Pol J Aviat Med Bioeng Psychol 2024; 30(4): 5-17
DOI: 10.13174/pjambp.25.08.2026.01

ORIGINAL ARTICLE

MODAFINIL AND GALANTAMINE FOR COUNTERACTING WAKEFULNESS-RELATED FATIGUE: ASSESSMENT VIA CRITICAL FLICKER FUSION

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Source of support: This work was supported by the National Centre for Research and Development (Poland) under Grant [No. OR00004208], titled: "Improving the psychophysical fitness of a soldier during combat tasks by means of pharmacological stimulation"

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Introduction: The critical fl icker fusion (CFF) threshold is a well-established neurophysiological marker of temporal visual resoluti on and corti cal excitability, with higher thresholds reflecting increased alertness and wakefulness. This study aimed to evaluate the eff ects of modafinil and galantamine on central nervous system arousal during sustained wakefulness using CFF as an objecti ve measure of stimulant-induced modulati on of perceptual processing.

Methods: Twelve healthy male volunteers (mean age = 24 years) parti cipated in a randomized, double-blind, placebo-controlled, crossover study consisti ng of three non-consecutive test sessions: modafinil (100 mg), galantamine (10 mg), and placebo. Each session included four testi ng points and simulated prolonged wakefulness. The drug was administered after ~27 hours of conti nuous wakefulness. CFF thresholds were measured in both ascending (fl icker-to-fusion) and descending (fusion-to-flicker) directi ons using a validated CFF device under controlled environmental conditions.

Results: Modafinil significantly elevated CFF thresholds compared to placebo in both ascending and descending paradigms, indicati ng enhanced corti cal arousal. Galantamine showed a signifi cant increase in the descending threshold at only one measurement point relative to placebo. No stimulant–measurement interacti on emerged, suggesti ng that the effect did not vary signifi cantly across sessions. However, ti me-course analyses showed a non-monotonic profile: aft er a 10:30 dose, CFF rose toward late morning then attenuated by early aft ernoon, likely reflecting circadian/homeostatic infl uences and individual pharmacokinetics/pharmacodynamics.

Conclusions: Modafi nil, but not galantamine, increased CFF thresholds in both ascending and descending paradigms, consistent with enhanced corti cal arousal. Operationally, dosing time and mission phase are critical considerati ons; aligning administrati on with rising circadian drive and pairing pharmacological treatment with non-pharmacological countermeasures may help sustain benefits.

Keywords: sleep deprivation, fatigue, alertness, military aviation, circadian rhythms, stimulants

Cite this article: Lewkowicz R, Przewodzka A, Łaszczyńska J. Modafi nil and Galantamine for Counteracting Wakefulness-Related Fati gue: Assessment Via Criti cal Flicker Fusion. Pol J Aviat Med Bioeng Psychol 2024; 30(4): 5-17. DOI: 10.13174/pjambp.25.08.2026.01

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INTRODUCTION

Fatigue is a pervasive and well-documented threat to safety and performance in both civilian and military aviation [14,30,58]. It impairs key cognitive functions such as attention, memory, situational awareness, and decision-making, all of which are essential for safe flight operations. Fatigue-related impairments have been implicated in numerous aviation incidents and accidents. In military aviation specifically, fatigue has been identified as a contributing factor in approximately 4-8% of mishaps, according to U.S. Air Force data [11]. These effects are exacerbated in operational environments involving sustained wakefulness, night operations, high-tempo deployments, or rapid time-zone shifts, where opportunities for restorative sleep are limited and circadian misalignment is common [12,13].

In response to the operational risks associated with fatigue, aviation authorities and military organizations have implemented a variety of countermeasures. These include crew resource management, strategic napping, optimized duty scheduling, light exposure control, and fatigue risk management systems [14]. In addition, technologies for monitoring wakefulness, such as microsleep detection and eye-movement tracking, can be integrated [20]. While these behavioral and organizational interventions can help mitigate fatigue-related risks, they are often insufficient during extended operations in which sleep deprivation is unavoidable. Consequently, there is growing interest in pharmacological countermeasures to sustain cognitive performance under such conditions.

Among the most studied pharmacological interventions is modafinil, a wakefulness-promoting agent that enhances alertness and executive functioning. This stimulant promotes alertness mainly through the activity of the dopaminergic system, and its effect on the histaminergic system contributes to the regulation of sleep and wakefulness [5]. Administration of modafinil is associated with relatively few adverse effects compared with traditional stimulants like amphetamine [39,54]. Furthermore, it carries a lower risk of addiction among aviation personnel, as the drug does not cause a sudden release of dopamine but increases its availability in the body in a more controlled manner [52].

While modafinil remains the most widely investigated wakefulness-promoting agent, interest has also grown in alternative pharmacological strategies that target different neurotransmitter systems. In this context, galantamine, a cholinesterase inhibitor commonly used in the treatment of Alzheimer's disease, has been explored for its potential to enhance memory and attentional processes through modulation of the cholinergic system [37,38,41]. Both compounds have shown promise in mitigating the cognitive deficits associated with sleep loss [44,45,54]; however, the neurocognitive domains they affect may differ, and their efficacy under real-world operational conditions remains incompletely understood.

