

The effects of bromazepam over the temporo-parietal areas during the performance of a visuomotor task: A qEEG study

Fernanda Araújo^{a,k}, Sergio Machado^{a,f,i}, Flávia Paes^{i,j}, Marlo Cunha^{a,f,g}, Henning Budde^h, Mauricio Cagy^c, Luis F. Basile^{d,e}, Oscar Arias-Carrión^l, Bruna Velasques^{a,f,k,m,*}, Roberto Piedade^a, Pedro Ribeiro^{a,b,f}

^a Brain Mapping and Sensory Motor Integration, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Brazil

^b School of Physical Education, Bioscience Department (EEFD/UFRJ), Brazil

^c Division of Epidemiology and Biostatistics, Institute of Community Health, Federal Fluminense University (UFF), Rio de Janeiro, Brazil

^d Division of Neurosurgery, University of São Paulo Medical School, Brazil

^e Laboratory of Psychophysiology, Faculty of Psychology and Phonology, Methodist University of São Paulo (UMESP), Brazil

^f Institute of Applied Neuroscience (INA), Rio de Janeiro, Brazil

^g School of Physical Education, Laboratory of Motor Behavior, Federal University of Vale do São Francisco (UNIVASF) – Pernambuco, Brazil

^h Department of Movement and Training Science, Institute of Sports Science, Humboldt University zu Berlin, Germany

ⁱ Panic & Respiration Laboratory, Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

^j Faculty of Psychology, Brazilian Institute of Medicine and Rehabilitation (IBMR), Rio de Janeiro, Brazil

^k Neurophysiology and Neuropsychology of Attention, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Brazil

^l Department of Neurology, Phillips University Marburg, Marburg, Germany

^m Neuromuscular Research Laboratory, National Institute of Traumatology and Orthopaedics (NITO), Rio de Janeiro, Brazil

ARTICLE INFO

Article history:

Received 2 February 2011

Received in revised form 28 March 2011

Accepted 30 March 2011

Keywords:

Bromazepam

Electroencephalography

Sensorimotor integration

Theta

Visuomotor task

ABSTRACT

This study investigated the effects of bromazepam on qEEG when 14 healthy subjects were asked to perform a visuomotor task (i.e., motor vehicle driving task). The subjects were exposed to two experimental conditions: the placebo (PL) and 6 mg of bromazepam (Br 6mg), following a randomized, double-blind design on different days. Specifically, we observe absolute power extracted from qEEG data for theta band. We expected to see a decrease in absolute theta power in the temporal and parietal areas due to the influence of bromazepam for the experimental group when compared with the placebo group. We found a main effect for the condition factor for electrodes T3, T4, P3 and P4. We also observed a main effect for the period factor for electrodes P3 and P4. We observed that the ingestion of 6 mg of bromazepam induces different patterns in theta power at the temporal and parietal sites. We concluded that 6 mg of bromazepam was an important factor in the fluctuation of the activities in the temporal and parietal areas. We then hypothesize about the specific role of this drug during the execution of a visuomotor task and within the sensorimotor integration process.

© 2011 Elsevier Ireland Ltd. All rights reserved.

A relevant issue in cognitive neuroscience is the sensitivity of EEG activity to detect changes produced by different substances, such as bromazepam, methylphenidate and modafinil [8,25,27]. Changes in qEEG variables can be used to explore the mechanisms of drug effects in order to investigate sensorimotor integration and cognitive processes [7,8,17]. Benzodiazepine, particularly bromazepam, is the most prescribed and abused pharmacologic group (worldwide) for the management of anxiety and insomnia [20,4]. Benzodiazepines have been used to understand how the cerebral cortex works during the performance of sensorimotor integration

tasks. However, this is still not entirely understood. For instance, some studies have shown that bromazepam may impair psychomotor capacity when individuals are submitted to neuropsychological testing, such as memory, attention, reaction time, and vigilance performance [5,4]. It has been suggested that the impairment caused by bromazepam takes place in the early stages of sensory-motor integration (i.e., stimulus identification), thereby undermining the entire system of identification of the stimulus to the execution of motor task [7,11]. This study is justified by the increase in the prescription of benzodiazepines and their use in addition there is a lack of studies on the effects of this drug on sensory-motor integration in healthy subjects.

