

The effects of bromazepam over the central and frontal areas during a motor task: an EEG study

Os efeitos do bromazepam nas áreas corticais central e frontal durante execução de uma tarefa motora: um estudo de EEG

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ABSTRACT

The present study investigates the influence of bromazepam while executing a motor task. Specifically, we intend to analyze the changes in alpha absolute power under two experimental conditions, bromazepam and placebo. We also included analyses of theta and beta frequencies. We collected electroencephalographic data before, during, and after motor task execution. We used a Two Way ANOVA to investigate the condition (PL × Br6 mg) and moment (pre and post) variables for the following electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, C3, CZ and C4. We found a main effect for condition on the electrodes FP1, F7, F3, Fz, F4, C3 and CZ, for alpha and beta bands. For beta band we also found a main effect for condition on the electrodes Fp2, F8 and C4; for theta band we identified a main effect for condition on C3, Cz and C4 electrodes. This finding suggests that the motor task did not have any influence on the electrocortical activity in alpha, and that the existing modifications were a consequence due merely to the drug use. Despite its anxiolytic and sedative action, bromazepam did not show any significant changes when the individuals executed a finger extension motor task.

Keywords: bromazepam, electroencephalography, sensorimotor integration, absolute alpha power, motor task.

RESUMO

O presente estudo investiga a influência do bromazepam durante a execução de uma tarefa motora. Especificamente, pretende-se analisar as mudanças na potência absoluta de alfa sob duas condições experimentais, bromazepam e placebo. Nós também incluímos as análises das frequências teta e beta. Foram coletados dados eletroencefalográficos antes, durante e depois da execução da tarefa motora. Usamos uma Anova de 2 fatores para investigar a condição (PL × Br6 mg) e variáveis no momento (pré e pós) para os seguintes eletrodos: Fp1, Fp2, F7, F3, Fz, F4, F8, C3, C4 e CZ. Encontramos um efeito principal para a condição e eletrodos FP1, F7, F3, Fz, F4, C3 e CZ para alfa e beta. Para beta também foi encontrado um efeito principal para condição nos eletrodos Fp2, F8 e C4; para theta nós identificamos um efeito principal para condition em C3, Cz e C4. Este achado sugere que a tarefa motora não tem qualquer influência sobre a atividade electrocortical alfa e que as modificações existentes foram uma consequência devido o uso de drogas. Apesar de sua ação ansiolítica e sedativa, o bromazepam não apresentou mudança significativa quando os indivíduos executaram uma tarefa motora.

Palavras-chave: bromazepam, eletroencefalografia, integração sensório-motora, potência absoluta alfa.

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Motor learning involves a group of processes which provoke relatively permanent changes in motor behavior¹. From this perspective, learning depends on the integrity of the sensorial processing, which is, on the ability of the individual to receive the sensorial information from the environment and from his/her body movements, and to process them and integrate them in the central nervous system (CNS), and utilize them to generate adequate adaptive responses². Previous studies showed that various cortex areas are part of the motor learning process^{3,4,5}. Among these areas, the frontal cortex and the somatomotor cortex should be highlighted, since these are the regions that directly participate in motor control. Specifically, the frontal cortex participates in the planning of sequential actions, in the standardization of motor behaviors, and in part of the automated emotional and memory behavior^{5,6,7}. The somatomotor cortex receives somatic information and controls the limb movements⁴. Other brain areas also participate in the movement, sending messages, dosing strength and agility, and constantly adjusting the movement through visual, auditory and tactile feedbacks coming from the environment⁸.

