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The influence of bromazepam on cortical power distribution

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ABSTRACT

The EEG has been widely employed in the assessment of electrophysiological changes induced by distinct medications. Its sensibility in detecting alterations produced by a specific substance may be enhanced by methods of quantitative analyses (qEEG). The present study aimed at investigating the modulatory effects of bromazepam on brain dynamics. The effects of bromazepam (3mg) on EEG power distribution were tested in 10 healthy individuals, in a double-blind experiment. The electrophysiological measure was analyzed across experimental conditions, moments, and electrodes, in the delta, theta, alpha and beta frequency bands separately. A significant decrease of relative power was observed in delta and theta (main effect of condition). No interactions were observed. Although the expected anxiolytic EEG profile was not observed (increased beta and decreased alpha activity), this specific result may be related to other factors such as dosage used and the subjects' general physiological state, and not necessarily to the drug itself.

Key words: benzodiazepine, bromazepam, quantitative EEG, relative power, brain dynamics.

INTRODUCTION

The investigation of cortical activity is essential for the understanding of the neural mechanisms related to psychoactive substances. In this context, electroencephalography (EEG) has been used to monitor the effects of distinct medications on brain dynamics since cortical activity is responsive to the unique characteristics of psychoactive substances (Saletu et al. 2002). The EEG sensibility in identifying changes produced by a specific substance may be improved by methods of quantitative analyses (qEEG) (Anghinah et al. 2000, Veiga et al. 2003). Once drugs have specific effects on wave morphology, changes in qEEG variables can be used to investigate

mechanisms of drug action as well as to monitor and possibly predict efficacy (Fink 1978). Although spectral attributes of the EEG are susceptible to changes under the influence of benzodiazepines, few studies have specifically analyzed the effects of bromazepam on qEEG variables. Saletu et al. (1989) compared the effects of single oral doses of a benzodiazepine agonist and diazepam (10 mg), on ten normal volunteers, and observed a "typical anxiolytic EEG profile", which is characterized by an increase in beta and a decrease in alpha. In another study, the same authors analyzed the effects of single oral doses of alpidem (an imidazo-pyridine derivative) and lorazepam, on ten normal volunteers, and the exact same pattern of results, i.e., EEG profile, was observed (Saletu et al. 1986). Specifically, studies employ-

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ing bromazepam are practically inexistent in the current literature. Bromazepam, possibly the most commonly employed benzodiazepine, has been used in the pharmacological treatment of anxiety since the early 60's. Its mechanism of action on the Central Nervous System is believed to be related to the ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter (Kopp et al. 2004, Puga et al. 2005).

One of the few studies that examined the effects of this particular drug on qEEG was conducted by Fink et al. (1976). The effects of single oral doses of bromazepam (9 mg) and diazepam (10 mg) in EEG data were analyzed for thirteen male adult volunteers and an analogous result was reached: increased beta and decreased alpha activity. Such changes seem to be characteristic for benzodiazepines (Saletu et al. 2006). Ohtani et al. (2002) conducted one of the few studies that specifically analyzed the effects of 3 mg bromazepam, on a sample of 12 healthy male volunteers. They observed increased beta activity that was directly proportional to an increase in the drug's plasmatic concentration (Ohtani et al. 2002). In this context, due to the lack of studies related to this topic, and with the intent of further exploring this issue, the present investigated the modulatory effects of this drug on brain dynamics. Specifically, the effects of bromazepam on cortical power distribution were analyzed.

MATERIALS AND METHODS

SUBJECTS

The sample consisted of 10 volunteers, 5 male and 5 female, with ages varying between 21 and 38 years (27 ± 5 years). All subjects were healthy, free of cognitive deficits and were not making use medication or any psychoactive or psychotropic substance at the time of the test. To ensure that subjects did not have any physical or mental health impairment, and to identify and exclude from the experiment any subjects who could contaminate future results, all participants were evaluated by a neuropsychiatrist. A questionnaire was developed and administered at the beginning of each test session to identify possible biological determinants, such as food intake, body temperature, fatigue, and drugs. Subjects signed a consent form, where the experimental condition

was thoroughly described. The experiment was approved by the Psychiatric Institute's Ethics Committee.

STUDY DESIGN AND PROCEDURES

Subjects received a capsule (bromazepam 3 mg or glucose) on three different occasions under a randomized, double-blind, crossover study. The procedures consisted of a three-day experiment: a day of bromazepam (B) and two of placebo (P1 and P2). On each day, the procedures were standardized in the following routine: 1) 10 minutes of EEG recording (5' eyes-closed / 5' eyes-open); 2) Administration of capsule (bromazepam or placebo); 3) The second EEG (10'), 20 minutes after drug ingestion; 4) The third EEG (10'), 60 minutes after drug ingestion.

