DOI: 10.1590/0004-282X20150140

ARTICLE

Alpha power oscillation in the frontal cortex under Bromazepam and Modafinil effects

Oscilações da potência alfa no córtex frontal sob influência do Bromazepam e Modafinil

Danielle Aprigio[2], Washington Adolfo[2], Juliana Bittencourt[2,3,4], Mariana Gongora[1], Silmar Teixeira[7], Luis Fernando Basile[8,9], Henning Budde[10,11], Mauricio Cagy[6], Pedro Ribeiro[1,4,5], Bruna Velasques[2,4,5]

ABSTRACT

Objective: Our aim was to investigate and compare the neuromodulatory effects of bromazepam (6 mg) and modafinil (200 mg) during a sensorimotor task analyzing the changes produced in the absolute alpha power. **Method:** The sample was composed of 15 healthy individuals exposed to three experimental conditions: placebo, modafinil and bromazepam. EEG data were recorded before, during and after the execution of the task. A three-way ANOVA was applied, in order to compare the absolute alpha power among the factors: Group (control, bromazepam and modafinil) Condition (Pre and Post-drug ingestion) and Moment (pre and post-stimulus). **Results:** Interaction was found between the group and condition factors for Fp1, F4 and F3. We observed a main effect of moment and condition for the Fp2, F8 and Fz electrodes. **Conclusion:** We concluded that drugs may interfere in sensorimotor processes, such as in the performance of tasks carried out in an unpredictable scenario.

Keywords: electroencephalography, central nervous system agents, brain mapping.

RESUMO

Objetivo: Investigar e comparar os efeitos neuromoduladores do bromazepam (6mg) e modafinil (200mg), durante a prática de uma tarefa sensoriomotora, analisando as modificações produzidas na potência absoluta de alfa. **Método:** A amostra foi composta por 15 indivíduos saudáveis, expostos a três condições experimentais: Placebo, modafinil e bromazepam. Dados eletroencefalográficos foram registrados antes, durante e após a execução da tarefa motora. Um ANOVA *three-way* foi aplicado para comparar a potência absoluta de alfa nos fatores Grupo (controle, bromazepam e modafinil), Condição (Pré e Pós ingestão da droga) e Momento (Pré e Pós estimulo). **Resultados:** Verificou-se interação entre os fatores grupo e condição para os eletrodos Fp1, F4 e F3. Observamos um efeito principal para momento e condição nos eletrodos Fp2, F8 e Fz. **Conclusão:** Concluímos que as drogas, podem interferir em processos sensoriomotores, como no desempenho de tarefas executadas em um cenário imprevisível.

Palavras-chave: eletroencefalografia, fármacos do sistema nervoso central, mapeamento cerebral.

Quantitative Electroencephalography (qEEG) is a tool that has been widely used to investigate the information and sensoriomotor integration processing[1,2]. Among other fields, qEEG studies investigate changes in cortical activity during motor processes related to task practice and they evaluate the electrophysiological changes resulting from administration of psychoactive substances[3,4,5]. Among the neuromodulation drugs, bromazepam and modafinil stand out.

Bromazepam is a benzodiazepine, which has anxiolytic, analgesic and hypnotic effects[6]. It acts as a neuromodulator

[1]Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria, Mapeamento Cerebral e Integração Sensorial Motor, Rio de Janeiro RJ, Brazil;
[2]Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria, Neurofisiologia e Neuropsicologia da Atenção, Rio de Janeiro RJ, Brazil;
[3]Universidade Veiga de Almeida, Rio de Janeiro RJ, Brazil;
[4]Instituto de Neurociência Aplicada, Rio de Janeiro RJ, Brazil;
[5]Universidade Federal do Rio de Janeiro, Faculdade de Educação Física, Departamento de Biociência, Rio de Janeiro RJ, Brazil;
[6]Universidade Federal do Rio de Janeiro, Programa de Engenharia Biomédica, Rio de Janeiro RJ, Brazil;
[7]Universidade Federal do Piauí, Mapeamento Cerebral e Laboratório de Plasticidade, Parnaíba PI, Brazil;
[8]Universidade de São Paulo, Faculdade de Medicina, Divisão de Neurocirurgia, São Paulo SP, Brazil;
[9]Universidade Metodista de São Paulo, Departamento de Psicologia e Fonoaudiologia, Laboratório de Psicofisiologia, São Bernardo do Campo SP, Brazil;
[10]Faculty of Human Sciences, Medical School Hamburg, Hamburg, Germany;
[11]Sport Science, Reykjavik University, Reykjavik, Iceland.
Correspondence: Bruna Velasques; Av. Venceslau Brás, 71/Fundos; 22290-140 Rio de Janeiro RJ, Brasil; E-mail: bruna_velasques@yahoo.com.br
Conflict of interest: There is no conflict of interest to declare.
Received 05 May 2015; Received in final form 17 July 2015; Accepted 10 August 2015.

