of depressive moods (Beck et al. 1996), ESS is a standardized tool for assessing daytime sleepiness (Johns 1991), and STAI is valuable for screening of anxiety disorders, consisting of two separate rating scales, one for “state” anxiety and the other for “trait” anxiety (Spielberger 1983). BDI, ESS, and STAI consist of 21, 8, and 40 question items rated by 4-point scales, respectively. Participants were asked to abstain from caffeine and alcohol intake for 2 days and 24 h, respectively, before the experiment. They were instructed not to eat or drink anything except water for 2 h prior to and throughout the experiment. The characteristics of the participants are summarized in Table 1. The present study was approved by the ethics committee of Nippon Medical School (approval number 223019). All participants gave written informed consent prior to the experiment.

Study design and procedure

This study adopted a randomized placebo-controlled within-subjects cross-over design. To carefully monitor adverse drug effects in the participants, we conducted the study, including the fMRI data analyses, in a single-blind manner. Each participant was tested on two separate days at least 2 weeks apart to allow for complete clearance of drugs. In the first series, modafinil (200 mg as a Modiodal 100-mg tablet formula,

Fig. 1 CONSORT flow diagram displaying the progress of all participants through the study



Alfresa Pharma, Japan; Minzenberg et al. 2008) or a placebo tablet was administered orally with water. In the second series, participants were crossed over to receive the opposite medication. The modafinil and placebo tablets were identical in appearance and taste so that participants were not aware which tablet was being administered. The order of administration was randomly decided. Any demographic characteristics were not significantly different between participants who were allocated to placebo first or modafinil first (Table 1). We asked the participants to infer which drug arm they were in. Ten of the 23 participants correctly answered the arm to which they belonged, indicating that their inference was at chance level ($p = 0.136$; binomial distribution). The fMRI scan was started 2.5 h after administration of the placebo or modafinil, based on pharmacokinetic data that a 200-mg dose of modafinil reaches a peak plasma level at 2.5 h after oral administration (Robertson and Hellriegel 2003). Blood oxygenation level-

dependent (BOLD) fMRI and behavioral data were acquired during performance of the ANT task. To assess subjective drug effects, subjective ratings were obtained before and at 2 h (just before fMRI scan) after the administration.

Drug effects on subjective ratings

Subjective assessments were collected using Profile of Mood States (POMS) (McNair et al. 1971), Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960) and Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton 1959), and visual analogue scales (VAS) (Bond and Lader 1974). POMS was used to assess various mood states by a 5-point self-administered scale consisting of 65 items measuring 6 factors: Tension–Anxiety, Depression–Dejection, Anger–Hostility, Vigor, Fatigue, and Confusion. Assessments of depression and anxiety status included HAM-D and HAM-A,

Table 1 Demographic characteristics of participants

	Total subjects (<i>n</i> = 23)	Range	Placebo first (<i>n</i> = 9)	Modafinil first (<i>n</i> = 14)	<i>p</i> value ^a
Age (years)	29.5 ± 5.0	20–38	30.4 ± 5.2	28.9 ± 5.1	0.474
Gender (males:females)	14:9		6:3	8:6	0.648 ^b
Body mass index (kg/m ²)	21.0 ± 1.7	18.7–24.5	20.6 ± 1.3	21.3 ± 1.9	0.403
Alcohol consumption (g/day)	3.9 ± 5.6	0–20	4.7 ± 6.4	3.4 ± 5.2	0.781 ^c
Caffeine consumption (mg/day)	75.7 ± 58.3	0–210	78.4 ± 63.3	73.9 ± 57.2	0.861
BDI	1.5 ± 2.0	0–7	2.1 ± 1.8	1.1 ± 2.0	0.141 ^c
ESS	4.0 ± 2.4	0–9	3.2 ± 2.1	4.4 ± 2.5	0.245
STAI (state)	32.1 ± 5.8	23–41	30.8 ± 5.3	33.0 ± 6.2	0.386
STAI (trait)	32.5 ± 6.0	23–43	32.4 ± 5.6	32.5 ± 6.9	0.983

Values are presented as mean ± standard deviation

BDI Beck Depression Inventory, *ESS* Epworth Sleepiness Scale, *STAI* State and Trait Anxiety Inventory

^a *p* values as compared between groups firstly treated with placebo and modafinil. Two-sample *t* test for unpaired data was used unless otherwise indicated

^b χ^2 test

^c Non-parametric Mann–Whitney's *U* test

which consisted of 21 and 14 items, respectively. VAS was applied to assess subjective mood by using 16 lines with an opposing adjective at either end: (1) alert–drowsy, (2) calm–excited, (3) strong–feeble, (4) muzzy–clear-headed, (5) well-coordinated–clumsy, (6) lethargic–energetic, (7) contented–discontented, (8) troubled–tranquil, (9) mentally slow–quick-witted, (10) tense–relaxed, (11) attentive–dreamy, (12) incompetent–proficient, (13) happy–sad, (14) antagonistic–amicable, (15) interested–bored, and (16) withdrawn–gregarious. For each scale, participants were asked to mark each line between the antonyms to indicate how they felt at the present time. Each mood VAS was measured in millimeters from the end of positive mood. Scores ranged from 0 to 100, with lower scores indicating more positive mood. These sub-scales were grouped into three factors: Alertness (1, 3, 4, 5, 6, 9, 11, 12, 15), Contentedness (7, 8, 13, 14, 16), and Calmness (2, 10). Item scores were summed and averaged to create total scores for each respective factor.

