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Electroencephalogram Effects of Armodafinil: Comparison With Behavioral Alertness

Daniela J. Conrado¹, Michael Bewernitz¹, Mingzhou Ding², Jean Cibula³, Christoph Seubert⁴, Sherwin K. B. Sy¹, Stephan Eisenschenk³, and Hartmut Derendorf¹

¹Department of Pharmaceutics, University of Florida, Gainesville, FL, USA

²J Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL, USA

³Department of Neurology, University of Florida, Gainesville, FL, USA

⁴Department of Anesthesiology, University of Florida, Gainesville, FL, USA

Abstract

Development of central nervous system-acting drugs would be enhanced by suitable biomarkers that reflect the targeted pathophysiologic brain state. The electroencephalogram (EEG) has several characteristics of an ideal biomarker and can be promptly adapted to pre-clinical and clinical testing. The aim of this study was to evaluate EEG as a measure of the wakefulness-promoting effect of armodafinil in sleep deprived healthy subjects. Armodafinil pharmacodynamics were simultaneously assessed by EEG- and behavioral-based measures including a well-established measure of alertness. Using two quantitative EEG-based measures—power spectral and event-related brain activity analyses—we observed that armodafinil mitigated the slowing of brain activity and the decrease of the event-related brain activity caused by sleep deprivation. Armodafinil-induced changes in EEG are in agreement and explain up to 73.1% of the armodafinil-induced changes in alertness. Our findings suggest that EEG can serve as a marker of the wakefulness-promoting drug effect.

Keywords

armodafinil; biomarker; electroencephalogram; event-related brain activity; power spectral analysis; alertness; psychomotor vigilance task; go/no-go association task

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Development of novel treatments for diseases of the central nervous system would benefit from sensitive and robust biomarkers that assess parameters close to the brain

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Corresponding Author: Hartmut Derendorf, PhD, PO Box 100494, 1600 SW Archer Rd, Gainesville, FL 32610, USA, hartmut@ufl.edu.

The Current address of Daniela J. Conrado is Neuroscience Clinical Pharmacology, Pfizer, Cambridge, MA, USA

The Current address of Michael Bewernitz is Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Conflict of Interest/Disclosure

The authors declare no conflict of interest.

pathophysiology. Electroencephalogram (EEG)-based measures have several desirable characteristics of an ideal pharmacodynamic measure. They yield an objective, nearly continuous, sensitive, non-invasive and direct assessment of neurotransmission-related activity without being affected by learning effects or requiring subjects' active cooperation.^{1,2} Moreover, EEG-based measures are relatively inexpensive and straightforward to implement in pre-clinical and clinical setting.

EEG has been systematically studied in a few drug classes. Changes in EEG power spectrum not only differentiated benzodiazepines with a wide range of intrinsic efficacy and affinity,³ but also reflected the depth of anesthesia caused by intravenous anesthetics.⁴ Remifentanyl development was expedited based on a well-established EEG power spectrum parameter (i.e., spectral edge) which was correlated with its analgesic efficacy.⁵⁻⁷ Event-related brain activity or event-related potentials, in turn, are voltage fluctuations in the EEG due to an internal or external event.² They are widely used to diagnose neurological (e.g., multiple sclerosis) and sensory (e.g., hearing impairments in neonates) disorders.² Preliminary studies demonstrated that event-related brain activity measures predicted response to clozapine and antidepressants in schizophrenia and mood disorders, respectively.^{8,9}

The greatest challenge is that the agreement between EEG parameters and drug effect is not yet clear in many situations.¹⁰ It has been claimed that a better understanding of the clinical meaning of EEG parameters would be obtained if an alternative measure of drug effect were performed in combination with EEG recording.¹ Although it has been noticed more than two decades ago, the number of studies investigating correlations between changes in EEG parameters and well-established measures of specific drug effects is still limited.