To effectively evaluate the impact of such pharmacological agents, sensitive and reliable measures of central nervous system (CNS) functioning are required. One such tool is the critical flicker fusion (CFF) test, a psychophysical assessment that measures the temporal resolution of visual perception. This test determines the frequency at which flickering light is perceived as steady (fusion) or begins to be perceived as flashing (flicker), referred to as the critical flicker fusion frequency threshold [50]. The CFF threshold is considered a robust indicator of cortical arousal, information processing speed, and overall CNS integrity [10,16,33]. Higher CFF threshold values reflect increased excitability of the visual cortex and improved temporal resolution, which have been associated with heightened states of alertness and wakefulness [19]. Importantly, the CFF threshold has been shown to decrease significantly with fatigue [29], sleep deprivation [7,25], and sedative drug use [22,24], making it a valuable tool for monitoring alertness and cognitive readiness in operational settings.

Previous studies have demonstrated that prolonged wakefulness leads to reductions in CFF thresholds, which correlate with subjective reports of fatigue and objective performance impairments in tasks requiring sustained attention and rapid decision-making [25,51,59]. A decline in the ability to distinguish between flickering light stimuli may indicate increasing psychophysiological stress and signal the need for a break from flight operations, rest, or even a nap [26]. Moreover, the CFF test has been successfully used to detect the effects of various psychoactive substances, including both sedatives and stimulants [22–24]. Despite this, few studies have directly examined the influence of modafinil or galantamine on temporal visual resolution as measured by the CFF test, particularly in the context of sleep deprivation. This represents a notable gap in the literature, as understanding how these compounds affect temporal processing may inform their application in high-risk environments such as military aviation and special operations.

This study was conducted as part of a broader program evaluating pharmacological methods for sustaining operational effectiveness in combat settings [32,46]. A companion objective of that program was to inform aviation fatigue management through rigorously tested drug-based countermeasures. Within this framework, we address the limited evidence on how modafinil and galantamine influence complex-task performance during sleep loss, exploring approaches that could help maintain aircrew capability. The objective of the present study was to assess the effects of modafinil and galantamine on temporal visual resolution using the CFF test in healthy individuals subjected to sustained wakefulness. By evaluating how these pharmacological agents modulate CFF thresholds under sleep-deprived conditions, this study aims to contribute to a deeper understanding of their potential utility as fatigue countermeasures in operational contexts.

Based on prior evidence linking CFF to cortical arousal and wakefulness-promoting interventions, we hypothesized that: (H1) modafinil would increase CFF thresholds (ascending and descending) relative to placebo during sustained wakefulness; (H2) galantamine would produce smaller or no increases in CFF compared with placebo; and (H3) the magnitude of any drug-related changes would vary over the course of the day, reflecting combined circadian and homeostatic influences on alertness.

METHOD

Participants

Twelve healthy male volunteers (aged 20-25 years; M = 24, SD = 2.5) participated in the study. Their anthropometric characteristics included height 172-186 cm (M = 179 cm), weight 71-88 kg (M = 80 kg), and BMI ranging from 23.5 to 26.5 kg/m². All participants had valid medical clearance from the Regional Military Aviation Medical Commission and underwent comprehensive pre-study evaluations, including internal medicine, neurology, ophthalmology, otolaryngology, electrocardiography (ECG), electroencephalography (EEG), audiometry, blood and urine analyses, cardiopulmonary exercise testing, and VO_2max assessment.

Exclusion criteria focused on medical conditions contraindicating use of modafinil or galantamine, such as asthma, epilepsy, significant hepatic, renal, or cardiac dysfunction, or bradycardia. Participants were screened for sleep disorders and instructed to abstain from alcohol, caffeine, tobacco, and vigorous exercise for 24 hours prior to testing. To ensure participant safety, participants were instructed to report any adverse health events, including anxiety symptoms or irritability, immediately to the attending physician before and during the study.

Each participant provided written informed consent. The study was approved by the Military Institute of Aviation Medicine (WIML) Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Study design

The study was a randomized, double-blind, placebo-controlled, crossover trial with a 3 (condition) × 4 (time point – tests described below) within-subjects design. Each participant completed three non-consecutive test sessions under different pharmacological conditions: (1) 100 mg modafinil (Vigil®), (2) 10 mg galantamine (Nivalin®), and (3) placebo. Sessions were separated by a 7-day washout period.

Each session followed the same schedule: participants arrived at 19:00 and remained under supervision for about 21 hours until the end of the session at 16:00 the following day. Drug administration occurred at 10:30, following approximately 27 hours of sustained wakefulness (participants began each session after a normal day of activity followed by a sleepless night). No napping was allowed. This protocol simulated extended operational wakefulness common in military aviation.

To control for circadian variation, testing occurred at fixed time points across all sessions:

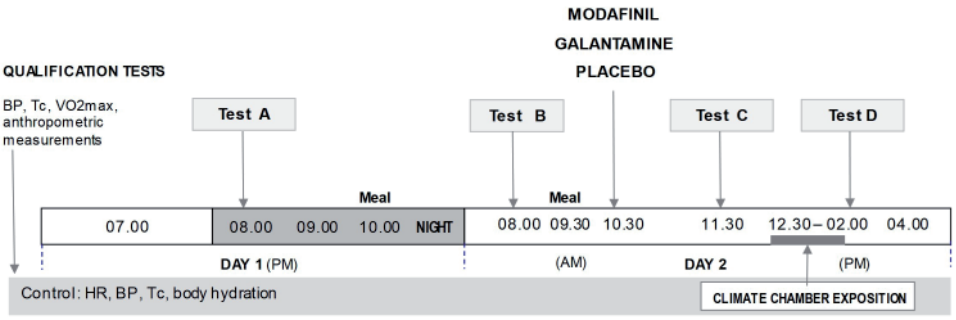
- Test A: 20:00 (baseline, before night without sleep),
- Test B: 08:00 (after ~25 h wakefulness, before drug intake),
- Test C: 11:30 (1 h post-dose),
- Test D: 14:00 (3.5 h post-dose).