Attention network test

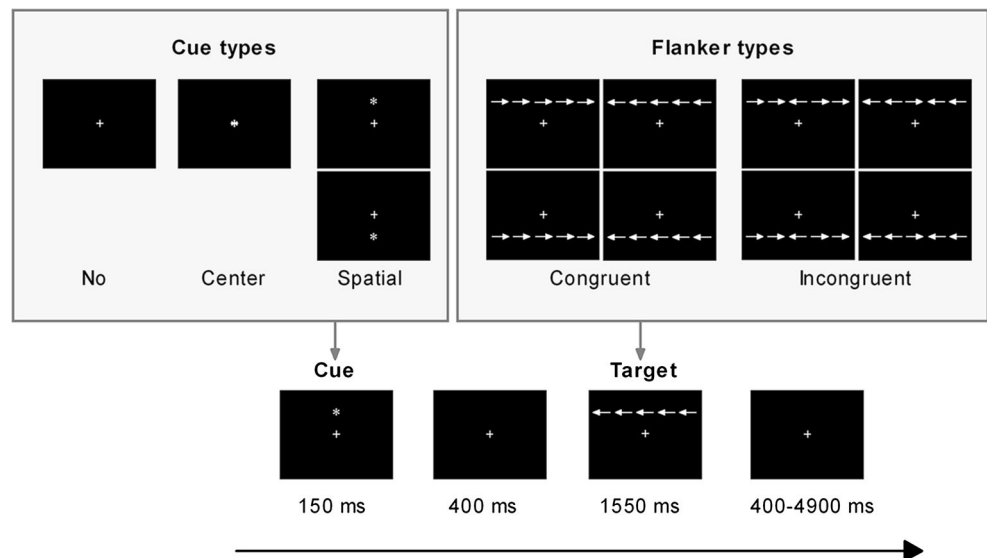
We used the attention network test (ANT) task designed as an event-related fMRI study (Fan et al. 2005; Thienel et al. 2009). The task paradigm is illustrated in Fig. 2. Each trial consisted of a cue period (150 ms), an interval (400 ms), a target period displaying target and flanker arrows (1550 ms), and an offset period (400–4900 ms). A fixation cross was shown in the center of the screen throughout the trial. The participants were instructed to maintain their gaze on the fixation cross. At the cue period, one of three cue types was presented: (1) no cue, only the central fixation cross; (2) the center cue, an asterisk displayed in the center with the fixation cross, alerting participants to the target onset; and (3) spatial

cue, an asterisk displayed either above or below the fixation cross, predicting both the onset and spatial location of the target. At the target period, the target arrow was flanked on both sides by two distracter arrows, pointing in the same (congruent condition) or opposite (incongruent condition) direction to the target. This set of arrows appeared at the same location (above or below the fixation cross) as the spatial cue was presented at the cue period in each trial. Subjects were instructed to identify whether the central (target) arrow pointed to the left or the right and to respond as quickly and accurately as possible by pressing a button for the left direction with the left index finger or another button for the right direction with the right index finger. After a 24-trial practice session for about 2 min outside the MRI scanner room, participants performed three experimental sessions with 240 trials within a total of 20 min with breaks. Throughout the sessions, 24 possible stimulus combinations (3 cue conditions, 2 flanker conditions, 2 target presentation sides, and 2 target pointing directions) were presented equally in the trials (10 times for each combination) in a pseudorandom order. The task was created and presented on a personal computer using E-prime (version 2.0; Psychology Software Tools, USA), displayed on a monitor situated at the foot of the scanner bed, and viewed by participants via mirrors mounted to a head coil.

Statistical analyses of demographic characteristics, subjective ratings, and behavioral data

The demographic characteristics were compared between the placebo first and the modafinil first groups. Unpaired *t* test and non-parametric Mann–Whitney's *U* test were used for the data with normal and non-normal distributions, respectively. The gender data were analyzed by chi-square test. As behavioral

Fig. 2 Schema of ANT task. Stimulus material and example for the course of one trial are presented. In each trial, a fixation cross was seen constantly in the center of the screen. A cue (no, center, or spatial cue) appeared randomly. After inter-stimulus interval, the target (the center arrow) and flankers of the left and right two arrows (congruent or incongruent flankers) were presented. During the target period, the participant was asked to indicate the direction of the arrow head of the target with a button press. After the target period, an inter-trial interval was given



measures, responses and reaction times (RTs) of the trials were recorded on E-prime, and the mean percent of correct responses (accuracy) and mean RT in correct responses for no-cue and center-cue conditions were calculated, respectively. According to previous studies (Fan et al. 2005), the alerting effect was calculated by subtracting the mean RT value in the center-cue condition from that in the no-cue condition. For the subjective ratings and behavioral data, paired *t* test and non-parametric Wilcoxon signed-rank test were used for data with normal and non-normal distributions, respectively, between the placebo and modafinil treatments. The threshold for significance was set at $p < 0.05$.