The present study evaluates EEG as a measure of the wakefulness-promoting effect of armodafinil. Armodafinil (Nuvigil®), a non-amphetamine stimulant medication, was approved by the FDA in 2007 to promote wakefulness in patients with excessive sleepiness related to obstructive sleep apnea/hypopnea syndrome (OSAHS), narcolepsy and shift work sleep disorder (SWSD).¹¹ Armodafinil is the R-enantiomer of modafinil (racemic mixture) and has an elimination half-life time, that is, three to four times longer than that of the S-enantiomer.^{12,13} The enantiomers seem to have similar pharmacodynamics, including reduced potential for abuse when compared to amphetamine-like stimulants.¹⁴ Several potential neurological and psychiatric indications have been investigated for modafinil¹⁵ and are likely to be extended to armodafinil.

To help evaluate the clinical significance of armodafinil-induced changes on EEG, we conducted EEG recording with simultaneous assessment of drug effect on a well-established measure of behavioral alertness (i.e., psychomotor vigilance task, PVT). In addition, a measure of impulsive behavior (i.e., go/no-go association task, GNAT) was performed to evaluate the effect of armodafinil on response inhibition, a parameter also known to be affected by excessive sleepiness. Two quantitative electroencephalogram-based measures were performed: power spectral analysis and event-related brain activity. Our main hypothesis was that armodafinil-induced changes in EEG are in agreement and can explain a substantial portion of armodafinil-induced changes in behavioral-based measures, especially

alertness. Ultimately, it provides insight into the clinical significance of EEG changes induced by stimulant drugs such as armodafinil.

Methods

Clinical Study

A double-blind, placebo-controlled, crossover clinical study was performed at the UF Clinical Research Center, Shands Hospital, University of Florida. The study protocol was in accordance with the Declaration of Helsinki and approved by the local Institutional Review Board. Six subjects were enrolled following a set of inclusion and exclusion criteria (see Supplementary Data online) and written informed consent was obtained from all subjects. The study consisted of three 48-hour visits separated by washout periods of at least 7 days. During each study visit, a set of pre-specified procedures were performed. In the morning of admission (day 1) subjects were interviewed about duration of sleep as well as inclusion and exclusion criteria. Urine drug screen (for all subjects) and pregnancy test (for female subjects) were also performed. Subjects had a training session on each neurobehavioral assay before the “resting baseline” session was performed. The subjects then underwent 24 hours of sleep deprivation after which a “fatigue baseline” session was performed (day 2). After that a single dose of the study drug was administered (placebo, 150 mg, or 250 mg armodafinil oral tablets). The subjects then underwent additional 12 hours of sleep deprivation during which 10 experimental sessions were performed. Pharmacodynamic measures were identical across all baseline and experimental sessions.

Behavioral-Based Measures

The subjects executed two neurobehavioral assays: a PVT and a GNAT. All output metrics were recorded by a dedicated computer (ERTS; BeriSoft Cooperation, Frankfurt, Germany) and then extracted for analysis (MATLAB; MathWorks, Inc., Natick, MA).

In the 10-minute PVT, the subjects were requested to focus on a cross symbol located at the center of a computer screen and respond to the appearance of a visual stimulus. The visual stimulus consisted of a bull's eye picture displayed at random time intervals. The subjects were instructed to respond as quickly as possible by pressing a response button on an external keyboard logic (EXKEY; BeriSoft Cooperation). PVT output was analyzed as in published literature¹⁶ (see Supplementary Data online). The final output metrics were then: (a) number of errors (i.e., errors of commission plus errors of omission), and (b) reciprocal response time (1/RT).

In the 10-minute GNAT, the subjects were requested to respond to one form of visual stimuli (go trials) and hold a response to another form (no-go trials)¹⁷ (see Supplementary Data online). The output metrics were: (a) 1/RT for go trials, (b) number of failures to respond for go trials (i.e., errors of omission), and (c) number of failures to inhibit a response for no-go trials (i.e., errors of commission).

