Effects Of Modafinil And Bromazepam On Decision-Making: A P300 Analysis

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Abstract

Drug influence on the decision making process has been scarcely studied. Researchers have driven the hypothesis that drugs might cause interference on cortical circuits. The aim of the present study is to evaluate the electrophysiological and behavioral changes occurring in the P300 after ingestion of modafinil (200mg), bromazepam (6mg) and placebo in healthy subjects exposed to a sensorimotor task based on the oddball paradigm. The sample for this study consisted of 10 subjects of both sexes, with ages ranging between 20 and 45, who were submitted to a quantitative electroencephalography. The experimental procedure was carried out in three visits, before and after drug ingestion. The results demonstrated a significant increase in the P300 latency and amplitude for the target condition, when compared to the non-target condition, for all analyzed electrodes. No significant difference was found for group or moment. A statistically significant difference was found for the group variable in the behavioral analysis. Such results suggest that the P300 is a measure, which is not sensitive to drug ingestion. On the other hand, the measure presented certain level of sensitivity when the subjects faced two different conditions in the decision making process orientation.

Keywords
Modafinil; Bromazepam; oddball; P300; quantitative electroencephalography; Reaction Time.

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Introduction

Decision making involves the entire process starting from the capacity of directing attention to a stimulus, going through its identification, all the way to the selection and planning of a motor response [1-4]. In particular, the event related potential (ERP) or evoked potential allows for a detailed organization of all the stages of information processing [5]. An extremely important potential for understanding cognitive processes during a motor task is the P300 which contains two distinguishable subcomponents represented by P3a and P3b [6]. The P3b wave peak is widely present in the central and parietal areas of the cortex, occurring approximately 300-500ms after the start of the stimulus [7, 8]. Specifically, such wave represents the endogenous attention in tasks which demand keeping the attentive focus on relevant targets, therefore allowing the working memory consolidation, and later making available a conscious access to information [6, 9].

For this reason, the P300 is of great importance in investigating the possible electro-cortical changes caused by the ingestion of substances, which have a stimulating or depressive effect on the central nervous system (CNS), among which are, respectively, modafinil and bromazepam. Modafinil is considered to be a cognitive amplifier, capable of modulating functional organization and brain communication, therefore resulting in the improvement of cognitive performance [10-14]. Some studies report cases of healthy subjects using this drug, with the main objective of producing cognitive improvement, especially with regards to memory and attention [14]. On the other hand, bromazepam, an anxiolytic drug with a depressive effect on the CNS, is therapeutically utilized to produce sedation, induce sleep, relieve anxiety and muscle spasms, in addition to preventing convulsions [15]. Studies prove its efficacy in treating anxiety disorder, although they highlight the drug side effects in tasks involving sensorimotor integration [16-21].

The present study is therefore relevant, considering the need of recognizing the electrophysiological changes caused by the modafinil and bromazepam effect during decision making. The database search showed that very few studies have investigated the influence of such drugs on the P300 wave through the visual evoked potential using the oddball paradigm. Considering this, our hypothesis is that modafinil and bromazepam ingestion can alter the P300 latency and amplitude, as well as produce changes in the reaction time for task execution. Therefore, our objective was to analyze the changes in P300 and reaction time of the components related to the events caused by the use of modafinil (200mg) and bromazepam (6mg) during decision making, through a sensorimotor task based on the oddball paradigm, in order to verify the changes caused by the different conditions imposed on the subjects.

Materials and Methods

Subjects

The sample for this study consisted of 10 subjects of both sexes, 7 women and 3 men, whose ages ranged between 20 and 45. The present study was conducted with healthy subjects, in order to homogenize the sample and avoid possible alterations, such as cortical and/or dynamics changes, due to various pathologies or to the constant use of medications. Therefore, the subjects had no physical or mental disease, including any type of cognitive deficit, and they were neither psychotropic nor psychoactive substance users. A previous evaluation was conducted through a detailed questionnaire, in order to guarantee such result and identify or exclude any subject, who could possibly contaminate future results. The objective of the questionnaire was also to identify possible ERP biological determinants, such as: diet, hours of sleep, physical activity, blood pressure and heart rate. The subjects
signed a free and clear consent form describing in detail all experimental procedures. In addition to this, the research was approved by the Ethics Committee of the Psychiatry Institute of the Federal University of Rio de Janeiro.