Hydration, blood pressure, core temperature, heart rate, and energy expenditure were monitored throughout the sessions. Meals were provided at 22:00 and 09:30 to standardize nutritional intake. The scheme of the study design is shown in Fig. 1.

Pharmacological Agents

Two psychoactive agents approved for use in the European Union were tested:

- modafinil (Vigil®, 100 mg) — a wakefulness-promoting agent with an onset of action within 30–60 min, peak effect at 2–4 h, and a half-life of 12–15 h [39,55];



Type of measurement	Test A	Test B	Test C	Test D
BP, Tc, weight, energy expenditure, **CFFT**, psychomotor performance and attention tests	x	x	x	x
Flight performence test	x	x		x
Boardwalk (isometric training station)		x		x
Bedford test, borg test				x

HR: heart rate, BP: blood pressure, Tc: core temperature, CFFT: Critical Flicker Fusion Test, V02max: maximal aerobic capacity

Fig. 1. Scheme of the study design (single test session).

– galantamine (Nivalin®, 10 mg) — a cholinesterase inhibitor with peak plasma concentration reached within 0.5–2 h and a half-life of ~5.5 h [1].

Capsules containing the psychoactive agents and placebo (which contained lactose) were visually identical and randomized in sequence for each participant.

Apparatus

The CFF thresholds were assessed at each of the four time points (tests A-D, Fig. 1) using the Flicker fusion unit (SCHUHFRIED, Austria), a widely used psychophysical device for measuring CNS functioning. The equipment is owned by the Military Institute of Aviation Medicine. This device was equipped with a CFF response panel (S/N: TE 1006) and a flicker tube (S/N: PF 0612).

The light stimulus was produced by a red, diffuse light-emitting diode (LED) with a peak wavelength of 655 nm and a luminous intensity of 5.4 millicandelas. The flicker frequency was adjusted in 0.1 Hz increments within a range of 25.0 to 60.0 Hz.

The optical system comprised two concave–convex lenses, each with a focal length of 250 mm, configured to generate a virtual image of the flickering stimulus that was perceived at a distance of 12 meters. This configuration ensured visual accommodation consistent with distance viewing, thereby minimizing the influence of near-focus convergence on threshold detection.

The visual angle of the central stimulus was 1.2°, while the surrounding ambient background subtended a visual angle of 10°, providing a stable luminance field during testing. The ambient environment was illuminated uniformly with a luminous intensity of 600 millicandelas, delivered over a 30 mm diameter area, ensuring controlled and consistent background lighting conditions throughout the experiment.

Procedure

Prior to the start of the study, all participants were thoroughly briefed on the experimental procedures, safety protocols, and the known side effects of the administered stimulants. Each participant completed the same set of tests during three separate sessions (Fig. 1), with a different stimulant administered in each one (modafinil, galantamine, placebo). The order of stimulant administration was randomized across participants. A washout period of seven days was maintained between sessions to minimize carryover effects.

To control for the influence of circadian variation on psychophysiological functioning, all testing sessions were conducted at the same time of day, in the evening, according to a standardized study schedule (Fig. 1). Prior to the first measurement (Test A) in the initial session, participants were instructed on how to operate the Flicker Fusion Unit (SCHUHFRIED, Austria) and practiced the task until they demonstrated full comprehension.

All CFF threshold assessments were conducted in a quiet, dimly lit room. Each trial involved both ascending and descending series of flicker frequencies. During ascending trials, participants were instructed to press a button the moment the flickering light appeared steady (fusion). In descending trials, they responded when the

steady light began to flicker. Five measurements were obtained for each series type, and the mean ascending and mean descending thresholds were calculated for analysis. Each test block was completed within 5–7 minutes.

Statistical analysis

Normality was assessed using Shapiro-Wilk tests for each stimulant and time point (Tests A-D), while Levene's test was used to assess homogeneity of variance across stimulant and measurement combinations for CFF thresholds (ascending and descending). A linear mixed-effects (LME) model was implemented to examine the effects of stimulant (galantamine, modafinil, placebo) and measurement time point (Test A–D) on the CFF thresholds, with random intercepts for participants.

An analysis of variance (ANOVA) on the LME model was used to examine the statistical significance of main effects (stimulant, measurement) and their interaction. To estimate effect sizes, we computed partial eta-squared (ηp2). Post-hoc pairwise comparisons were performed using estimated marginal means with the Benjamini-Hochberg procedure to control the false discovery rate. Post-hoc tests focused on between-stimulant comparisons at each measurement time point and within-stimulant comparisons across measurement time points. The significance of differences was set at $p < 0.05$.

