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Absolute Theta Power in the Frontal Cortex During a Visuomotor Task: The Effect of Bromazepam on Attention

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Abstract

Bromazepam is a benzodiazepine, which has been widely employed in the treatment of anxiety. We investigated the electrophysiological changes in absolute theta power within the frontal cortex when individuals performed a visuomotor task under bromazepam. The sample of 17 healthy individuals was randomized into 2 experimental conditions, under which bromazepam 6 mg and placebo were administered on different days. All subjects were right -handed, with no mental or physical illness and were not using any psychoactive or psychotropic substance during the entire period of the study. We found an increase in reaction time under bromazepam compared with placebo . With regard to the electrophysiological variable, we found a lower theta power value in the prefrontal cortex prior to task execution, compared with after. We therefore suggested that this could be an increase of neural activity in this region, because of the subjects' readiness to perform the task, that is, because of their higher alertness. The right lateral frontal region showed lower theta power under bromazepam for pre- and post-finger movement. This could have occurred because of more effort to execute the task. In the left frontal region: premovement did not demonstrate any difference between conditions, possibly because the proposed task was simple to execute. In conclusion, theta power plays an important role in the analysis of visuomotor performance, assuming that bromazepam causes impairment on sustained attention and sensory perception.

Keywords

absolute theta power, bromazepam, sensorimotor integration, visuomotor task, quantitative electroencephalography

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Introduction

Sensorimotor integration is responsible for identification of several sources of stimuli, selection, and action planning.[1,2] This ability to associate external sources with an internal model is how the central nervous system creates harmonic actions.[3] Such dynamic interaction has already been highlighted in various studies, and is regarded as a transformation process of the sensorial information into motor commands, looking for a desired response.[4-6] Cognitive neuroscience has been trying to understand how this stream of processes occurs under the effect of anxiolytic drugs,[7-10] since increasing evidence is showing that these drugs could shift cognitive functions.[11-13]

Benzodiazepines have been used in several neurophysiological trials because of their constant use in anxiety symptoms.[14-16] The most prescribed and used benzodiazepine around the world is bromazepam; this drug has been employed in several trials to understand how the brain areas involved in cognitive processes operate under its influence.[17-19] Studies have shown impaired psychomotor ability at the first stage of information processing (stimulus identification/detection and attention),under bromazepam.[20] Long-standing and continuous use of benzodiazepines increased the reaction time because of sedative effects

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and loss of short-term memory.[21,22] On the other hand, positive effects on task performance were demonstrated when low doses were administered because of their power to decrease internal stress and anxiety.[13,22]

To evaluate the electrophysiological changes resulting from the administration of drugs, quantitative electroencephalographic (qEEG) recordings have been used together with sensorimotor integration tasks to investigate cognitive processes.[16] These tasks play an important role in understanding attention and sensoriomotor integration processes.[23] qEEG analysis was used to investigate the changes in the theta band absolute power within frontal areas, when subjects were exposed to visuomotor tasks, under the influence of bromazepam. Theta has been associated with cognitive functions: this frequency was corelated with stimuli encoding and attention mechanisms.[24] In this context, we hypothesized that bromazepam 6 mg would affect theta, promoting a decrease in absolute theta power, when compared with placebo. We also expected to find an increase in reaction time under bromazepam, considering that this drug produces muscle relaxation and reduces alertness.

Materials and Methods

Sample

The sample was 17 healthy individuals, of both sexes with ages varying between 18 and 30 years, right-handed, with no mental or physical illness (previous anamnesis), not using any psychoactive or psychotropic substances during the study. We utilized the Edinburgh Inventory[25] to indentify left-handed individuals, who were excluded from the experiment. All subjects signed consent 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 task was performed in a sound- and light-attenuated room, in order to minimize sensory interference. Each subject was exposed to the experimental conditions: placebo and 6 mg of bromazepam (Br_6mg), following a randomized, double-blind design on different days. Each subject was exposed to one condition on the first day and to the other after 48 hours. After capsule ingestion, subjects remained at rest for 1 hour.[10] Then, a computer monitor (Sansung-SyncMaster 550v) was positioned in front of the subjects, as they sat on a comfortable chair with armrest, to minimize muscular artifacts, while EEG data were recorded before, during, and after the visuomotor task. Under both conditions, the task was developed in 6 blocks of 15 trails each (a flexion/extension movement of the index finger in a rhythmic way), with 8-minute intervals between blocks to avoid muscular fatigue. An accelerometer sensor was positioned on the index finger to measure acceleration[26] and, together with visual feedback, was synchronized with the EEG window. The accelerometer was connected to the EEG through an additional channel (ie, channel 21).