Tasks and Procedures
The data collection was supervised by a psychiatrist and it was conducted in a soundproof room. During the task, the lights were turned off, in order to minimize any possible visual interference, apart from the video monitor. The experiment followed a randomized, double-blind design on three different days: one day having ingested placebo (starch), one having ingested bromazepam (6 mg) and one with modafinil (200 mg). It is important to clarify that the researcher acquired and paid for the drug in a specialized drugstore. The medication was prescribed by the psychiatrist, who was responsible for the researcher. Furthermore, the capsules which were not used in the experiment were incinerated. Initially, blood pressure and heart rate were measured; then, an electroencephalography acquisition was recorded at rest, during six minutes divided as follows: three minutes with the eyes closed and three more minutes with the eyes open. After this, the Evoked Potential (P300) was executed. Each subject was submitted to 10 target stimulations, that is, a square was showed 10 times in one block. For each block, there was 95% probability of 1 in 4 non-target stimuli preceding a target stimulus. Each stimulus lasted 2.5 seconds, being this the same interval time between stimuli, with the screen turned off.

After applying the Evoked Potential, a D2 Test of Attention was also applied. This test evaluates various aspects of selective attention and concentration. Apart from measuring the subject’s processing speed, the D2 Test also allows to evaluate the quality and relation between speed and performance precision. Once this stage (baseline) was over, the individuals received a capsule, containing placebo (starch), bromazepam (6 mg) or modafinil (200 mg). Eighty minutes after the capsule ingestion, the same neuropsychological test was applied; then, one more electroencephalography acquisition was recorded for three minutes, to configure rest, proceeding then onto the use of the P300.

EEG data acquisition
The electroencephalography signal acquisition was recorded using the 20-channel BrainTech3000 (EMSA) EEG system, together with the ERP Acquisition program already described. This program was employed to filter the data: Notch (60 Hz), high-pass of 0.3 Hz and low-pass of 25 Hz (order 2 Butterworth).

Twenty-one electrodes were arranged on a lycra cap (EletroCap Inc., Fairfax, VA) along the scalp on the frontal, temporal, parietal and occipital areas, according to the 10/20 system protocol [22], and two more electrodes were positioned on the earlobes, set as a reference point, yielding 20 mono-pole derivations to them (using Fpz as ground electrode). The caps were individually adjusted and put on each subject, according to each individual’s circumference and anatomy proportions. The signal correspondent to each EEG derivation resulted from the electric potential difference between each electrode and the pre-established reference (earlobes).

First, the impedance levels of each electrode were calculated, and they were kept below 10 kΩ. The ocular electric activity was estimated by attaching two 9-mm-diameter electrodes in a bipolar montage. The electrodes were positioned, respectively, above and below the right eye orbit, in order to register vertical ocular movements, and on the external corner of the same eye, in order to register horizontal ocular movements. Visual artifacts were a priori inspected through a data visualization program using the Matlab 5.3® (The Mathworks, Inc.).
Data processing and analysis
The electroencephalographic signals collected during the experiment were processed using methods developed by the Brain Mapping and Sensorimotor Integration Laboratory of the Psychiatry Institute of the Federal University of Rio de Janeiro in a Matlab 5.3® environment.

Statistical Analysis
A three-way ANOVA and a post hoc Scheffé test were applied to compare the P300 latency and amplitude for the factors group (control, bromazepam and modafinil), Condition (target and non-target stimulus) and Moment (pre and post capsule administration). In addition to this, a two-way ANOVA and a post hoc Scheffé test were also applied to analyze the behavioral data represented by the reaction time, comparing the group and moment factors. Furthermore, a one-way ANOVA was applied to prove that no statistically significant difference was found among the groups for the pre-moment.

Results
In order to verify possible electrophysiological changes in the cortex, caused by the use of bromazepam and modafinil during an oddball paradigm, three measures were analyzed: latency, amplitude and reaction time. A Three-way ANOVA test was applied to conduct a statistical analysis of latency and amplitude, considering the following independent variables: group (bromazepam X control X modafinil), moment (pre-task X post-task) and condition (target X non-target). A statistically significant difference was found in the amplitude for the condition variable (target X non-target) for the variations: C3 (p < 0.001; F = 13,088), Cz (p < 0.000; F = 20,855), C4 (p < 0.000; F = 22,125), Fz (p = 0.001; F = 10,562), F3 (p = 0.002; F = 9,305), F4 (p < 0.001; F = 26,761), P3 (p < 0.001; F = 25,029), P4 (p < 0.001; F = 24,030) e Pz (p < 0.001; F = 68,575). With regards to the latency results, statistically significant differences were found also for the condition variable for the variations: C3 (p = 0,001; F = 11,272), C4 (p < 0,001; F = 89,605), Cz (p = 0,001; F = 10,242), F4 (p < 0,001; F = 14,962), Fz (p = 0,049; F = 3,916), Pz (p < 0,001; F = 68,575), P3 (p < 0,001; F = 42,718), P4 (p < 0,001; F = 49,998).