EEG-Based Measures

Scalp-EEG recordings were acquired using a battery-operated 128-channel amplifier with a 1,024 Hz sampling rate and a 24-bit converter (Biosemi, Amsterdam, The Netherlands). One hundred twenty eight scalp electrodes were placed using a spandex electrode cap. Four electro-oculogram electrodes – below and above the left eye and in the left and right side of the eyes – were attached to control for eye artifacts. EEG recording was quantitatively analyzed by two different approaches: (a) power spectral analysis, which determined brain activities in different frequency ranges during the 2-minute resting EEG recording; (b) event-related brain activity analysis, which determined brain activities during the execution of the two aforementioned neurobehavioral assays. The EEG signal was pre-processed prior to both analyzes (see Supplementary Data online).

In the power spectral analysis, EEG data were split into contiguous 4-second intervals (0.25 Hz of frequency resolution). Fast Fourier transform was applied and power estimates were obtained in each interval (BESA 5.3; BESA GmbH, Gräfelfing, Germany). Power estimates were then averaged within the following frequency ranges: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–25 Hz). Visual inspection of the data indicated treatment-related differences for power estimates in the delta frequency range (i.e., delta power); particularly, in the frontal (F3 and F4 electrodes), temporal (T7 and T8 electrodes) and occipital (O1, Oz, and O2 electrodes) regions of the brain (see Supplementary Figure S1 online for electrodes location). The final output metrics were delta power in the aforementioned electrodes. Given the exploratory nature of the present study, delta power was not combined across different electrodes in order to investigate any tendency of localization or lateralization of treatment-related differences.

In the event-related brain activity analysis, stimulus-locked average was performed (BESA 5.3; BESA GmbH). The data were epoched from –500 to 1,000 ms with 0 ms corresponding to the stimulus onset. Baseline value was defined as the mean voltage of the pre-stimulus period between –200 and 0 ms. Grand average across all subjects were computed for each treatment during the execution of the PVT and GNAT. For the PVT, the conditions were correct- and incorrect-response trials; for the GNAT, conditions were correct- and incorrect-response trials for each stimuli category, go- and no-go trials. This selective averaging, for instance, prevented error-related interference in correct-response trials. Treatment-related differences in PVT and GNAT were evidenced for the late positive peak at around 380 ms post-stimulus (P3) during correct-response trials in the central region of the brain (Cz electrode). P3 was identified as the maximum peak between 250 and 650 ms and its amplitude, measured against the baseline value, was extracted for each subject. The final output metrics were: (a) P3 amplitude for correct-response trials in Cz during PVT; (b) P3 amplitude for correct-response go trials in Cz during GNAT; (c) P3 amplitude for correct-response no-go trials in Cz during GNAT.

Statistical Analysis

Final output metrics for each behavioral- and EEG-based measure were compared using a generalized linear mixed effect model (SAS 9.3; SAS Institute, Inc., Cary, NC). Metrics were previously checked for normality and appropriately transformed if necessary. RT and

delta power were reciprocal- and log-transformed, respectively. Count data (i.e., number of errors of omission or commission) were analyzed using Poisson distribution via a logarithm link function. The fixed effects of treatment, time, fatigue baseline, prior treatment (i.e., carry-over) and treatment $\times$ time interaction were investigated. Carry-over effect was not significant in any of the tested output metrics. The level of significance of the other fixed effects is presented in the Results Section. Subject and visit were set as random effects. Appropriate covariance structures were selected to account for the repeated measures performed on each subject. Tukey's test was used for post-hoc multiple comparisons in order to control the type I error rate. t-Statistics were calculated by subtracting the sample mean from each observation and, subsequently, dividing it by the sample standard deviation (normal distributions with different sample mean and standard deviation were observed for each type of measure). Tukey mean-difference plots were constructed by designating the average of the t-statistics of two measurements as the x-axis, and the difference between the two values as the y-axis. The distribution of the differences between the two measurements were checked for normality and the 95% limits of agreement were calculated as the mean difference ± 1.96 multiplied by the standard deviation of the differences. Two measures were considered to be in agreement if the 95% limits of agreement were between ± 3 ordinate units.