The protocol for each day of the experiment consisted of 5 stages. During the first, we conducted signal acquisition through qEEG for 2 minutes with eyes opened. Then, subjects ingested a capsule containing placebo or bromazepam and remained at rest for 1 hour. After that, a 2-minute EEG with eyes opened was recorded. At stage 4, simultaneously with qEEG acquisition, the individual started the visuomotor task with flexion and extension of the index finger at the same time that the visual feedback was being generated on the monitor. The last stage consisted of qEEG for 2 minutes with eyes opened.

Data Acquisition

EEG. The international 10/20 system for electrodes[27] was used with a 20-channel Braintech-3000 EEG system (EMSA-Medical Instruments, Brazil). The 20 electrodes were arranged on a nylon cap (ElectroCap, Inc, Fairfax, VA), yielding monopole derivations to linked earlobes, set as reference points. In addition, two 9-mm diameter electrodes were attached above and on the external corner of the right eye, in a bipolar electrode montage, in order to monitor eye movements (electro-oculography or EOG). Impedance of EEG and EOG electrodes was kept below 5 kohm. The data acquired had total amplitude of less than 100 μV. The EEG signal was amplified, with a gain of 22 000, analogically filtered between 0.01 Hz (high-pass) and 100 Hz (low-pass), and sampled at 240 Hz. The software Data Acquisition (Delphi 5.0), developed at the Brain Mapping and Sensorimotor Integration Laboratory, was employed to filter the raw data: notch (60 Hz), high-pass of 0.3 Hz, and low-pass of 100Hz.

Accelerometer. To obtain signals from the accelerometer, we used the MMA7340 model of Freescale Semiconductor, Inc (Austin, TX). This system is composed of a microelectronic device, which explores the mechanical proprieties of silicone to create movable structures and to detect distinct movement directions.[26,28] The capture of movements was conducted in an actual time system, with the interaction of EEG software signal acquisition. As the movement was performed, the accelerometer showed a curve with acceleration variability providing information about velocity and time.

Data Processing

To quantify reference-free data, a visual inspection and independent component analysis (ICA) were applied to identify and remove eye blinks and ocular movements.[29] Data from individual electrodes exhibiting loss of contact with the scalp or high impedances (>10 kohm) were not considered, and data from single-trial epochs exhibiting excessive movement artifacts (±100 μV) were also eliminated. The ICA-filtered data were then reinspected for residual artifacts, using the same

rejection criteria described above. Then, a classic estimator was applied to the power spectral density (PSD), or directly from the square modulus of the Fourier transform, which was performed by MATLAB (Mathworks, Inc, Natick, MA). qEEG parameters were reduced to 4-second periods (the selected epoch started 2 seconds before and ended 2 seconds after the trigger, ie, the moment preceding index finger movement and the moment after index finger movement).

Spatial Electrode Localization and Frequency Band

The frontal cortex was the region of interest in this study. The prefrontal area, represented by electrodes Fp1, Fp2, F7, and F8, was analyzed because of its relationship with executive functions, such as attention and planning.[30] The F3, FZ, and F4 electrodes corresponding to the premotor cortex, responsible for movement selection, preparation, and voluntary action control were also inspected.[31] Theta (4-7 Hz) was chosen because of its association with cognitive function and attention.[21,32] Although other EEG frequencies, such as alpha and gamma[33,34] are related with attention process, theta is more specific, since this frequency is also related to sensorimotor integration and information processing.[35-39] This aspect demonstrates that theta represents in more detail the main process of our investigation.

Statistical Analysis

Absolute theta power was analyzed under the 2 conditions (Placebo vs Br_6mg) during 5 periods of the study: Rest 01, Rest 02, premovement, postmovement, and Rest 03, using a 2-way analysis of variance. This analysis was corrected by multiple comparisons, using the post hoc test with Bonferroni's correction procedure. Additionally, a paired *T* test was performed to compare the moments within each condition, aimed at exploring their interaction (Condition vs Moment). The significance criterion was $P \leq .05$ for all analyses.

