Error-related Alpha Suppression: Scalp Topography and (Lack of) Modulation by Modafinil

Hans S. Schroder[1,2*], Ann M. Iturra-Mena[1*], Micah Breiger[1], Samantha R. Linton[1], Mykel A. Robble[1], Brian D. Kangas[1], Jack Bergman[1], Stefanie Nickels[1], Gordana Vitaliano[1], Andre Der-Avakian[3], Samuel A. Barnes[3], William A. Carlezon Jr.[1], and Diego A. Pizzagalli[1]

Abstract

■ Errors in performance trigger cognitive and neural changes that are implemented to adaptively adjust to fluctuating demands. Error-related alpha suppression (ERAS)—which refers to decreased power in the alpha frequency band after an incorrect response—is thought to reflect cognitive arousal after errors. Much of this work has been correlational, however, and there are no direct investigations into its pharmacological sensitivity. In Study 1 (n = 61), we evaluated the presence and scalp distribution of ERAS in a novel flanker task specifically developed for cross-species assessments. Using this same task in Study 2 (n = 26), which had a placebo-controlled within-subject design, we evaluated the sensitivity of ERAS to placebo (0 mg), low (100 mg), and high (200 mg) doses of modafinil, a wakefulness promoting agent. Consistent with previous work, ERAS was maximal at parieto-occipital recording sites in both studies. In Study 2, modafinil did not have strong effects on ERAS (a significant Accuracy × Dose interaction emerged, but drug–placebo differences did not reach statistical significance after correction for multiple comparisons and was absent after controlling for accuracy rate). ERAS was correlated with accuracy rates in both studies. Thus, modafinil did not impact ERAS as hypothesized, and findings indicate ERAS may reflect an orienting response to infrequent events. ■

INTRODUCTION

Errors elicit a suite of psychophysiological responses, including increased pupil dilation (Wessel, Danielmeier, & Ullsperger, 2011), heart rate deceleration (Hajcak, McDonald, & Simons, 2003), and ERPs that index rapid error detection (error-related negativity) and attention allocation (error positivity; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). Moreover, power in the theta frequency band (4–7 Hz) is increased immediately after errors (Cavanagh, Zambrano-Vazquez, & Allen, 2012). Together, these responses are thought to reflect parts of a generic response-monitoring system capable of detecting response errors, orienting to these and other novel events, and eventually signaling the need for behavioral adjustment (Cavanagh & Frank, 2014; Ullsperger, Danielmeier, & Jocham, 2014; Yeung, Botvinick, & Cohen, 2004; Holroyd & Coles, 2002).

A less well-studied phenomenon is the reduction in power within the alpha frequency band (8–12 or 10–14 Hz) occurring after errors relative to correct responses (Carp & Compton, 2009). This error-related alpha suppression (ERAS)—which refers to the alpha power on correct trials minus alpha power on error trials—is most pronounced at parietal electrode sites (Navarro-Cebrian, Knight, & Kayser, 2013; van Driel, Ridderinkhof, & Cohen, 2012; Compton, Arnstein, Freedman, Dainer-Best, & Liss, 2011; Carp & Compton, 2009), maximal approximately 200–500 msec after response onset, and not strongly correlated with error-related theta, error-related negativity, or error positivity (Carp & Compton, 2009).

Given the inverse relationship between alpha power and cerebral activity (Davidson, Jackson, & Larson, 2000), the tendency for greater alpha power on correct trials implies a relative decrease in cognitive arousal when performance is successful. Thus, ERAS is thought to reflect an increase in cognitive arousal after response errors (Carp & Compton, 2009). A recent study indirectly implicated the locus coeruleus and norepinephrine (LC/NE) system in the emergence of ERAS (Compton et al., 2021). Located in the brain stem, the LC is the main site of synthesis of NE, a monoamine neurotransmitter involved in basic sleep and wakefulness (i.e., arousal) functions (Samuels & Szabadi, 2008). Compton et al. (2021) found that greater pupil dilation, an index of arousal thought to be regulated by the LC/NE system, systematically covaried with less

[1]McLean Hospital/Harvard Medical School, Boston, MA, [2]University of Michigan Medical School, [3]University of California San Diego
*Hans S. Schroder and Ann M. Iturra-Mena contributed equally to this work and are co-first authors.

alpha power on a trial-to-trial basis. Other work implies that ERAS may reflect activity of the default mode network (DMN), a network of functionally connected regions most active during rest and off-task processing (Buckner, Andrews-Hanna, & Schacter, 2008), given that alpha power also covaries with self-reported moments of mind wandering (Compton, Gearinger, & Wild, 2019).

An alternative possibility is that ERAS reflects an orienting response to infrequent events. Indeed, despite findings that alpha power is reduced on error relative to correct trials (e.g., Compton et al., 2011; Carp & Compton, 2009), nearly all error-monitoring studies use tasks that elicit far fewer errors than correct responses. It is therefore possible that a reduction in alpha power is not specific to "errors," but to "infrequent events." Indeed, when participants performed a task in which errors were much more frequent, alpha power was reduced on the less frequent correct trials compared with the more frequent errors (Pezzetta, Nicolardi, Tidoni, & Aglioti, 2018).

Despite these findings, the functional significance of ERAS remains poorly understood, particularly owing to the mostly correlational nature of previous studies. Here, we investigated the arousal hypothesis pharmacologically with modafinil before participants completed a flanker task. Modafinil is well suited to examine arousal and alpha power, as it is used to promote wakefulness for individuals with narcolepsy (Bastoji & Jouvet, 1988) and has been related to greater pupil dilation (Hou, Freeman, Langley, Szabadi, & Bradshaw, 2005), an indirect marker of arousal.

In Study 1, we evaluated the scalp topography of ERAS in a novel flanker task within a sample of healthy volunteers. In Study 2, using a within-subject design, we examined modafinil's effects on ERAS by randomly assigning healthy volunteers to placebo, 100 mg, or 200 mg of modafinil using a within-subject, cross-over design. Given alpha's inverse relationship to wakefulness, we hypothesized that modafinil would decrease alpha power, resulting in reduced ERAS.

STUDY 1

Methods

Participants

Data from 61 participants (37 women, 24 men; *M* age = 23 years, *SD* = 5 years) who identified as white (n = 36), Asian (n = 20), Black (n = 3), or more than one race (n = 2; six participants identified as Hispanic or Latino) were reanalyzed from a previous report (Schroder et al., 2020) that validated the current version of the flanker task (see below for details). The prior report focused on posterror slowing and traditional error-related ERPs, and thus, all analyses focusing on ERAS are novel.