We used a paradigm similar to the S1–S2 paradigm to investigate sensorimotor integration during a visuomotor task. The paradigm involves a warning stimulus (S1) and an imperative

* Corresponding author at: Rua Paula Brito 350/1102, Andaraí, CEP 20541-190, Rio de Janeiro, RJ, Brazil. Tel.: +55 21 25714134.

E-mail address: bruna.velasques@yahoo.com.br (B. Velasques).

stimulus (S2), however, we did not analyze the contingent negative variation (CNV). One of the most influential neurophysiological theories about the S1–S2 paradigm is that it readies the cortex for processing the next stimulus and response, i.e., S2 stimulus, due to an advisory signal, i.e., S1 stimulus [11]. According to those principles and considering the features of each area, we expected to see the effects of bromazepam in the left and right temporal and parietal cortices. Several studies demonstrated that the temporal areas are involved in the transmission of multimodal sensory information, i.e., neurons in these areas are sensible to stimuli of different modalities, enabling multisensory interactions [1,9,17]. Moreover, the parietal lobe integrates sensory information from several channels [9,21].

Thus, our objective is to investigate the effects of bromazepam on qEEG when subjects were submitted to a visuomotor task (i.e., motor vehicle driving task). Specifically, we observed absolute power extracted from qEEG data for theta band. The increase of theta power has been related to increases in mental effort during the encoding of sensory information, attention demand, higher task difficulty and increasing cognitive load [18,19,31]. We expected to see a decrease in absolute power for the experimental group when compared with the placebo group in the left and right temporal and parietal areas due to the drug's influence. Thus, the assessment of qEEG may unveil how the temporal and parietal areas participate in the organization and integration of sensory information, in other words, the performance of cognitive operations and the achievement of motor control during the performance of multiple complex tasks under the effect of bromazepam.

The sample was composed of 14 healthy subjects (nine male and five female; mean age: 32.5, SD: 9.5). The inclusion criteria included the absence of mental or physical impairments and no history of psychoactive or psychotropic substance use (screened by a previous anamnesis and a clinical examination). All subjects were also right handed, according to the Edinburgh inventory [24]. Moreover, they had no less than 6–8 h of sleep prior to the experiment and no previous experience with the task. All subjects signed a consent form and were aware of the experimental protocol. The experiment was approved by the Ethics Committee at the Federal University of Rio de Janeiro according to the principles of Helsinki Declaration [13].

The task was performed in a sound and light-attenuated room, to minimize sensory interference. Each subject was exposed to both the experimental conditions: the placebo (PL) and 6 mg of bromazepam (Br 6 mg), following a randomized, double-blind design on different days. (Thus, each subject was exposed to one condition on the first day and the other condition on the second day. The subjects performed the conditions in one week interval.) After the capsule ingestion, subjects remained at rest for 1 h [23]. Then, a computer monitor (Samsung-SyncMaster 550v) was positioned in front of the subjects as they sat on a comfortable chair to minimize muscular artifacts, while electroencephalography (EEG) data were recorded before, during and after the motor task execution.

Subjects were asked to perform a visuomotor task (S1–S2 paradigm – motor vehicle driving task). The task was controlled and synchronized with the qEEG recording by the software Car Acquisition (Delphi 5.0). The visuomotor task consisted of driving a car at a slow and fixed speed. Subjects were instructed to pay attention to curves and to respond as quickly possible when an action command appeared. The proper response was to press the anterior button of the joystick (Model Quick Shot-Crystal CS4281) which was fixed onto a support attached under the chair, to avoid hand instability. Each subject was submitted to 50 trials under each experimental condition. The task was composed of 0.5 ms periods, before and after the appearance of each stimulus (i.e., pre-S1, post-S1, pre-S2 and post-S2). The warning stimulus (S1 – yellow square)

and the action stimulus or command (S2 – red triangle) appeared at a fixed interval of 2.5 s (intra-stimulus interval). However, the interval between the re-appearance of S2 and S1 varied randomly from 2.5 and 15 s (inter-stimulus interval) to avoid providing cues for the occurrence of S1.