Behavioral data were evaluated using the *T* test for independent groups (Br_6mg and Placebo). Reaction time, between visual stimuli presentation and motor response (ie, lower the index finger), was measured for the 6 blocks of the task, under both study conditions.

Results

Behavioral Variable

Independent *T*-test results of behavioral analysis demonstrated that the Br_6mg and Placebo conditions presented a significant difference in the parameter reaction time during motor task execution. When compared with Placebo, there was an increase in the reaction time under the Br_6mg condition ($P = .001$; Figure 1).

Neurophysiologic Variables

This study investigated the modulatory effects of bromazepam on cerebral dynamics before and after task execution (finger movement), through the inspection of theta absolute power. The 2-way analysis of variance revealed a significant interaction between study period and condition for the frontal electrodes Fp1 ($F = 7.370$; $P = .000$), Fp2 ($F = 4.596$; $P = .001$), F3 ($F = 3.415$; $P = .008$), F7 ($F = 15.221$; $P = .000$), and F8 ($F = 37.276$; $P = .000$). A detailed inspection using a paired *T* test between study periods for each subfactor (Placebo vs Br_6mg) was conducted to test for the nature of the interactions. The electrodes F4 ($F = 1.388$; $P = .239$) and Fz ($F = 1.967$; $P = .097$) did not show any significant interaction among the factors.

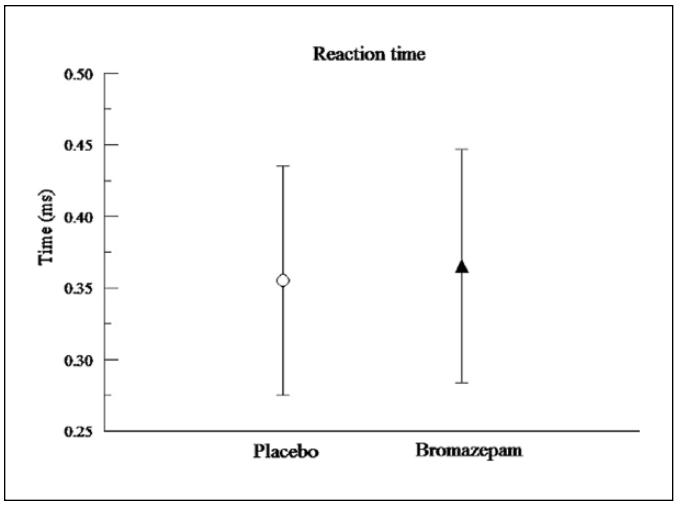


Figure 1. Mean and standard deviation of the parameter reaction time during execution of the motor task. The statistical analysis revealed increase in the reaction time for bromazepam 6 mg when compared with the placebo condition ($P < .05$).

For the electrode Fp1, "Rest 1" ($F = 0.17$; $P = .89$) and "premovement" ($F = 0.190$; $P = .663$) did not show significant differences between conditions. However, for "Rest 2" ($F = 36.024$; $P = .000$), "postmovement" ($F = 11.898$; $P = .001$), and "Rest 3" ($F = 15.038$; $P = .000$), significant differences were found, with an increase of absolute theta under the placebo condition (Figure 2A).

For the Fp2 electrode, the difference between Placebo and Br_6mg was detected for "Rest 2" ($F = 28.910$; $P = .000$), "premovement" ($F = 15.544$; $P = .000$), "postmovement" ($F = 21.799$; $P = .000$), and "Rest 3" ($F = 13.425$; $P = .000$), with increased theta under placebo. "Rest 1" did not differ between conditions ($F = 0.397$; $P = .529$; Figure 2B).

For the F7 electrode, "Rest 1" ($F = 3.647$; $P = .056$), "Rest 2" ($F = 1.529$; $P = .217$), and "postmovement" ($F = 2.025$; $P = .155$) did not show any difference between placebo and Br_6mg. Differences were found only for "premovement" ($F = 4.280$; $P = .039$) and "Rest 3" ($F = 18.300$; $P = .000$), with increased theta under placebo (Figure 3A).