MRI data acquisition

Brain imaging data were obtained using an Intera Achieva 1.5 T Nova scanner (Philips Electronics, The Netherlands). Functional images were acquired with the following parameters: repetition time (TR) = 3000 ms, echo time (TE) = 60 ms, flip angle = 90°, field of view (FOV) = 200 mm, and matrix = 64 × 64 (Thienel et al. 2009). A total of 339 functional images were acquired from each participant with a T2*-weighted gradient-echo echo-planer imaging sequence sensitive to BOLD contrast. Whole brain coverage was obtained with 4-mm slice thickness and 35 axial slices. After the functional scans, a high-resolution T1-weighted structural image was also acquired for accurate spatial normalization with the following parameters: TR = 9.3 ms, TE = 4.6 ms, flip angle = 8°, FOV = 250 mm, matrix = 256 × 256, slice thickness = 1.2 mm, and number of slices = 160.

fMRI data analysis

Imaging data were preprocessed and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, UK)

running with MATLAB (Mathworks, USA). The structural T1 image and the functional images were manually reoriented to the anterior commissure–posterior commissure line. To correct for between-scan movements, the functional images were realigned to the first image of each session and again realigned to the mean image created after the first realignment. No participant had moved more than 2 mm in any direction during fMRI acquisition. The individual structural T1 image was then co-registered to the mean functional image. The transformed structural image was then segmented to create spatial normalization parameters that were applied to functional images in the next normalization step. The functional images were spatially normalized into the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans were resampled at a resolution of 2 × 2 × 2 mm. The functional images were spatially smoothed with an isotropic Gaussian kernel (full width at half maximum of 8 mm) to increase the signal-to-noise ratio.

For subject-level statistical analyses, correct trials were modeled in the context of the general linear model using δ functions convolved with a canonical hemodynamic response function. Six regressors (related to the onset of the targets) were defined according to the permutation of all conditions comprising three cues (no, center, and spatial) and two flankers (congruent and incongruent). Incorrect and no-response trials were modeled separately as a regressor of non-interest. The six head movement parameters estimated during realignment were included as confounds. Low frequency noise was removed by applying a high-pass filter (cutoff period, 128 s) to the fMRI time-series data of each voxel. The statistical parametric map for each contrast, (a) alerting (central cue > no cue), (b) orienting (spatial cue > center cue), and (c) executive control (incongruent flanker > congruent flanker) of the *t* statistic, was calculated on a voxel × voxel basis.

For group-level analyses, the one-sample *t* test was performed to determine group-level activation for each contrast. Then, for group comparisons, paired *t* test was performed to assess the difference between the placebo and modafinil administrations. The contrast images obtained from subject-level statistical analyses were entered into paired *t* test analyses. All results on activation in the whole brain were reported at $p < 0.001$, uncorrected, with a minimum cluster size of 20 voxels. The cluster size threshold was determined using a cluster-extent correction procedure as implemented in SPM8. Only results surviving the cluster correction ($p < 0.05$) were reported.

According to the group comparison analysis, we focused on the changes in BOLD responses in the alerting contrast because significant difference in brain activity was shown between placebo and modafinil treatments in alerting contrast, but not in orienting and executive control contrasts. We set a priori ROIs with a sphere of 10 mm radius, centered at the maximum peak coordinates of the regions showing significant differences between the placebo and modafinil treatments using the Wake Forest University (WFU) PickAtlas. These ROIs were similar to a priori regions set in previous fMRI studies using the ANT task in healthy untreated controls (Backes et al. 2011; Muto et al. 2012; supplementary Table 1). The percent signal changes within the ROIs were calculated for the alerting contrast using MarsBar and were analyzed using the paired *t* test between the placebo and modafinil treatments and linear correlation (as below).

To investigate the correlation between BOLD activation (percent signal changes) and behavioral measures (RT and accuracy), we performed linear correlation analysis. Pearson's correlation was used for RT analysis, and Spearman's rank correlation method was used for accuracy analysis because these values did not follow normal distribution. The threshold for significance was set at $p < 0.05$.

Results

Effects of modafinil on subjective ratings

Changes in subjective ratings were calculated by subtracting the values before the drug administration from those at 2 h after the drug administration. There were no significant drug effects on the depression status as measured by HAM-D ($p = 0.147$) or the anxiety status as measured by HAM-A ($p = 1$) between the placebo and modafinil treatments. With regard to mood states as measured by POMS (Table 2), modafinil treatment demonstrated a significant increase in the score for vigor compared to the placebo treatment ($p = 0.021$). With regard to subjective mood as measured by VAS (Table 2), subjects with the modafinil treatment were significantly more alert ($p = 0.016$), energetic ($p = 0.018$),

Table 2 Changes in mood in placebo and modafinil treatments

	Placebo	Modafinil	<i>p</i> value ^a
POMS			
Tension–Anxiety	−0.4 ± 0.5	0 ± 0.6	0.396
Depression–Dejection	−0.9 ± 0.4	−0.7 ± 0.6	0.735
Anger–Hostility	−0.9 ± 0.4	−1.2 ± 0.5	0.720
Vigor	−0.3 ± 0.9	1.1 ± 1.2	0.021*
Fatigue	−0.7 ± 0.4	−1.6 ± 0.9	0.273
Confusion	−0.3 ± 0.5	−0.5 ± 0.6	0.860
VAS (mm)			
1. Alert	6.0 ± 5.0	−12.7 ± 5.4	0.016*
2. Calm	8.8 ± 4.1	10.2 ± 4.5	0.958
3. Strong	−2.6 ± 1.6	−6.2 ± 3.2	0.398
4. Clear-headed	1.5 ± 3.3	−10.1 ± 5.2	0.071 ^b
5. Well-coordinated	0.9 ± 1.5	−1.0 ± 3.4	0.684
6. Energetic	3.7 ± 2.4	−3.2 ± 2.5	0.018*
7. Contented	0.2 ± 2.4	−0.9 ± 3.5	0.808 ^b
8. Tranquil	−1.0 ± 3.5	−5.5 ± 3.9	0.248
9. Quick-witted	−0.6 ± 2.8	−8.7 ± 3.5	0.015*
10. Relaxed	0.4 ± 3.2	4.7 ± 3.6	0.288 ^b
11. Attentive	−1.8 ± 4.0	−7.3 ± 2.7	0.224
12. Proficient	−0.9 ± 2.3	−3.8 ± 2.6	0.353
13. Happy	2.2 ± 1.9	−2.6 ± 2.4	0.179 ^b
14. Amicable	3.3 ± 3.1	6.8 ± 4.1	0.267
15. Interested	4.9 ± 3.4	−3.0 ± 3.0	0.085
16. Gregarious	3.0 ± 3.7	−5.3 ± 3.0	0.126
Factor 1 (Alertness)	1.2 ± 1.7	−6.2 ± 2.4	0.005** ^b
Factor 2 (Contentedness)	1.5 ± 1.4	−1.5 ± 1.5	0.218
Factor 3 (Calmness)	4.6 ± 2.7	7.5 ± 3.3	0.313 ^b