Studies about motor learning have used electroencephalographic measures (EEG) in order to analyze motor processes related to practice, in addition to evaluating electrocortical alterations derived from drug administration with some effect on the CNS^{4,9,10}. Among the investigated drugs, bromazepam can be highlighted. Bromazepam is an anxiolytic drug from the family of benzodiazepines, capable of producing important alterations in the CNS; some of the main symptoms caused by the drug are relevant for motor learning and control, such as sleep induction, muscle relaxation and alertness reduction¹¹. The benzodiazepines are psychoactive substances used in the treatment of insomnia, anxiety, agitation, muscle spasms and other dysfunctions related to the CNS¹¹. Despite the existence of some results related to the influence of bromazepam in learning and motor task execution^{4,9,10,12}, there are still some gaps to be filled within the topic. Several studies report the influence of bromazepam in the EEG during a motor task, most of these studies investigated beta and theta frequency^{4,9,10,11,13,14}. The papers that we found investigating the influence of bromazepam in absolute alpha power during a motor task show incongruence in the results. Thus, in order to better understand the participation of other frequency band in motor task execution under influence of bromazepam, we choose to analyse absolute alpha power. With this in mind, the main purpose of the present study is to analyze alpha frequency, however, we included the analysis of theta and beta frequencies. Therefore, the present study has the objective to investigate the influence of bromazepam (6 mg) during the practice of a simple motor task, that is, the extension movement of the index finger. Specifically, we analyze alpha absolute power under two experimental conditions: bromazepam and placebo. The hypothesis is that the subjects under the effect of the drug will tend to be slower

and more relaxed, and will experience lower neural recruitment, represented by a greater alpha activity in the frontal and central areas.

METHOD

Sample

Sixteen healthy individuals, (seven men and nine women with average age of 32.5, SD: 9.5) participated of the study. We choose as exclusion criteria: mental or physical illness, and history of psychoactive or psychotropic substances use. For this reason all participants went through anamnesis and a clinical exam. All individuals were right-handed, in agreement with the Edinburgh inventory¹⁵. In addition to this, they were not allowed to sleep for less than 6-8 hours on the night before the experiment. All subjects signed a consent form and were aware of the experimental protocol. The study is in agreement with the Declaration of Helsinki and was approved by the Ethics Committee of the Federal University of Rio de Janeiro.

Experimental procedure

The subjects performed the task in a sound and light-attenuated room, to minimize sensory interference. Each subject realized two experimental conditions: placebo (Pl) and 6 mg of Bromazepam (Br_6 mg), following a randomized, double-blind design on different days. Thus, each subject executed one condition on the first day and to the other condition on the second day, one week apart. First, we collected EEG data for each subject during three minutes. After the capsule ingestion, subjects remained at rest for 2 hour. Then, the subjects sat in front of a computer monitor (Samsung-SyncMaster 550v), they sat on a comfortable chair with armrest, in order to minimize muscular artifacts, while we recorded the electroencephalography (EEG) data before, during and after the motor task execution. Under both conditions, the subject performed 6 blocks of 15 trails each (a flexion/extension movement of the index finger in a rhythmic way), with 8-second intervals between blocks. The individuals executed the extension of the right index finger after a stimulus appeared on the computer monitor many times, as fast as possible. We positioned a sensor called accelerometer (an electro-mechanic device utilized to measure velocity alterations over time) on the index finger to measure the acceleration and, together with the visual feedback, we synchronized the accelerometer with the EEG window. We calculated the average of the six blocks together, and we analyzed the initial and final measures, respectively determining the pre and post period.

The protocol adopted for each day of the experiment consisted of five stages. During the first moment, we conducted the signal acquisition through qEEG for 2 minutes

with the eyes opened. Then, the subjects ingested a capsule containing placebo or bromazepam, and remained at rest for 1 hour. After that, we recorded another 2-minute EEG signal acquisition with the eyes opened. At stage four, simultaneously with qEEG signal acquisition, the individual started the motor task with flexion and extension of the index finger at the same time that the visual feedback was being generated on the monitor screen. The last stage consisted of another signal acquisition through qEEG for 2 minutes with eyes opened.