Results

Six healthy subjects were eligible and completed the study out of the eight screened subjects. In this sample, with equal distribution of sex, the median age was 24.8 years (range 23.0–31.0 years), the median body mass index was 25.1 kg m⁻² (range 20.1–28.9 kg m⁻²), two subjects were African American and four subjects were non-Hispanic whites. Armodafinil was generally well tolerated with one subject having headache and nausea. All subjects underwent 24 hours of sleep deprivation before a single administration of the study drug followed by additional 12 hours of post-dosing sleep deprivation during which pharmacodynamic assessments (i.e., EEG- and behavioral-based measures) were carried out. Baseline assessments of the pharmacodynamic measures were performed for all subjects prior ("resting baseline") and after 24 hours of sleep deprivation ("fatigue baseline").

Effects on Behavioral-Based Measures

Armodafinil increased the PVT performance, as reflected by the increased reciprocal response time (1/RT) and reduced number of errors, when compared to placebo. The least square means (95% confidence interval, CI) of both metrics for placebo, armodafinil 150 and 250 mg, respectively, were as follows: (a) 1/RT, 3.55 (3.04–4.05), 3.89 (3.38–4.39), and 3.80 (3.30–4.30) ms⁻¹; (b) number of errors, 59.2 (32.7–107), 15.1 (8.09–28.1), and 16.9 (8.98–31.8); (armodafinil 150 mg vs. placebo: 1/RT, $P < .0001$, number of errors, $P = .0081$; armodafinil 250 mg vs. placebo: 1/RT, $P = .0254$, number of errors, $P = .0218$). The two doses of armodafinil were not significantly different from each other with respect to both PVT metrics (1/RT: $P = .5095$; number of errors: $P = .9644$). Fatigue baseline adjustment was performed in order to account for the significantly different baseline values across the different treatment groups (1/RT: $P < .0001$; number of errors: $P < .0001$). Average 1/RT and number of errors over time for the three treatment groups are shown in Figure 1.

Armodafinil increased the GNAT performance, as reflected by the increased 1/RT and reduced number of errors of omission and commission, when compared to placebo. The least square means (95% CI) of the three metrics for placebo, armodafinil 150 and 250 mg, respectively, were as follows: (a) 1/RT, 2.15 (2.03–2.26), 2.45 (2.33–2.56), and 2.43 (2.31–2.54) ms⁻¹; (b) errors of omission, 8.80 (4.37–17.7), 1.46 (0.67–3.19), and 1.41 (0.64–3.13) ms⁻¹; (c) errors of commission, 35.1 (25.6–48.1), 23.0 (16.8–31.6), and 22.0 (16.0–30.2) (armodafinil 150 mg vs. placebo: 1/RT, $P < .0001$, errors of omission, $P = .0038$, errors of commission, $P < .0001$; armodafinil 250 mg vs. placebo: 1/RT, $P < .0001$, errors of omission, $P = .0048$, errors of commission, $P < .0001$). The two doses of armodafinil were not significantly different from each other with respect to the three GNAT metrics (1/RT: $P = .9362$; errors of omission: $P = .9979$; errors of commission: $P < .5417$). Fatigue baseline adjustment was performed for the three metrics given their significant difference across the treatments (1/RT: $P = .0001$; errors of omission: $P < .0021$; errors of commission: $P < .0001$). Average 1/RT, number of errors of omission and commission over time for the three treatment groups are shown in Figure 2.

