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Modafinil Decreased Thalamic Activation in Auditory Emotional Processing: A Randomized Controlled Functional Magnetic Resonance Imaging Study

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Background: Modafinil improves wakefulness and attention, is approved in Japan for treatment of narcolepsy, and was reported to be effective for attention-deficit/hyperactivity disorder. However, it was reported to induce emotional instability, including mania, depression, and suicidal ideation. Such side effects may be related to changes in cognitive behavior caused by the effects of modafinil on emotional recognition. However, the effects of modafinil on the neural basis of emotional processing have not been fully verified. We used functional magnetic resonance imaging to investigate the effects of modafinil on the neural basis of auditory emotional processing.

Methods: This study adopted a placebo-controlled within-subject crossover design. Data from 14 participants were analyzed. The effects of modafinil on cerebral activation and task performance during an emotional judgement task were analyzed.

Results: Task accuracy decreased significantly and response time of emotional judgement was significantly delayed by modafinil, as compared with placebo. Right thalamic activation in auditory emotional processing was significantly less in the modafinil condition than in the placebo condition. In addition, reduction of right thalamic activation by modafinil was positively correlated with accuracy of emotional judgement.

Conclusions: Our findings suggest that modafinil acts on the right thalamus and changes behavior and brain function associated with auditory emotional processing. These results indicate that modafinil might change emotional recognition by reducing emotional activation related to social communication.
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Key words: emotion, fMRI, modafinil, psychopharmacology, thalamus

Introduction

Modafinil promotes wakefulness and is an effective medication for narcolepsy[1]. Modafinil has also been reported to improve attentional function in patients with attention-deficit/hyperactivity disorder, when used off-label[2,3]. As an adjunct to antidepressants and antipsychotics, modafinil improved psychomotor inhibition and general fatigue in depression, as well as cognitive impairment and adverse symptoms in schizophrenia[4–6]. In addition to these therapeutic effects, recent neuroimaging studies have demonstrated an effect of modafinil on the neural basis of cognitive function, such as the reward system[7] and working memory[8]. These findings indicate that modafinil could improve cognitive function by modulating the dopamine and noradrenergic brain systems[9–11].

However, modafinil was found to induce manic and depressive states, even in patients with no history of psy-

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chiatric illness[12–16]. These symptoms are related to emotional instability and could be caused by the effect of modafinil on the neural basis of emotional processing. However, how modafinil affects brain activities in emotional processing has not been fully explained. Two previous studies of healthy participants reported that modafinil affected emotional processing. One study showed that modafinil increased miscategorization of facial emotions, i.e., miscategorizing sad as angry[17]. Another study reported that, as compared with placebo, modafinil increased brain activity during recognition of fearful faces at the limbic-cortical-striatal-pallidal-thalamic circuit, including the amygdala, anterior cingulate cortex, and thalamus. By contrast, no significant change was observed in the accuracy of a facial emotion recognition task[18]. However, it remains unclear how modafinil affects brain functions related to auditory emotional recognition.

A number of studies have used facial recognition tasks to confirm pharmacological effects on emotional recognition[19–21]. Facial expressions transfer our emotions precisely, and skill in recognizing facial expressions is essential in our social life. In addition, of course, besides facial expressions, the voice also conveys emotions[22,23]. Recognizing emotions in the voice is critical in communicating with others. However, to our knowledge, few studies have investigated voice-based emotional recognition. In these modern times, we do not need to see in order to communicate with each other, and opportunities that depend only on vocal communication are obviously increasing[24,25]. Since auditory communication is inseparable from social life, revealing pharmacological effects on auditory emotional processing is gaining in importance.

This study investigated the effects of modafinil on the neural basis of auditory emotional processing. Before beginning the study, we hypothesized that modafinil would modulate auditory emotional recognition by increasing brain activity in emotion-related areas, such as the cingulate cortex, amygdala, and thalamus.

Materials and Methods

Participants

Thirty-four healthy Japanese volunteers were enrolled in this study, 33 of whom satisfied the inclusion criteria (**Fig. 1**). Enrolment took place between February 2012 and August 2013, when the target number of participants was reached. The allocation ratio was 1:1. Exclusion criteria were a medical history of psychiatric disorders, cardiac disorders, epilepsy, or modafinil allergy; diseases such as hypertension, hepatic dysfunction, or renal dysfunction; any drug intake for at least 2 weeks before the experiment; any contraindications to functional magnetic resonance imaging (fMRI); excessive consumption of alcohol or caffeine; pregnancy; and smoking. Baseline measurements of depressive mood, anxiety, and daytime sleepiness were evaluated by the Beck Depression Inventory (BDI)[26], State-Trait Anxiety Inventory (STAI)[27], and Epworth Sleepiness Scale (ESS)[28], respectively[29]. Participants with a BDI score >11, a STAI-state score >45, or a STAI-trait score >46 were excluded from the study, as high depression and anxiety scores may affect brain activity in emotional processing[30,31]. Participants were instructed to avoid caffeine for 2 days, alcohol for 24 hours, and food intake for 2 hours before and during the experiment. Participants who tested positive for urine drug screening (des-methyl-sertraline) or who had a urinary caffeine level >2 μg/mL were excluded from the analysis because of possible effects on subjective mood and brain activity. The characteristics of the participants are summarized in **Table 1**. The final sample size was 14 participants. A post-hoc power analysis of fMRI and behavioral data of the 14 participants by G*Power[32] showed a power of >80%, a potentially meaningful degree of reliability.