Values are presented as mean ± standard error of mean. *p* values as compared between placebo and modafinil conditions

* $p < 0.05$; ** $p < 0.01$

^aNon-parametric Wilcoxon signed-rank test unless otherwise indicated

^bPaired *t* test

and quick-witted ($p = 0.015$) compared to those with the placebo treatment. Among the three mood factors, the modafinil treatment resulted in a significant increase in alertness factor compared to the placebo treatment ($p = 0.005$). The results were consistent with previous reports (Pringle et al. 2013; Rasetti et al. 2010). Thus, the results from subjective ratings confirmed that the modafinil treatment increased vigor and alertness.

Effects of modafinil on task performance

The effects of modafinil on reaction time, accuracy, and alerting effect were investigated during performance of the ANT task during MRI. Modafinil treatment showed significantly faster reaction times in no-cue condition (placebo 595.4 ± 18.6 ms; modafinil 531.5 ± 10.7 ms; $p = 0.002$) and

in center-cue condition (placebo 565.2 ± 19.9 ms; modafinil 496.9 ± 10.9 ms; $p = 0.001$) (Fig. 3a). The modafinil treatment showed higher accuracy (placebo $94.1 \pm 2.1\%$, median 98.1% ; modafinil $98.3 \pm 0.6\%$, median 98.8% ; $p < 0.001$) than the placebo treatment (Fig. 3b). We also assessed the alerting effect by subtracting the mean RT values in the center-cue condition from those in the no-cue condition. The alerting effect was 30.2 ± 4.4 ms (median 34.0 ms) in the placebo treatment, consistent with a previous report (Abdullaev et al. 2010), and 34.6 ± 3.8 ms (median 34.8 ms) in the modafinil treatment. No treatment difference was found for the alerting effect ($p = 0.230$) (Fig. 3c). As for orientation, the orienting effect was 57.7 ± 5.5 ms (median 55.4 ms) and 36.2 ± 3.3 ms (median 32.3 ms) in the placebo and modafinil treatments (Supplementary Fig. 1), respectively, showing that modafinil decreased the orienting effect. In addition, there was no difference in executive control effect between the modafinil (14.3 ± 3.3 ms, median 17.8 ms) and the placebo treatments (17.6 ± 5.6 ms, median 17.2 ms).

Effects of modafinil on BOLD activation in the alerting network

For each treatment, whole-brain analysis was performed to determine brain regions showing BOLD activation in the alerting network. In the placebo treatment (Fig. 4a and Table 3), alerting network activity was found in the right superior parietal lobule, left inferior parietal lobule, bilateral middle occipital gyri, left fusiform gyrus, bilateral temporo-occipital cortices, and left cerebellum, consistent with previous fMRI studies using the ANT task in healthy untreated controls (Backes et al. 2011; Fan et al. 2005; Liu et al. 2013; Muto et al. 2012; Zheng et al. 2012; supplementary Table 1). The placebo treatment also showed activation in the left supplementary motor area, bilateral middle temporal gyri, right inferior temporal gyrus, right postcentral gyrus, right precuneus, left inferior occipital gyrus, and right caudate

($p < 0.001$, uncorrected). In the modafinil treatment (Fig. 4b and Table 3), a similar, but more pronounced activation pattern was shown as compared with that of the placebo treatment. Modafinil treatment showed alerting network activity in the left inferior temporal gyrus, bilateral middle occipital gyri, right inferior occipital gyrus, bilateral lateral temporo-occipital cortices, and bilateral cerebellum, activations that were also observed in previous fMRI studies using the ANT task in healthy untreated controls (supplementary Table 1). Modafinil treatment also activated the left middle temporal gyrus, right inferior temporal gyrus and left inferior occipital gyrus ($p < 0.001$, uncorrected).

Next, whole-brain paired t test analysis was performed to compare alerting network activity between the placebo and modafinil treatments. The modafinil treatment showed significantly stronger activation in the left middle and inferior occipital gyri than the placebo treatment ($p < 0.001$, uncorrected; Fig. 5a and Table 4). No regions showed greater alerting network activity in the placebo than in the modafinil treatments. In the orienting and executive control contrasts in fMRI, there were no differences in regional brain activation between the placebo and modafinil treatments (threshold for significance, $p < 0.001$, uncorrected).