Data acquisition

Electroencephalography

The International 10/20 system for electrodes¹⁶ was used with a 20-channel Braintech-3000 EEG system (EMSA-Medical Instruments, Brazil). We used 20 electrodes arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA), yielding mono-pole derivations to linked earlobes, set as reference points. In addition, we attached two 9 mm-diameter electrodes above and on the external corner of the right eye, in a bipolar electrode montage, to monitor artifacts on eye-movements (EOG). We kept the impedance of EEG and EOG electrodes between 5 and 10 k Ω . The data acquired had total amplitude of less than 100 μ V. We amplified the EEG signal, with a gain of 22,000, analogically filtered between 0.01 Hz (high-pass) and 100 Hz (low-pass), and sampled at 240 Hz. For the reference data analysis, we applied a visual exam and an independent component analysis (ICA) to eliminate the possible sources of artifacts produced by the task. We excluded data of individual electrodes which lost contact with the scalp or which showed high impedance (> 10 k Ω), as well as data from blocks with movement artifact excess (\pm 100 μ V). Then, we applied ICA to identify and remove any remaining artifacts after the initial visual inspection. ICA is a group of blind source separation methods, which aim at estimating the maximum independent components from a statistic point of view. The ICA-filtered data were then re-inspected for residual artifacts, using the same rejection criteria described above. We applied a classic estimator for the power spectral density (PSD), or directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB (Matworks, Inc.).

Statistical analysis

This study analyzed the frontal (Fp1, Fp2, F7, F3, Fz, F4 and F8) and central (C3, CZ and C4) areas. EEG absolute power values underwent a logarithmic transformation through the SPSS software (version 16.0), in order to get closer to a normal distribution. We performed a two way ANOVA test to analyze the results between the conditions (PL \times Br 6mg) and between the moments (pre and post) for the following electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, C3, CZ e C4. We analyzed each electrode

separately. We applied the Scheffé test to analyze the significant differences between the moments ($p \leq 0.05$).

RESULTS

Alpha

We found a main effect for condition on the electrodes Fp1 ($p < 0.05$; $F = 4.67$), F7 ($p < 0.001$; $F = 18.96$), F3 ($p < 0.001$), Fz ($p < 0.001$; $F = 18.72$), F4 ($p < 0.001$; $F = 10.24$), C3 ($p < 0.001$; $F = 26.47$) and CZ ($p < 0.001$; $F = 12.79$) (Figure 1). For all the electrodes the bromazepam condition showed a greater alpha absolute power when compared to the placebo condition.

Beta

We found a main effect for condition on the electrodes Fp1 ($p < 0.005$; $F = 7.91$), Fp2 ($p < 0.001$; $F = 117.43$), F7 ($p < 0.001$), F3 ($p < 0.009$; $F = 6.91$), Fz ($p < 0.012$; $F = 6.33$), F4 ($p < 0.001$; $F = 54.41$), F8 ($p < 0.001$; $F = 19.66$) (Figure 2), C4 ($p < 0.009$; $F = 6.82$) e C3 ($p < 0.047$; $F = 3.92$) (Figure 3). For all the electrodes the bromazepam condition showed a greater alpha absolute power when compared to the placebo condition.

Theta

We found a main effect for condition on the electrodes C3 ($p < 0.001$; $F = 20.25$), Cz ($p < 0.001$; $F = 28.25$) e C4 ($p < 0.001$; $F = 32.49$) (Figure 4). For all the electrodes the bromazepam condition showed a greater alpha absolute power when compared to the placebo condition.

DISCUSSION

Our objective was to verify the bromazepam influence on alpha band absolute power during the execution of a simple motor task (the index finger extension movement). Our hypothesis is that the subjects, under the effect of the drug, will show a reduced neural recruitment, represented by a greater alpha activity in the frontal and central areas involved in the task. We considered two factors for analysis: condition (placebo vs. bromazepam) and moment (pre and post motor task). We verified a main effect for condition for the electrodes FP1, F7, F3, FZ, F4, C3 and CZ. We did not find significant effect for the moment factor; this finding suggests that the executed task did not influence absolute alpha power, and that the existing modifications are related to the drug use. In order to expand the investigation, we included the analysis of theta and beta frequencies. The results in beta and theta are similar to the results found in the alpha frequencies, a main factor for condition with a greater power in the bromazepam condition.