and some studies have shown that it triggers changes in neuropsychological functions such as memory, attention, psychomotor activity, reaction time and alertness[7]. Modafinil has already been used for the treatment of narcolepsy and other sleep disorders[8,9,10]. In recent years, psychostimulants have been used to promote cognitive enhancement, since they help the performace in areas such as attention and memory[11]. Previous studies have shown that this drug can significantly improve the performance in tests for executive functions, such as working memory, cognitive flexibility and planning, in healthy volunteers who were not sleep deprived[8].

Although some results related to the influence of these drugs on learning and performing motor tasks have been found, there is a gap in the literature when we intend to seek information regarding the analysis of absolute alpha power (8-13Hz) after the ingestion of placebo, modafinil and bromazepam. Studies show that alpha reflects an "idle" state of the brain, best seen in the waking state and physical and mental relaxation conditions. It reflects cognitive functions, memory, creativity and academic performance[1]. Thus, the present study aims to investigate and compare the neuromodulatory effects of bromazepam and modafinil, during the practice of a sensorimotor task based on the oddball paradigm. Therefore, we try to execute a task that requires decision making and ability to inhibit irrelevant stimuli in individuals under the influence of drugs that seem to activate and depress the central nervous system. We decided analyze the frontal cortex due to related to executive functions and to the subject's capacity of engaging in behavior-oriented goals[12]. It is believed that absolute alpha power will show changes in the frontal areas during the execution of a sensorimotor integration task after ingestion of drugs such as modafinil and bromazepam. With regards to the absolute alpha power, it is expected that it will increase after ingestion of modafinil and that neuronal recruitment will decrease, since this drug is considered to be a cognitive potentiating. The opposite result is expected after the use of bromazepam.

METHOD

Sample

The sample was composed of 15 healthy individuals, twelve women and three men, mean age: 29.78 SD: ± 6.89. All individuals were right-handed, in agreement with the Edinburgh inventory and with higher education[13]. This study was conducted with healthy participants in order to homogenize the sample and avoid possible biases such as changes in the cortical dynamics, due to various diseases or continued use of drugs. Thus, all subjects showed no physical or mental health impairment, including any kind of cognitive impairment, and did not use any psychotropic or psychoactive substance. In order to accomplish this, an assessment was carried out through a detailed questionnaire to identify and exclude from the experiment any subject that could contaminate future results. The questionnaire also aimed to identify possible biological determinants that could influence EEG activity, such as: food, sleep, physical activity, blood pressure and heart rate. All subjects signed a free and informed consent form, where the experimental conditions were described in detail. In addition, the study was approved by the Ethics Committee of the Institute of Psychiatry at Universidade Federal do Rio de Janeiro (CAAE: 0010.0249.000-06).

Experimental procedure

The subjects performed the task in a sound and light-attenuated room, to minimize sensory interference. The experimental was randomized and double-blind designed on three different days with an interval of at least one week, in each day the subject ingested one substance: i.e., 1 gelatin capsule with 500 mg of starch (placebo), 1 gelatin capsule with 6 mg of bromazepam, and 1 gelatin capsule with 200 mg modafinil. It is important to clarify that the researcher acquired and paid for the drug in a specialized drugstore and the capsules which were not used in the experiment were incinerated. Thus, on each experimental day, participants were submitted to an electroencephalography acquisition at rest, executed the Oddball Paradigm task and after that, another EEG at rest was recorded. Then, participants ingested a capsule of placebo, 6 mg bromazepam or 200 mg modafinil and, two hours later from ingestion, the same previous steps were repeated.