All participants were right-handed according to the Edinburgh Handedness Inventory[33], nonsmokers, and normal consumers of caffeine. They were normal in terms of baseline depression, anxiety, and daytime sleepiness. All participants provided informed consent for this study, which was approved by the ethics committee of Nippon Medical School (approval number: 223019). The complete experiment and data analysis were performed at Nippon Medical School.

Experimental Design

A randomized placebo-controlled, within-subject, crossover design was adopted for this study. The study was conducted in a single-blind manner, to identify adverse drug effects in participants. Each participant was examined on 2 separate days at least 2 weeks apart, so as to wash out the drug completely. In the first session, modafinil (200 mg as 2 tablets of a Modiodal 100-mg formula, Alfresa Pharma, Japan[34]) or placebo tablets were administered orally with water. In the second session, participants were crossed over to receive the other medicine. The modafinil and placebo tablets were indistinguishable in appearance and taste so that participants were not aware which tablet was being administered. One experimenter randomly decided the order of administration by simple randomization, to avoid age and gender bias. The

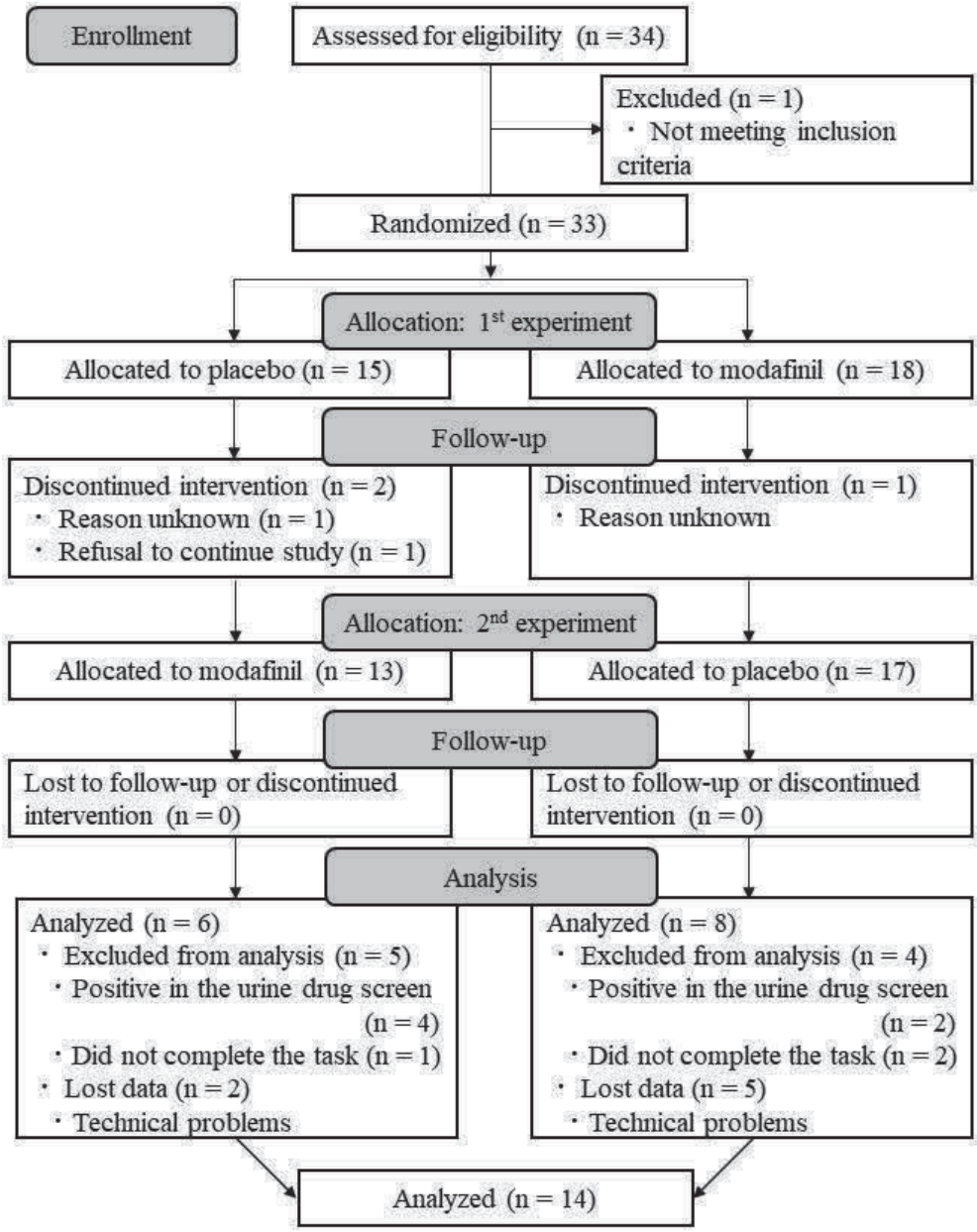

Fig. 1 CONSORT flow diagram of participant progress through the study.

Table 1 Characteristics of participants

	Mean (SD) n = 14
Age (years)	31.2 (4.1)
Gender (male:female)	7 : 7
Body mass index (kg/m^2)	20.7 (2.1)
Alcohol consumption (g/day)	5.2 (5.4)
Caffeine consumption (mg/day)	85.6 (53.2)
BDI	1.6 (1.6)
ESS	3.7 (2.2)
STAI (state)	31.4 (5.4)
STAI (trait)	31.9 (6.3)

Abbreviations: SD, standard deviation; BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; STAI, State-Trait Anxiety Inventory

fMRI scan was started 2.5 hours after medication, as pharmacokinetic data indicate that 200 mg of modafinil reaches a peak plasma level at 2.5 hours after oral administration[35].