Participants completed a modified version of the Eriksen flanker task (Eriksen & Eriksen, 1977), which has been previously described (Schroder et al., 2020) and has been developed for cross-species (humans, rats) assessment of cognitive control (Robble et al., 2021). Participants used a Cedrus response pad (model RB-740 m, Cedrus Corporation) to indicate the color of the center image (target) in between two flanking images. The images (violet flowers and green leaves; see Figure 1) and their corresponding button assignments were counterbalanced across participants. During each of 350 trials, the flanking images were presented 100 msec before the target and could match the target image (congruent trial) or not match (incongruent trial). All three images remained on the screen for another 50 msec, for a total trial time of 150 msec. The intertrial interval was presented next, and then the next trial started (see Figure 1). After every 70 trials, the participants were given a short break (and the task was self-initiated again by the participant), which divided the task into five blocks.

For every correct response, participants earned 5 cents, but if they responded outside their 85th percentile RT from the previous block, they received the following feedback message: "TOO SLOW!!!" For approximately half of the participants, there was additional trial-to-trial feedback

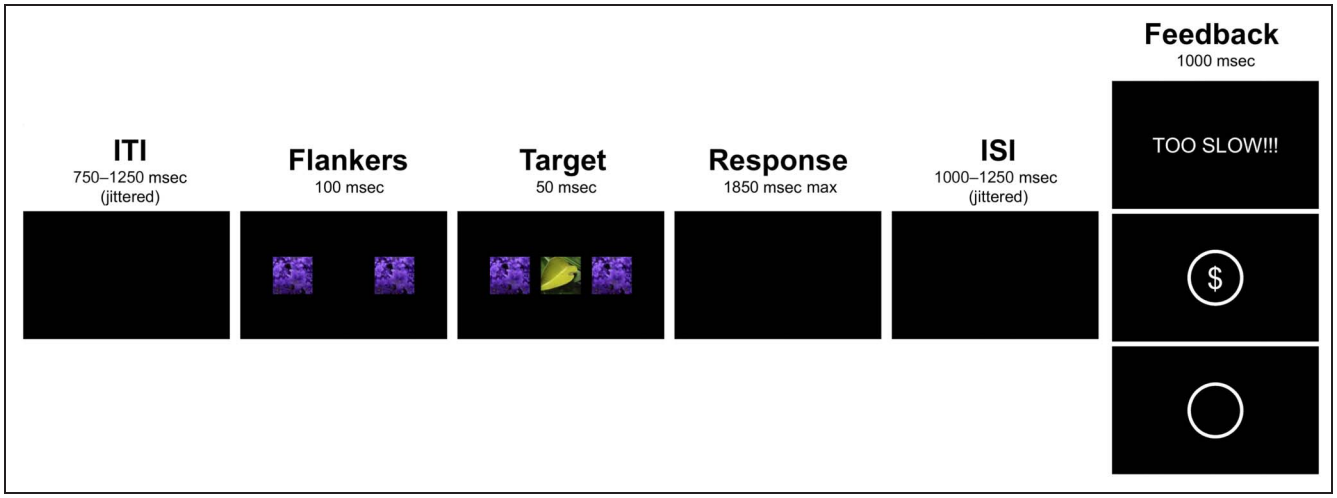

Figure 1. Flanker task design used in the current studies.

after responses; participants were presented with a blank screen for 1000–1250 msec before presentation of a dollar sign enclosed in a circle (correct responses) or an empty circle (incorrect responses) for 1000 msec. Note that analysis time windows, described below, occurred before the presentation of trial feedback.

In an electrically and acoustically shielded booth, participants were seated 70 cm in front of a 22.5-in. (diagonal) VIEWPixx monitor (VPixx Technologies). PsychoPy software (Pierce, 2007) was used to control presentation and timing of the stimuli. All images were displayed on a black background subtending 4.16° of visual angle vertically and 17.53° horizontally.

Continuous EEG activity was recorded from a customized 96-channel actiCAP system using an actiCHamp amplifier (Brain Products GmbH) with impedances kept below 25 kΩ. The ground channel was embedded in the cap and located anterior and to the right of Channel 10, which roughly corresponds to electrode AFz. The reference used during data acquisition was Channel 1 (Cz). All signals were digitized at 500 Hz using BrainVision Recorder software (Brain Products).

Offline analyses were performed with BrainVision Analyzer 2.2 (Brain Products). First, a visual inspection was used to remove gross muscle artifacts and EEG data during the breaks separating blocks. The data were then band-pass filtered with cutoffs of 0.1 and 30 Hz, 24 dB/oct roll-off. An independent component analysis was conducted to remove any blinks, horizontal eye movements, and electrocardiogram, and corrupted channels were interpolated using spline interpolation. Scalp electrode recordings were re-referenced to the average activity of all electrodes.

We then extracted response-locked data (−1500 to 1500 msec) for correct responses and errors separately. To deconfound congruency and RT effects, only incongruent trials were considered and the RT for the trial was required to be within the individually determined 95% confidence interval for incongruent RTs. Epochs were then rejected if there was a voltage step exceeding 50 μV in 200-msec time intervals, or a maximum voltage difference of more than 150 μV or less than 0.5 μV within a trial on an individual channel basis.

Time–Frequency Decomposition

Power spectra were processed using a continuous wavelet transformation in Brain Vision Analyzer 2.2. A complex Morlet wavelet transformation was applied using a Morlet parameter *c* (which refers to the cycle number per frequency) of 3.5 applied to the data from 1 to 30 Hz in 30 frequency steps distributed on a logarithmic scale. A percentage change baseline correction (BVA 2.0 Solution by Dr. Ingmar Gutberlet) was implemented by first averaging the amplitude in a −500 to −200 msec preresponse window for the response-locked data. Thus, subsequent power values reported below are calculated based on the percentage change of power relative to the baseline period according to the formula: *prctchange (tf) = (activity tf – baseline f) / baseline f* (Cohen, 2014). This percentage change function was performed on a trial-by-trial basis.

To isolate the alpha frequency band in the intertrial interval (Carp & Compton, 2009), wavelet layers were extracted from 10 to 14 Hz (wavelet scale center frequencies: 10.44, 11.74, 13.20, and 14.84 Hz; wavelet scale frequency bandwidth: 5.97, 6.71, 7.54, and 8.48 Hz). This alpha range was chosen to directly replicate the one used by Compton and colleagues (Compton et al., 2011; Carp & Compton, 2009). Informed by visual inspection and previous literature (Carp & Compton, 2009), the alpha power values were exported 200–500 msec post-response. Power was examined along the midline at the following electrode sites: 9, 2, 1, 33, an average of sites 34 and 35, 40, and 45, which correspond roughly to Fz, FCz, Cz, CPz, Pz, POz, and Oz, respectively. Data were normalized using a log transformation (see also Carp & Compton, 2009). In terms of the number of clean EEG epochs included in the analysis, averaged across all electrode sites included in the analysis, there were an average of 88 correct trials (SD = 16, range: 47–112) and an average of 28 error trials (SD = 15, range: 7–59).