When analyzing the Cz, C3, C4, Fz, F3, F4, Pz, P3 and P4 derivations, a main effect for condition was found. The results pointed out greater latency for the target condition when compared to the non-target one. A main effect for condition was also found for the Cz, C3, C4, Fz, F3, F4, Pz, P3 and P4 electrodes, when amplitude was observed. The results also suggest greater amplitude for the target condition when compared to the non-target one (Fig. 1, 2 and 3).

On the other hand, a One-way ANOVA test was applied for the statistical analysis of the reaction time behavioral variable, considering the group and moment variables. A statistically significant difference was found for the group variable (p = 0.005; F = 5,309). The results highlighted greater reaction time for the control group when compared to the modafinil group, and for the bromazepam group when compared to the modafinil one, with no difference found between the control and bromazepam groups (Fig. 4).
Figure 1: Control group, indicating greater P300 latency and amplitude for the target compared to the non-target.
Figure 2: Bromazepam group, indicating greater P300 latency and amplitude for the target compared to the non-target.
Figure 3: Modafinil group, indicating greater P300 latency and amplitude for the target compared to the non-target.
Discussion
The aim of the present study was to investigate the changes occurring in the ERP, analyzing the P300 changes and reaction time starting from two experimental conditions (i.e., modafinil and bromazepam ingestion) and a control condition (i.e., placebo) during an oddball paradigm [23, 24]. Therefore, our hypothesis was that modafinil and bromazepam ingestion could alter the P300 latency and amplitude, and produce changes in the reaction time for task execution. We expected to find greater amplitude and lower latency and reaction time in the patients under the effect of modafinil, when compared to the control group. The opposite was expected for the individuals under the effect of bromazepam. Therefore, in order to better analyze the results, our discussion will be separated into topics. First, we will discuss the results related to reaction time, and after the results of each P300 measure.

Reaction Time
Our results demonstrated a main effect for group and interaction between group and moment; specifically, a difference was found between the control and modafinil groups and between bromazepam and modafinil, with no difference found between the control and bromazepam groups. It was possi-
ble to verify that the use of modafinil lowered the reaction time in the solicited task, when compared to the control and bromazepam groups. The result found is in agreement with the literature [12], since modafinil was able to improve the response performance to the stimulus, making the individuals faster; this is probably due to the capacity of this drug to improve cognitive performance, therefore facilitating activities related to working and episodic memory, attention, and processes which demand cognitive control, when compared to the control and bromazepam groups [12, 16, 20, 25].

When comparing the bromazepam group with the control group, no differences were found in the task performance. Then, when administered in relatively low doses, bromazepam seems to not cause any damage to the performance of individuals who are experiencing an attention and learning situation during a motor task. Such findings can be associated to the effect of the medication, which facilitated the activation and improvement of the motor control mechanisms, by “reducing” the anxiety levels occasioned by the task situation [17]. Further justifying the result of our study, another research’s did not find any significant difference in the reaction time between the bromazepam and control groups, through a visual discrimination task, also using the oddball paradigm and visuomotor task [15, 26].

Latency
The electrophysiological variables were observed through the analysis of the F3, F4, FZ, C3, C4, CZ, P3, P4, PZ electrodes. The results will be discussed dividing the analysis into anterior (frontal and central) and posterior (parietal) areas. The results obtained showed a main effect for condition (i.e., target x non-target) when P300 latency was analyzed in both areas. In particular, greater latency was found for the target condition, when compared to the non-target one. No main effect for group was found (i.e., control x bromazepam x modafinil), demonstrating that the P300 latency does not identify the utilized drugs. Greater latency for the target condition was observed in this study. Such finding seems to be related to the fact of this stimulus appearing less frequently than the non-target stimulus, therefore causing a delay in the sensorimotor integration process, which is common in the presence of a rare stimulus [27]. In addition to this, the lower P300 latency for the non-target condition may be associated to the fact of the subjects having to inhibit their motor response (i.e., press the joystick). Such finding may be associated to the other processing stages. That is, during the stimulus-identification stage, an inhibition occurs when identifying the stimulus as a non-target one, consequently provoking a postponing or finalization of the other stages. This process would use a lower P300 latency for the non-target condition.

Considering this, the non-target condition seems to be similar to a distracting stimulus needing to be inhibited. The distracting stimulus inhibition is recognized by the decision making process, with no need for a motor response. A study described that the P300 fronto central component plays a critical role in the response inhibition of the non-target stimulus during a Go/NoGo visual task. Therefore, the pre-motor area (involved in the response inhibition), sends projections to two sub-cortical regions, which are acting in behavior inhibitory control [28]. Some researches affirm that this is a fundamental process for adaptation and self-organization [29]. Despite the fact of the author highlighting the role of the anterior component in the inhibition, therefore agreeing with the present study, it is also important to point out that we observed a similar result in the posterior regions.