The International 10/20 EEG System for electrodes [16] was used with the 20-channel EEG Braintech-3000 system (EMSA-Medical Instruments, Brazil). The 20 electrodes were arranged in a nylon cap (ElectroCap Inc., Fairfax, VA, USA) yielding monopolar derivations referred to linked earlobes. In addition, two 9-mm diameter electrodes were attached above and on the external corner of the right eye, in a bipolar electrode montage, for the monitoring of eye-movement (EOG) artifacts. Impedance of EEG and EOG electrodes was kept between 5 and 10 k Ω . The amplitude of the data acquired totaled less than 100 μ V. 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 Car Acquisition (Delphi 5.0) at the Brain Mapping and Sensory Motor Integration Lab was employed with the following digital filters: notch (60 Hz), high-pass of 0.3 Hz and low-pass of 25 Hz.

To quantify reference-free data, a visual inspection and independent component analysis (ICA) were applied to remove as many sources of artifacts produced by the task as possible [15]. Data from individual electrodes exhibiting loss of contact with the scalp or high impedances (>10 k Ω) were deleted and data from single-trial epochs exhibiting excessive movement artifacts (\pm 100 μ V) were also deleted. ICA was then applied to identify and remove any remaining artifacts after the initial visual inspection. ICA is an information maximization algorithm that is derived from spatial filters through the blind source separation of EEG signals into temporally independent and spatially fixed components. Independent components resembling eye-blink or muscle artifacts were removed and the remaining components were then back-projected onto the scalp electrodes by multiplying the input data by the inverse matrix of the spatial filter coefficients derived from ICA using established procedures. The ICA-filtered data were then re-inspected for residual artifacts using the same rejection criteria described above. Then, a classic estimator was applied for the power spectral density (PSD), or directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB 5.3 (Matworks, Inc.). Quantitative EEG parameters were extracted from 2 s periods (the selected epoch started 0.5 ms before and after the appearance of each stimulus, i.e., S1 and S2, respectively), for consecutive (non-overlapping) artifact-free, 2-s EEG epochs (spectral resolution: 0.25 Hz), with rectangular windowing. In this manner, based on artifact-free EEG epochs, the threshold was defined by mean plus three standard deviations. Epochs with a total power higher than this threshold were not integrated into the analysis.

We analyzed the anterior-temporal (T3 and T4) and the parietal (P3 and P4) areas. The first one plays an important role in supplying multimodal sensory information for the performance of voluntary movements and sensorimotor integration [12]. The parietal areas are functionally related to the integration of sensory information from different modalities [21], manipulation of objects, attention and visuospatial processing [2,6]. The theta band (4.5–8 Hz), was chosen due to its association with cognitive functions such as stimuli encoding [3], attention mechanisms [29] and information transmission [19].

The qEEG absolute power values were log₁₀-transformed by SPSS software (version 16.0) to approximate a normal distribution. A two-way ANOVA was used to analyze between the conditions (i.e., PL \times Br 6 mg), and between the periods (i.e., pre-S1, post-S1, pre-S2, post-S2) for each electrode (i.e., T3, T4, P3, P4). A Scheffé test was applied to analyze significant differences between the periods ($p < 0.05$).