Oddball paradigm consists of two stimuli presented randomly, with one occurring relatively infrequently. Subjects were asked to discriminate target (infrequent) from non-target or standard stimuli (frequent). In the present experiment, target stimuli were represented by a square and non-target stimuli by a circle. Subjects were instructed to respond as quickly as possible to the target stimulus by pressing a button in a joystick (Model Quick Shot- Crystal CS4281). Each stimulus lasted 2.5 seconds, being this the same interval time between stimuli, with the screen turned off. The visual stimulus was presented on the monitor by the event-related potential (ERP) acquisition software, developed in Delphi 5.0 (Inprise Co.). Each subject was submitted to 10 target stimuli. The square was presented 10 times in a single block. The task was composed by five blocks. In each block there were 95% probability 1 to 4 non-target stimuli preceding a target stimulus and 5% having between 5 and 7 non-target before 1 target. Approximately 2.375 non-target stimuli were expected before 1 target. Each stimulus duration was 2.5 seconds, the same time intervals with the screen turn off between stimuli.

Data acquisition

The capture of the EEG signal was performed using the 20-channel Braintech-3000 EEG system (EMSA-Medical Instruments, Brazil) in conjunction with the ERP Acquisition program described in the previous section. Its configuration

uses 60 Hz Notch digital filtering between 0.3 Hz (high-pass) and 25 Hz (low-pass) (order Butterworth 2).

Twenty-one electrodes were mounted on a Lycra cap (EletroCap Inc., Fairfax, VA) over the frontal, temporal, parietal and occipital areas of the scalp, according to the 10/20 system protocol[14]. and two electrodes were positioned on earlobes with the reference function (bi-auricular) for a 20 monopolar derivation assembly (Fpz electrode used as ground). Several cap sizes were placed and adjusted individually for each participant, following the circumference and proportion of individual anatomy. The signal for each EEG derivation results from the electric potential difference between each electrode and the preset reference (earlobes). First, the impedance levels of each electrode were observed, and were maintained below 10 kΩ. The ocular electric activity was estimated by placing two 9 mm-diameter electrodes assembled bipolarly. The electrodes were placed respectively above and below the right eye socket to record vertical eye movements and on the external corner to register the same horizontal eye movements. Visual artifacts were inspected in advance with a data visualize tion program using Matlab 5.3® (The Mathworks, Inc.).

Data analysis and processing

The EEG signals collected during the experiment were processed through routines developed by the Brain Mapping Laboratory of Sensory-Motor Integration at the Psychiatric Institute of the Federal University of Rio de Janeiro in a Matlab 5.3® environment. Power in alpha band was estimated using trapezoidal integration of the Power Spectral Density (PSD) between 8 and 12Hz. PSD estimation was achieved using the Bartlett Periodogram applied throughout 50 epochs per subject synchronized by the target stimuli with 1-s length each one. The EEG was digitalized at 200 samples per second. 5 x 10 epochs per subject. Each epoch has a 1 second of duration and is synchronized with the onset of the stimulus.

Statistical analysis

A three-way ANOVA and a post hoc Scheffé test were applied, in order to compare the alpha absolute power among the factors: Group (control, bromazepam and modafinil), Condition (Pre and Post-drug ingestion) and Moment (pre and post-stimulus). A paired T-test was used in order to investigate any possible interaction, considering different moments for each condition. Moreover, a one-way ANOVA was performed, in order to verify that no statistically significant differences among groups were found in the pre- drug ingestion condition.

RESULTS

Our results demonstrate an interaction between the group and condition factors for the electrodes Fp1 ($p < 0.05$; $F = 3.143$) (Figure 1A), F4 ($p < 0.05$; $F = 3.359$) (Figure 1B), and F3 ($p < 0.05$; $F = 4.041$) (Figure 1C). In order to investigate the interactions, a significant difference was found between the moments in the modafinil and bromazepam groups for the Fp1 electrode. As for F3 and F4, the paired t-test showed a difference between moments only for the modafinil group. Furthermore, a main effect of moment was found for the electrodes Fp2 ($p < 0.05$; $F = 31.742$) (Figure 2A), F8 ($p < 0.05$; $F = 27.932$) (Figure 2B) and Fz ($p < 0.05$; $F = 18.554$) (Figure 2C), and a main effect of condition was also observed for the same electrodes: Fp2 ($p < 0.05$; $F = 5.189$) (Figure 3A), F8 ($p < 0.05$; $F = 4.304$) (Figure 3B) and Fz ($p < 0.05$; $F = 4.156$) (Figure 3C). We did not find statistical difference for the electrode F7. Our results showed an interaction between group and condition for Fp1, F3 and F4. For the Fp1 electrode, a difference was found between the pre and post-drug ingestion moments for the two groups, i.e., bromazepam and modafinil; we noticed a higher alpha power after drug ingestion for both groups. In addition to this, no difference was found between the modafinil and bromazepam groups for the moments before and