Effects of modafinil on BOLD signal changes in the left middle and inferior occipital gyri

Further, we focused on the left middle and inferior occipital gyri as ROIs for analyses of BOLD signal changes, as these regions showed significant differences in BOLD activation between the placebo and modafinil treatments in the alerting network in whole-brain analysis. Correspondingly, these regions have been reported to be involved in the alerting network in several previous studies (Backes et al. 2011; Muto et al. 2012; supplementary Table 1). The percent BOLD signal changes were larger in the modafinil than in the placebo treatments in the left middle occipital gyrus ($p = 0.006$) and left

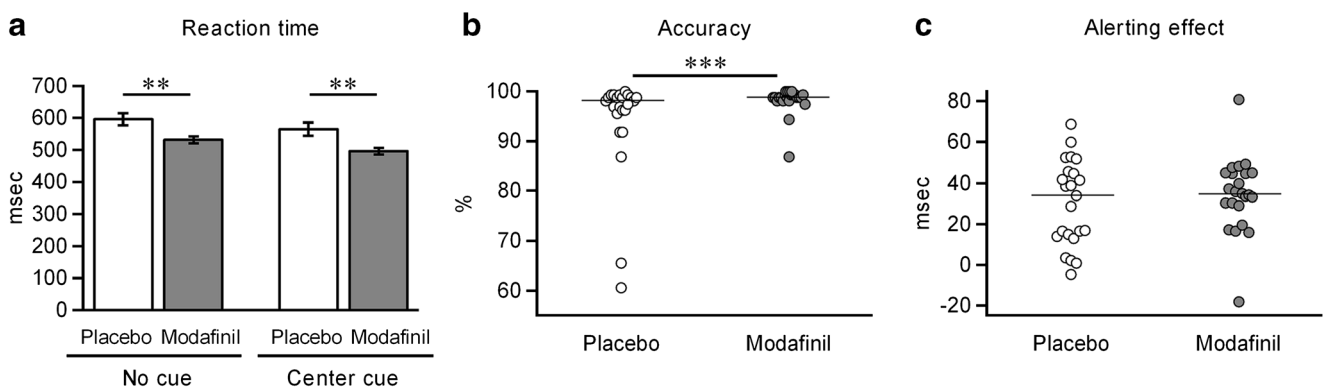


Fig. 3 Effects of modafinil on task performance. There were significant differences between the placebo and modafinil treatments for reaction time (a) and accuracy (b) in the no- and center-cue conditions, indicating that modafinil increased attention performance. c The score

of the alerting effect did not show a significant difference between placebo and modafinil treatments. Error bars show standard error of mean. Each symbol indicates individual subject. Horizontal lines indicate median values. ** $p < 0.01$; *** $p < 0.001$

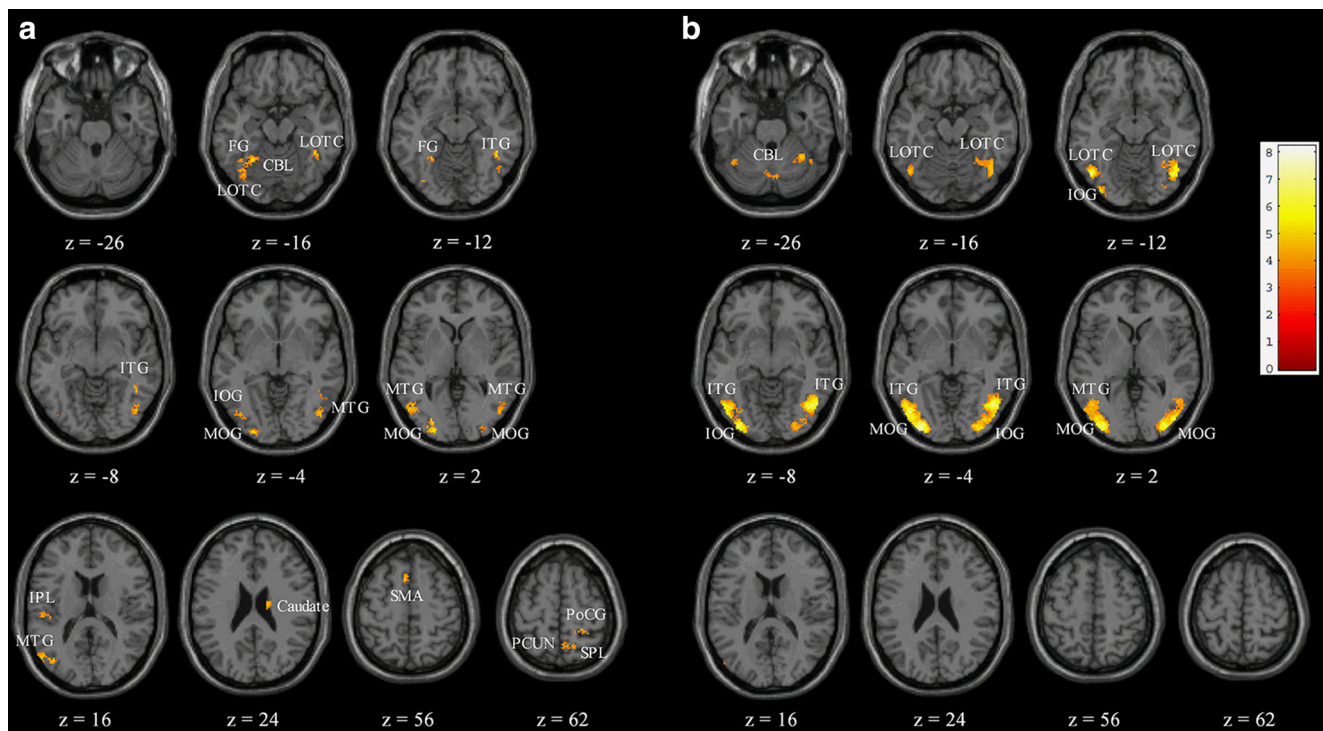


Fig. 4 Neural responses in alerting network. Group-level activations are shown in the alerting network in placebo (a) and modafinil (b) treatments. Axial slices are shown at $z = -26$ to $z = 62$ in the MNI template. The left side of these images corresponds to the left hemisphere. $p < 0.001$, uncorrected, with a minimum cluster size of 20 voxels. Color bar