Participants were required to listen to voice stimulation and determine the valence of each voice during fMRI scanning. On the basis of blood oxygen level-dependent (BOLD) contrast, cerebral response to emotional processing was compared between the modafinil and placebo conditions. We used MRI-derived measurements of brain function to compare brain responses during the emotional judgement task. Mood was measured before and after (just before fMRI scan) medication by using the profile of mood scales (POMS)[36] and Bond-Lader mood

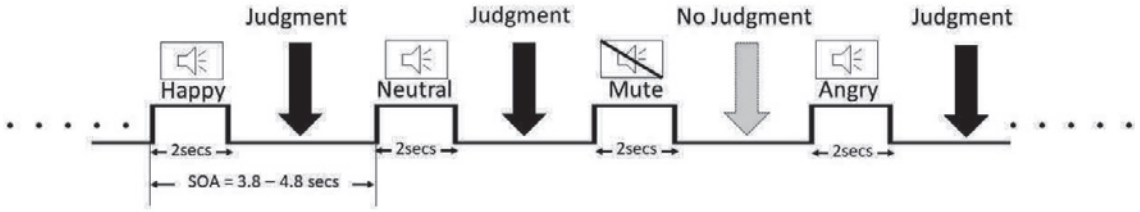

Fig. 2 Schema of the emotional judgment task. During the fMRI experiment, participants were asked to listen to and assess the valence of affective voices (neutral, happy, sad, angry).
Abbreviations: SOA, Stimulus onset asynchrony

scales[37].

Mood Ratings

We used the POMS and Bond-Lader mood scales to evaluate the subjective mood of each participant. POMS is a 5-point self-administered scale consisting of 65 items measuring 6 factors: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor, Fatigue, and Confusion. The Bond-Lader mood scales consist of 16 visual analogue scales with end points anchored by pairs of antonyms: 1) Alert-Drowsy, 2) Calm-Excited, 3) Strong-Feeble, 4) Clear-headed-Muzzy, 5) Well-coordinated-Clumsy, 6) Energetic-Lethargic, 7) Contented-Discontented, 8) Tranquil-Troubled, 9) Quick-witted-Mentally-slow, 10) Relaxed-Tense, 11) Attentive-Dreamy, 12) Proficient-Incompetent, 13) Happy-Sad, 14) Amicable-Antagonistic, 15) Interested-Bored, and 16) Gregarious-Withdrawn. Participants marked on a 100-mm line how they felt at that particular moment. Scores ranged from 0 to 100, and lower scores indicated more positive mood. In the Bond-Lader mood scales, the sub-scales were grouped into 3 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 factor. Drug effect was evaluated for each scale by comparing scores obtained by subtracting the pre-medication rating scores from post-medication scores. Changes in the rating of each item in the POMS and Bond-Lader mood scales, were evaluated with the paired *t* test and nonparametric Wilcoxon signed-rank test for data with normal and non-normal distributions, respectively. The statistical threshold for significance was set at $p < 0.05$.

Emotional Judgement Task

Montreal Affective Voices[38] were used as stimuli. This is a validated dataset of non-verbal human voices expressing typical emotions, such as happy and angry. The stimuli used in this study were happy, sad, angry, and affectively neutral voices. An event-related design was adopted as the test design (**Fig. 2**). The voices were presented for 2 seconds, 30 times with each emotion, in a randomized sequence. In addition to these vocal stimuli, 12 mute sections were randomly inserted between the voices. The stimulus onset asynchrony was 4.3 ± 0.5 seconds. During fMRI scanning, each participant assessed the emotional valence (positive/neutral/negative) of the voices. Three participants did not evaluate more than 10 of 30 voices of each emotion and were thus excluded from all analyses including mood rating and BOLD analysis, as it was possible they had fallen asleep during the fMRI scanning or had not understood the task explanation. Accuracy and reaction time under placebo and modafinil conditions were analyzed by paired *t* test and nonparametric Wilcoxon signed-rank test for normal and non-normal distributions, respectively. The statistical threshold for significance was set at $p < 0.05$.

In the analysis of accuracy, deviation data (from a range of mean ± 2 SD for each emotion) were ruled out of the analysis of task performance, including reaction time, because of the possibility that participants had pressed a wrong button. We excluded the task performance data from 1 participant for neutral voices, 2 for sad voices, and 1 for angry voices in the placebo condition, and data from 1 participant for neutral voices, 1 for happy voices, and 1 for angry voices in the modafinil condition. fMRI data from these participants were nevertheless retained for the analysis of brain activity.

Image Acquisition

An Intera Achieva 1.5 T Nova scanner (Philips Electronics, The Netherlands) was used to obtain brain imaging data. Parameters for functional images were repetition time (TR) = 2,500 ms, echo time (TE) = 50 ms, flip angle = 90°, field of view (FOV) = 200 mm, and matrix = 64 × 64. From each participant, 312 functional images were acquired with a T2*-weighted gradient-echo echo-planar imaging sequence sensitive to BOLD contrast. Whole-brain coverage was obtained with a 6-mm slice

thickness and 20 axial slices. After the functional scans, a high-resolution T1-weighted structural image was obtained 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.