EEG ACQUISITION

The study design respected the International Pharmacoelectroencephalography group guidelines (Harrison and Horne 2000). International 10/20 System (Jasper 1958) for electrode placement (referred to linked earlobes) was used with a 20-channel Braintech-3000 (EMSA-Medical Instruments, Brazil). The 20 monopolar electrodes were arranged in a nylon cap (ElectroCap Inc., Fairfax, VA). Impedance for EEG and EOG electrodes were under 5 K Ω and 20 K Ω , respectively. Visual inspection was employed for detection and elimination of artifacts. The data acquired had total amplitude of less than 100 μ V. The signal was amplified with a gain of approximately 22,000. Eye-movement (EOG) artifact was monitored with a bipolar electrode montage using two 9-mm diameter electrodes attached above and on the external canthus of the right eye. Moreover, Independent Component Analysis (ICA) was applied to remove possible sources of artifacts. The EEG signal was analogically filtered between 0.16 Hz (high-pass) and 35 Hz (low-pass), and sampled at 200 Hz. The acquisition software, developed at the Brain Mapping and Sensorimotor Integration Lab, was employed with the following digital filters: Notch (60 Hz), high-pass of 0.3 Hz and low-pass of 25 Hz.

DATA PROCESSING AND ANALYSIS

At least 2 min of artifact-free data were extracted from the EEG record for quantitative analysis. A Matlab 5.3[®] (Mathworks Inc., Natick, MA, USA) routine was implemented to perform a spectral analysis and estimate the

specific parameter of interest: band-limited EEG Relative Power, for delta (1.0-3.5 Hz), theta (4.0-7.5 Hz), alpha (8.0-12.0 Hz), and beta (13-25 Hz) frequency bands, between all pair combinations of electrodes. Power is a measure of amplitude and is analogous to the concept of signal strength; the greater the amplitude, the greater the amount of power in the EEG signal. Relative Power reflects the percentage of total power found in a specific band. Relative Power measures were log-transformed ($X' = \log [X/(1.0-X)]$) to acquire Gaussianity.

SPATIAL LOCALIZATION

Electrodes located over frontal, central and parietal areas were selected. Specifically, frontal areas were analyzed due to their association with attentional mechanisms, motivation and planning. Central and parietal electrodes were analyzed since they are representative of premotor and primary motor areas, as well as primary somatosensory and higher order somatosensory areas (Kandel et al. 2000).

STATISTICAL ANALYSIS

A total of four three-way ANOVAs, condition \times moment \times electrode ($3 \times 3 \times 3$), were performed for the electrophysiological measure, i.e., relative power, in each frequency band separately. A Post Hoc (Scheffé) was applied a posteriori. Experimental conditions were established as Bromazepam (B), Placebo 1 (P1), and Placebo 2 (P2), and experimental moments as 0' (before drug administration), 20' (twenty minutes after drug administration), and 60' (sixty minutes after drug administration). The selected electrodes were F3, F4, C3, C4, P3, P4 and four frequency bands were analyzed: delta, theta, alpha, and beta.

RESULTS

LOG RELATIVE POWER

In delta, the three-way ANOVA revealed significant main effects of condition [$F_{(2,537)} = 6.775$; $p = 0.001$], moment [$F_{(2,537)} = 7.314$; $p = 0.001$], and electrode site [$F_{(5,534)} = 20.525$; $p = 0.000$]. The Post Hoc indicated the following differences: P1 and P2 ($p = 0.001$); 0' and 20' ($p = 0.001$); F3 and F4 ($p = 0.043$), F3 and P3 ($p = 0.000$), F3 and P4 ($p = 0.002$), F4 and C3 ($p = 0.000$), F4 and C4 ($p = 0.000$), F4 and P3 ($p = 0.000$), F4 and P4 ($p = 0.000$), C4 and P3 ($p = 0.011$).

In theta, the analysis revealed significant main effects of condition [$F_{(2,537)} = 8.929$; $p = 0.000$] and electrode site [$F_{(5,534)} = 18.205$; $p = 0.000$]. The Post Hoc indicated the following differences in: B and P2 ($p = 0.006$), P1 and P2 ($p = 0.000$); F3 and F4 ($p = 0.017$), F3 and C3 ($p = 0.018$), F3 and P3 ($p = 0.000$), F3 and P4 ($p = 0.000$), F4 and P3 ($p = 0.004$), F4 and P4 ($p = 0.007$), C3 and P3 ($p = 0.000$), C3 and P4 ($p = 0.001$), C4 and P3 ($p = 0.004$), C4 and P4 ($p = 0.007$).