indicates t statistics. CBL cerebellum, FG fusiform gyrus, IOG inferior occipital gyrus, IPL inferior parietal lobule, ITG inferior temporal gyrus, LOTC lateral temporo-occipital cortex, MOG middle occipital gyrus, MTG middle temporal gyrus, PCUN precuneus, PoCG postcentral gyrus, SMA supplementary motor area, SPL superior parietal lobule

inferior occipital gyrus ($p = 0.006$) in the alerting network (Fig. 5b).

Correlations between RT and the percent BOLD signal changes in the left middle or inferior occipital gyri were calculated in the alerting network in both placebo and modafinil treatments. As shown in the results in Fig. 6, a greater number of data points were distributed in an area with higher signal changes and shorter reaction time in the modafinil treatment as compared to the placebo treatment. Further, we found negative correlations between RT and BOLD activations in the left middle occipital gyrus ($r = -0.423$, $p = 0.003$, Fig. 6a) and left inferior occipital gyrus ($r = -0.387$, $p = 0.008$, Fig. 6b). Thus, more intense activations in the left middle and inferior occipital gyri were associated with faster reaction time in the alerting network.

Discussion

In this study, we employed an fMRI study combined with the ANT task and investigated the components of attention that are affected by modafinil and the neural substrates that are responsible for the drug effects. Our main findings were that modafinil distinctly enhances alerting performance and mood in the attention networks and that BOLD responses in the left middle and inferior occipital gyri are significantly increased in

the alerting network following modafinil treatment in association with enhanced alerting performance. On the other hand, there were no differences in regional brain activation between the placebo and modafinil treatments in the orienting and executive control contrasts in fMRI. Consistently, previous fMRI studies using the ANT task showed differential effects on individual components of the attentional network, although these discrepancies could not be fully explained. Passive hyperthermia impaired executive function but did not change alerting and orienting in behavior, while it altered three networks in brain activity (Liu et al. 2013). Carriers of an alpha 1C subunit of the L-type voltage-gated calcium channel (*CACNA1C*) with the risk allele for psychosis showed impaired behavioral performance in alerting and orienting, while neural activities in fMRI were reduced in the right inferior parietal lobule during orienting and in the medial frontal gyrus during executive control of attention (Thimm et al. 2011). Thus, brain activity in each network is independently affected by external and endogenous factors.

Neurotransmitter systems responsible for enhanced alerting by modafinil remain elusive. The mechanism of action of modafinil is unique and complex (Mereu et al. 2013; Minzenberg and Carter 2008). Modafinil acts not only through dopaminergic and noradrenergic mechanisms similar to traditional psychostimulants (Wisor 2013) but it also affects other neurotransmitter systems including glutamate, GABA,

Table 3 Brain regions activated by alerting network in placebo and modafinil treatments

Treatment	Region	BA	MNI coordinates			<i>t</i> value	
			<i>x</i>	<i>y</i>	<i>z</i>		
Placebo	R Inferior temporal gyrus	37	46	−44	−12	6.29	
	L Middle occipital gyrus	18/19	−26	−92	−2	5.59	
	R Middle temporal gyrus	37/39	50	−68	12	5.39	
	L Cerebellum		−34	−66	−18	5.29	
	L Middle temporal gyrus	37/39	−50	−70	14	5.28	
	L Fusiform gyrus	37	−26	−52	−16	5.13	
	R Postcentral gyrus	1/2/3	24	−40	60	5.01	
	L Supplementary motor area	6	−4	14	56	4.85	
	R Caudate		18	−12	24	4.80	
	L Inferior parietal lobule	40	−50	−26	16	4.47	
	L Lateral temporo-occipital cortex	19/37	−36	−70	−16	4.44	
	R Middle occipital gyrus	18	28	−86	6	4.38	
	L Inferior occipital gyrus	18/19	−36	−76	−6	4.30	
	R Precuneus	7	10	−58	62	4.20	
	R Superior parietal lobule	5/7	18	−58	62	4.13	
	R Lateral temporo-occipital cortex	37	40	−42	−18	3.80	
	Modafinil	L Inferior temporal gyrus	37	−44	−72	−4	8.21
		L Middle occipital gyrus	18/19	−32	−88	−4	7.64
R Inferior temporal gyrus		37	46	−64	−4	7.51	
L Lateral temporo-occipital cortex		19/37	−46	−68	−12	7.29	
L Inferior occipital gyrus		18/19	−32	−84	−6	6.95	
R Middle occipital gyrus		19	46	−80	2	6.85	
R Inferior occipital gyrus		18/19	44	−80	−2	6.57	
R Lateral temporo-occipital cortex		19/37	44	−68	−14	6.27	
R Cerebellum			36	−52	−30	5.56	
L Middle temporal gyrus		37	−40	−62	8	5.20	
L Cerebellum			−4	−78	−40	4.77	