Image Processing

Imaging data were preprocessed and analyzed by Statistical Parametric Mapping (SPM12) (Wellcome Department of Imaging Neuroscience, UK) running with MATLAB (Mathworks, USA). Because the MRI scanner was temporally synchronized to the time schedule of the experimental tasks by E-Prime (Psychology Software Tools, USA), our fMRI dataset did not include dummy scans. A total of 312 echo-planar images (EPIs) were obtained, and all images were used for typical preprocessing. First, to correct for participant motion, all EPI volumes were realigned to the first image of the entire EPIs in this fMRI experiment. Then, the mean image of the EPIs was spatially co-registered with the anatomical T1 images. This anatomical T1 image was segmented into an image of gray matter and white matter. On the basis of this segmented T1 image, the anatomical template of diffeomorphic anatomical registration through an exponentiated Lie algebra (DARTEL)[39] was created. All realigned EPIs were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template with the DARTEL template and flow field of each participant. The functional images were then spatially smoothed with an isotropic Gaussian kernel (full width at a half maximum of 8 mm) to increase the signal-to-noise ratio.

The significance of hemodynamic changes in each condition was examined by using a general linear model with boxcar functions convoluted with a hemodynamic response function. The t-values were then transformed to a unit normal distribution, resulting in z-scores. In the present study, while the participants were assessing emotional valence, cerebral activation was investigated by comparing the modafinil and placebo conditions. Because the neural basis of modafinil in emotional processing is unclear, we used whole-brain analysis to identify brain regions showing a BOLD signal during the emotional judgement task.

Statistical Analysis

Group analysis (second-level analysis with spm12) of the data was performed. fMRI data were calculated by analysis of variance (ANOVA) based on the 2 × 5 full factorial model with the factors drug (modafinil/placebo) and emotion (Mute/Neutral/Happy/Sad/Angry). The statistical threshold was set at a familywise error rate (FWE)-corrected, multiple comparison p of < 0.05 (height threshold of F = 8.16, and extent threshold of ke = 243 voxels). To verify the effect of modafinil, for the peak of the significantly activated area in the main effect of the drug, bar plots were examined using the beta value, which is estimated by the main effect of drug, and also by using a 90% confidence interval for the main drug effect.

Correlation between Behavioral Performance and Brain Activity

A region of interest (ROI) was selected at the brain region showing BOLD change during modafinil administration. To investigate the relationship between change in brain activity and change in behavioral performance by modafinil, the correlation coefficients between change in BOLD intensity in the ROI and change in behavioral measures (accuracy and reaction time) were calculated. For the analysis, Pearson's correlation and nonparametric Spearman's rank correlation were used. The significance threshold was set at $p < 0.05$.

Results

Mood Rating

For each of the items for mood rating, the effect of modafinil on subjective mood was statistically evaluated by calculating changes in the ratings. Changes in the ratings were computed by subtracting values before medication from those at 2 hours after medication (**Table 2**). Concerning the rating of POMS, modafinil was significantly associated with higher scores for vigor (p = 0.008) and confusion (p = 0.032), as compared with placebo. As for the Bond-Lader mood scales, participants during modafinil treatment were more energetic (p = 0.033) and more quick-witted (p = 0.023). There was no significant drug effect on the 3 mood factors of Alertness, Contentedness, and Calmness.

Emotional Judgement Task

The effects of modafinil on accuracy and reaction time during the emotional judgement task were investigated. There was no order effect on accuracy or reaction time. Regarding the accuracy of the emotional judgement task, accuracy was significantly lower for modafinil than for placebo (p = 0.024) in all-emotion analysis. However, analysis of discrete emotions revealed no significant differences in accuracy between placebo and modafinil (**Fig. 3a**). With regard to reaction time, reaction time was significantly slower for modafinil than for placebo (p =

Table 2 Change in mood during placebo and modafinil treatment

	Placebo	Modafinil	*p* value[a]
POMS			
Tension-Anxiety	−0.6±1.4	0.6±1.9	0.263[b]
Depression-Dejection	−0.5±1.3	0.0±1.4	0.776[b]
Anger-Hostility	−0.9±1.8	−0.7±1.4	0.796[b]
Vigor	−1.8±2.5	0.1±2.3	0.008**[b]
Fatigue	−0.6±0.6	−0.5±1.1	0.564[b]
Confusion	−0.4±0.6	0.6±1.2	0.032*[b]
Bond-Lader mood scales (mm)			
Alert	5.2±19.3	−2.3±14.5	0.191
Calm	9.6±19.7	5.2±14.7	0.288[b]
Strong	0.9±4.8	−2.0±7.6	0.310[b]
Clear-headed	4.8±13.6	−3.6±23.4	0.375
Well-coordinated	0.1±7.6	2.6±16.6	0.615[b]
Energetic	2.4±7.3	−2.5±11.8	0.033*[b]
Contented	0.2±9.5	−0.5±15.9	0.896
Tranquil	−0.6±10.7	−0.8±15.7	0.977
Quick-witted	7.3±10.6	−5.6±17.3	0.023*
Relaxed	−4.3±9.0	−2.8±12.5	0.692
Attentive	4.3±10.5	−5.9±13.4	0.107
Proficient	−1.3±7.5	−2.4±14.0	0.837
Happy	0.3±12.9	−3.9±13.3	0.382
Amicable	−2.3±6.8	1.2±10.7	0.273
Interested	−0.2±11.9	−0.5±12.4	0.701[b]
Gregarious	0.7±10.2	−1.6±10.6	0.582
Factor 1 (Alertness)	2.6±11.5	−2.5±15.3	0.451[b]
Factor 2 (Contentedness)	−0.3±10.3	−1.1±13.5	0.594[b]
Factor 3 (Calmness)	2.7±16.9	1.2±14.2	0.231[b]