In alpha, main effects of moment [$F_{(2,537)} = 5.535$; $p = 0.004$] and electrode site [$F_{(5,534)} = 17.612$; $p = 0.000$] were found. The Post Hoc pointed out to the following differences: 0' and 20' ($p = 0.014$), 0' and 60' ($p = 0.019$); F3 and P3 ($p = 0.000$), F3 and P4 ($p = 0.000$), F4 and C3 ($p = 0.002$), F4 and C4 ($p = 0.004$), F4 and P3 ($p = 0.000$), F4 and P4 ($p = 0.000$).

In beta, the ANOVA did not reveal any main effects. No interactions were observed among the variables in any of the bands analyzed.

Figure 1 demonstrates differences among conditions (B, P1, P2), moments (0', 20', 60'), and electrode sites (F3, F4, C3, C4, P3, P4), in each frequency band (delta, theta, alpha and beta).

Figure 2 illustrates the cortical dynamics across the experimental conditions (B, P1 and P2) and moments (0', 20' and 60'), in delta, theta, alpha and beta.

DISCUSSION

The present study aimed at investigating the effects of bromazepam (3 mg) through a specific qEEG variable: relative power. The study was designed to combine three factors. The conjunction of experimental groups (i.e., conditions), drug intake (i.e., moment), and cortical areas (i.e., electrode sites) was established in the attempt to encompass possible sources of variability on brain neuroelectrical fluctuations. Given that patients and normal controls, in certain instances, respond differently to the changes induced by a drug, the understanding of drug-induced qEEG changes becomes imperative (Saletu et al. 2002). Since the late 1960's it has been reported that the intake of benzodiazepines generates a typical anxiolytic pharmac-EEG profile, which is characterized by increased beta and decreased alpha activity (Saletu et al. 1989, 1986, Herrmann 1982, Itil 1974, Matejcek and