$p < 0.001$ uncorrected

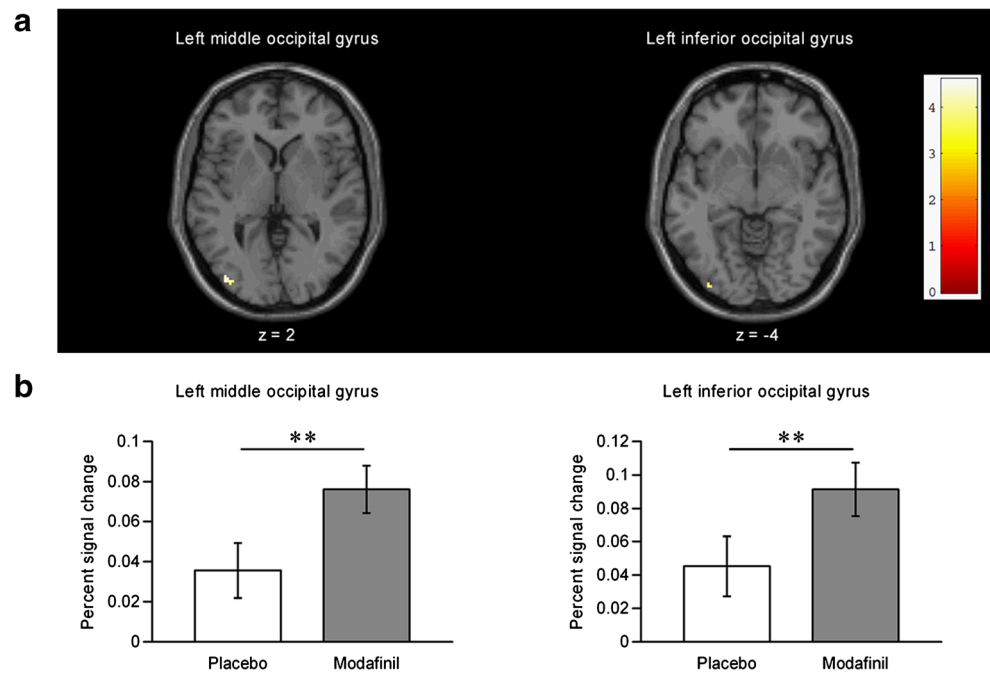
BA Brodmann area, MNI Montreal Neurological Institute, L left, R right

histamine, and serotonin (Ferraro et al. 1999, 2000; Ishizuka et al. 2010). Pharmacological studies have shown that noradrenaline affects the efficiency of alerting, while orienting and executive control are affected by acetylcholine and dopamine, respectively (Green et al. 2008). The α_2 -adrenoreceptor agonist clonidine impaired behavioral measures and attenuated the activity of the alerting effect (Coull et al. 2001). Noradrenaline-containing fibers originate from the locus coeruleus and innervate a broad range of cortical and subcortical regions including the occipital cortex (Berridge and Waterhouse 2003). Extracellular noradrenaline in the rat occipital cortex was increased by electrical stimulation of the locus coeruleus and administration of the α_2 -adrenoreceptor antagonist mirtazapine or the NET inhibitors reboxetine and desipramine (Devoto et al. 2004; Devoto and Flore 2006; Valentini et al. 2006). NET is distributed in the occipital cortex in human brain (Schou et al. 2007), and modafinil actually binds to NET (Madras et al. 2006). In contrast, the density

of DAT is very low in the occipital cortices (Shih et al. 2006). Thus, the enhanced alerting by modafinil may be mediated at least partly by increased noradrenergic activity in the occipital cortex through the inhibition of noradrenaline reuptake.

Our results showed increases in BOLD responses in the left middle and inferior occipital gyri following modafinil treatment. Further, the BOLD signal changes in the occipital gyri were negatively correlated with reaction time during alerting. A previous fMRI study reported that alerting effects were observed in the occipital gyrus, suggesting that increased alertness results in a top-down modulation of activity in visual processing areas (Thiel et al. 2004). Top-down attention involves voluntary allocation of attention to locations or features mediated by dorsal frontoparietal areas (Vossel et al. 2014), which can modulate the activity of occipital areas (Corbetta and Shulman 2002; Vossel et al. 2014). In the present study, however, dorsal frontoparietal activity during alerting was not detected in either placebo or modafinil treatment. It is

Fig. 5 Effects of modafinil on brain activations in alerting network. The modafinil treatment showed significantly stronger activation in the alerting network than the placebo treatment. **a** Colored regions show the areas identified by group comparison analysis. Color bar indicates t statistics. **b** Percent BOLD signal changes for the alerting network calculated from a priori ROIs. Error bars indicate the standard error of mean. $**p < 0.01$



noteworthy that, according to a previous report, sleep deprivation reduced BOLD responses in occipital areas without changes of dorsal frontoparietal areas, suggesting that wakefulness could modulate occipital activity in the alerting network without top-down regulation (Muto et al. 2012). Further research would confirm whether modafinil induced the occipital activity through top-down modulation of the dorsal frontoparietal area by analyzing effective connectivity between these areas.

The enhancing effect of modafinil on alerting was significant among the three attention networks. Alerting is defined as achieving and maintaining a state of high sensitivity to incoming stimuli, consisting of intrinsic (tonic) and phasic alertness (Sturm and Willmes 2001). Intrinsic alertness refers to an internal control of arousal in the absence of an external cue, whereas phasic alertness represents an ability to increase response for a short time period following an external warning stimulus. In the present study, modafinil treatment showed significantly faster reaction times than placebo treatment in both no-cue and center-cue conditions, suggesting that modafinil enhances both intrinsic and phasic alertness.