Results

Behavior

Typical flanker task effects were observed in this task (see Schroder et al., 2020, for full details). For example, RTs were longer on incongruent trials than congruent trials, $t(60) = 28.14$, $p < .001$, Cohen's $d = 3.60$, and accuracy was lower on incongruent trials, $t(60) = 14.57$, $p < .001$, Cohen's $d = 1.87$.

Alpha Suppression

The time–frequency plot of ERAS is shown in Figure 2, and alpha power values are summarized in Table 1. A Site (Fz, FCz, Cz, CPz, Pz, POz, Oz) × Accuracy (error vs. correct) × Feedback (absent vs. present) repeated-measures ANOVA on post-response alpha power confirmed a significant main effect of Accuracy, $F(1, 59) = 51.81$, $p < .001$, $\eta_p^2 = .47$, because of significantly lower alpha power after errors compared with correct responses, consistent with the ERAS effect. A significant main effect of Site, $F(6, 354) = 15.91$, $p < .001$, $\eta_p^2 = .21$, indicated that overall alpha power was largest at parieto-occipital electrode sites. Likewise, a significant Site × Accuracy interaction, $F(6, 354) = 3.44$, $p = .003$, $\eta_p^2 = .055$, revealed that the magnitude of the difference between error and correct trials varied across the scalp. Bonferroni-corrected post hoc tests clarified that the ERAS difference was significant ($p < .001$) at every electrode site and the absolute mean difference was greatest at POz (electrode 40, Cohen's $d = 1.13$), Pz (Cohen's $d = 1.03$), and Oz (electrode 45, Cohen's

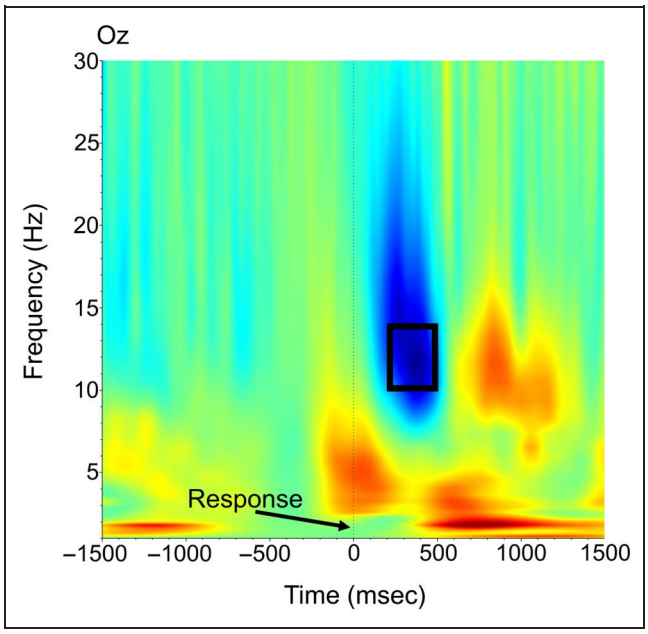

Figure 2. Time–frequency plot of ERAS (Study 1). n = 61. Data are taken from Channel 45 (Oz). Depicted is the error minus correct contrast, such that blue values indicate less power on error trials versus correct trials and red indicates more power on error trials. Time 0 is response onset. Box indicates regions of statistical analysis.

d = 0.86). There were no significant main effects or interactions involving Feedback (Fs < 1.67, ps > .13). These results confirm previous results of the spatial distribution of ERAS being largest in parieto-occipital sites (Carp & Compton, 2009) and indicate that trial-to-trial feedback had no impact on ERAS. Overall, errors committed during this version of the flanker task were associated with a reduction in alpha power.

Correlations between Alpha Suppression and Accuracy

Finally, we computed bivariate correlations between alpha suppression and accuracy on incongruent trials (the trials used to compute alpha power). Alpha suppression (alpha power on correct trials minus alpha power on error trials) was positively related to accuracy at all electrode sites: Fz (r = .35, p = .009), FCz (r = .36, p = .004), Cz (r = .48, p < .001), CPz (r = .52, p < .001), Pz (average of 35/34; r = .44, p < .001), POz (r = .40, p = .002), and Oz (r = .38, p = .003). Conclusions were identical when considering nonparametric Spearman's rho correlations: Fz (ρ = .32, p = .012), FCz (ρ = .37, p = .004), Cz (ρ = .45, p < .001), CPz (ρ = .52, p < .001, Pz (ρ = .42, p = .001), POz (ρ = .37, p = .004), and Oz (ρ = .36, p = .004). These correlations indicate that the ERAS effect was greatest for those with higher accuracy (i.e., fewer errors). These data are consistent with an orienting account of ERAS, such that a larger signal corresponds to fewer errors. Figure 3 (left) shows the correlation between ERAS at channel Pz and accuracy.

STUDY 2

Study 1 confirmed the presence of parieto-occipital alpha suppression on error trials in the modified flanker task. In Study 2, we assessed the effects of placebo, low (100 mg), and high (200 mg) doses of modafinil on alpha suppression in an independent sample of healthy participants.

Methods

An independent sample of 30 adults, who were all psychologically healthy (determined by the semistructured clinical interview; SCID-5), right-handed, and recruited from the greater Boston area, participated in Study 2. Participants provided written informed consent before all study procedures in the presence of a physician, who described the potential risks of modafinil. A total of four participants were excluded before statistical analysis due to having too few error trials for reliable ERP analysis (fewer than six, per Olvet & Hajcak, 2009), leaving a final sample of 26 participants (12 women, 14 men; M age = 23.81 years, SD = 4.82 years, range: 19–34 years). The Mass General Brigham institutional review board approved all procedures.