Effects on EEG-Based Measures

Armodafinil increased the event-related brain activity during execution of the PVT and GNAT, as reflected by the increased amplitude of the late positive peak (P3) over the central region of the brain (Cz electrode), when compared to placebo (Figure 3). During PVT, the respective least square means (95% CI) of P3 amplitude for placebo, armodafinil 150 and 250 mg were 1.28 (–1.41–3.98), 1.80 (–0.89–4.49), and 2.18 (–0.52–4.87) μV (armodafinil 150 mg vs. placebo: $P = .0526$; armodafinil 250 mg vs. placebo: $P = .0001$); during GNAT go condition, they were 3.53 (–1.02–8.07), 5.36 (0.82–9.91), and 5.40 (0.85–9.94) μV , and during GNAT no-go condition, they were 4.71 (0.09–9.33), 7.55 (2.93–12.2), and 7.30 (2.68–11.9) μV (armodafinil 150 mg vs. placebo: go condition, $P < .0001$, no-go condition, $P < .0001$; armodafinil 250 mg vs. placebo: go condition, $P < .0001$, no-go condition, $P < .0001$). The two doses of armodafinil were not significantly different from each other with respect to P3 amplitude during PVT ($P = .2006$) and GNAT (go condition: $P = .9943$; no-go condition: $P = .8583$). Fatigue baseline adjustment was performed in order to account for the significantly different baseline values across the different treatments during the GNAT no-go condition ($P < .0001$); for consistency, it was kept in the model even when no significant difference was observed (PVT: $P = .7199$; GNAT go condition: $P = .2625$). Average P3 amplitude over time for the three treatment groups during PVT and GNAT are shown in Figure 4.

Armodafinil decreased the EEG power in the delta frequency range (i.e., EEG delta power) over the frontal (F3 and F4 electrodes), temporal (T7 and T8 electrodes) and occipital (O1, Oz, and O2 electrodes) regions of the brain when compared to placebo. The least square means (95% CI) of the delta power in the different brain regions for placebo, armodafinil 150 and 250 mg, respectively, were as follows: (a) F3, 1.07 (0.85–1.29), 0.94 (0.72–1.16), and 0.98 (0.76–1.20); (b) F4, 1.11 (0.88–1.35), 0.99 (0.76–1.23), and 1.00 (0.77–1.24); (c) T7, 0.92 (0.73–1.12), 0.81 (0.62–1.01), and 0.84 (0.64–1.04); (d) T8, 0.93 (0.66–1.19), 0.82 (0.56–1.08), and 0.85 (0.59–1.11); (e) O1, 1.12 (0.97–1.28), 1.03 (0.87–1.19), and 0.97 (0.81–1.13); (f) Oz, 1.15 (1.00–1.30), 1.04 (0.89–1.19), and 0.99 (0.83–1.14); (g) O2, 1.16

(0.98–1.34), 1.02 (0.84–1.20), and 1.00 (0.82–1.18) μV (armodafinil 150 mg vs. placebo: F3, $P = .0018$, F4, $P = .0008$, T7, $P < .0001$, T8, $P < .0001$, O1, $P = .0081$, Oz: $P = .0018$, O2: $P < .0001$; armodafinil 250 mg vs. placebo: F3, $P = .0348$, F4, $P = .0032$, T7, $P = .0040$, T8, $P = .0173$, O1, $P < .0001$, Oz: $P < .0001$, O2: $P < .0001$). The two doses of armodafinil were not significantly different from each other with respect to delta power at any tested region (F3: $P = .5233$; F4: $P = .9200$; T7: $P = .5120$; T8: $P = .2841$; O1: $P = .2173$; Oz: $P = .3264$, O2: $P < .8441$). Fatigue baseline adjustment was performed in order to account for the significantly different baseline values across the different treatments (T7: $P = .0216$; O1: $P < .0001$; Oz: $P < .0002$; O2: $P = .0026$); for consistency, it was kept in the model even when no significant difference was observed (F3: $P = .6507$; F4: $P = .2744$; T8: $P = .6074$). Average delta power over time for the three treatment groups in the occipital region is shown in Figure 5; analogous representations for the frontal and the temporal regions are shown in the Supplementary Figures S2 and S3 online, respectively.