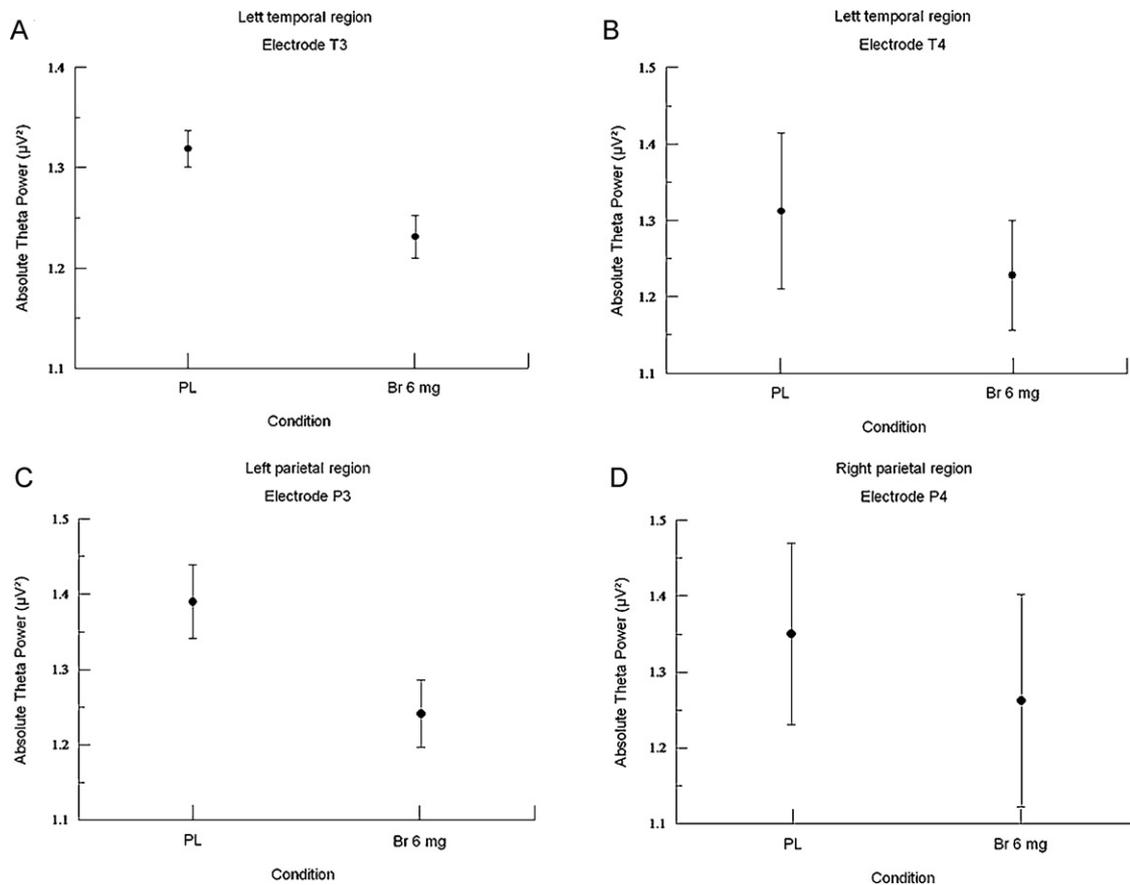


Fig. 1. (A) Main effect for factor condition observed in the electrode T3 by mean and SD (significant difference; $p < 0.003$). (B) Main effect for factor condition observed in the electrode T4 by mean and SD (significant difference; $p < 0.006$). (C) Main effect for factor condition observed in the electrode P3 by mean and SD (significant difference; $p < 0.001$). (D) Main effect for factor condition observed in the electrode P4 by mean and SD (significant difference; $p < 0.001$).

The two-way ANOVA with repeated measures indicated a main effect for the condition factor at T3 ($p = 0.003$; $F = 7.070$; Fig. 1A), T4 ($p = 0.006$; $F = 5.921$; Fig. 1B), P3 ($p = 0.001$; $F = 55.793$; Fig. 1C) and P4 ($p = 0.001$; $F = 13.764$; Fig. 1D) electrodes. The analysis of the T3 and T4 electrodes demonstrated a lower power value for Br 6 mg when compared to PL. The analysis of the P3 and P4 electrodes showed a lower power for Br 6 mg when compared to PL.