A blood analysis reviewed by a physician determined normal medical status and safety to administer the medication. Following these screening procedures, participants completed three EEG sessions at least 1 week apart structured using a double-blind, within-subject, placebo-controlled design. At each session, participants were administered a single placebo (0 mg), low (100 mg), or high (200 mg) dose of modafinil. Doses were given 2 hr before the session so as to achieve peak plasma concentration during the cognitive tasks (Robertson & Hellriegel, 2003). EEG sessions included an 8-min baseline recording of resting EEG, completion of the flanker task (described

Table 1. Log-transformed Alpha Power Values in Study 1

	"Fz" (9)		*"FCz" (2)*		*"Cz" (1)*		*"CPz" (33)*		*"Pz" (34/35)*		*"POz" (40)*		*"Oz" (45)*	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Error	2.09	0.26	2.06	0.25	2.04	0.22	2.01	0.26	2.00	0.27	2.06	0.26	2.16	0.26
Correct	2.20	0.19	2.26	0.18	2.23	0.17	2.21	0.18	2.25	0.19	2.33	0.23	2.39	0.26

n = 61. Conventional 10/20 system names in quotes; channel numbers in the custom cap in parentheses.

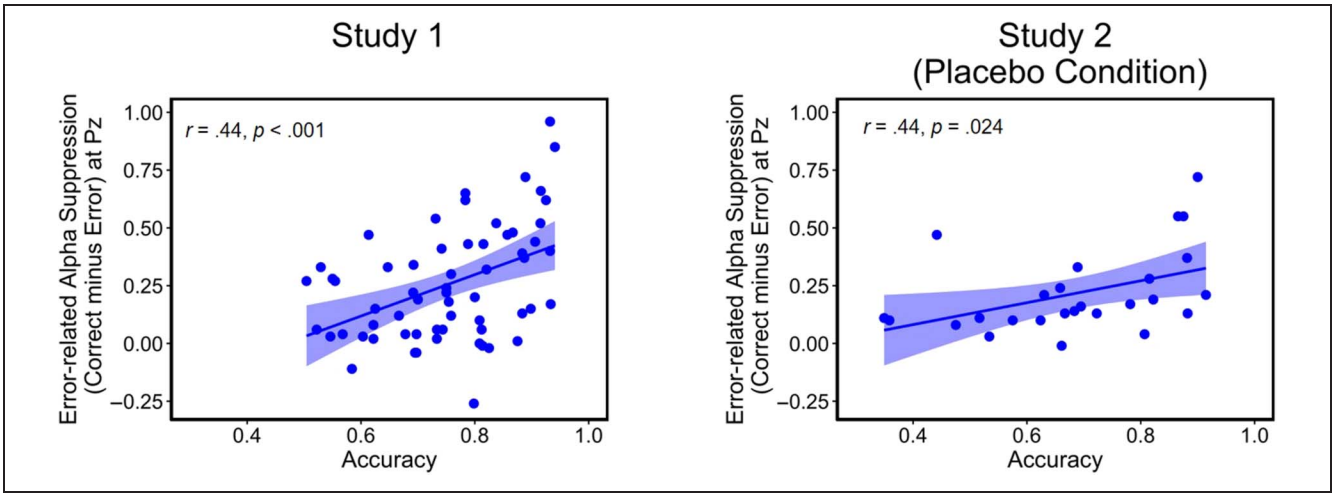

Figure 3. Correlation between alpha suppression and accuracy. *y*-axis for both graphs depicts log-transformed values of the difference between alpha power on correct trials minus alpha power on error trials.

above), and a probabilistic reversal learning task (not considered here). Button assignments were kept consistent within participants across the EEG sessions to prevent response-switching effects (Schroder, Moran, Moser, & Altmann, 2012). The order of tasks was randomized, and there were no significant effects of task order. EEG acquisition, preprocessing, and analyses were identical to Study 1. The task in Study 2 was identical to the feedback version of the task in Study 1, and all participants received trial-to-trial feedback.

Self-report Assessments

Participants completed a battery of self-report measures (for the full list, contact corresponding author), including two particularly relevant for this study. First, participants completed a side effects scale using a 1 (*not at all*) to 5 (*severe*) Likert scale, rating 12 different side effects (e.g., sleepiness, headache, feel hot or flushed, and dizziness) both before drug administration and at peak drug time. We report the full sum of the side effect scale (with a possible range of 12–60).

To specifically index arousal before and after drug administration, we also report on the "sleepiness" item in a separate analysis. Responses were summed to compute a side effects metric with possible range of 12–60. As another index of arousal, participants also completed the State–Trait Anxiety Inventory–State Version (STAI-S; Spielberger, 1983), a well-validated index of state anxiety. The STAI-S was administered before drug administration, during peak drug time, and before participants left the laboratory.

Baseline Alpha Recording

To assess whether modafinil had a differential impact on resting-state alpha activity, we examined the baseline recording data, which were collected after peak drug dose time but before the flanker task. Resting data (eyes closed) were subjected to a visual inspection of gross artifacts (movement) and filtered 0.1–100 Hz with a 60-Hz notch filter and then subjected to an independent component analysis to remove ocular and cardiac components. Topographic interpolation using spline interpolation, when necessary, was computed next. EEG data were then re-referenced to the average of all electrodes. Data were segmented based on equal-sized segments (2.048 sec each), then a fast Fourier transform was computed (with noncomplex data, hamming window 10%, window variance correction, period window, no compression, resolution: 0.48828 Hz), and data from the same 10–14 Hz spectral range were extracted for analysis for Pz, POz, and Oz.

Results

Behavioral Measures

As in Study 1, typical flanker effects were observed. A 2 congruency × 3 dose repeated-measures ANOVA on RT revealed a main effect of Congruency, $F(1, 25) = 321.20$, $p < .001$, $\eta_p^2 = .93$, such that RTs on incongruent trials were significantly slower than RTs on congruent trials. There were no effects of modafinil on RT, main effect of Dose, $F(2, 50) = 1.26$, $p = .29$, $\eta_p^2 = .048$, and no Congruency × Dose interaction, $F(2, 50) = 0.15$, $p = .86$, $\eta_p^2 = .006$.

A similar picture emerged for accuracy. The Congruency × Dose ANOVA revealed a main effect of Congruency, $F(1, 25) = 115.84$, $p < .001$, $\eta_p^2 = .82$, such that accuracy on incongruent trials (estimated marginal $M = 68\%$, $SE = 3\%$) was significantly lower than accuracy on congruent trials ($M = 94\%$, $SE = 1\%$). As with RT, there were no significant effects of modafinil on accuracy, main effect of Dose, $F(2, 50) = 2.54$, $p = .097$, $\eta_p^2 = .092$, and the Congruency × Dose interaction was not significant,

$F(2, 50) = 2.71, p = .092, \eta_p^2 = .098$. Numerically, incongruent accuracy was lowest in the low-modafinil condition ($M = 64\%$, $SE = 4\%$) compared with the placebo ($M = 69\%$, $SE = 3\%$) and high-modafinil condition ($M = 72\%$, $SE = 3\%$). In summary, the flanker task elicited expected flanker interference effects on behavior. However, modafinil did not have any significant impacts on behavior in this task.