Relative Power

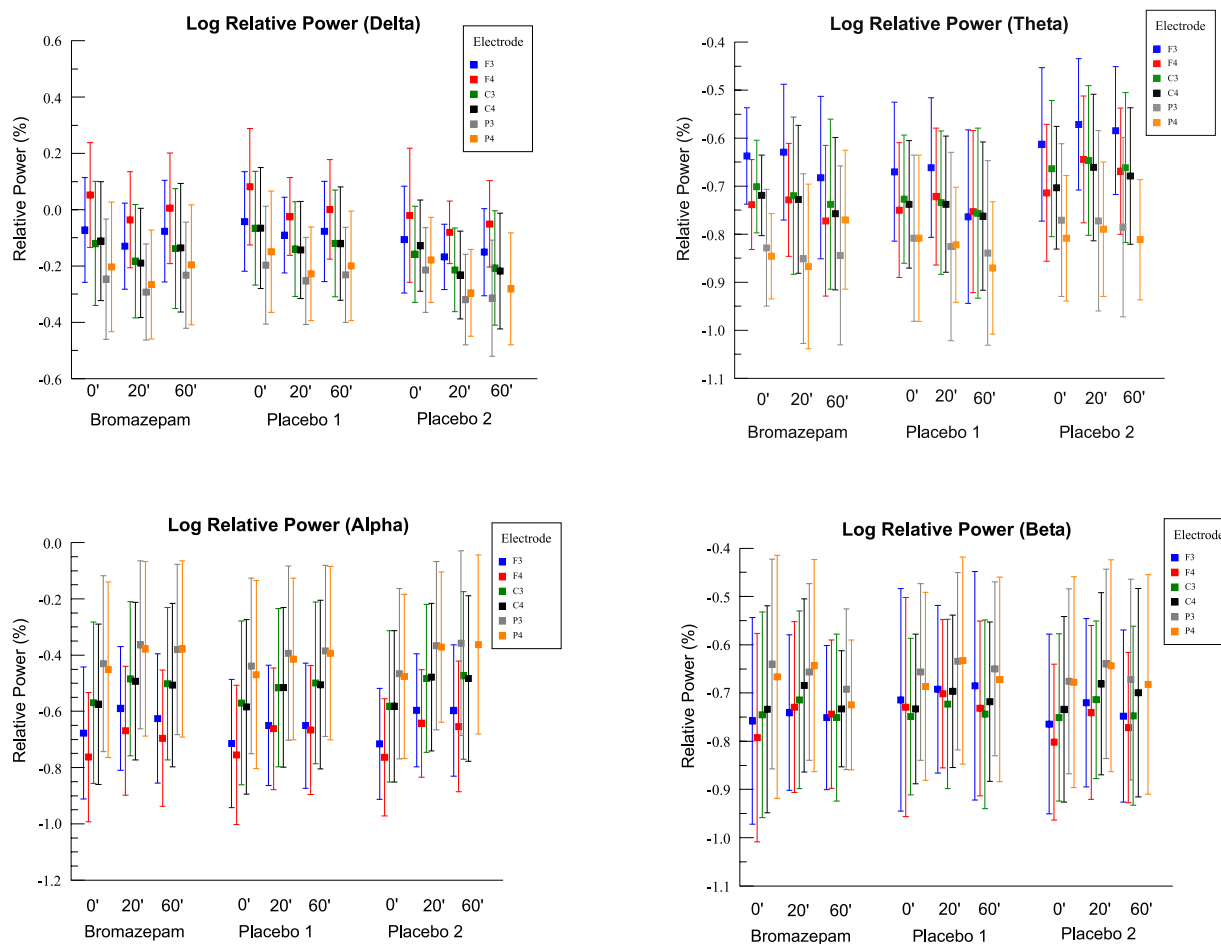


Fig. 1 – Log Relative Power variations across conditions (B, P1, P2), moments (0', 20', 60'), and electrodes (F3, F4, C3, C4, P3, P4), in each frequency band (delta, theta, alpha and beta).

Devos 1976). Saletu et al. (1986) and Fink et al. (1976) observed this specific pattern using higher dosages in their studies (diazepam 10 mg and bromazepam 9 mg). In addition, studies have shown that bromazepam does not induce augmentation of slow waves in the clinical dosage range, even if they are administered in extremely high doses (Saletu et al. 2002).

Such profile was not observed in the present study. The results of the statistical analyses pointed out to a main effect of condition in delta and theta, a main effect of moment in delta and alpha, and a main effect of electrode in all the analyzed bands. The main result of

the study was reflected by a significant decrease of relative power in delta and theta. However, this specific pattern was observed not only between the bromazepam group and the placebos (in theta), but also between the two placebo groups (in delta). Furthermore, in theta, relative power values were greater in the bromazepam group when compared to P1 but less when compared to P2. In delta, the opposite pattern was seen ($B < P1$ and $B > P2$). It must be stressed that, in delta, such differences between the bromazepam group and the placebos was not statistically significant. Therefore, these results represent only a trend of decrease/increase of relative