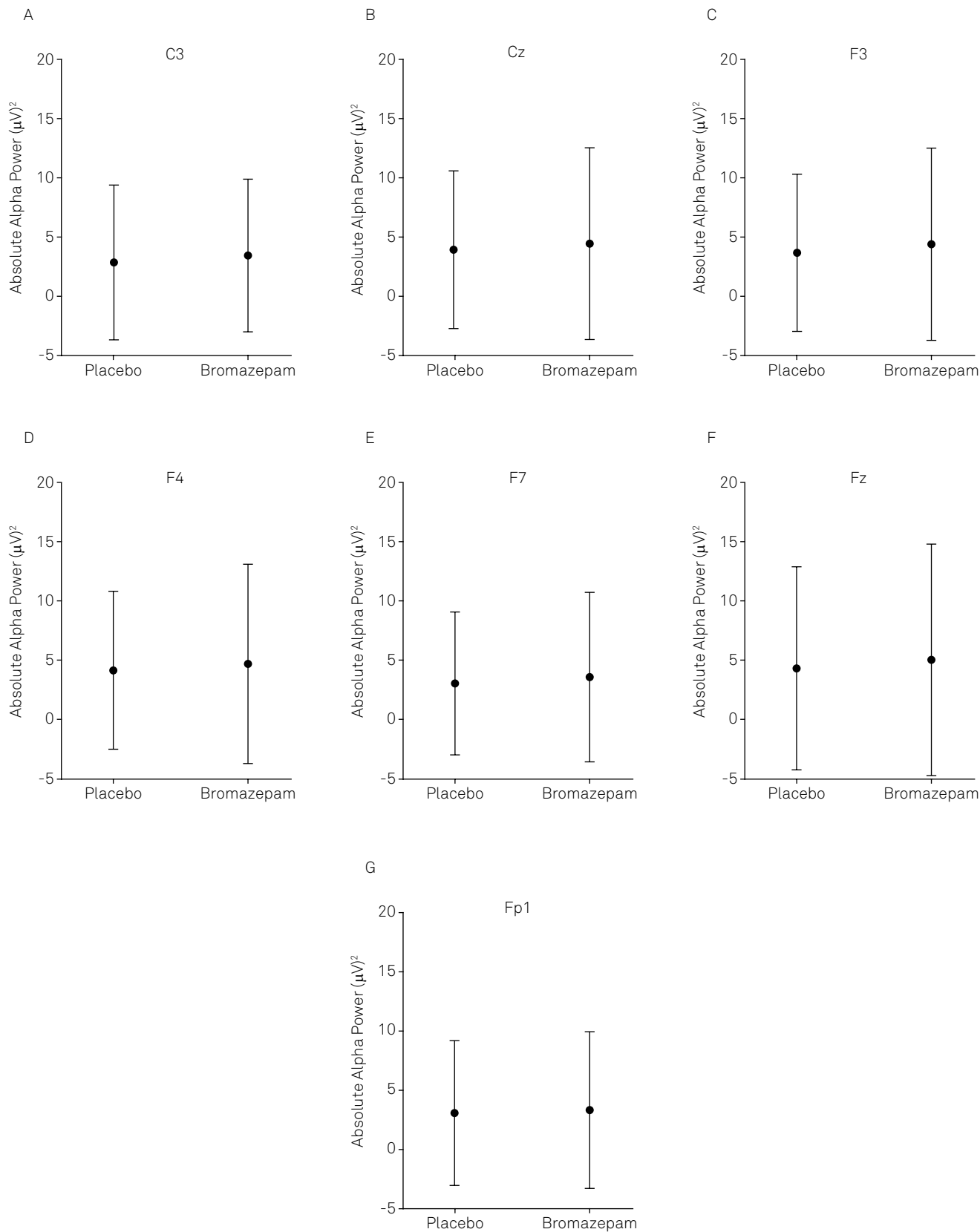


Figure 1. (A) The results highlight a significant difference: between conditions ($p < 0.05$) for C3; (B) The results highlight a significant difference between conditions ($p < 0.05$) for Cz; (C) The results highlight a significant difference between conditions ($p < 0.05$) for F3; (D) The results highlight a significant difference between conditions ($p < 0.05$) for F4; (E) The results highlight a significant difference between conditions ($p < 0.05$) for F7; (F) The results highlight a significant difference between conditions ($p < 0.05$) for Fz; (G) The results highlight a significant difference between conditions ($p < 0.05$) for Fp1.