Notes: Values are presented as mean ± SD of the mean. *p* values are indicated for comparison between the placebo and modafinil conditions.
*$p < 0.05$; ** $p < 0.01$
[a] Paired *t* test unless otherwise indicated
[b] Nonparametric Wilcoxon signed-rank test
Abbreviations: POMS, Profile of Mood States

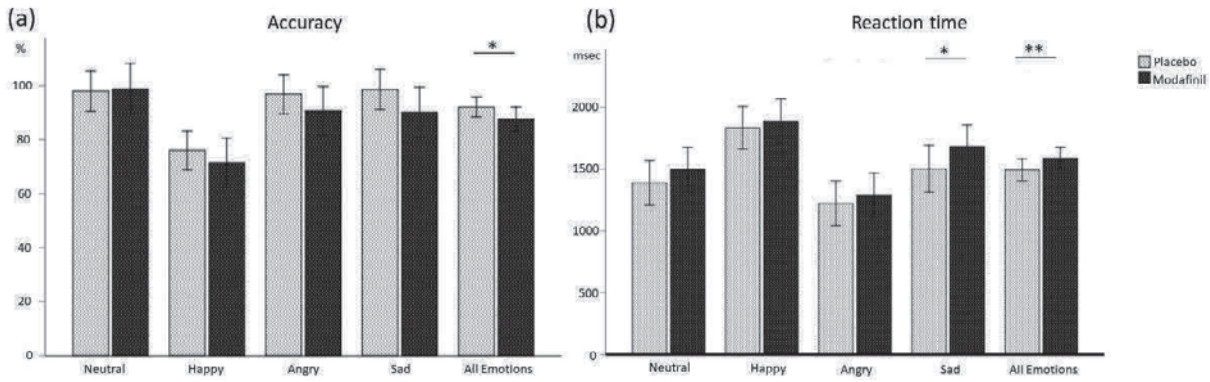

Fig. 3 Effects of modafinil on task performance. As compared with placebo, modafinil was associated with significantly lower accuracy (a) and slower reaction time (b) in all-emotion analysis. In the analysis of discrete emotions (neutral, happy, angry, sad), no significant difference was observed in accuracy (a), although modafinil was associated with significantly slower reaction time for sad voices (b).
Notes: *$p < 0.05$; ** $p < 0.01$

Table 3 Brain regions activated by emotional judgment during placebo minus modafinil condition

Brain Regions	Talairach Coordinates in MNI space			F (1,130)	z-value	Cluster size	*p* (FWE-corrected)
	x	*y*	*z*				
Modafinil < Placebo							
R thalamus	14	−11	8	21.19	4.27	431	0.023

Abbreviations: MNI, Montreal Neurological Institute; FWE, familywise error rate; R, right

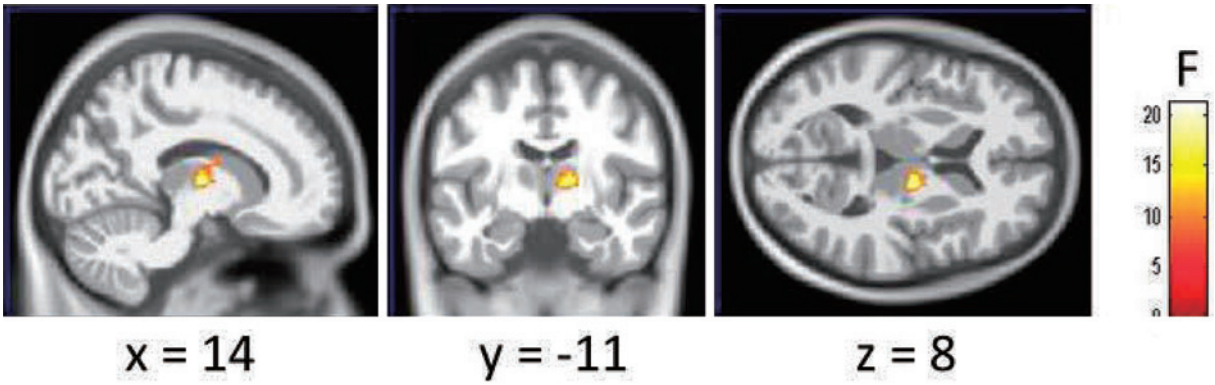

Fig. 4 BOLD signal during emotional judgment task under the placebo minus modafinil condition. Modafinil was associated with significantly less activation than placebo in the right thalamus.

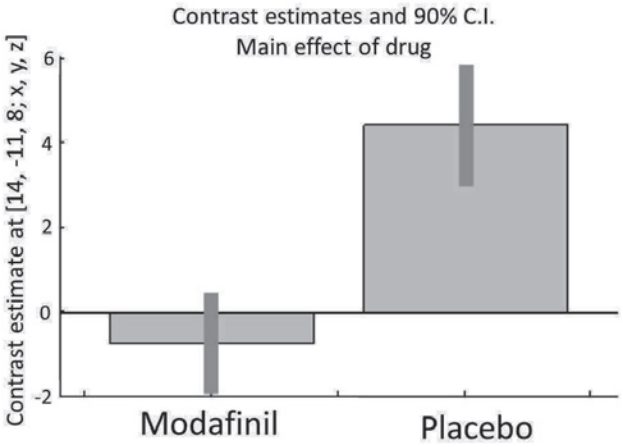

Fig. 5 Contrast estimates and 90% confidence intervals for the main effect of the drug in the right thalamus (Talairach coordinates in MNI space: [x, y, z]: [14, −11, 8]).