For the F8 electrode, theta absolute power was higher under placebo for "Rest 2" ($F = 19.989$; $P = .000$), "premovement" ($F = 6.535$; $P = .011$), and "postmovement" ($F = 12.189$; $P = .000$). For "Rest 1," theta decreased under placebo, when

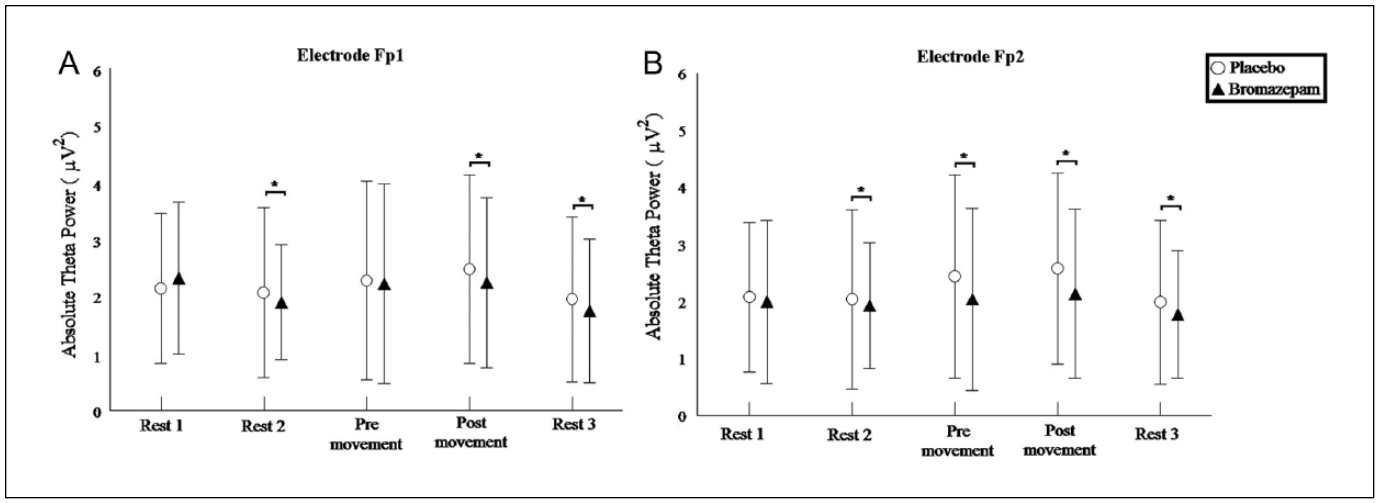


Figure 2. (A) Interaction between bromazepam and placebo conditions for electrode Fp1 by mean and standard deviation for theta band ($P < .05$). (B) Interaction between bromazepam and placebo conditions for electrode Fp2 by mean and standard deviation for theta band ($P < .05$).