All analyses were performed using R (version 4.4.2) [47] with the rstatix package version 0.7.2 [27], dplyr package version 1.1.4 [56], effectsize package version 1.0.1 [6], ggplot2 [57], and ggpubr package version 0.6.1 [28].

RESULTS

CFF ascending threshold

The LME model revealed a significant main effect of stimulant ($F(2,121) = 5.02$, $p = 0.008$), but no significant effect of measurement ($F(3,121) = 1.76$, $p = 0.158$) or the stimulant × measurement interaction ($F(6,121) = 0.98$, $p = 0.44$). Post hoc comparisons (Benjamini-Hochberg procedure) across stimulants at each measurement indicated that, at Test C, the CFF threshold was significantly higher for participants receiving modafinil compared to placebo (estimate = 10.92, SE = 4.29, $p = 0.037$, Fig. 2). A similar significant difference was observed at Test A, where modafinil again yielded higher values than placebo (estimate = 10.75, SE = 4.29, $p = 0.041$). No other pairwise comparisons reached statistical significance across measurement time points. This pattern was consistent with H1.

The effect size (η2) for the stimulant factor was moderate (0.08), indicating a meaningful impact of the stimulant type on CFF threshold. Measurement and the interaction effect demonstrated smaller effect sizes (0.04 and 0.05, respectively).

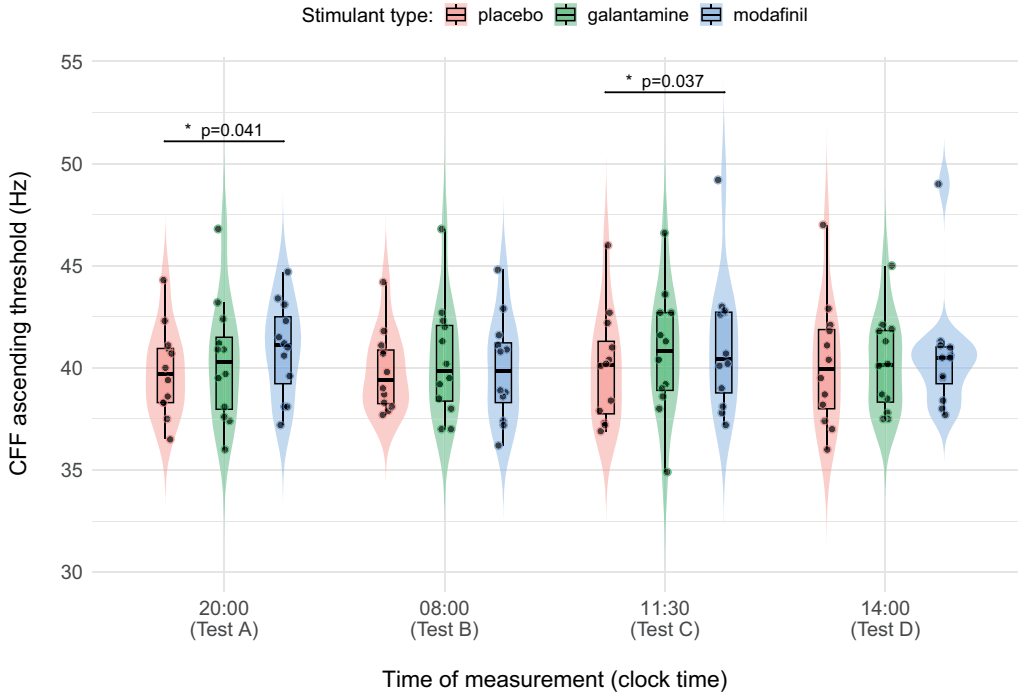


Fig. 2. Stimulant comparisons within each measurement for the critical flicker fusion (CFF) ascending threshold (transition from flicker to fusion). The violin plot represents distribution shape/density; the box indicates the median and IQR (whiskers to 1.5×IQR); jitter indicates individual observations.