Blinding Success and Side Effect Profile

At the end of the third and final EEG assessment, participants were asked to guess which assessments corresponded with placebo, low, and high doses. Overall, participants guessed correctly less than 50% for each of the conditions (high: 46% correct, low: 39% correct, placebo: 35% correct). Just seven participants (26%) correctly guessed all three conditions accurately. Side effects were very low (grand mean across all conditions and time points [pre- and postdrug] = 12.73, $SE = 0.17$ on range of 12–60) and did not differ among drug conditions (Fs < 0.57, ps $> .62$). Together, these findings indicate that blinding was successful.

Vital Sign Indicators of Arousal[1]

Heart rate. Heart rate, measured in beats per minute (pulse), was evaluated using a Dose (placebo, low, high) × Time (predrug vs. postdrug) ANOVA. A significant main effect of Dose, $F(2, 48) = 6.66, p = .003, \eta_p^2 = .22$, and Time, $F(1, 24) = 33.54, p < .001, \eta_p^2 = .58$, indicated that the high-dose condition was associated with greater pulse overall and that pulse decreased across the session. There was no significant Dose × Time interaction, $F(2, 48) = 1.09, p = .34, \eta_p^2 = .044$.

Blood pressure. Systolic blood pressure, measured in millimeters of mercury (mm Hg) was evaluated with a Dose (placebo, low, high) and Time (predrug vs. postdrug) ANOVA. Significant main effects of Dose, $F(2, 48) = 5.92, p = .005, \eta_p^2 = .20$, and Time, $F(1, 24) = 16.35, p < .0001, \eta_p^2 = .41$, indicated that, overall, blood pressure was highest in the high-dose condition and after drug administration. A near-significant Dose × Time interaction, $F(2, 48) = 3.04, p = .057, \eta_p^2 = .11$, indicated that the largest increase in systolic blood pressure from pre- to postdrug administration was observed in the high-dose condition, an intermediate increase in the low-dose condition, and the lowest increase in the placebo condition. Indeed, there was a significant linear trend for this interaction, $F(1, 24) = 8.77, p = .007, \eta_p^2 = .27$. In other words, a dose-dependent increase in systolic blood pressure was observed with modafinil.

A somewhat different pattern emerged with respect to diastolic pressure; main effects of Dose, $F(2, 48) = 6.80, p = .003, \eta_p^2 = .22$, indicated by the highest diastolic blood pressure in the high-dose condition, and Time, $F(1, 24) = 61.54, p < .001, \eta_p^2 = .72$, with diastolic blood pressure higher at postdrug than predrug assessment; however, there was no interaction between Dose and Time, $F(2, 48) = 0.21, p = .81, \eta_p^2 = .009$.

Self-report. For the self-reported sleepiness item, no significant effects of Time or Dose emerged (all Fs < 2.40, ps $> .13$). For the STAI, no significant effects of Time or Dose emerged (all Fs < 2.18, ps $< .15$). Thus, modafinil had no effects on self-reported indicators of arousal.

Alpha Suppression

Given that the parietal distribution of alpha suppression was confirmed in Study 1, we focused analyses on the three parieto-occipital sites with the largest effect sizes in Study 1. In terms of the number of clean EEG epochs for the final analysis of ERAS (again averaged across the electrode sites included in the analysis), these were the following: correct placebo ($M = 81$, $SD = 20$, range: 37–107), correct low dose ($M = 75$, $SD = 25$, range: 18–107), correct high dose ($M = 85$, $SD = 19$, range: 42–107), error placebo ($M = 37$, $SD = 20$, range: 10–77), error low dose ($M = 41$, $SD = 22$, range: 10–93), and error high dose ($M = 33$, $SD = 19$, range: 9–77).

As before, the average of electrodes 34/35 was used to represent site Pz. Study 2 alpha power values are summarized in Table 2. A Site (34/35, 40, 45 [Pz, POz and Oz]) × Accuracy (error vs. correct) × Dose (placebo, low, high) ANOVA was conducted on log-transformed alpha power data. Figure 4 presents log-transformed alpha power values for all conditions in this ANOVA. Figure 5 presents the time–frequency plot of alpha suppression (error minus correct) across the three doses at channel 45 (Oz). Replicating Study 1, the main effect of Accuracy, $F(1, 25) = 40.47, p < .001, \eta_p^2 = .62$, confirmed reduced alpha power on errors compared with correct responses. There was a significant interaction between Accuracy and Dose, $F(2, 50) = 4.09, p = .023, \eta_p^2 = .14$, indicating a differential impact of dose depending on the accuracy of the response. Post hoc Bonferroni-corrected tests indicated that numerically correct trials in the placebo condition (averaged across the three electrode sites) had higher alpha power than correct trials in the low-dose (M difference = 0.069) and high-dose (M difference = 0.060) conditions, although neither comparison survived the correction procedure (ps = .079 and .091 for placebo-low, placebo-high Bonferroni-adjusted comparisons, respectively). None of the error trial comparisons approached significance (ps $> .90$). Thus, these data indicate that the small accuracy by modafinil dose effect was driven by correct trial alpha power.

As alpha suppression may reflect an orienting response to novel events, we also controlled for error rate in the low-dose condition. As noted above, the low-dose condition had nonsignificantly higher error rates on incongruent trials. If ERAS reflects orienting, the numerically

Table 2. Log-transformed Alpha Power Values in Study 2

	"Pz" (34/35)						"POz" (40)						"Oz" (45)					
	Placebo		*Low*		*High*		*Placebo*		*Low*		*High*		*Placebo*		*Low*		*High*	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Error	2.11	0.26	2.12	0.25	2.07	0.26	2.15	0.30	2.17	0.27	2.15	0.30	2.18	0.35	2.23	0.36	2.22	0.36
Correct	2.32	0.22	2.28	0.22	2.26	0.22	2.39	0.25	2.32	0.24	2.32	0.29	2.41	0.31	2.33	0.30	2.37	0.30

n = 26. Conventional 10/20 system names in quotes; channel numbers in the custom cap in parentheses.

lower ERAS in the low-modafinil condition may simply be an artifact of increased error rate in that condition (more errors = less orienting = less ERAS). Consistent with this notion, controlling for low-dose incongruent accuracy by adding it as a continuous covariate in the Site × Accuracy × Dose ANOVA abolished any effects of dose (all Fs < 1.28, ps > .28). Thus, the small effect of modafinil on correct trial alpha is likely explained by an orienting response because of the high error rate in the low-modafinil condition.