The two-way ANOVA also revealed a main effect for the period factor for electrodes P3 (Fig. 2A) and P4 (Fig. 2B). Further post hoc analyses revealed a significant difference among periods for both electrodes. The analysis of the electrode P3 demonstrated a lower power value in pre-S1 when compared to post-S1 ($p = 0.007$) and post-S2 ($p = 0.007$). Post-S1 demonstrated a higher value when compared to pre-S2 ($p = 0.012$). And the power value in pre-S2 was lower than post-S2 ($p = 0.012$). The analysis of the electrode P4 showed a lower power value in pre-S1 when compared to post-S1 ($p = 0.007$) and post-S2 ($p = 0.035$). Post-S1 demonstrated a higher value when compared to pre-S2 ($p = 0.005$). And the power value in pre-S2 was lower than post-S2 ($p = 0.024$).

This study aimed to verify the effects of bromazepam on qEEG absolute theta power when subjects were submitted to a visuo-motor task (i.e., motor vehicle driving task). Our task involved unpredictable situations where a car must be controlled on a virtual track with different types of curves at different velocities. In this manner, the assessment of qEEG may unveil how the cerebral cortex participates in the organization and integration of sensory information, thus the performance of cognitive operations and the achievement of motor control during the performance of multiple complex tasks under the effects of bromazepam.

We observed a decrease in theta power for the Br 6 mg group when compared with the PL group for the T3, T4, P3 and P4 electrodes. It is well-documented that the temporal areas are influenced by the somatosensory cortex, which plays an important role in supplying multimodal sensory information to sensorimotor integration processes (supplying the right hemisphere) and voluntary movements (i.e., supplying the left hemisphere) [12,28]. The reduction in theta power for Br 6 mg appears to be strongly associated with the encoding of sensory integration, such as stimulus detection and attention (i.e., stimuli appearance – S1–S2) based on its temporal relation to the onset of targets and its spatial distribution over the left temporal areas (i.e., T3 electrode). Moreover, the temporal region is involved with the formation of new memories, and in this case, those of a spatial nature (i.e., T4 electrode). The subjects were submitted to a task that involved unpredictable situations demanding attention in order to control a car on a virtual track that presents various forms and types of curves at different speeds, thus creating an increasing cognitive load (i.e., spatial and temporal perception) [17]. We observed a reduction of activity over temporal area in the presence of bromazepam when compared to placebo. This finding is interpreted as an interference of bromazepam in the multimodal transmission demanded by the task, producing changes in the communication of different sensory modalities.

For the parietal cortex we found the same result seen in the temporal cortex. However, the changes produced by the bromazepam over the cortex parietal suggest an interference in the integration of sensory information, particularly those associated with the identification of spatial features due to the characteristics of the task. In the right parietal areas, we observed a decrease in absolute theta

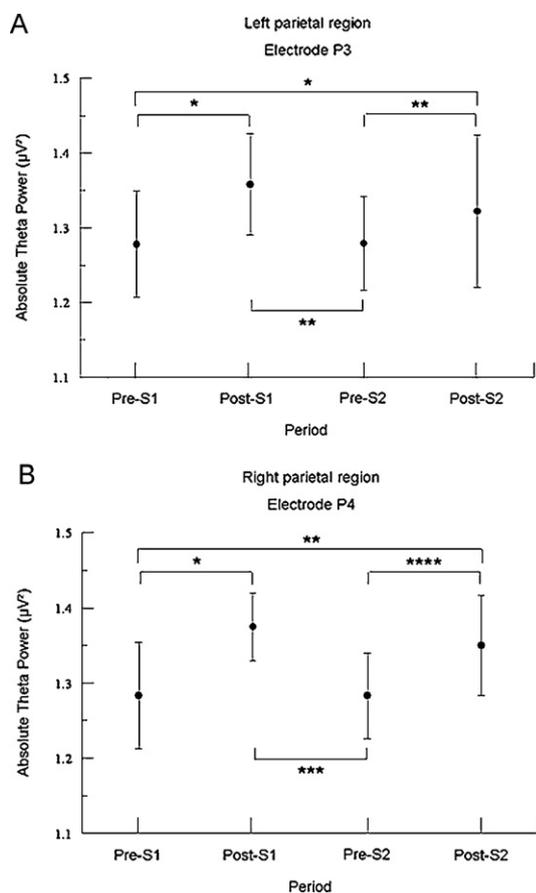


Fig. 2. (A) Main effect for factor period observed in the electrode P3 by mean and SD. *Significant difference (Scheffé test; $p < 0.007$). **Significant difference (Scheffé test; $p < 0.012$). (B) Main effect for factor period observed in electrode P4 by mean and SD. *Significant difference (Scheffé test; $p < 0.007$). **Significant difference (Scheffé test; $p < 0.035$). ***Significant difference (Scheffé test; $p < 0.005$). ****Significant difference (Scheffé test; $p < 0.024$).