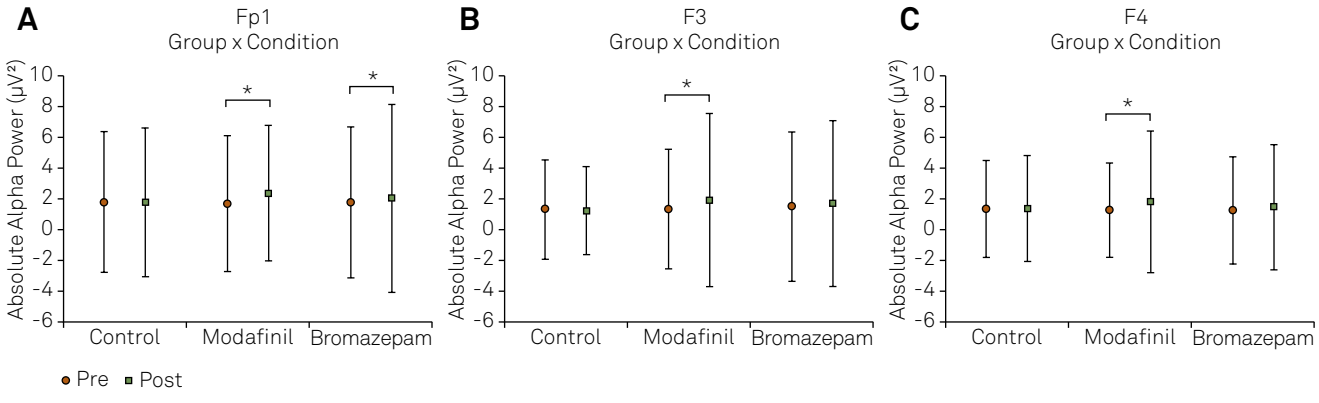

Figure 1. Mean and standard deviation of absolute alpha power over frontal cortex. The figure illustrates the group and condition factors interaction. (A) for Fp1 the statistical analysis revealed that pre and post conditions differs for Modafinil and Bromazepam groups ($p < 0.05$); (B) for F3 the statistical analysis revealed that pre and post conditions differs for Modafinil group ($p < 0.05$); (C) for F4 the statistical analysis revealed that pre and post conditions differs for Modafinil group ($p < 0.05$).

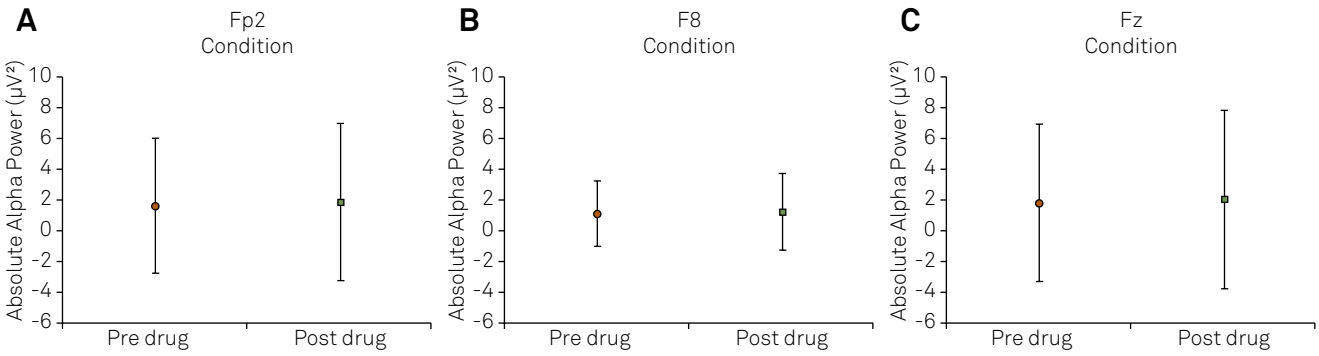

Figure 2. Mean and standard deviation of absolute alpha power over frontal cortex. The figure illustrates the main effect for condition. (A) for Fp2 the statistical analysis revealed higher absolute alpha power after drug ingestion ($p < 0.05$); (B) for F8 the statistical analysis revealed higher absolute alpha power after drug ingestion ($p < 0.05$); (C) for Fz the statistical analysis revealed higher absolute alpha power after drug ingestion ($p < 0.05$).