Bayesian Analysis of Variance

To verify the evidence for the null effect of modafinil on ERAS, we reanalyzed the data from Study 2 in JASP v 0.15.0.0 statistical software that allows for Bayesian analyses. In the Bayesian approach to ANOVA in JASP, the principal objective is model comparison. The 3 Site × 2 Trial Type × 3 Dose ANOVA resulted in comparisons of 19 different models, including the null model where no independent variables are specified. The results indicated that only one model showed significant improvement after observing the data (i.e., an increase in posterior odds from the prior odds): the model that included main effects of Site and Trial Type, BF_M = 111.812. None of the other models had a BF_M substantially above 1 (the next best model with Site + Trial Type + Dose + Trial Type × Dose yielded a BF_M = 1.187). The notation of Bayes factor (model; BF_M) indicates the relative increase in odds after the data have been observed; BF_M = 1.00 indicate no change in the posterior odds. In terms of model comparisons, using the BF_{01} Bayes factor, which compares the best model with each subsequent model with respect to explaining the data, the best model was 13.93 times better at explaining the data than the next best model (see Table 3 for full model results). Thus, these Bayesian analyses indicate evidence for the null hypothesis (i.e., that dose had no impact on ERAS).

Correlations between Alpha Suppression and Accuracy

As in Study 1, we computed correlations between alpha suppression (alpha power on correct trials minus alpha power on error trials) and incongruent trial accuracy. In the placebo condition, the correlation between accuracy and ERAS was identical to that in Study 1 at electrode sites 34/35 (Pz, r = .44, p = .024) and similar at sites 40 (POz, r = .38, p = .053) and 45 (Oz, r = .33, p = .098). The correlation between ERAS at Pz and accuracy is shown in Figure 3 (right). Although the latter two correlations failed to reach statistical significance, they are similar in effect size to the correlations observed in Study 1. As in Study 1, the direction of these correlations indicates that as accuracy increases, so does alpha suppression, an effect consistent with an orienting account of ERAS. None of the correlations with incongruent accuracy were significant in the low-modafinil (rs = −.066, .087, and −.20, ps =

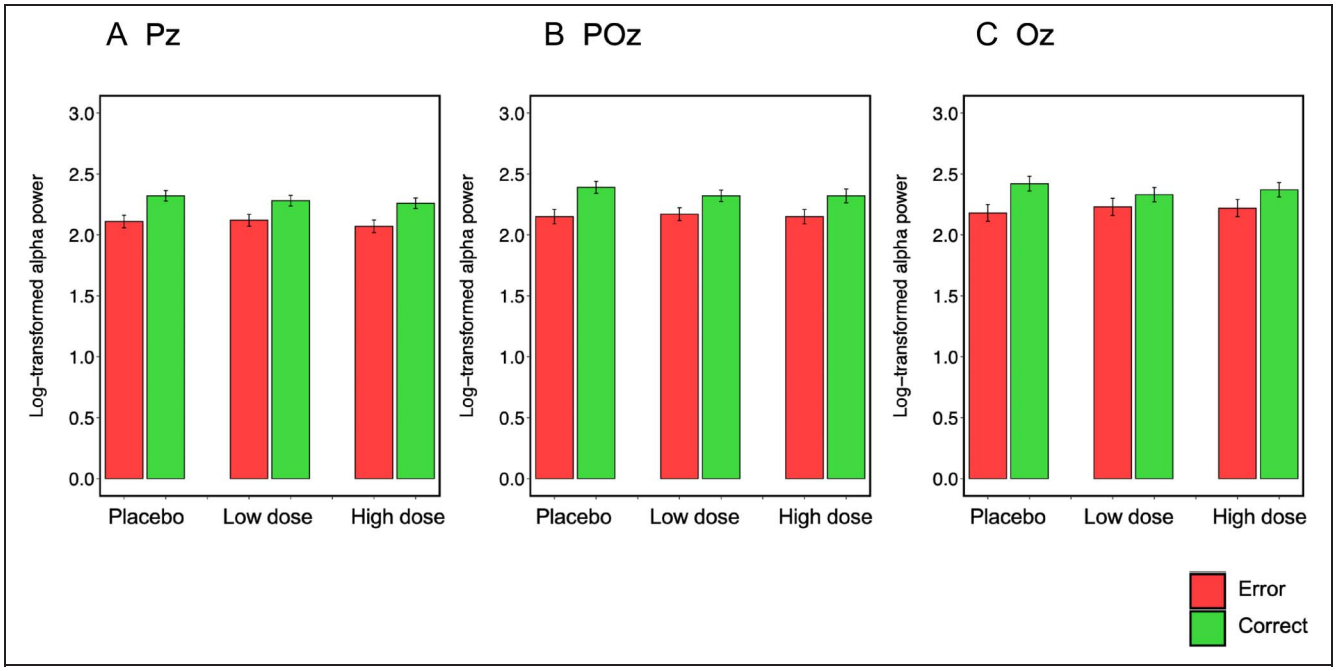

Figure 4. Log-transformed alpha power values in Study 2. Data shown at (A) Pz (Channels 34/35), (B) POz (Channel 40), and (C) Oz (Channel 45) for error and correct trials. Bars represent *SEM*.

.75, .67, and .34, for Pz, POz, and Oz, respectively) and high-modafinil (*r*s = .084, .02, and −.10, *p*s = .68, .94, and .64, for Pz, POz, and Oz, respectively) conditions. Conclusions were identical when using nonparametric Spearman's rho correlations: placebo (ρs = .53, .50, and .30, *p*s = .001, .009, and .13, for Pz, POz, and Oz, respectively), low-modafinil (ρs = .007, .12, and −.20, *p*s = .97, .55, and .32, for Pz, POz, and Oz, respectively), and high-modafinil (ρs = .07, .08, and −.03, *p*s = .72, .71, and .91, for Pz, POz, and Oz, respectively) conditions.

Baseline Alpha Activity and Modafinil

In a final supplemental analysis, we examined whether modafinil impacted baseline (non-task-based) alpha activity (10–14 Hz), which was recorded before the flanker task.