power. The control of spatial attention involves several processes for both the right and left visual fields and monitoring function in conflict situations, when experiencing a mismatch between motor intention, proprioception and/or visual feedback [10,22,30]. In this context, the increase of absolute theta power for the PL condition revealed that it is likely associated with the several visuospatial mechanisms presented in the experimental task, the integration among these mechanisms and the motor response required by the task. Theta band is largely related to attention mechanisms and information transmission [18,19,31]. Specifically, we observed a decrease of absolute theta power for the Br 6 mg condition in the right parietal cortex. Thus, our results suggest a reduction of mental effort for sensorial information detection and spatial attention caused by the drug administration [11]. In conclusion, our results demonstrate that 6 mg of bromazepam interferes in the multisensory integration process, and indicates that the drug affects the integration process and attention mechanism.

The left parietal area (electrode P3) is guided by internal representations [28]. Particularly, we observed a reduction of absolute theta power in the left parietal area for the bromazepam 6 mg condition, and an increased absolute theta power for the placebo condition. This result is associated with a decrease in attention, resulting in a processing impairment of internal representations. The decrease of absolute theta power represents the reduction of attention during the task, specifically the attention related to the voluntary control of the motor task [14,26]. For our task,

subjects have to pay attention on the curves, and to respond as quickly as possible, when the action command appears. To execute this task, an improvement of spatial attention is necessary. It requires integration and coordination between the sensorial information and motor control over the joystick. Six milligrams (6 mg) of bromazepam impaired the early stages of sensorimotor integration, hindering the detection of stimulus and attention. This result demonstrates a decrease in attention for the detection of stimuli S1 and S2, resulting in an increased difficulty in performing the task and a delayed onset of motor action. We conclude that bromazepam affects the processing of information. It probably suggests that the drug interferes in the transmission of different multimodal sensitive information in the temporal areas and then in the integration of these information in the parietal areas, thereby slowing all the mechanisms for the execution of motor task.

We found a main effect for the factor period at electrodes P3 and P4. We found the same result for both electrodes. We observed a lower absolute theta power in pre-S1 when compared to post-S1 and -S2. We also verified a higher value in post-S1 when compared to pre-S2 and a lower value in pre-S2 when compared to post-S2. The S1 stimulus is a warning to the next stimulus and the S2 stimulus is imperative, in other words, the subject must perform a motor task when S2 appears (for more detailed information see Ref. [11]). Our results are explained by the characteristics of each stimulus (S1 and S2). We will focus on the differences between pre-S1 and post-S1, and the pre-S2 and post-S2. Although, we observed a difference between post-S1 and pre-S2, our discussion is concerned with the main stimuli.

Our findings demonstrated a decrease in absolute theta power before the stimuli when compared with the post-stimuli, for both warning and imperative. The increase in post-stimulus may be associated with a decoding of information. Thus, the warning and imperative stimuli are processed similarly to the parietal cortex. However, the explanation of the stimulus processing becomes differentiated due to the features of each stimulus. The function of the S1 stimulus is to warn that something will happen (i.e., the appearance of imperative stimulus). As a result of the S1 presentation, we observed a period of alertness, expectation and highest attention. The alertness is related to the expectation of the appearance of the next stimulus (i.e., S2). Our result demonstrates a peak of absolute theta power 0.5 s after the warning stimulus and we interpreted as an increase in spatial functions with the approximation of the imperative stimulus. Previous studies demonstrated that an increase in theta power is associated with mental effort during the encoding of information and increasing cognitive load [18,19,31]. When we observe a highest absolute theta power over the parietal cortex after the warning stimulus, we interpret it as an increase in attention in order to recognize the appearance of the S2 stimulus.