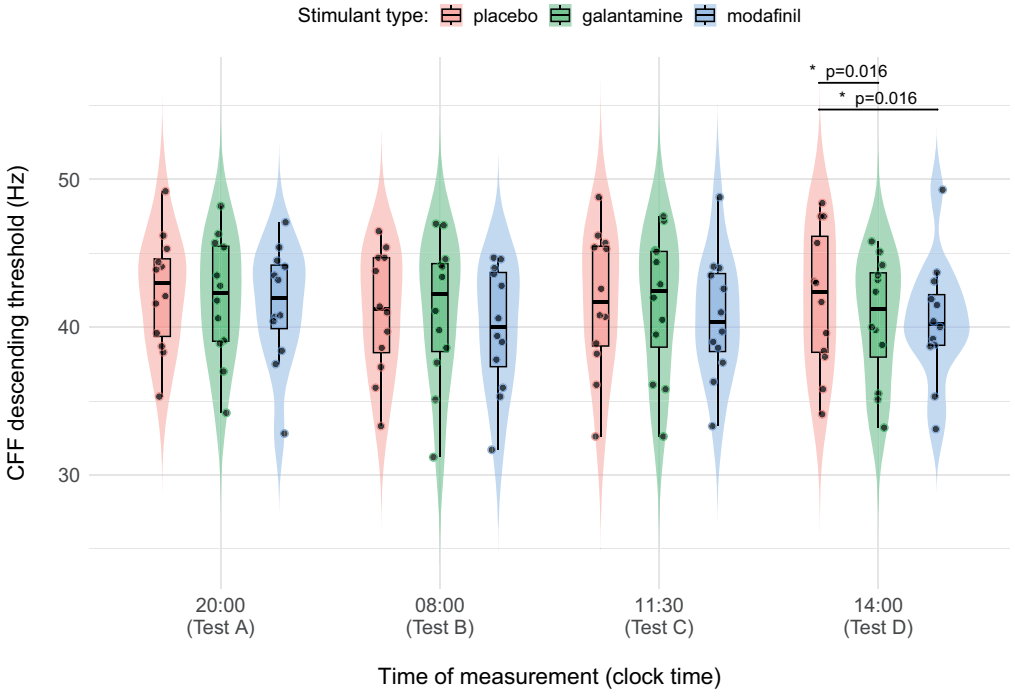


Fig. 3. Stimulant comparisons within each measurement for the critical flicker fusion (CFF) descending threshold (transition from fusion to flicker). The violin plot represents distribution shape/density; the box indicates the median and IQR (whiskers to 1.5×IQR); jitter indicates individual observations.

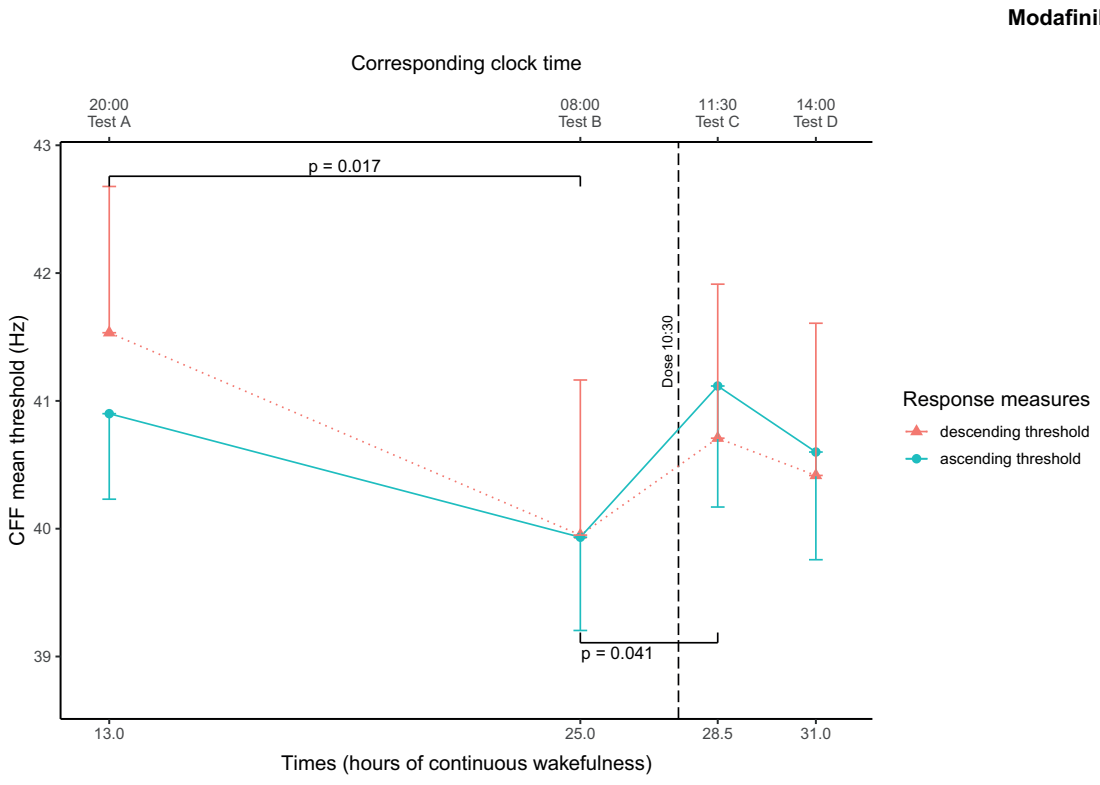


Fig. 4. Effects of modafinil on critical flicker fusion (CFF) mean threshold (ascending and descending) measures. The upper x-axis indicates clock time, while the lower x-axis indicates hours of continuous wakefulness. Error bars represent the standard error of the mean (SEM).

CFF descending threshold

A separate LME model fitted for the CFF descending threshold revealed significant main effects of both stimulant ($F(2,121) = 9.34$, $p < 0.001$) and measurement ($F(3,121) = 6.64$, $p < 0.001$), with no significant stimulant × measurement interaction ($F(6,121) = 0.83$, $p = 0.548$). Post hoc analyses (Benjamini-Hochberg procedure) showed several statistically significant pairwise differences. Under Test D, participants receiving modafinil showed a significantly higher CFF threshold than those receiving placebo (estimate = -14.83, SE = 5.21, $p = 0.016$, Fig. 3). At the same time point (D), galantamine also differed significantly from placebo (estimate = -13.50, SE = 5.21, $p = 0.016$). The modafinil–placebo differences were consistent with H1. The galantamine findings did not provide clear support for H2.