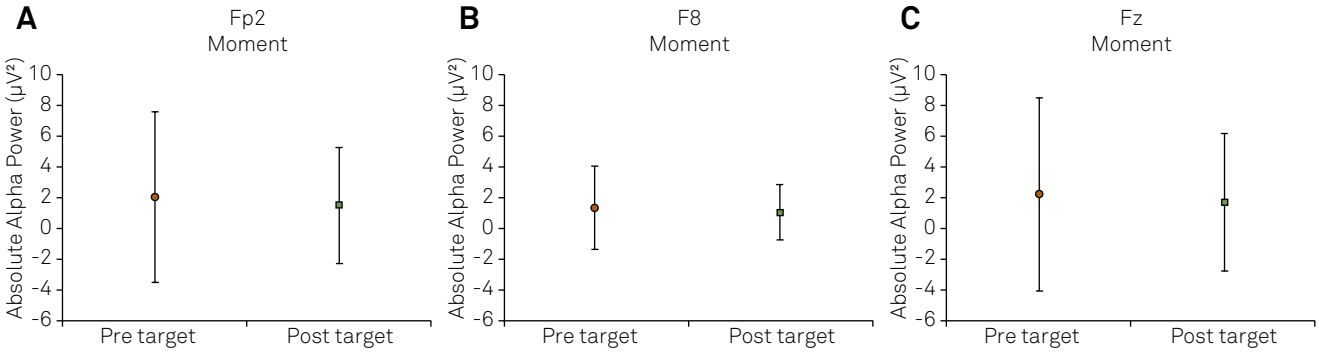

Figure 3. Mean and standard deviation of absolute alpha power over frontal cortex. The figure illustrates the main effect for moment. (A) for Fp2 the statistical analysis revealed higher absolute alpha power before stimulus presentation ($p < 0.05$); (B) for F8 the statistical analysis revealed higher absolute alpha power before stimulus presentation ($p < 0.05$); (C) for Fz the statistical analysis revealed higher absolute alpha power before stimulus presentation ($p < 0.05$).

after ingestion. As for the F3 and F4 electrodes, we found a difference between the pre and post-drug ingestion moments only for the modafinil condition, where an increase in the absolute alpha power was observed after using the drug.

DISCUSSION

This study compared the neuromodulatory effects of bromazepam and modafinil, while performing the oddball paradigm; specifically, we analyzed absolute alpha power in the frontal cortex (i.e., electrodes F3, F4, Fp1, Fp2, F7, F8 and Fz). We hypothesized that subjects under the effect of modafinil presented lower neuronal recruitment, represented by greater alpha activity in the frontal areas involved in the task, and we expected to find an inverse effect after the bromazepam ingestion. However, our results demonstrate that both modafinil and bromazepam produce an attenuation of the cortical activity[15], but that only the left prefrontal cortex (Fp1) was sensitive to bromazepam.

It is important to emphasize that the behavioral data, i.e. the task execution reaction time was analyzed in a previous study. Studies reported a statistically significant difference between groups ($p = 0.005$)[16] The results showed a greater reaction time for the control group compared with modafinil group, and for the bromazepam group when compared with the modafinil group and no difference was found between the control and bromazepam groups.

Alpha has been an important tool for analysis of brain functions and it is widely associated with attention processes, decision making and learning[17,18]; it is noteworthy that alpha (8-13 Hz) is a frequency whose amplitude is inversely proportional to the amount of recruited neurons, i.e. the alpha rhythm will reflect an attenuation of cortical activity[17,19,20]. In addition to this, the investigated area (frontal cortex) is also related to executive functions and to the subject's capacity of engaging in behavior-oriented goals[20].

The results for modafinil corroborate the hypothesis of this study; however, a different and unexpected effect was found for bromazepam for the Fp1 electrode. Therefore, in the left prefrontal cortex, both drugs optimized the subjects' cortical activity, demanding less effort from the brain.

Modafinil has been categorized as a brain stimulant, because of its wakefulness-promoting properties[10], and it acts

on cognitive improvement, including working memory, episodic memory and other processes, which are dependent on the pre-frontal cortex and cognitive control. This potentiating effect of cognitive aspects would lead to the lower recruitment observed at the moment of drug ingestion. In a recent study, Gilleen et al.[21], included modafinil into cognitive training in healthy subjects, in order to determine the gains obtained from this combination of approaches. The subjects were trained with language tasks, working memory and verbal learning, and they were administered modafinil (200 mg) or placebo for ten days after the training. The results demonstrated that the combination of modafinil with cognitive training promoted better learning, suggesting that modafinil may act specifically on enhancing learning mechanisms. The results from such study showed cognitive improvement achieved with the use of modafinil in healthy subjects, therefore confirming our hypothesis regarding this drug. However, no study sought to understand the role this drug plays on EEG activity in healthy subjects.