0.003) in all-emotion analysis. In analyses of discrete emotions, reaction time for the sad voice was significantly slower for modafinil (p = 0.047), but there were no significant differences for happy, angry, or neutral voices (**Fig. 3b**).

Brain Activity

In the 2 × 5 full factorial design analysis, the main effect of the drug was significant in the right thalamus (**Table 3**, **Fig. 4**). In the bar plot of the strength of cerebral activation at the peak coordinate of the right thalamus (Talairach coordinates [x, y, z]:[14, −11, 8]), modafinil was associated with significantly less activation than placebo in the right thalamus (**Fig. 5**). The main effect of emotion was observed in regions that included the right cerebellum, bilateral superior temporal gyrus, right medial temporal gyrus, and left postcentral gyrus. No interaction effects (drug × emotion) were observed in relation to BOLD response.

Correlation between Behavioral Measurements and Brain Activity

Correlation between behavioral measures (placebo minus modafinil) and brain activity in ROI was calculated. We set the ROI at [x, y, z]:[14, −11, 8] (Talairach coordinates) in the right thalamus, where the peak coordinate of activation was observed under placebo minus modafinil conditions. Accuracy and thalamic activation were strongly positively correlated. Reaction time and thalamic activation were not correlated (**Table 4**, **Fig. 6**).

Discussion

In this study, we investigated the effect of modafinil on subjective mood and cerebral activation during a vocal emotional valence judgement task. Ratings of vigorous, confused, energetic, and quick-witted were significantly higher for modafinil than for placebo. The accuracy of

Table 4 Correlation coefficients between behavioral measurements and BOLD signal in the thalamus at [x, y, z]:[14, −11, 8]

	Accuracy		Reaction time	
	r	*p* value	r	*p* value
Neutral	0.555	0.061	0.406	0.190
Happy	0.896	< 0.001***	0.257	0.397
Angry	0.887[a]	< 0.001***	0.565	0.044
Sad	0.670[a]	0.017*	0.154[a]	0.633
All emotions	0.872	< 0.001***	0.261	0.067

Notes: Pearson's correlation unless otherwise indicated
*$p < 0.05$; *** $p < 0.001$
[a]Spearman's rank correlation

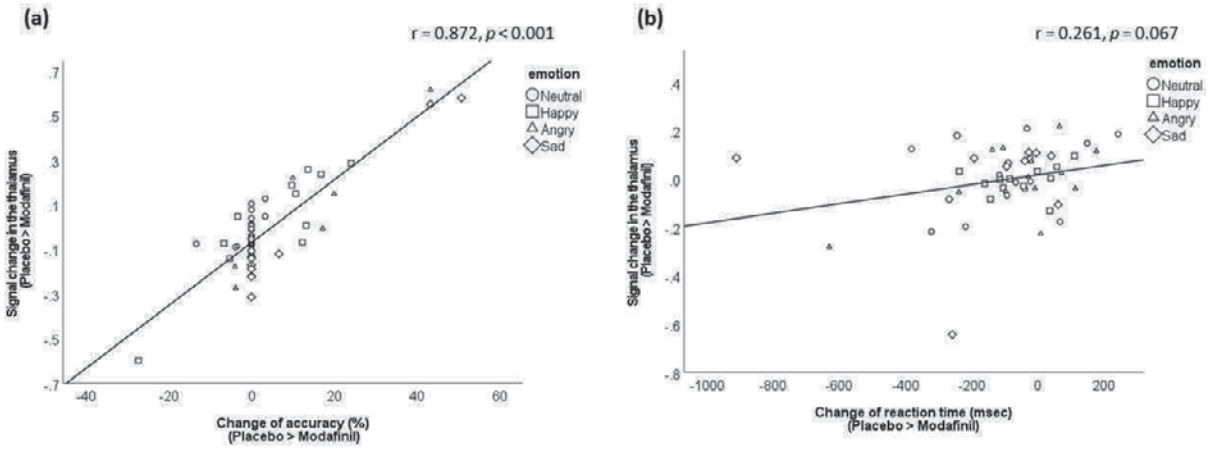

Fig. 6 Correlation between brain activation and task performance in emotional judgment. Scatterplots show a significant positive correlation between BOLD signal change in the thalamus and accuracy (a) during the emotional judgment task. However, no correlation was observed between BOLD signal change in the thalamus and reaction time (b).

assessment of emotional valence was significantly decreased by modafinil, and response time for emotional judgement was significantly delayed. As compared with placebo, modafinil was associated with a significant decrease in thalamic activation during emotional processing. Accuracy in assessing emotional valence was significantly positively correlated with thalamic activation by modafinil.

Effects of Modafinil on Thalamic Activation during Auditory Emotional Processing

We found a positive correlation between the reduction of thalamic activation and the decline in accuracy of assessment of emotional valence for modafinil, which indicates that modafinil particularly affects cerebral response in the thalamus during emotional assessment. The thalamus is composed of a series of neural nuclei that are responsible for relaying various sensory signals[40]. In sensory relay nuclei, such as the medial and lateral geniculate nuclei, sensory stimuli are relayed from receptors located throughout the body to the cerebral cortex[41]. Sensory stimuli travel from sensory organs to the thalamus and are transmitted to the cerebral cortex to be perceived as sensation. Previous studies have shown that when sensory stimuli pass the thalamus the thalamus acts as a `gate' to filter information from various channels and control its transmission to the cortex[42,43].