Within the modafinil condition (Fig. 4), the CFF descending threshold at Test B was significantly lower than at Test A (estimate = -15.83, SE = 5.21, $p = 0.017$). For the CFF ascending threshold, Test C was significantly higher than Test B (estimate = -11.83, SE = 4.29, $p = 0.041$).

In the galantamine condition (Fig. 5), the CFF threshold was significantly lower at Test D compared to Test A (estimate = -14.08, SE = 5.21, $p = 0.047$).

In the placebo condition (Fig. 6), no pairwise comparisons of ascending or descending CFF thresholds reached statistical significance across measurement time points.

In summary, across all conditions, modafinil exhibited a trend toward a higher mean CFF ascending threshold compared to galantamine and placebo, particularly at measurement C, taken immediately after stimulant administration. The stimulant × measurement interaction was not significant in either model, which did not support H3.

DISCUSSION

The present study investigated the extent to which pharmacological stimulation with modafinil or galantamine mitigates the detrimental effects of sleep deprivation on temporal visual resolution and cortical processing. Overall, the data supported H1: modafinil increased CFF thresholds relative to placebo in both ascending and descending paradigms, consistent with wake-promoting effects reported under sleep loss [5,7]. In contrast, H2 was not supported, as galantamine did not yield a robust or consistent elevation of CFF compared

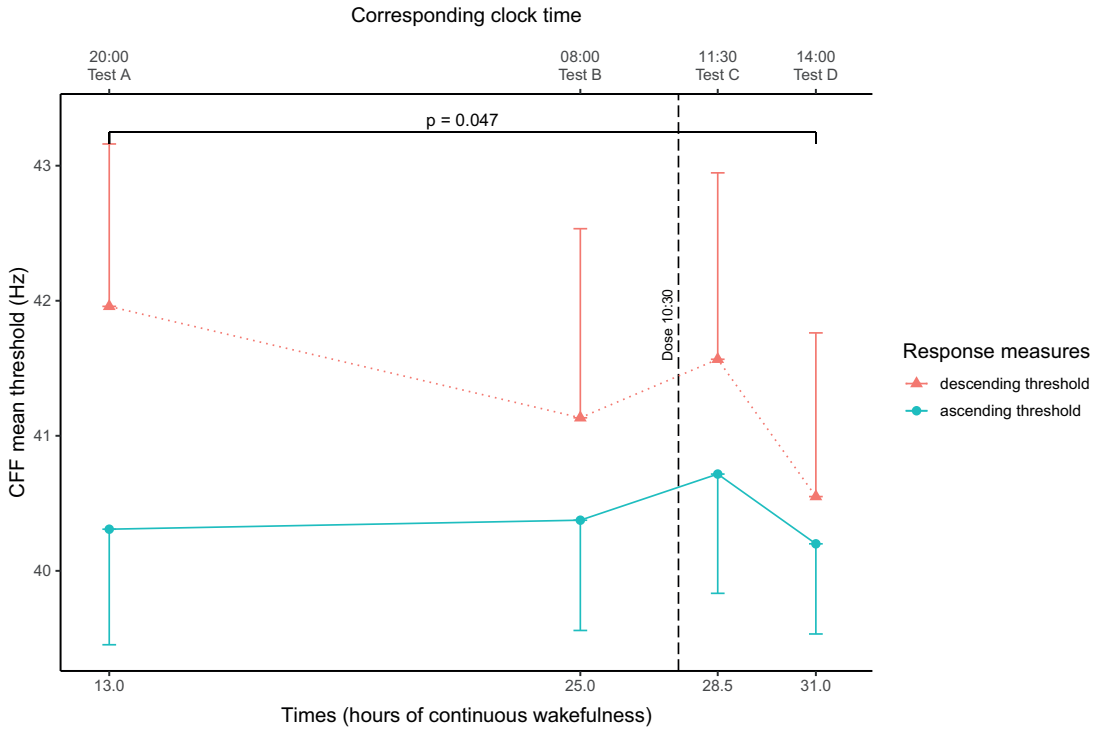


Fig. 5. Effects of galantamine on critical flicker fusion (CFF) mean threshold (ascending and descending) measures. The upper x-axis indicates clock time, while the lower x-axis indicates hours of continuous wakefulness. Error bars represent the standard error of the mean (SEM).