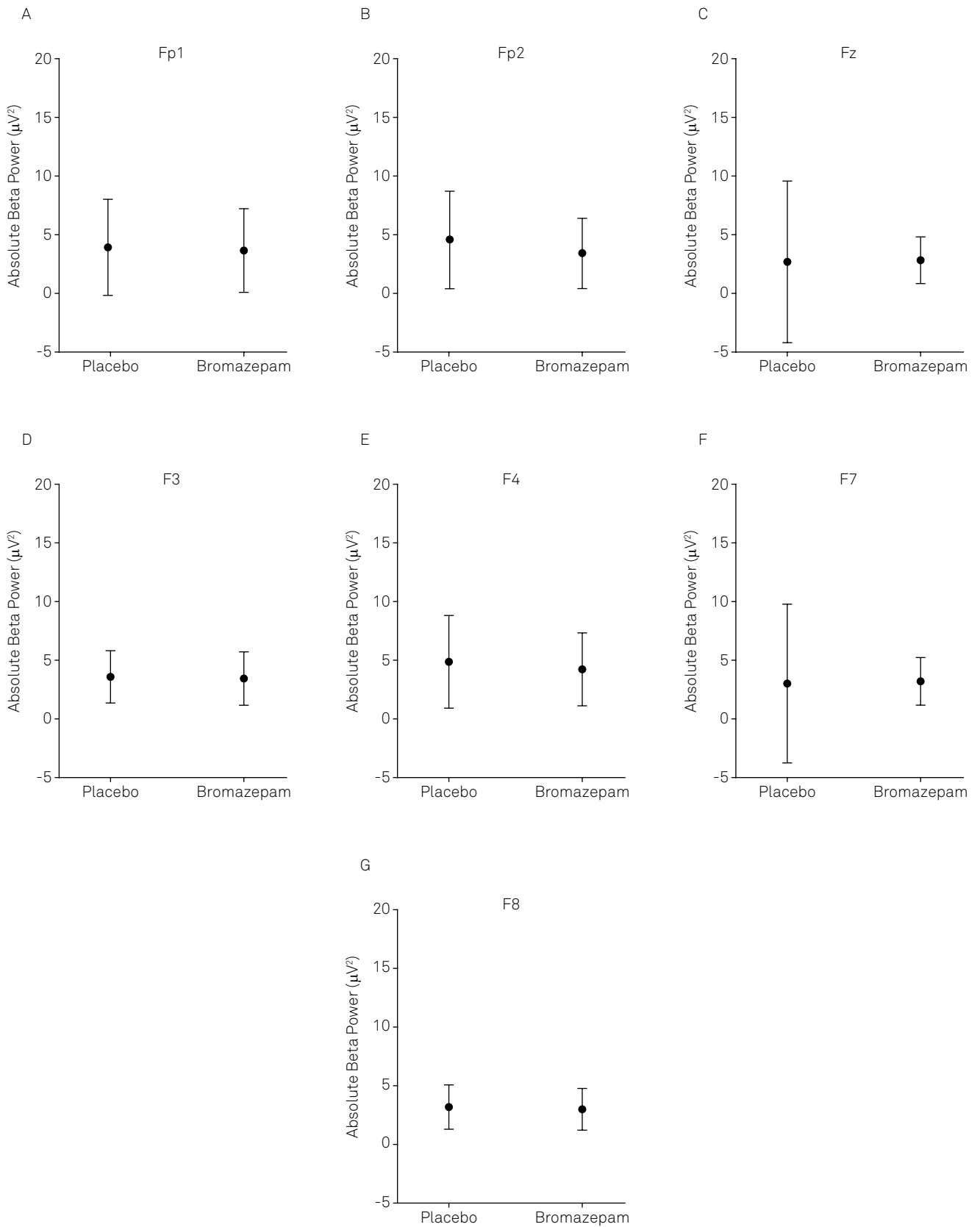


Figure 2. Mean and standard deviation for Absolute Beta Power. (A) The results highlight a significant difference between conditions ($p < 0.05$) for Fp1; (B) The results highlight a significant difference between conditions ($p < 0.05$) for Fp2; (C) The results highlight a significant difference between conditions ($p < 0.05$) for Fz; (D) The results highlight a significant difference between conditions ($p < 0.05$) for F3; (E) The results highlight a significant difference between conditions ($p < 0.05$) for F4; (F) The results highlight a significant difference between conditions ($p < 0.05$) for F7; (G) The results highlight a significant difference between conditions ($p < 0.05$) for F8.