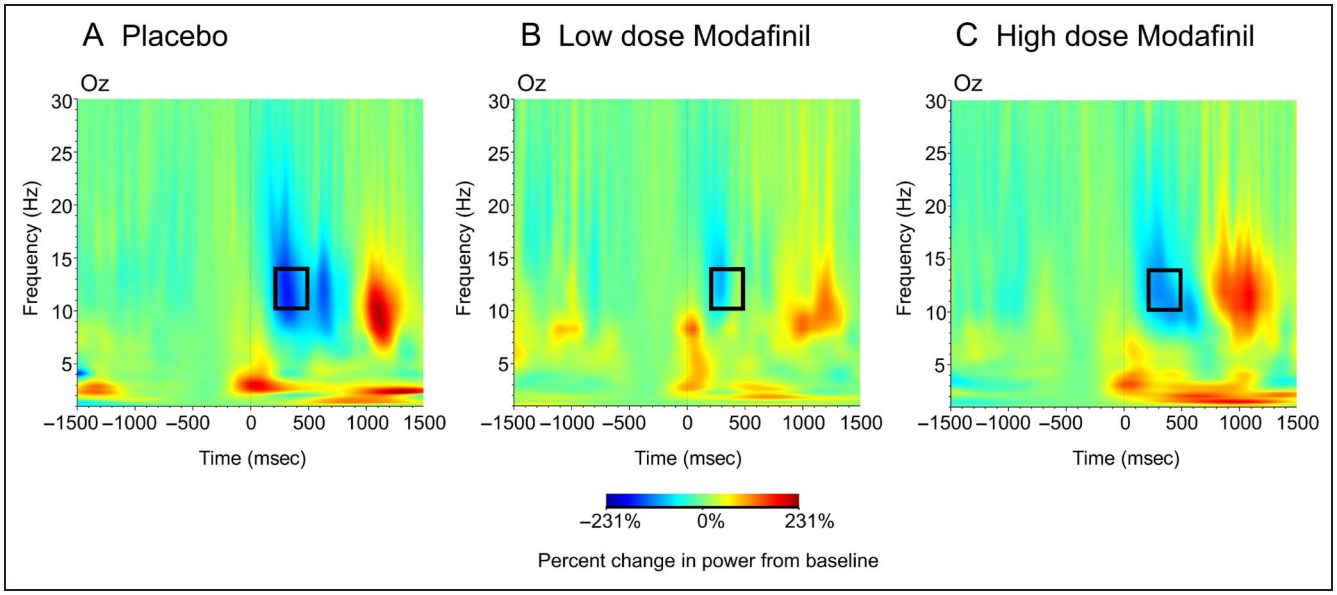

Figure 5. Time–frequency plots of ERAS (Study 2). n = 26, within-subject design. Data shown at Channel 45 (Oz). Doses refer to (A) placebo (0 mg), (B) low (100 mg), and (C) high (200 mg) doses of modafinil. Depicted is the error minus correct contrast, such that blue values indicate less power on error trials versus correct trials and red indicates more power on error trials. Time 0 is response onset. Boxes indicate regions of statistical analysis.

Table 3. Model Comparison from the Bayesian Approach to ANOVA (Study 2)

Models	*P(M)*	*P(M|data)*	BF_M	BF_{01}	*Error %*
Site + Trial Type	0.053	0.861	111.812	1.000	
Site + Trial Type + Dose + Trial Type × Dose	0.053	0.062	1.187	13.927	51.797
Site + Trial Type + Dose	0.053	0.043	0.806	20.092	51.778
Site + Trial Type + Site × Trial Type	0.053	0.026	0.473	33.667	51.817
Site + Trial Type + Dose + Site × Trial Type + Trial Type × Dose	0.053	0.004	0.064	242.653	51.794
Site + Trial Type + Dose + Site × Trial Type	0.053	0.002	0.043	359.212	51.782
Site + Trial Type + Dose + Site × Dose + Trial Type × Dose	0.053	0.001	0.024	649.984	51.805
Site + Trial Type + Dose + Site × Dose	0.053	9.33e−4	0.017	923.276	51.821
Site + Trial Type + Dose + Site × Trial Type + Site × Dose + Trial Type × Dose	0.053	8.08e−5	0.001	10665.605	51.942
Site + Trial Type + Dose + Site × Trial Type + Site × Dose	0.053	5.47e−5	9.85e−4	15740.549	51.864
Trial Type	0.053	1.51e−5	2.71e−4	57187.396	51.885
Site + Trial Type + Dose + Site × Trial Type + Site × Dose + Trial Type × Dose + Site × Trial Type × Dose	0.053	2.70e−6	4.86e−5	319011.962	51.796
Trial Type + Dose + Trial Type × Dose	0.053	1.58e−6	2.84e−5	545513.702	51.798
Trial Type + Dose	0.053	1.35e−6	2.43e−5	638495.517	51.775
Site	0.053	4.53e−28	8.16e−27	1.900e+27	51.759
Site + Dose	0.053	3.08e−29	5.55e−28	2.795e+28	51.760
Site + Dose + Site × Dose	0.053	5.64e−31	1.01e−29	1.528e+30	51.779
Null model (incl. Subject)	0.053	5.24e−31	9.44e−30	1.643e+30	51.752
Dose	0.053	3.47e−32	6.25e−31	2.479e+31	51.774

All models include Subject.

We computed a 3 site (Pz, POz, Oz) × 3 dose (placebo, low, high) repeated-measures ANOVA on the resting alpha activity. Similar to the ERAS findings above, modafinil had no impact on baseline alpha activity: main effect of Dose, $F(2, 50) = 0.52$, $p = .52$, $\eta_p^2 = .020$; Site × Dose interaction, $F(4, 100) = 1.14$, $p = .34$, $\eta_p^2 = .04$. A significant main effect of Site, $F(2, 50) = 24.63$, $p < .001$, $\eta_p^2 = .50$, indicated alpha power was greater at sites POz and Oz compared with Pz. Thus, modafinil had no impact on alpha activity either during the task (ERAS) or at baseline.

GENERAL DISCUSSION

Alpha suppression following errors is relatively understudied, and its functional significance remains elusive. Indirect evidence using pupil dilation raises the possibility that alpha suppression reflects a nonspecific arousal signal after errors (Compton et al., 2021). The current work more closely tested this hypothesis by examining ERAS in a novel flanker task and assessing its sensitivity to modafinil, a medication used to promote wakefulness (i.e., arousal). Although ERAS was observed in our task in two separate studies of healthy participants, modafinil had a negligible effect on ERAS that did not survive corrections for multiple comparisons or a sensitivity analysis controlling for error rate (Figure 4). Thus, modafinil did not influence ERAS. Instead, we found consistent evidence that ERAS closely tracked error rate, pointing to a potential orienting explanation of ERAS (see Figure 3).

We replicated the classic alpha suppression finding in humans using a novel flanker task designed specifically for cross-species use (Robble et al., 2021). The effect replicated those from previous findings (Carp & Compton, 2009) in three ways: in direction (power was greater on correct trials compared with errors), spatial topography (the effect was largest at parieto-occipital sites), and timing (beginning approximately 200 msec after error onset). Moreover, the alpha suppression effect was highly similar for both Studies 1 and 2, confirming that ERAS is a robust and reproducible phenomenon across independent samples.