Regression and Agreement Analyses Between EEG- and Behavioral-Based Measures

Figure 6 shows the univariate linear regression analyses between behavioral alertness (i.e., PVT performance) and each of the EEG-based measures. The event-related brain activity during execution of the PVT was a statistically significant explanatory variable of the PVT performance. Using observed data, the event-related brain activity explained 53.7% of the PVT performance (Figure 6a, left panel). Using the fatigue baseline adjusted least squares means, the event-related brain activity explained 73.1% of the PVT performance (Figure 6a, right panel). The EEG delta power explained 51.0% of the PVT performance when the fatigue baseline adjusted least squares means were used in the regression analysis (Figure 6b, right panel); however, this measure did not reach statistical significance when observed data were used which could be attributed to its high within-subject variability (i.e., residual error) (Figure 6b, left panel). Tukey mean-difference plots for the t-statistics of behavioral- and EEG-based measures were created to evaluate the agreement between the two types of assessments. The mean differences for the t-statistics of PVT performance and brain activity during PVT (Figure 6c) as well as PVT performance and delta power (Figure 6d) were zero, which indicates the absence of any systematic difference between the measurements. The 95% limits of agreement for both EEG-based measures were within the ± 3 ordinate threshold for agreement with the event-related brain activity having a better agreement with the behavioral alertness (± 1.43) than the EEG delta power (± 2.87). Regression analyses between GNAT performance and event-related brain activity together with respective Tukey mean-difference plots are shown in the Supplementary Figure S4 online. The event-related brain activity during GNAT was a statistically significant explanatory variable of the GNAT performance ($P < .0001$). Using observed data and fatigue baseline adjusted least squares means, the event-related brain activity during GNAT no-go trials explained, respectively, 34.8% and 78.6% of the GNAT performance; similarly, the respective values for the event-related brain activity during GNAT go trials were 26.3% and 71.8%. The mean differences for the t-statistics of GNAT performance and brain activity during GNAT (go and no-go trials) were zero, indicating the absence of any systematic difference. The 95% limits of agreement for both brain activity during GNAT go and no-go trials were ± 1.93 and ± 1.78 , respectively.

Discussion

To our knowledge, the present study is the first to simultaneously assess and compare the armodafinil effects on EEG- and behavioral-based measures. PVT a well-established behavioral measure of alertness with civilian and military applications in road, air and International Space Station transportation^{18,19} was chosen as the reference measure for the wakefulness-promoting effect of armodafinil. We observed that armodafinil increased the subject's behavioral performance and event-related brain activity and decreased the EEG delta power when compared to placebo. Overall, the drug groups started to differentiate from the placebo group at around 2 hours post-dose with the difference becoming less evident toward the last experimental time point. The results of the regression and agreement analyses between drug-induced changes on EEG metrics and alertness suggests that EEG is a potential maker of the wakefulness-promoting effect of armodafinil.

In the present study, armodafinil mitigated the slowing of the brain activity due to sleep deprivation. In other words, it decreased the EEG power in the delta frequency range (1–4 Hz; i.e., EEG delta power) over the frontal, temporal and occipital region of the brain when compared to placebo. Drug-related effects on either theta, alpha or beta frequency ranges were not observed. Our findings are virtually consistent with the results of published studies where modafinil effect on the EEG power spectrum was reported^{20–23}; in those studies, though, correlation between the drug-related EEG changes and alertness was not investigated. For instance, in a helicopter simulation study, modafinil reduced EEG activity in the delta and theta frequency ranges of sleep deprived healthy pilots.²⁰ In that study, three repeated doses of modafinil 200 mg were administered to the subjects; therefore, the absence of armodafinil effect on the theta activity in our study could be related to the different study design. Another study in healthy subjects showed that modafinil 300 mg also increased the EEG power in the alpha frequency.²¹ This effect, though, was only observed after the first dose, which was given prior to sleep deprivation with the intention to prevent a decrease in vigilance. Similar to modafinil,²¹ the armodafinil-induced increase in EEG alpha power is less apparent in situations when the alpha activity is reduced (i.e., after a period of sleep deprivation).

PVT, a widely used measure of behavioral alertness, fulfills the requirements for a meaningful assessment of the neurocognitive effect of sleep deprivation in that¹⁶: (a) it reflects an aspect of waking cognitive function (e.g., ability to use attention); (b) it is easy to perform and can be completed in a matter of minutes; (c) it has negligible learning effects; (d) it is sensitive; (e) the output metrics have a clear interpretation; (f) it is believed to be reflective of performance on “real world” tasks such as drowsiness-related impaired driving.¹⁹ Both armodafinil doses produced a significant increase in the level of alertness; subjects not only responded faster to the appearance of the stimulus but also with improved accuracy. PVT was used as a secondary pharmacodynamic endpoint in a large phase 1 clinical trial of armodafinil in healthy subjects undergoing acute sleep deprivation with the onset of armodafinil effect being consistent with our results.²⁴ Likewise, modafinil improved PVT performance in studies conducted in sleep deprived healthy subjects²⁵ as well as OSAHS²⁶ and SWSD²⁷ patients.