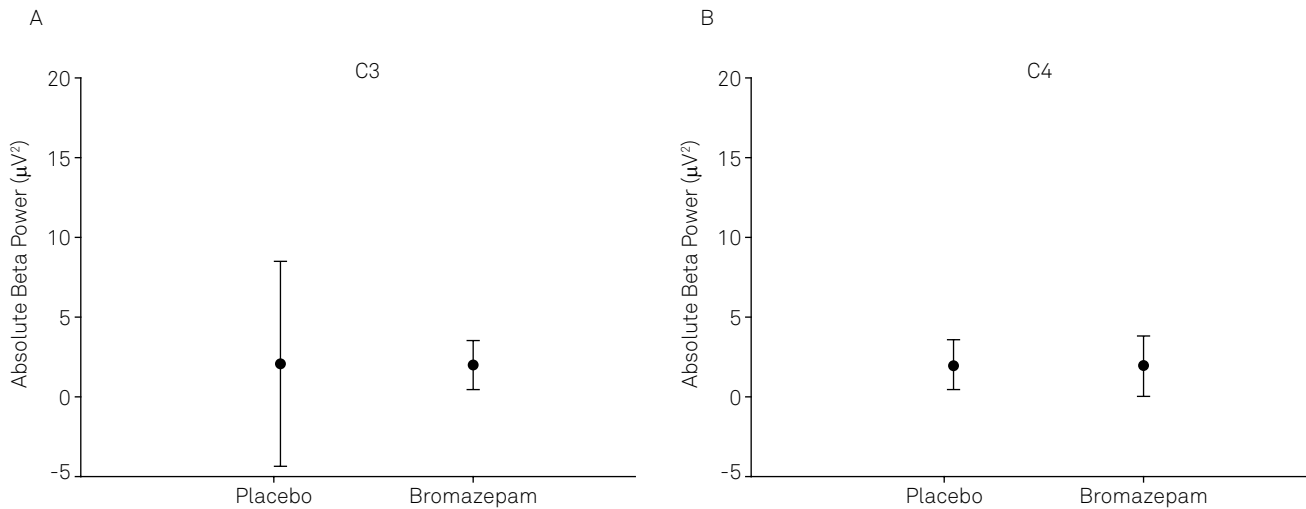


Figure 3. Mean and standard deviation for Absolute Beta Power. (A) The results highlight a significant difference between conditions ($p < 0.05$) for C3; (B) The results highlight a significant difference between conditions ($p < 0.05$) for C4.