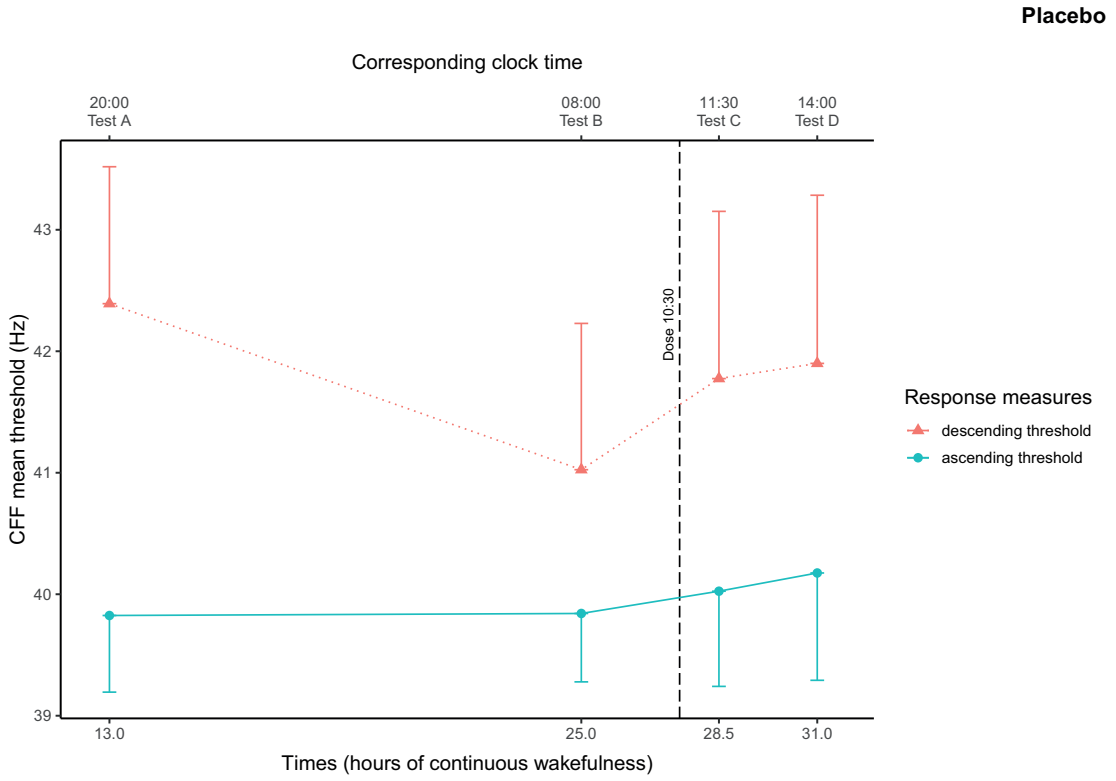


Fig. 6. Effects of placebo on critical flicker fusion (CFF) mean threshold (ascending and descending) measures. The upper x-axis indicates clock time, while the lower x-axis indicates hours of continuous wakefulness. Error bars represent standard error of the mean (SEM).

with placebo across tests, in line with evidence that cholinergic enhancement shows task- and state-dependent effects and may not directly shift CFF [8–10,23]. H3 received partial support: although the stimulant × measurement interaction was not significant, the across-day trajectories (including early-afternoon attenuation) were compatible with circadian and homeostatic modulation during sustained wakefulness [15,17,59], and with reports that ascending and descending thresholds can diverge under high neurocognitive load [58].

Our analyses showed a significant main effect of stimulant on both ascending and descending CFF thresholds, with no stimulant × measurement interaction. Thus, drug effects were broadly present across sessions, although their magnitude varied by time point. In line with prior work [53], modafinil produced overall higher CFF thresholds, consistent with enhanced cortical arousal and improved temporal visual resolution, whereas galantamine did not yield a robust elevation (Figs. 2 and 3). The moderate effect size for the stimulant factor in the ascending model ($\eta p2 = 0.08$) indicates a meaningful, time-general influence on arousal and is consonant with evidence that CFF is a valid, sensitive index of cerebral/behavioral arousal [4,34,53].

Ascending (flicker-to-fusion) and descending (fusion-to-flicker) thresholds are often treated as interchangeable indices of temporal visual resolution; however, they can differ systematically because they rely on partially distinct perceptual decision criteria and neural computations (e.g., temporal integration vs transient detection), and the method-of-limits procedure can introduce hysteresis and response bias. These differences may become more apparent when the CNS operates under high load or stress, where top-down attentional control and sensory gating are challenged, potentially yielding larger divergence between ascending and descending CFF patterns [36].

The time-course plots refine this picture (Figs. 4–6). In the placebo arm, CFF followed the expected diurnal/homeostatic pattern under sustained wakefulness: relatively preserved evening levels (20:00), a nadir after a sleepless night (08:00), and a late-morning/early-afternoon rebound—a trajectory well documented for human alertness and performance [15,17]. In both modafinil and galantamine conditions, CFF rose shortly after dosing at 10:30 (peak near 11:30) and then declined by 14:00. The initial rise is consistent with modafinil pharmacokinetics (Tmax ≈ 2–4 h

in healthy adults), while the subsequent decline is plausibly explained by the early-afternoon decline in circadian drive (the "post-lunch dip") interacting with continuing homeostatic pressure from prolonged wakefulness [17,40,48].

The observed within-day CFF profile is also consistent with prior work showing measurable daytime variation in CFF and related subjective alertness indices under standardized conditions, with the lowest levels typically occurring during circadian low points and transient decrements around early afternoon (the "post-lunch dip") [49]. Accordingly, our results support interpreting CFF as a marker jointly shaped by circadian phase and homeostatic sleep pressure rather than as a purely pharmacodynamic readout.

Notably, a post-dose decline in CFF does not necessarily imply a loss of drug efficacy. Performance–arousal relationships often follow an inverted-U pattern: as arousal rises above the individual's optimal range, temporal integration can worsen despite continued pharmacological activation. This pattern is grounded in the adaptive-gain theory of locus–coeruleus norepinephrine function and the broader Yerkes-Dodson framework, both of which predict decrements when tonic arousal becomes too low or too high for the task demands [2,3].