The GNAT has been extensively used to study the neural mechanisms underlying response inhibition.^{17,28} Deficit in response inhibition has been associated with not only sleep deprivation, but also attention deficit and hyperactivity disorder (ADHD).^{29–32} Indeed, a study comparing adult patients with narcolepsy, idiopathic hypersomnia and ADHD demonstrated a high percentage of overlapping symptoms between sleep disorders and ADHD which may lead to misdiagnosing.³³ In this context, response inhibition tasks have been applied to study the effect of stimulant drugs in children with ADHD.^{34–36} Methylphenidate, a classical stimulant drug, was able to improve the GNAT performance by reducing the number of errors of commission.³⁵ In the present study, both armodafinil doses improved the GNAT performance. Several studies proposed modafinil as an effective therapy in the management of ADHD in children and adults.^{36–41}

Event-related brain activity offers a direct measure of neurotransmission-related activity with a millisecond time resolution.² In the present study, the event corresponded to the external visual stimuli presented in the behavioral-based measures during which the brain activity was monitored. Armodafinil increased brain activity in the central region, as reflected by the increased P3 amplitude. Similarly, a study in children with ADHD demonstrated that methylphenidate was also able to increase P3 amplitude when compared to placebo,³⁴ corroborating the potential overlapping pharmacodynamic profiles of methylphenidate and armodafinil. We observed higher between-subject variability for the metrics of brain activity when compared to behavioral-based measures. While noise may have contributed, this variability may reflect the differences in the cognitive-neural-pharmacological process among the subjects.² Conversely, we observed lower within-subject variability for event-related brain activity, which is consistent with previous report.⁴²

Our findings indicate that EEG-based measures, especially the event-related brain activity, are in agreement and explain up to 78.6% of armodafinil-induced changes in behavioral-based measures, including alertness (up to 73.1%). EEG-based measures assess parameters close to the brain pathophysiology. Event-related brain activity, in particular, offers an assessment of each brain processing stage between a stimulus and a response (e.g., sensory, cognitive, motor process); conversely, the output of a behavioral measure comes from innumerable individual cognitive processes.⁴² It is then reasonable to assume that an EEG-based measure that reflects the effects of sleep deprivation and armodafinil can be used as one of the explanatory variables for the subject's performance during PVT and GNAT. In addition, the Tukey mean difference plots did not identify any systematic difference between t-statistics for PVT/GNAT performance and brain activity as well as PVT performance and delta power. The 95% limits of agreement were less than ± 3 ordinate units for all EEG-based measures with event-related brain activity showing relatively narrow limits.

The present study has some limitations that need to be considered. First, we conducted this study in a relatively small sample size. We made efforts to increase the power by designing a placebo-controlled cross-over study. Second, we studied healthy subjects who underwent a total of 36 hours sleep deprivation in the context of a single dose study. Thus, further studies are needed before extrapolation of our findings to patient populations with chronic excessive daytime sleepiness receiving multiple doses of armodafinil. Third, we did not find a significant difference between both armodafinil doses with respect to all pharmacodynamic

measures investigated in this study. Although it could be attributed to limited study power or to the non-patient subjects, no consistent increase in effect with increased dose was observed when armodafinil was tested in OSAHS, narcolepsy and SWSD patient populations during phase 3 trials.²⁴