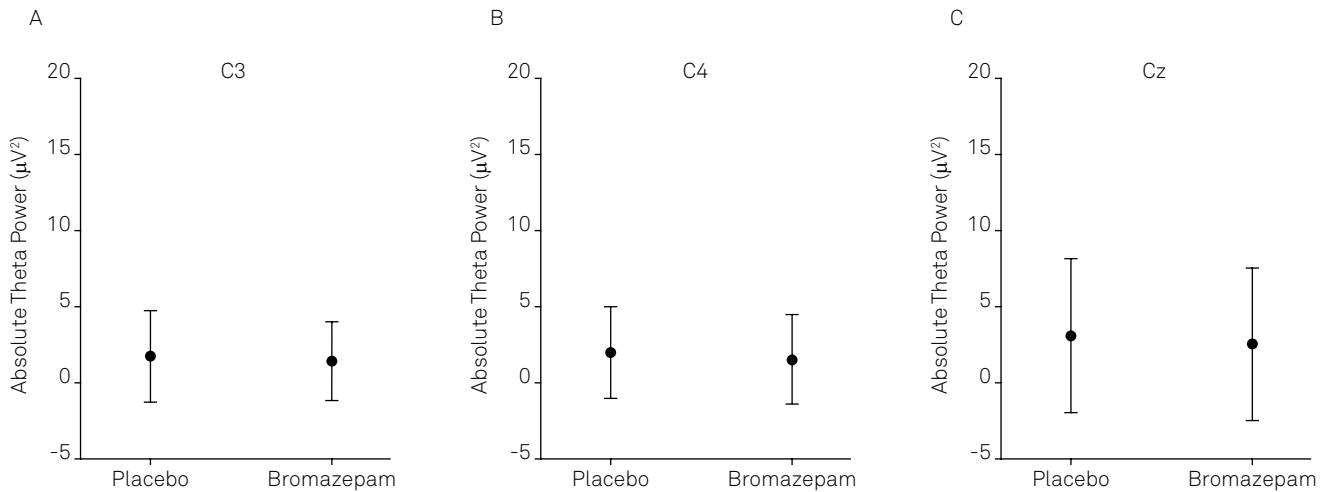


Figure 4. Mean and standard deviation for Absolute Theta Power. (A) The results highlight a significant difference between conditions ($p < 0.05$) for C3; (B) The results highlight a significant difference between conditions ($p < 0.05$) for Cz; (C) The results highlight a significant difference between conditions ($p < 0.05$) for C4.

It is worth highlighting that the behavioral data, that is, task execution reaction time, was analyzed in a previous study. A statistically significant difference was found in the analyzed behavioral parameter ($p = 0.001$)¹⁷. They observed a greater reaction time for the Br_6 mg condition, when compared to the placebo one; the subjects who used bromazepam showed a slower response to the stimulus. Other researchers analyzed behavioral studies after bromazepam intake, identifying this way some distinct results. In their study, Bourin¹⁸ investigated the bromazepam and other benzodiazepines (3 mg) effects in 20 healthy volunteers. The authors observed that the longest motor reaction time was noticed 6 hours after the drug ingestion. Montenegro¹⁹ tried to verify whether there would be reaction time changes after ingestion of 3 mg of bromazepam. The authors believed that a longer reaction time would occur,

but the expected result was not found. This study highlights that the results can be influenced by the administered dose. Jansen²⁰ also examined the bromazepam (6 mg and 12 mg) effects on the reaction time 65 minutes after the drug administration, and a lower performance was observed.

However, in the present study, the analysis of the behavioral data demonstrated a statistically significant difference between the Br_6 mg and placebo conditions, proving that the Br_6 mg condition promoted a slower response of the individuals when presented with a stimulus. It is worth pointing out that alpha (8-13 Hz) is a frequency with inversely proportional amplitude to the quantity of recruited neurons, that is, the alpha rhythm will reflect a lowering of cortical action²¹. Our results will be discussed according to the analyzed areas.

Frontal Cortex

The frontal region performs an essential role in the formation of objectives and goals, strategy planning, selecting the cognitive abilities required for the implementation of motor plans and coordinating them to apply them in the correct order, in addition to specific actions related to movement^{6,7,22}. Therefore, the execution of a simple motor task allows for a more detailed investigation of the processes associated with planning and motor coordination. We verified a greater alpha absolute power for the bromazepam condition for the electrodes Fp1, F7, F3, Fz e F4. This result corroborates with our hypothesis of a lower neural recruitment produced by bromazepam. We also identified a decrease of absolute beta power for the electrodes Fp1, Fp2, F7, F3, F4 and F8. In a previous study, Portella¹² investigated alterations of the attention levels in the motor performance using typing, and electroencephalographic parameters because of the administration of 6 mg of bromazepam. Specifically, they analyzed coherence differences in the alpha, beta, and theta bands in the frontal, central and parietal areas during the execution of four blocks of motor task. According to the same author referred to above, the processes of attention are related to the frontal area and are indicated by beta rhythm increase; however specifically in this band there was decrease between the electrodes F3-Fz in the experimental group, suggesting neuronal specialization for such mechanisms. The results demonstrated a main effect for the condition factor in the frontal F3-Fz and central C3-Cz. Despite the difference between the task executed in the study by Portella¹² and the task executed in the present research, our results in the frontal area are similar to the ones found in his study.