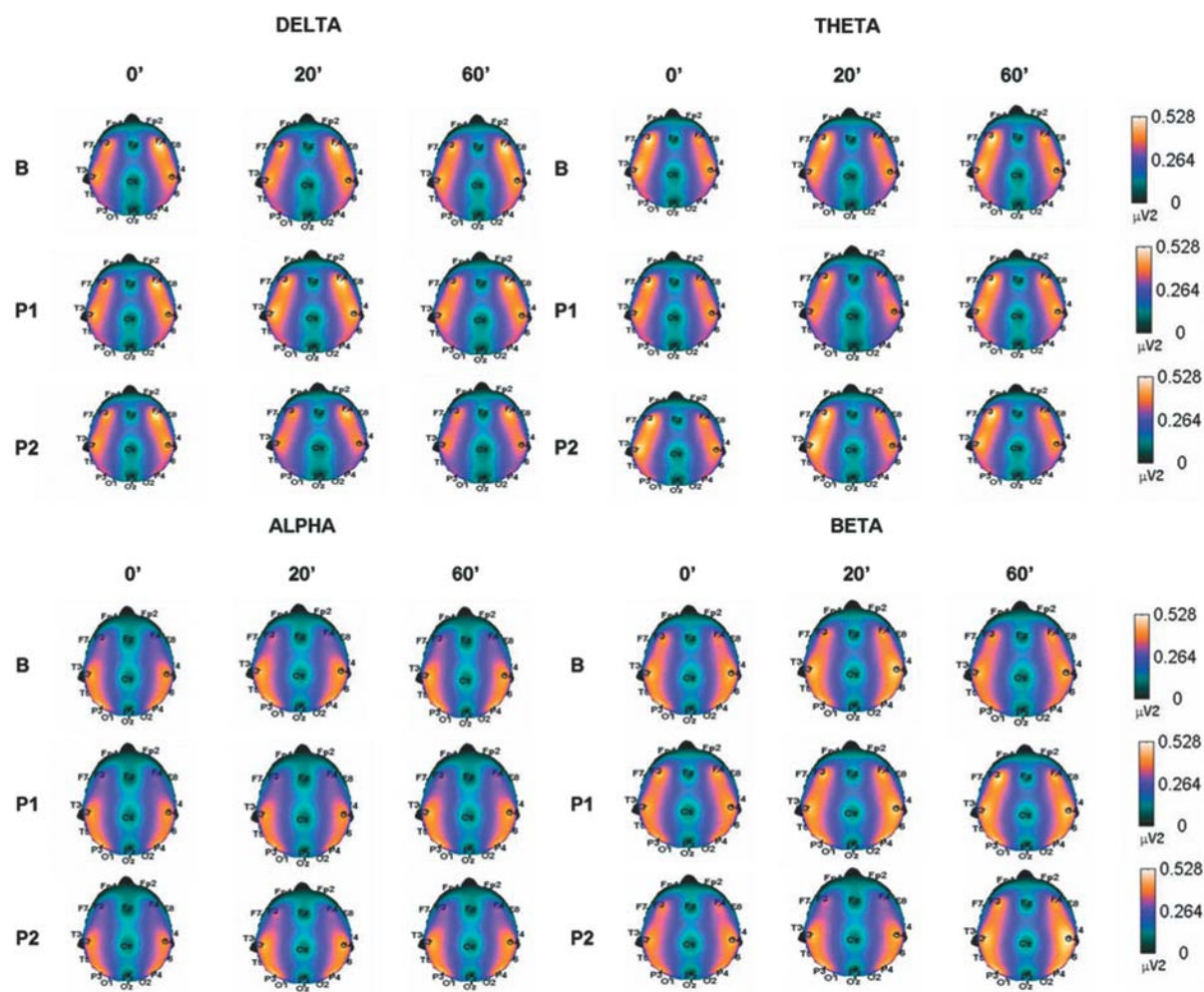


Fig. 2 – Cortical dynamics of EEG Relative Power variation across conditions (B, P1, P2) and moments (0', 20', 60'), in delta, theta, alpha and beta.

power values. In this sense, the administration of the drug per se may not account for such results. The moment and electrode main effects corroborate this line of reasoning. In other words, cortical dynamics may have differed between groups, moments, and electrodes due to factors such as study design and subjects' motivation, other than the drug itself. In the present study we specifically wanted to observe if small doses of bromazepam promoted any changes on brain dynamics, once previous studies had already analyzed higher doses. However the absence of a significant increase in beta and decrease in alpha may also be related to the low dosage administered, which may be regarded as a limitation of the study. It's possible that the typical anxiolytic pharmaco-EEG pro-

file only occurs with higher doses. However, Ohtani et al. (2002) observed an increase in beta with 3 mg bromazepam, showing that even low doses may promote an anxiolytic profile. In this sense, it is possible that in the present study the experimental design might have influenced the results (3 days of treatment). Other factors, such as participants' motivation and individual psychological characteristics (anxiety) might also account for the results observed.

In a general sense, further studies, using different doses of bromazepam and controlling variables such as motivation and anxiety levels, are necessary for a better understanding of the effects of this benzodiazepine on power distribution and other qEEG variables. Additional

studies are also necessary to thoroughly understand how different medications affect cortical brain dynamics.

RESUMO

O EEG tem sido amplamente empregado na avaliação de mudanças eletrofisiológicas induzidas por medicações distintas. A sensibilidade desta técnica em detectar alterações produzidas por uma substância pode ser aprimorada por métodos de análise quantitativa (EEGq). O presente estudo teve por objetivo investigar os efeitos modulatórios do bromazepam na dinâmica cerebral. Os efeitos de 3mg de bromazepam na distribuição de potência cortical foram observados em 10 indivíduos saudáveis, em um desenho duplo-cego. A medida eletrofisiológica foi analisada nas diferentes condições experimentais, momentos e eletrodos, em delta, teta, alfa e beta separadamente. Uma diminuição significativa de potência relativa foi observada em delta e teta (efeito principal para condição). Não foram observadas interações. Embora o perfil ansiolítico do EEG (aumento de beta e diminuição de alfa) não tenha sido observado, este resultado específico pode estar relacionado a outros fatores, tais como dose utilizada e estado fisiológico dos sujeitos, e não necessariamente à droga propriamente dita.

Palavras-chave: benzodiazepínico, bromazepam, EEG quantitativo, potência relativa, dinâmica cerebral.

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