The cholinergic findings fit a similarly nuanced view. Cholinergic enhancement can modulate attention and sensory processing in a task- and state-dependent manner rather than yielding a uniform "more is better" benefit; selective effects on visual attention and gating have been demonstrated with cholinesterase inhibitors in humans [31]. Thus, the lack of a consistent CFF elevation, and the late decline, in the galantamine arm likely reflects context-dependent cholinergic influences interacting with time of day and accumulating sleep pressure [8,9].

Taken together, these observations suggest that modafinil elevates CFF overall, but its benefit is non-monotonic across the day and may attenuate by early afternoon; galantamine shows no consistent enhancement and may be associated with a later decline under some circumstances. The placebo pattern confirms that CFF closely tracks circadian and homeostatic influences, providing a necessary backdrop against which drug effects should be interpreted. Operationally, these results argue that time of administration and mission phase should be considered explicitly when using pharmacological countermeasures: dosing that aligns with circadian increases in alertness may maximize benefit, whereas early-afternoon windows may require adjustment (e.g., timing, dose, or adjunct non-pharmacological countermeasures) [17,40].

Finally, because sustained wakefulness increases state instability (moment-to-moment variability in alertness), future studies should sample more densely across the post-dose interval, control meals/light exposure, and pair CFF with pharmacokinetics/pharmacodynamics and physiological measures (e.g., EEG) to test the predicted inverted-U pattern for the circadian–arousal interaction and to determine whether the mid-day attenuation reflects pharmacology, circadian physiology, or their interaction [18].

Study limitations

While these results support the utility of the CFF threshold as a neurobehavioral biomarker of stimulant-induced arousal, several limitations should be noted [35,42,43]. First, the sample comprised healthy, medically screened volunteers tested under controlled laboratory conditions; therefore, generalizability to operationally fatigued or clinically heterogeneous populations remains uncertain.

Second, although the protocol involved sustained wakefulness from evening to the following day, we did not objectively index sleep–wake history or circadian phase (e.g., actigraphy/PSG, dim-light melatonin onset), nor did we tightly control potential zeitgebers such as light exposure or meal timing. Consequently, the relative contributions of homeostatic sleep pressure versus circadian modulation, particularly the early-afternoon dip, cannot be fully disentangled from drug effects.

Third, we did not acquire pharmacokinetics/pharmacodynamics measures (e.g., plasma modafinil/galantamine concentrations or time-varying CFF–exposure modeling), and our post-dose sampling was relatively coarse; thus, the observed mid-day attenuation after the 10:30 dose cannot be conclusively attributed to pharmacokinetics, circadian physiology, or their interaction (including a potential inverted-U relationship between arousal and temporal resolution).

Fourth, although we analyzed both ascending (flicker-to-fusion) and descending (fusion-to-flicker) thresholds, the study was underpowered for interaction tests (stimulant × measurement × threshold type), and we lacked electrophysiological markers (e.g., EEG alpha/beta) that could clarify neural mechanisms and help adjudicate method-specific versus state-dependent effects [21].

Fifth, CFF is a proximal sensory/perceptual endpoint; we did not concurrently assess higher-

order cognition (e.g., sustained attention, executive control) or real-world performance, limiting inferences about functional impact. Future work should incorporate objective sleep/circadian assessments, denser post-dose sampling with pharmacokinetics/pharmacodynamics measures, and tighter control (or manipulation) of time-of-day factors to test the predicted circadian–arousal inverted-U and to determine whether the early-afternoon decline reflects pharmacology, physiology, or both.

CONCLUSIONS

In summary, this study demonstrates that pharmacological stimulation exerts a measurable effect on temporal visual resolution indexed by CFF. Across both ascending (flicker-to-fusion) and descending (fusion-to-flicker) paradigms, we observed a significant main effect of stimulant, with modafinil, but not galantamine, producing overall higher CFF thresholds, consistent with enhanced cortical arousal. The absence of an interaction between stimulant and measurement indicates that modafinil's benefit was broadly present across sessions, while the time-course analyses reveal an important nuance: after dosing at 10:30, CFF rose toward late morning and then attenuated by early afternoon, suggesting a non-monotonic profile likely shaped by circadian/homeostatic influences as well as individual pharmacokinetics/pharmacodynamics variability.

These findings also indicate early-afternoon attenuation, which underscores that the timing of administration and mission phase are critical. Aligning dosing with rising circadian drive and/or combining pharmacological and non-pharmacological countermeasures may help maintain benefits across the duty day.

Future work should integrate objective sleep/circadian assessments and dense post-dose sampling with pharmacokinetics/pharmacodynamics to disentangle pharmacological from physiological contributions to the observed non-linearity and to test the predicted circadian–arousal inverted-U. Furthermore, future studies should include an in-depth neuropsychological assessment and EEG/ECG monitoring to more precisely capture the neural mechanisms underlying the observed pharmacological effects and to better determine the practical implications for operational applications.

AUTHORS' DECLARATION

Concept of the article: Rafał Lewkowicz. **Theoretical input:** Rafał Lewkowicz. **Research methods:** Rafał Lewkowicz, Joanna Łaszczyńska. **Execution of research:** Rafał Lewkowicz, Anna Przewodzka. **Data processing:** Rafał Lewkowicz. A**nalysis and interpretation of the results:** Rafał Lewkowicz. **Manuscript preparation:** Rafał Lewkowicz, Anna Przewodzka. **Project administration:** Joanna Łaszczyńska. The Authors declare that there is no conflict of interest.

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