Observing the pre- and post-S2 periods, we found a decrease of absolute theta power 0.5 s before the appearance of S2 and an increase of absolute theta power 0.5 s after the presentation of the S2 stimulus. In our task, the participants had to control a car on a virtual track, so they had to encode sensory information to store and to recover route information (i.e., different forms and types of curves). Although the subjects need some level of attention before S2, they are at rest waiting for the imperative stimulus. After the appearance of S2, the subjects begin the motor task. When these two periods are compared, we verified an increase in the period that occurs 0.5 s after the S2 stimulus. As a result, we identified that the post-S2 period demands more spatial attention and integration among sensorial information because the subjects need to start the motor task requested. According to our results, the subjects probably employed unexplored attention mechanisms to drive the car on different types of curves. We conclude that bromazepam changes the stimulus processing in the initial phase of sensorimotor

tor integration, i.e., identification of stimulus, therefore retard the identification of S1 and S2 stimulus.

References

- [1] T. Allison, A. Puce, G. McCarthy, Social perception from visual cues: role of the STS region, *Trends Cogn. Sci.* 4 (7) (2000) 267–278.
- [2] M. Avillac, S. Deneve, E. Olivier, A. Pouget, J.R. Duhamel, Reference frames for representing visual and tactile locations in parietal cortex, *Nat. Neurosci.* 8 (7) (2005) 941–949.
- [3] M. Bastiansen, J. Berkum, P. Hagoort, Event-related theta power increases in the human EEG during online sentences processing, *Neurosci. Lett.* 323 (2002) 13–16.
- [4] C. Blanco, S.X. Antia, M.R. Liebowitz, Pharmacotherapy of social anxiety disorder, *Biol. Psychiatry* 51 (1) (2002) 109–120.
- [5] M. Bourin, J.L. Auget, M.C. Colombel, C. Larousse, Effects of single oral doses of bromazepam, buspirone and clobazam on performance tasks and memory, *Neuropsychobiology* 22 (3) (1989) 141–145.
- [6] C.A. Bueno, R.A. Andersen, The posterior parietal cortex: sensorimotor interface for the planning and online control of visually guided movements, *Neuropsychologia* 44 (13) (2006) 2594–2606.
- [7] M. Cunha, D. Machado, V.H. Bastos, C. Ferreira, M. Cagy, L. Basile, R. Piedade, P. Ribeiro, Neuromodulatory effect of bromazepam on motor learning: an electroencephalographic approach, *Neurosci. Lett.* 407 (2006) 166–170.
- [8] M. Cunha, C. Portela, V.H. Bastos, D. Machado, S. Machado, B. Velasques, H. Budde, M. Cagy, L. Basile, R. Piedade, P. Ribeiro, Responsiveness of sensorimotor cortex during pharmacological intervention with bromazepam, *Neurosci. Lett.* 448 (2008) 33–36.
- [9] M. Dapretto, M.S. Davies, J.H. Pfeifer, A.A. Scott, M. Sigman, S.Y. Bookheimer, M. Iacoboni, Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders, *Nat. Neurosci.* 9 (1) (2006) 28–30.
- [10] G.R. Fink, J.C. Marshall, P.W. Halligan, C.D. Frithet, J. Driver, R.S. Frackowiak, R.J. Dolan, The neural consequences of conflict between intention and the senses, *Brain* 122 (1999) 497–512.
- [11] S. Fridman, S. Machado, M. Cunha, B. Velasques, F. Pompeu, H. Budde, M. Cagy, L.F. Basile, R. Piedade, P. Ribeiro, Effects of bromazepam in frontal theta activity on the performance of a sensorimotor integration task: a quantitative electroencephalography study, *Neurosci. Lett.* 451 (2009) 181–184.