Our results suggest that modafinil reduces thalamic activation, thereby decreasing assessment of emotional recognition. The thalamus is important in emotional perception as a relay nucleus of sensory signals, including auditory signals[41]. In light of these previous findings, our results suggest that modafinil might reduce thalamic activation and the ability of the thalamus to process auditory emotional information, which leads to lower accuracy and slower response. Our findings indicate that modafinil might make mood unstable by affecting emotional processing.

Contrary to our hypothesis, modafinil decreased brain

activation in the thalamus. Previous studies of patients with schizophrenia reported emotional cognitive impairment and brain dysfunction that included the thalamus during emotional processing. The dopamine level in the thalamus in patients with schizophrenia was significantly higher than in control participants[44]. In addition, the accuracy of a facial expression task and thalamic activation were significantly lower in schizophrenia patients than in controls[45]. These previous studies of schizophrenia suggest that high dopamine levels in the thalamus might reduce thalamic activation and cause dysfunction of emotional processing. We previously reported that modafinil significantly increased dopamine level by occupying dopamine transporters in the basal ganglia[10]. Dopamine transporters on the pre-synapse act to increase dopamine level by inhibiting re-uptake of dopamine[46]. These previous findings suggest that modafinil affects emotional cognitive function by increasing dopamine level in the thalamus, decreasing thalamic activation, and inducing subjective mood instability. This brain mechanism may be associated with the pathophysiology of side effects of modafinil, such as manic and depressive states.

Modafinil promotes wakefulness and increases vigor, while also possibly inducing anxiety[47,48]. In addition, the effect of modafinil on vigor was suggested to be dependent on the genotype of catechol-O-methyltransferase, which metabolizes dopamine in the brain[49]. Past and present findings thus suggest that modafinil increases vigor and confusion by modulating dopamine in certain brain regions, including the thalamus.

Limitations

This study clarified the effects of modafinil on emotional processing and subjective mood. In light of previous findings, changes in emotional cognitive function and the neural basis of emotional processing may be modulated by a reduction in thalamic activation, which is related to changing dopamine levels in the brain. However, because we did not measure dopamine levels in this study, the role of dopamine in relation to the effect of modafinil on emotional processing and subjective mood could not be clarified. The pharmacological action of modafinil is believed to be associated with various subnuclei in the thalamus; thus, neurotransmitters other than dopamine might also have a role in the therapeutic effects of modafinil. A future study using molecular imaging, such as positron emission tomography, should examine correlations between changes in cognitive functions and changes in molecular levels in the brain. Other limitations of this study are the small sample size and the fact that it was conducted in a single-blind manner, to allow for rigorous monitoring of side effects.

Regarding the single-dose administration in this study, although we found an effect of modafinil on brain activity and cognitive ability, 1 dose may not be sufficient to identify its effects on brain activity and cognitive function in relation to executive control.

Conclusion

This study of the effects of modafinil on subjective mood and brain activity during auditory emotional processing revealed the effect of modafinil on emotional cognitive function and the neural basis of emotional processing. Modafinil modulated emotional cognitive function and subjective mood by reducing thalamic activation during auditory emotional processing. Our findings indicate that modafinil acts on cognitive function and the neural basis related to social communication, including auditory emotional processing.

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References

1. Minzenberg MJ, Carter CS. Modafinil: A review of neurochemical actions and effects on cognition. Neuropsychopharmacology. 2008 Jun 1;33(7):1477−502.
2. Peñaloza RA, Sarkar U, Claman DM, Omachi TA. Trends in on-label and off-label modafinil use in a nationally representative sample. JAMA Internal Medicine. 2013;173(8): 704−6.
3. Wang SM, Han C, Lee SJ, et al. Modafinil for the treatment of attention-deficit/hyperactivity disorder: A meta-analysis. J Psychiatr Res. 2017 Jan;84:292−300.
4. Turner DC, Clark L, Pomarol-Clotet E, McKenna P, Robbins TW, Sahakian BJ. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. Neuropsychopharmacology. 2004 Jul;29(7):1363−73.
5. Orr K, Taylor D. Psychostimulants in the treatment of depression : a review of the evidence. CNS drugs. 2007;21 (3):239−57.
6. Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR. A randomized, double-blind, placebo-