Attentional impairment is observed in a variety of neuropsychiatric disorders such as ADHD and schizophrenia (Millan et al. 2012). Cognitive impairment in sustained attention has been shown to be an endophenotype in ADHD (Pironti et al. 2014). Imaging studies on patients with ADHD or schizophrenia showed alterations in the anatomy and function of the occipital lobe (Schneider et al. 2006; Tohid et al. 2015). These patients also demonstrated behavioral deficits in alerting when the ANT task was applied (Johnson et al. 2008; Backes et al. 2011). Although modafinil has been reported to be effective in improving attention in patients with ADHD (Turner 2006) and schizophrenia (Turner et al. 2004), the underlying mechanism has not been clarified. The present result may provide insight into the clinical availability of modafinil and the pathogenesis of attentional impairment in neuropsychiatric disorders. Methylphenidate has also been used for the treatment of ADHD, and it was reported that it improved poor attentional performance in both ADHD and control groups, irrespective of diagnosis (del Campo et al. 2013). In contrast to modafinil, methylphenidate improves the performance of executive function, which depends on

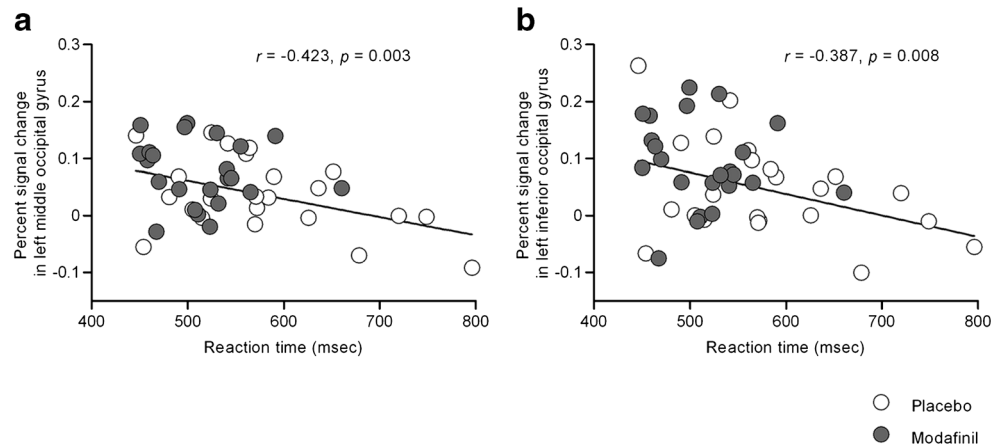
Table 4 Comparison of brain regions activated by alerting network between placebo and modafinil treatments

Treatment	Region	BA	MNI coordinates			t value
			x	y	z	
Modafinil > placebo	L Middle occipital gyrus	18/19	-38	-84	2	4.58
	L Inferior occipital gyrus	19	-44	-82	-4	3.76
Placebo > modafinil	None					

$p < 0.001$ uncorrected

BA Brodmann area, MNI Montreal Neurological Institute, L left

Fig. 6 Linear correlation between brain activation and task performance in alerting network. Scatterplots show significant negative correlation between BOLD signal changes in the left middle (a) and inferior (b) occipital gyri in alerting and reaction time during the ANT task



dopaminergic transmission (Kratz et al. 2012). Taken together, modafinil and methylphenidate may preferentially act on the noradrenergic and dopaminergic systems, respectively, although DAT occupancy and extracellular dopamine level under modafinil and methylphenidate treatments at clinical doses have appeared similar in positron emission tomography (PET) studies (Kim et al. 2014; Volkow et al. 2009). It is known that patients with ADHD often show impairment of alerting and executive functions (Oberlin et al. 2005), but some suffer more severely from either function. Given the characteristics of the drugs, modafinil and methylphenidate could be differentially used according to the major clinical conditions of the patients.

The present study has limitations in terms of interpreting the results. Because the pharmacological actions of modafinil are complicated, the possibility of the involvement of other neurotransmitters cannot be ruled out. Some studies using the ANT task in the alerting network reported that an antihistamine caused less alerting as indicated by longer reaction time and decreased BOLD response, and that a single nucleotide polymorphism in *GRIN2B* encoding the NR2B subunit of NMDA receptors showed faster reaction time (Conen et al. 2013; Schulz et al. 2012). Further studies are needed to identify which neurotransmitter systems are substantially responsible for the effects of modafinil on the alerting network in combination with other measures such as use of receptor antagonists and PET imaging studies for responsible neurotransmitter receptors. In addition, methodological limitations, including the single-blind study and the volunteer number, and the single-dose administration study, may affect the behavioral and fMRI analyses. Especially, single-dose treatment may not be effective enough to identify the modafinil effects on orienting and executive control in fMRI data analysis. In fact, in previous human studies on task performance, chronic administration with modafinil showed different effects on attentional measures from those with single-dose administration (Minzenberg and Carter 2008; Repantis et al. 2010).

In conclusion, healthy subjects showed enhanced performance and increased activation in the occipital lobe by a single dose of modafinil, especially in the alerting network possibly relevant to noradrenergic activity during the ANT task. The fMRI study combined with the ANT task could provide a rationale for characterizing the cognitive effects of central-acting drugs and select appropriate drugs for individual patients with distinct symptoms of impaired attention.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing financial interests.

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