- [12] J.M. Fuster, The cognit: a network model of cortical representation, *Int. J. Psychophysiol.* 60 (2) (2006) 125–132.
- [13] S. Giordano, The 2008 Declaration of Helsinki: some reflections, *J. Med. Ethics* 36 (October (10)) (2010) 598–603.
- [14] K. Haaland, Left hemisphere dominance for movement, *Clin. Neuropsychol.* 20 (2006) 609–622.
- [15] J. Iriarte, E. Urrestarazu, M. Valencia, M. Alegre, A. Malanda, C. Viteri, J. Artieda, Independent component analysis as a tool to eliminate artifacts in EEG: a quantitative study, *J. Clin. Neurophysiol.* 20 (2003) 249–257.
- [16] H. Jasper, The ten-twenty electrode system of the international federation, *Electroencephalogr. Clin. Neurophysiol.* 10 (1958) 371–375.
- [17] S.E. Kerick, L.W. Douglass, B.D. Hatfield, Cerebral cortical adaptations associated with visuomotor practice, *Med. Sci. Sports Exerc.* 36 (1) (2004) 118–129.
- [18] M. Kimura, J. Katayama, H. Murohashi, Probability-independent and probability-dependent ERPs reflecting visual change detection, *Psychophysiology* 43 (2006) 180–189.
- [19] W. Klimesch, EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis, *Brain Res. Brain Res. Rev.* 29 (1999) 169–195.
- [20] M. Llorente, D. David, A. Galden, M. Silverman, Defining patterns of benzodiazepines use in older adults, *J. Geriatr. Psychiatry Neurol.* 13 (2000) 150–160.
- [21] W.P. Medendorp, H.C. Goltz, T. Vilis, J.D. Crawford, Gaze-centered updating of visual space in human parietal cortex, *J. Neurosci.* 23 (15) (2003) 6209–6214.
- [22] M.M. Mesulam, Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events, *Philos. Trans. R. Soc. Lond. B: Sci.* 354 (1999) 1325–1346.
- [23] Y. Ohtan, T. Kotegawa, K. Tsutsumi, T. Morimoto, Y. Hirose, S. Nakano, Effect of fluconazole on the pharmacokinetics and pharmacodynamics of oral and rectal bromazepam: an application of electroencephalography as the pharmacodynamic method, *Clin. Pharmacol.* 42 (2) (2002) 183–191.
- [24] R. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, *Neuropsychology* 9 (1) (1971) 97–113.
- [25] F. Paes, S. Machado, O. Arias-Carrón, C.A. Domingues, S. Teixeira, B. Velasques, M. Cunha, D. Minc, L.F. Basile, H. Budde, M. Cagy, R. Piedade, S. Kerick, M. Menéndez-González, S.D. Skaper, B.A. Norwood, P. Ribeiro, A.E. Nardi, Effects of Methylphenidate on performance of a practical pistol shooting task: a quantitative electroencephalography (qEEG) study, *Int. Arch. Med.* 4 (1) (2011) 6.
- [26] M.F.S. Rushworth, H. Johansen-Berg, S.M. Gobel, J.T. Devlin, The left parietal and premotor cortices: motor attention and selection, *NeuroImage* 20 (2003) S89–S100.
- [27] M.T. Saletu, P. Anderer, G.M. Saletu-Zyhljarz, M. Mandl, O. Arnold, D. Nosiska, J. Zeithofer, B. Saletu, EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil, *Eur. Arch. Psychiatry Clin. Neurosci.* 255 (1) (2005) 20–32.
- [28] D. Serrien, R. Ivry, S. Swinnen, Dynamics of hemispheric specialization and integration in the context of motor control, *Nat. Rev. Neurosci.* 7 (2) (2006) 160–167.
- [29] M. Smith, L. McEvoy, A. Gevins, Neurophysiological indices of strategy development and skill acquisition, *Cogn. Brain Res.* 7 (1999) 389–404.
- [30] N. Wenderoth, F. Debaere, S. Snaert, P. Van Hecke, S.P. Swinnen, Parieto-premotor areas mediate directional interference during bimanual movements, *Cereb. Cortex* 14 (2004) 1153–1163.
- [31] G.F. Wilson, C.A. Russell, Real-time assessment mental workload using psychophysiological measures and artificial neural networks, *Hum. Factors* 45 (2003) 635–643.