controlled trial of modafinil for negative symptoms in schizophrenia. J Clin Psychiatry. 2007 May;68(5):705–10.
7. Funayama T, Ikeda Y, Tateno A, et al. Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens. Psychopharmacology (Berl). 2014 Aug;231(16):3217–28.
8. Müller U, Steffenhagen N, Regenthal R, Bublak P. Effects of modafinil on working memory processes in humans. Psychopharmacology (Berl). 2004 Dec;177(1-2):161–9.
9. Volkow ND, Fowler JS, Logan J, et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA. 2009;301(11):1148–54.
10. Kim W, Tateno A, Arakawa R, et al. In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [18F]FE-PE2I. Int J Neuropsychopharmacol. 2014;17(5):697–703.
11. Madras BK, Xie Z, Lin Z, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. J Pharmacol Exp Ther. 2006;319(2):561–9.
12. Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry. 2005 Apr;162(4):813–4.
13. Oulis P, Kouzoupis AV, Kontoangelos K, Pachou E, Masdrakis VG, Soldatos CR. Visual and coenesthetic hallucinations associated with modafinil. J Clin Psychopharmacol. 2008 Apr;28(2):251–2.
14. Yasui-Furukori N, Kusunoki M, Kaneko S. Hallucinations associated with modafinil treatment for narcolepsy. J Clin Psychopharmacol. 2009 Aug;29(4):408.
15. Kanal MG, Ozkan C, Doganavsargil O, Eryılmaz M. Late onset mania possibly related to modafinil use: A case report. Klinik Psikofarmakol Bülteni. 2012 Mar 1;22(1):71–4.
16. Aytaş Ö, Dilek Yalvaç H. Modafinil-induced psychosis: A case report. Noro Psikiyatr Ars. 2015;52(1):99–101.
17. Dolder PC, Müller F, Schmid Y, Borgwardt SJ, Liechti ME. Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. Psychopharmacology (Berl). 2018 Feb;235(2):467–79.
18. Schmidt A, Müller F, Dolder PC, et al. Acute effects of methylphenidate, modafinil, and MDMA on negative emotion processing. Int J Neuropsychopharmacol. 2018 Apr 1;21(4):345–54.
19. Assogna F, Pontieri FE, Caltagirone C, Spalletta G. The recognition of facial emotion expressions in Parkinson's disease. Eur Neuropsychopharmacol. 2008 Nov 1;18(11):835–48.
20. Zhu B, Chen C, Moyzis RK, et al. Genetic variations in the dopamine system and facial expression recognition in healthy chinese college students. Neuropsychobiology. 2012;65(2):83–9.
21. Dan R, Růžička F, Bezdicek O, et al. Impact of dopamine and cognitive impairment on neural reactivity to facial emotion in Parkinson's disease. Eur Neuropsychopharmacol. 2019 Nov 1;29(11):1258–72.
22. Belin P, Fecteau S, Bédard C. Thinking the voice: neural correlates of voice perception. Trends Cogn Sci. 2004 Mar;8(3):129–35.
23. Tiwari M, Tiwari M. Voice - How humans communicate? J Nat Sci Biol Med. 2012;3(1):3–11.
24. Axelsson A-S. Perpetual and personal: Swedish young adults and their use of mobile phones. New Media Soc. 2010;12(1):35–54.
25. Drago E. The effect of technology on face-to-face communication. Elon Journal of Undergraduate Research in Communications. 2015;6(1):13–9.
26. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory. (2nd ed.). Texas: Pearson; 1996.
27. Spielberger CD. Manual for the State-Trait Anxiety Inventory, STAI-form Y. California: Consulting Psychologists Press; 1983.
28. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540–5.
29. Suzuki C, Ikeda Y, Tateno A, Okubo Y, Fukayama H, Suzuki H. Acute atomoxetine selectively modulates encoding of reward value in ventral medial prefrontal cortex. J Nippon Med Sch. 2019;86(2):98–107.
30. Lepping RJ, Atchley RA, Chrysikou E, et al. Neural processing of emotional musical and nonmusical stimuli in depression. PLoS One. 2016;11(6):e0156859.
31. Schienle A, Schäfer A, Stark R, Walter B, Vaitl D. Relationship between disgust sensitivity, trait anxiety and brain activity during disgust induction. Neuropsychobiology. 2005;51(2):86–92.
32. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007 May 01;39(2):175–91.
33. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971 Mar 1;9(1):97–113.
34. Minzenberg MJ, Watrous AJ, Yoon JH, Ursu S, Carter CS. Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science. 2008;322(5908):1700–2.
35. Robertson P Jr, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet. 2003;42(2):123–37.
36. McNair DM, Lorr M, Droppleman LF. Manual for the Profile of Mood States: . San Diego, CA: Educational and Industrial Testing Services; 1971.
37. Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Med Psychol. 1974;47:211–8.
38. Belin P, Fillion-Bilodeau S, Gosselin F. The Montreal Affective Voices: a validated set of nonverbal affect bursts for research on auditory affective processing. Behav Res Methods. 2008 May;40(2):531–9.
39. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007 Oct 15;38(1):95–113.
40. Sherman SM, Guillery RW. Exploring the thalamus and its role in cortical function. 2nd ed. Cambridge MA, US: MIT Press; 2006.
41. Guillery RW. Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review. J Anat. 1995 Dec;187(Pt 3):583–92.
42. Crick F. Function of the thalamic reticular complex: the searchlight hypothesis. Proc Natl Acad Sci U S A. 1984 Jul;81(14):4586–90.
43. Sherman SM, Guillery RW. Functional organization of thalamocortical relays. J Neurophysiol. 1996 Sep;76(3):1367–95.
44. Oke AF, Adams RN, Winblad B, von Knorring L. Elevated dopamine/norepinephrine ratios in thalami of schizophrenic brains. Biol Psychiatry. 1988 May;24(1):79–82.
45. Yang C, Qi A, Yu H, et al. Different levels of facial expression recognition in patients with first-episode schizophre-

nia: A functional MRI study. General psychiatry. 2018;31 (2):e000014.
46. Sotnikova TD, Beaulieu JM, Gainetdinov RR, Caron MG. Molecular biology, pharmacology and functional role of the plasma membrane dopamine transporter. CNS Neurol Disord Drug Targets. 2006 Feb;5(1):45–56.
47. Randall DC, Shneerson JM, Plaha KK, File SE. Modafinil affects mood, but not cognitive function, in healthy young volunteers. Hum Psychopharmacol. 2003 Apr;18 (3):163–73.
48. Taneja I, Haman K, Shelton RC, Robertson D. A randomized, double-blind, crossover trial of modafinil on mood. J Clin Psychopharmacol. 2007 Feb;27(1):76–9.
49. Bodenmann S, Xu S, Luhmann UF, et al. Pharmacogenetics of modafinil after sleep loss: catechol-O-methyltransferase genotype modulates waking functions but not recovery sleep. Clin Pharmacol Ther. 2009 Mar;85 (3):296–304.

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