The increased alpha power observed in Fp1, F3 and F4 demonstrates that modafinil produces a decrease in cortical activity. In a study using positron emission tomography (PET), Mehta et al.[22], investigated the action of methylphenidate during the execution of a spatial working memory task. Methylphenidate is a psychostimulant, which produces cognitive improvement similar to modafinil[23]. The authors found that methylphenidate improves working memory performance, since they observed a reduction in the cerebral blood flow in the dorsolateral prefrontal cortex and posterior parietal cortex. The reduced activation in the dorsolateral prefrontal cortex is related to the action of the drug in response to a cognitive task. Although this study does not use EEG, they also found a reduction in the frontal cortical activity. Thus, this study provides support for our result, since the use of psychostimulants in healthy subjects produces lower neural recruitment. This lower recruitment has been interpreted as "cognitive enhancement", in healthy subjects[22,24]. Such improvement in cognitive performance induced by psychostimulants is triggered by changes in dopaminergic activity. After ingesting the psychostimulant, there seems to be an increased synaptic concentration of dopamine, and this process can increase excitatory mechanisms in the brain. Dopamine projections are seen in the areas of the midbrain, striatum and prefrontal cortex, which are involved in the regulation of working memory and cognitive enhancing flexibility[22]. Therefore, it is believed that, in healthy subjects, the availability of dopamine is near the optimum level. Enhanced dopamine activity may stimulate an already existing capacity, in the case of individuals without cognitive impairment.

With respect to bromazepam, we found that this drug influences alpha power only in the left prefrontal cortex (i.e., Fp1), similarly to what we observed with modafinil. The left prefrontal cortex plays a dominant role in the planning and execution of movement[21,25,26,27]. Generally, hemispheric action varies according to the pattern of brain activation, and thus according to the degree of information processing[28]. In particular, bromazepam is a benzodiazepine used to treat disorders related to the central nervous system (CNS), and it is used more and more with the intention to facilitate cognitive and motor development[3]. Considering this, the increase in absolute alpha power for the Fp1 electrode produced by bromazepam is related to the role this drug plays in task planning and execution. Such effect was also observed by Cunha et al.[5], who found fewer failures and lower reaction time, as well as greater cortical activity in the left frontal lobe, in the group that had ingested 3 mg of bromazepam; this was understood by researchers as an attenuation of the anxiety state, facilitating the focus of attention on the task relevant information. Our findings suggest that a 6 mg-dose x of this drug allows for greater mental "relaxation", directing the cortical activity to the dominant hemisphere for task planning and execution. The lower neural recruitment produced by bromazepam (represented by the increase in alpha power) may be associated with a decrease in anxiety levels and, consequently, to an increase in concentration. This result has been shown in previous studies[29,30]. In a recent study, Dionis et al.[3], investigated the effect of bromazepam (3mg and 6mg) on relative alpha power while executing a typing task. They noted that the doses employed facilitated motor development in the task performance, contributing to greater concentration and mental effort in the task. This fact favored the effectiveness of brain operations performed during coding mechanisms and information storage.

In conclusion, the results confirmed the initial hypothesis that modafinil (200 mg) and bromazepam (6 mg) may interfere in sensorimotor processes, such as in the performance of tasks carried out in an unpredictable scenario, involving decision making and the ability to inhibit irrelevant stimuli. It was believed that, under the effect of modafinil, the subjects would present lower neural recruitment, represented by an increase in alpha power, and this was the actual result found. However, under the condition in which bromazepam was expected to have the opposite effect of modafinil, a similar result was found, despite its depressant action on the CNS. In particular, this also contributes to a reduction of neuronal activity in the analysis of the Fp1 electrode. We concluded that modafinil is a drug that can optimize cognitive function, improving task performance, as evidenced by statistically significant results among the drugs observed in this experiment, as well as by studies that supported this research. Since this study was limited to healthy subjects as experimental subjects, future experiments using the same variables with different subjects and methods are needed, in order to increase knowledge about the alpha behavior and the effects of neuromodulating drugs. The present study has limitations related to the population investigated. Our focus was analyzing the acute effect of bromazepam and modafinil in healthy individuals; we did not investigate the clinical effects of the drugs.

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