A previous study showed an increase in the P300 latency in anterior and posterior regions in younger individuals, when compared to older ones; furthermore, greater latency was found in posterior areas, when compared to anterior cortex areas. The P300 latency increase is considered to be a delay in the information processing, translating the neu-
ron transmission speed and the memory reload and alertness in the subjects [30]. Results from another research are also in agreement with the findings showed in the present study. Such research analyzed the contribution of anterior cortical areas during a decision making task, similar to the one used in our experiment. The results demonstrate a P300 latency increase in the frontal area when detecting the target stimulus, as compared to the inhibition of distracting stimuli. The authors suggest that the frontal areas are directly involved in the target detection [31]. Other researchers report a P300 latency increase when the target stimulus is presented to the cortex anterior region, which is associated with the learning process [32, 33].

Amplitude
The P300 amplitude analysis identified a main effect for condition both in the anterior (frontal and central) and posterior (parietal) areas. Greater amplitude was found for the target condition when compared to the non-target one. During task execution, the subjects were instructed to present a motor response only when the target stimulus appeared on the computer screen. Such process required decision making [27, 34]. Studies show that this finding is commonly observed during an active stimulus, since the processing of a passive and more frequent stimulus produces lower P300 amplitude, due to the fact of the task involving simplified attention strategies for amplitude reduction [7].

Our research has not found a main effect for group and moment. Therefore, the amplitude seems to not be affected by the drugs. Such finding is in agreement with the result from another study, which analyzed electrophysiological and behavioral measures under the influence of bromazepam, during a visual discrimination task, using the oddball paradigm. The results did not show any interaction among the group (placebo 1, placebo 2 and bromazepam), moment (pre and post drug ingestion) and electrode (Fz, Cz, Pz and Oz) factors. Such results suggest that the utilized dose (3mg) of bromazepam did not have any effect on the cognitive processes evaluated by the ERP measures [21]. In our study, the subject ingested 6 mg of bromazepam. Therefore, we can observe that the absence of P300 changes is independent from the administered dose.

One more study utilized the same paradigm, however with the intention to compare the neuro-modulating effects of caffeine and bromazepam, starting from a normative database of the visual evoked potential (P300). With regards to the amplitude values, the results did not show any interaction between condition (caffeine, bromazepam and normative database) and electrode location (Fz, Cz and Pz). However, lower amplitude was observed for the caffeine condition, when compared to the normative database and bromazepam. Therefore, the authors stated that caffeine seemed to increase the P300 only when the individuals were tired [35]. Such results suggest that both the caffeine and the modafinil effects, with the utilized dose (200mg), do not improve the cognitive processes, evaluated by the P300 measures. Therefore, it is possible to observe that a single dose of modafinil would not be enough to cause changes in the P300 measures.

Despite some of the results in the literature being similar to the ones found in our research, it is important to highlight that there is great result variability in the P300 investigation. Such modifications occur, due to the fact of this wave being easily influenced by specific parameters such as task, paradigm and stimulus [30].

Conclusion
The present study has indicated that the bromazepam and modafinil ingestion did not cause any changes in the P300 during an oddball paradigm. Therefore, this does not seem to be a sensitive measure to investigate the drug influence on the CNS during the decision making process. On the other hand, such measure showed to be sensitive when
the subjects were facing two different types of information: the target stimulus and the non-target stimulus. Furthermore, the results showed that the reaction time was significantly influenced by modafinil to improve the subjects’ performance.

It is important to highlight that few studies have been conducted about this topic, and that so far conflicting results were found. We suggest that other potentials involved in the decision making process, as well as the P100, should be investigated under drug influence, since the first phases of information processing are probably more sensitive to pharmacological effects [36-38].

Acknowledgments
We wish to thank Fabiana Eramo for reviewing the English translation and Olga Lima from the EEG department of IPUB for kindly acquiring and preparing the EEG. Thanks for your special support. OA-C is supported by CONACYT-BMBF 2013 (Grant 208132).

Competing interests
None of the authors have actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, our work.

Authors’ contributions
PR, BV and OAC designed and conducted the experiment and 1drafted most of the manuscript. ALN, JB, WBA, MG, ST, FAMSP, ASC, JSP, AHS, LFB and MC performed the experiment and the drafting of the manuscript. All authors read and approved the final manuscript.

References


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