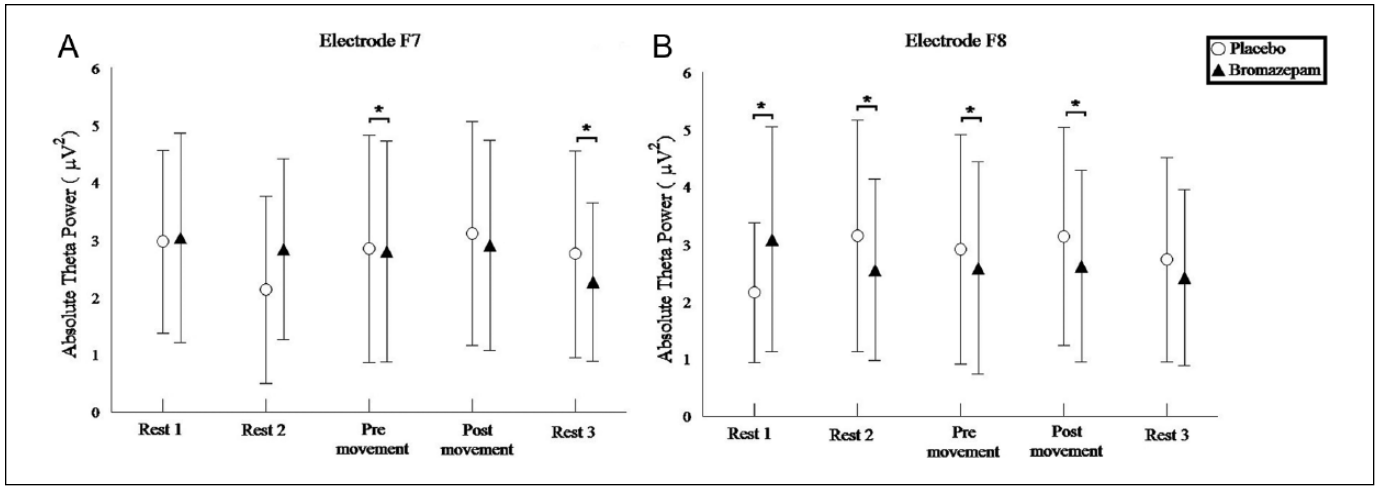


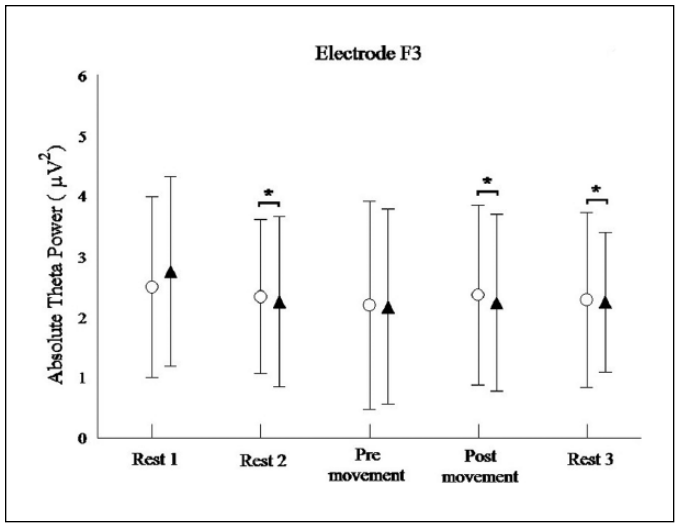
Figure 3. (A) Interaction between bromazepam and placebo conditions for electrode F7 by mean and standard deviation for theta band ($P < .05$). (B) Interaction between bromazepam and placebo conditions for electrode F8 by mean and standard deviation for theta band ($P < .05$).

compared with Br_6mg ($F = 112.992$; $P = .000$). Only "Rest 3" did not show any difference between conditions ($F = 1.819$; $P = .178$; Figure 3B).

For electrode F3, theta absolute power was lower under Br_6mg for "Rest 2" ($F = 7.437$; $P = .007$), "postmovement" ($F = 2.773$; $P = .096$), and "Rest 3" ($F = 2.997$; $P = .084$). "Rest 1" ($F = 3.630$; $P = .057$) and "premovement" ($F = 1.714$; $P = .191$) did not show significant differences between conditions (Figure 4).

Discussion

Within the behavioral domain, we found longer reaction times when subjects were under the effect of bromazepam 6 mg. This is a new result, which had not yet been demonstrated in other bromazepam studies by our group.[9,11,17,19,20] This finding is in agreement with the properties of the task proposed by this study, which focused only on the motor response after an unpredictable stimulus and did not involve any kind of learning or memorization. Increased reaction time under Br_6mg may be associated with a decrease in attention, probably caused by the anxiolytic effect of bromazepam. Several researchers have shown different reaction times with bromazepam at different times after ingestion. Jansen et al[40] reported an effect on the reaction time and a decrease in performance after 65 minutes from 6 or 12 mg bromazepam. Bourin et al[41] found greater reaction times 2 hours after ingestion.



Figures 4. Interaction between bromazepam and placebo conditions to electrode F3 by mean and standard deviation for theta band ($P < .05$).

The neurophysiological focus was on the variable absolute theta power. Especially, we searched for potential variations in the cortical areas involved with sensorimotor integration processes, with or without anxiolytic drugs, through qEEG. The results will be discussed in relation to the frontal region and according to the variables "condition" and " study period."

Theta Band Implications for the Frontal Region: Comparison and Motor Response

After observing different electrodes in the frontal region, an interaction was found between the experimental conditions and study periods for the following electrodes: Fp1, Fp2, F7, F8, and F3. The electrodes were grouped into frontopolar (Fp1 and Fp2), lateral–frontal (F7 and F8), and medial–frontal (F3).

" Rest" periods were analyzed to control the characteristics of baseline EEG, owing to the possible spontaneous variations of circadian rhythm.[42] Frontal electrodes did not present differences between conditions for "Rest 1," before drug ingestion. Conversely, the dynamics for "Rest 2," 1 hour after drug administration, and "Rest 3," after visuomotor task execution, varied for each electrode.