Hubl¹⁴ investigated the changes in the brain electrical activity in individuals who ingested olanzapine, using EEG and P300. The study verified the influence of the drug in individuals with no addiction, and if there was any alteration in the attention mechanisms during the information processing. The author found an increase in the quantity of alpha 2 waves (10-11.5 Hz) in the frontal region, and a decrease in occipital areas. Therefore, our results are in agreement with these findings, demonstrating that the benzodiazepines tend to increase the alpha power in these areas. Despite the present study having found an increase in the alpha activity in these areas after the administration of bromazepam, there are contradictions, such as the ones found in the study by Liley²³. In this research they verified the influence of lorazepam, a type of benzodiazepine in the alpha band, specifically alpha 1 (8-9.5 Hz), finding a negative correlation between alpha 1 and the drug use. The literature also points out that there is a decrease in the relative alpha power after the administration of benzodiazepines²⁴.

Somatomotor Cortex

The somatomotor cortex is responsible for sending signals in order to make motor activity control possible; its

function is to coordinate and execute body movements, especially the finest, most complex and varied movements^{25,26,27}. When analyzing this region, represented by the electrodes C3 and Cz, we found greater alpha absolute power under the bromazepam condition. Although this region is responsible for motor task control, it was not affected by the movement execution. Such result suggests that alpha absolute power cannot be considered as a sensible measure to analyze the effects caused by the task. This might have occurred because the alpha band is associated with cognitive aspects^{28,29}.

Studies that investigate motor tasks and electroencephalography traditionally investigate the beta frequency band, our study intend to elucidate the alpha power role during motor task execution. Alpha is known for its correlation with cognitive and attention aspects, when executing and/or re-learning a motor task, and not with the motor act itself²⁸. It is considered to be sensible to variations in perception, cognition and motor action²⁹. Even though we were not able to observe an effect caused by the task on alpha, i.e., we did not find a main effect for moment, our data demonstrate that the laterality (i.e., all individuals were right-handed and executed the task with their right hand) interfered in the bromazepam action on the electrocortical activity. This can be explained by the fact that a difference was found between the placebo and bromazepam conditions only on the middle line of the somatomotor cortex (Cz) and in the somatomotor cortex contralateral to the movement (C3), with no significant result found in the ipsilateral motor cortex (C4), specifically, for the C3 electrode, which is located above the area responsible for the cortical representation of the right hand¹². In a previous study, Silva³⁰ aimed at investigating bromazepam modulating effect on alpha and beta bands in primary motor areas (M1). The subjects were submitted to a motor task, in which they had to rapidly identify a ball thrown horizontally, and they had to catch it with their right hand, while electroencephalographic activity was captured. The findings showed that the bromazepam effects caused changes in the information processing within the left M1, represented by the C3 electrode. Our study found a result for alpha, which is similar to the one Silva³⁰ observed for beta. Therefore, our results confirm that bromazepam acts differently in the somatomotor cortex, demonstrating an involvement in the hemisphere directly related to motor action, that is, the left motor cortex, which is the area contralateral to the movement.

In conclusion, our results confirm the initial hypothesis, which stated that, under the effect of the drug, the subjects would show a lower neural recruitment, represented by alpha power increase and beta and theta power decrease. Specifically, we found these results in the frontal and somatomotor areas. In addition to this, the role of bromazepam was also highlighted as concerning the reaction time, making the motor act slower. Starting from our

findings, we can conclude that bromazepam, despite its anxiolytic and sedative action does not cause any significant changes when performing a finger extension motor task, that is, a not very complex task. Even though our result showed a main effect for condition, agreeing with the fact that bromazepam interferes in alpha absolute power, no difference was found between the pre and post-task moments; this makes us doubt about how exactly bromazepam has an influence on motor action. These data

show that, although the drug has an effect on the electrocortical activity, specifically on alpha absolute power, more researches need to be conducted, in order to explain how bromazepam acts and interferes in a simple motor action. Therefore, new researches are also necessary to elucidate how other brain regions would act within the alpha frequency, since this is a slower wave, and to clarify the relation with the drug dosage as well as the energy band activity alterations during a more complex task.

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