In summary, the present study demonstrates, for the first time, that armodafinil-induced changes in EEG are in agreement and explain up to 73.1% of the armodafinil-induced changes in alertness. Sleep deprivation is associated with delta frequency slowing and decreased event-related brain activity. Using two quantitative EEG-based measures, we observed a mitigation of the delta frequency slowing and a mitigation of the decreased event-related brain activity in sleep deprived subjects taking armodafinil compared to placebo. The wide availability and low cost make EEG-based measures promptly adaptable to drug development having the potential to bridge pre-clinical and clinical stages. Likewise, their ability to assess underlying neural mechanisms in a non-invasive, sensitive and robust manner suggests that EEG deserves to be evaluated as a marker of wakefulness-promoting drug effect. Ultimately, it could expedite the development of novel compounds with an analogous mechanism of action to armodafinil. Furthermore, the potential pathophysiological overlap between chronic sleep disorders and other cognition aspects or neurological/psychiatric disorders suggest the potential use of EEG to guide dose selection for phase 3 clinical trials pursuing new indications for armodafinil.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Psychomotor vigilance task performance mean ($\pm$ SEM) observed data (left panel), and fatigue baseline-adjusted least square means (right panel). (a) Reciprocal response time and (b) number of errors. Simple effect comparisons of treatment $\times$ time by time are shown for the right panels: specific time points represented by different letters are statistically significant different (adj. Tukey $P < .05$). rBL, resting baseline; fBL, fatigue baseline.

Figure 2.

Go/no-go association task performance mean ($\pm$ SEM) observed data (left panel), and fatigue baseline-adjusted least square means (right panel). (a) Reciprocal response time, (b) number of errors of omission and (c) number of errors of commission. Simple effect comparisons of treatment $\times$ time by time are shown for the right panels: specific time points represented by different letters are statistically significant different (adj. Tukey $P < .05$). rBL, resting baseline; fBL, fatigue baseline.

Figure 3.

Event-related brain activity. (a) Grand average during the execution of the psychomotor vigilance task (upper panel, time window: -200 to 500 ms), and topographic map at approximately 6 hours after the treatment administration (lower panel). (b) Grand average during the execution of the go/no-go association task no-go condition (upper panel, time window: -200 to 700 ms), and topographic map at approximately 6 hours after the treatment administration (lower panel). Zero millisecond corresponds to the appearance of the visual stimulus and positive potentials are plotted downward.

Figure 4.

Event-related brain activity mean ($\pm\text{SEM}$) observed data (left panel), and fatigue baseline-adjusted least square means (right panel). (a) Average P3 amplitude during the execution of the psychomotor vigilance task (PVT), (b) average P3 amplitude during the execution of the go/no-go association task (GNAT) go condition, and (c) average P3 amplitude during the execution of the GNAT no-go condition. Simple effect comparisons of treatment $\times$ time by time are shown for the right panels: specific time points represented by different letters are

statistically significant different (adj. Tukey $P < .05$). rBL, resting baseline; fBL, fatigue baseline.

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Figure 5.

Electroencephalogram delta band spectral power mean ($\pm$ SEM) observed data (left panel), and fatigue baseline-adjusted least square means (right panel). Electrodes (a) O1, (b) Oz, and (c) O2 of the occipital region. Simple effect comparisons of treatment $\times$ time by time are shown for the right panels: specific time points represented by different letters are statistically significant different (adj. Tukey $P < .05$). rBL, resting baseline; fBL, fatigue baseline.

Figure 6.

Univariate linear regression and agreement analyses between EEG-based measures and alertness (psychomotor vigilance task, PVT, performance). (a) Regression analysis between event-related brain activity during the execution of the PVT and PVT reciprocal response time (observed data were used in the left panel, and fatigue baseline-adjusted least square means were used in the right panel). (b) Regression analysis between EEG delta power and PVT mean reciprocal response time (observed data were used in the left panel, and fatigue baseline-adjusted least square means were used in the right panel). (c) Tukey mean-

difference plots for the t-statistics of PVT reciprocal response time and event-related brain activity during the execution of the PVT (observed data after administration of placebo, 150 and 250 mg armodafinil). (d) Tukey mean-difference plots for the t-statistics of PVT reciprocal response time and EEG delta power (observed data after administration of placebo, 150 and 250 mg armodafinil).