The frontopolar region is related to superior executive functions, such as planning, problem solving, reasoning and fact retrieval by episodic memory, when executing several cognitive paradigms.[43] After examining the interaction between conditions within the frontopolar regions, we observed a difference for each of the following: "Rest 2," "postmovement," and "Rest 3," in the left frontopolar region (Fp1); we also observed a difference in the right frontopolar region for each of the following: "Rest 2," "premovement," "postmovement," and "Rest 3." Specifically, we found a decrease in theta for the Br_6mg condition, when compared with placebo, during each of the periods. This demonstrates that theta is sensitive to bromazepam within this region. This finding supports our initial hypothesis, that bromazepam would interfere in information processing and in sensorimotor integration.

Niedermeyer and Silva[42] highlight the side effects produced by benzodiazepines, such as mental impairment, lack of motor coordination and changes in several cognitive domains, such as visuospatial, attention, processing speed and verbal learning, which can occur after long-term treatment.[44,45]

Within the frontopolar region, we observed a difference between conditions for "premovement" only for Fp2; this shows how bromazepam interferes in motor task preparatory and planning phases. The study by Elk et al[46] analyzed motor action planning using familiar and nonfamiliar objects and found that the frontopolar region was activated when the individuals executed familiar actions, such as brushing their teeth. This study partially supports our finding, since the activation found was bilateral, without any difference between the left and right frontopolar regions.

Dreher et al[47] analyzed functions attributed to the frontopolar cortex through motor tasks executed by individuals with impaired right and left frontopolar regions. The lesion impaired task execution, because of the deactivation of the frontopolar cortex, which is responsible for cognitive functions, such as planning and working memory. Therefore, the difference between conditions in the right region cannot be attributed exclusively to the characteristics of the frontopolar region, since both frontopolar regions are related to motor planning. This difference in theta between conditions within the right region can be related to the functions attributed to the right hemisphere, which are associated with attention control for visual representations[48,49] and sustained attention.[50] Therefore, theta reduction can be associated with the interference provoked by benzodiazepines in these cognitive domains.

When we looked at the interaction of electrodes in the lateral frontal area, we found different dynamics in the right and left regions during initial and final visuomotor task execution. In the left frontal region (F7), theta was higher under placebo than under Br_6mg prefinger movement; however, after motor action, the conditions did not discern. With regard to the right frontal region (F8), theta increased under placebo, compared with the Br_6mg, both before and after movement.

The activity of the lateral prefrontal cortex has been related to the regulation of voluntary actions.[51] Studies highlight that this region might be highly involved in the initial processes of comparison and response selection to action.[17,52] Our findings are in agreement with these studies, when showing a different behavior in this region for the moment prior to the finger movement, under the different research conditions. When comparing conditions in the motor action period, we found a lower absolute theta power under the effect of Br_6mg. This could be because greater effort is required to keep executing the motor task, that is, individuals had to increase their cognitive engagement to maintain the task, trying to compensate for the possible impairments caused by the drug on the alertness state and executive functions. Specifically, the difficulty to plan a response under Br_6mg could be related to a possible attention and

working memory reduction. Thus, the process of retaining information for planning and behavioral response may have been affected by the sedative effect of bromazepam, and a greater effort would be required to sustain attention during the task.

Within the left frontal region (F3), responsible for movement action selection, preparation and voluntary control, "pre-movement" did not show any difference between conditions. A possible explanation for this finding could be that the proposed task was simple, that is, it required neither detailed decision-making nor complex motor action. Thus, under both conditions, the subjects showed a similar activation pattern during the task, and executive functions were not impaired in this region.

Conclusion

We concluded that 6 mg bromazepam caused cortical changes in the frontal region. All electrodes in this region suffered activity reduction during the task. Our findings are in agreement with previous studies, which demonstrated alteration of the cerebral dynamics when bromazepam was administered during sensorimotor integration tasks.[9,11,17,20] Through analysis of absolute theta power, we highlighted how bromazepam interferes in areas related with motor planning and movement selection. Specifically, for visuomotor task execution, the activity decrease under bromazepam was possibly correlated with alertness reduction, as well as with higher effort to keep executing the task. Furthermore, behavioral data demonstrated a longer reaction time, when the subjects were under the drug influence. Therefore, for a better comprehension of possible impairments caused by bromazepam on frontal region dynamics, our laboratory may use tasks which require more effort and higher attention in future research.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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