However, ERAS was not influenced by modafinil, a noteworthy finding. This suggests that the arousal hypothesis of ERAS may be more nuanced and not sensitive to overall levels of arousal. Indeed, previous studies of ERAS reveal that it is most related to moment-to-moment changes of arousal (e.g., pupil dilation on a trial-to-trial basis; Compton et al., 2021). We are unaware of any studies examining ERAS in a sleep deprivation experiment or comparing those with and without sleep disorders.

Alternatively, it is possible that modafinil did not have strong effects on arousal. Although promoted as a wakefulness agent, our data provide limited support that participants felt more aroused with modafinil compared with the placebo. Arousal because of modafinil would only be indicated by significant Dose × Time interactions on variables of arousal. Only one such interaction emerged (for systolic blood pressure). Modafinil did not have significant interaction effects on heart rate, diastolic blood pressure, nor any of the self-reported measures of arousal and wakefulness. Whether this reflects a weaker effect of modafinil on arousal or a ceiling effect observed in healthy, non-sleep-disordered participants remains to be ascertained. Our data are also inconsistent with modafinil's purported "cognitive enhancement" effects: At least, when using in single doses, modafinil had no impact on behavior or any error-related ERPs consistently linked with cognitive control (see also Robble et al., 2021). This is more in line with recent meta-analytic evidence that modafinil has negligible effects on task performance (Kredlow, Keshishain, Oppenheimer, & Otto, 2019). Thus, it is possible ERAS does reflect cognitive arousal on a moment-to-moment basis, but the medication used herein was not strong enough to test this hypothesis in healthy humans.

Our results may instead be consistent with the account that ERAS reflects an orienting response, as it was correlated with accuracy in both studies (Figure 3). That is, participants who made fewer errors also had the largest ERAS effect. Orienting accounts have been previously used to explain other error-monitoring processes, including those that lead to posterror behavioral adjustments (Wessel, 2018; Notebaert et al., 2009), and recent work illustrates that alpha activity in attentional tasks may reflect orienting as well (Popov, Langer, Gips, Weisz, & Jensen, 2021). Notably, both arousal and orienting responses may be mediated by the same LC/NE system (Gabay, Pertzov, & Henik, 2011). Interestingly, modafinil—primarily considered a dopamine reuptake inhibitor (Volkow et al., 2009)—also occupies NE transporter sites (Minzenberg & Carter, 2008; Madras et al., 2006) and directly shifts NE output of the LC (Minzenberg et al., 2010). Given that we did not directly manipulate specific neurotransmitter systems in this study, we cannot speak to underlying neurobiological systems. However, future studies should continue to examine the potential orienting properties of ERAS.

It is also possible that alpha power on correct trials represents activation of the DMN, a network of brain regions associated with off-task processing and internal cognition (Smallwood, Brown, Baird, & Schooler, 2012; Buckner et al., 2008). Indeed, properties associated with DMN also overlap with increased alpha power (Brueggen et al., 2017). Conceptually, this would indicate that correct responses are associated with greater DMN activity than on error trials. It is intuitive that error trials would be associated with the highest DMN activity, to the extent that DMN activity corresponds to less on-task processing. In fact, several studies have documented such an increase in DMN or DMN-like responding on trials leading up to errors (Eichele et al., 2008; Hajcak, Nieuwenhuis, Ridderinkhof, & Simons, 2005). It would also be intuitive that immediately after the processes that lead one to commit a mistake, DMN activity would be suppressed by the onset of task processes. If ERAS is generated by DMN, further study of clinical applications is warranted. In particular, several lines of evidence indicate DMN is relevant for the understanding and treatment of depression (Pizzagalli, 2011) and anxiety (Sylvester et al., 2012), including aberrant error-preceding brain activity among anxious individuals (Schroder, Glazer, Bennett, Moran, & Moser, 2017). The current scalp ERP data do not speak to the possibility that ERAS represents output of the DMN, and future studies utilizing simultaneous EEG and fMRI may help test this possibility.

Limitations and Conclusion

These findings should be considered in light of several limitations. First, all participants were psychologically healthy, which limits generalizability to clinical populations and may have contributed to potential ceiling effects. Second, although the modafinil dose range of 100–200 mg in humans is consistent with recommendations for clinical treatment of narcolepsy, doses up to 400 mg have been previously evaluated (Broughton et al., 1997). It is possible that the null effects observed here represent the maximal effects that can be obtained with these relatively lower doses of modafinil in healthy participants. We finally acknowledge that null effects are difficult to interpret and may be the result of several factors. However, our study provides the first ever pharmacological investigation of ERAS, showing no effect of modafinil. Future studies examining ERAS in the context of other wakefulness-promoting medications, particularly those more directly targeting the LC/NE system, will be helpful in adjudicating between some of the possibilities raised here.

Reprint requests should be sent to Diego A. Pizzagalli, McLean Hospital/Harvard Medical School, 115 Mill St., Belmont, MA 02478, or via e-mail: dap@mclean.harvard.edu.

Author Contributions

Hans S. Schroder: Conceptualization; Formal analysis; Methodology; Project administration; Writing—Original draft. Ann M. Iturra-Mena: Data curation; Formal analysis; Investigation; Writing—Review & editing. Micah Breiger: Data curation; Formal analysis; Investigation; Writing—

Review & editing. Samantha R. Linton: Data curation; Formal analysis; Writing—Review & editing. Mykel A. Robble: Conceptualization; Formal analysis; Investigation; Writing—Review & editing. Brian D. Kangas: Conceptualization; Investigation; Writing—Review & editing. Jack Bergman: Conceptualization; Investigation; Writing—Review & editing. Stefanie Nickels: Conceptualization; Data curation; Formal analysis; Writing—Review & editing. Gordana Vitaliano: Investigation; Methodology; Writing—Review & editing. Andre Der-Avakian: Conceptualization; Investigation; Methodology; Writing—Review & editing. Samuel A. Barnes: Data curation; Formal analysis; Methodology; Writing—Review & editing. William A. Carlezon, Jr.: Conceptualization; Investigation; Writing—Review & editing. Diego A. Pizzagalli: Conceptualization; Investigation; Methodology; Project administration; Writing—Review & editing.

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Declarations of Interest

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes, and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics and Compass Pathways. Over the past 3 years, Dr. Carlezon has received consulting fees from Psy Therapeutics. Dr. Der-Avakian holds equity ownership in PAASP US. With the exception of NIMH, no funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors declare that they have no disclosures in association with this work.

Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

Note

1. A total of 25 participants had usable heart rate and blood pressure data.

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