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Research Report

A neurophysiological study of the detrimental effects of alprazolam on human action monitoring

Jordi Riba [a,c,*], Antoni Rodríguez-Fornells [b], Thomas F. Münte [c], Manel J. Barbanoj [a]

[a] Centre d'Investigació de Medicaments, Institut de Recerca, Servei de Farmacologia Clínica, Hospital de la Santa Creu i Sant Pau (HSCSP), Departament de Farmacologia i Terapèutica, Universitat Autònoma de Barcelona, Barcelona 08025, Spain
[b] Institució Catalana de Recerca i Estudis Avançats (ICREA) and Faculty of Psychology, University of Barcelona, Barcelona 08035, Spain
[c] Department of Neuropsychology, Otto von Guericke University, Universitätsplatz 2, 39106 Magdeburg, Germany

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Abstract

In order to adapt their behavior to different unexpected situations, humans need to be able to monitor their performance and detect and correct errors. Benzodiazepines have long been shown to impair performance in humans, but the performance-related neurophysiological processes targeted by these drugs remain largely unknown. In the present article, we assessed the impact of alprazolam administration on relevant aspects of action monitoring, i.e., the monitoring of response conflict and the detection and correction of errors by means of neurophysiological measures. Multichannel event-related brain potentials (ERPs) were recorded to assess the impact of the benzodiazepine alprazolam (0.25 mg and 1.00 mg) on action monitoring and motor preparation in a group of twelve healthy male volunteers who participated in a double-blind cross-over placebo-controlled clinical trial involving a letter flanker task. Error detection was evaluated using the error-related negativity (ERN); response conflict on correct trials was measured by means of the N2 amplitude difference between congruent and incongruent trials; motor preparation was assessed by means of the lateralized readiness potentials (LRPs); and post-error adjustments were assessed by measuring post-error slowing in reaction time. Alprazolam significantly reduced the amplitude of the ERN and the number of corrective responses and increased reaction time and LRP latencies. The drug had no effect on amplitude differences in the N2 component between congruent and incongruent trials or on post-error slowing. Thus, alprazolam was shown to affect brain correlates of error detection (ERN) and motor preparation (LRPs), while it did not disturb conflict monitoring on correct trials (N2) or post-error adjustments of behavior.

Theme: Neural basis of Behavior
Topic: Psychopharmacological agents

Keywords: Action monitoring; ERN; Benzodiazepine; Alprazolam; Human

1. Introduction

Error monitoring and error correction are important executive functions which help humans to adapt to their environment and anticipate, learn, correct and mend the consequences of their actions [35]. These functions are useful to avoid possible accidents (e.g., while driving) and to monitor error-prone situations [39]. The assessment of benzodiazepine effects on action monitoring appears especially relevant considering the negative impact of these drugs on alertness and driving abilities [54] and the increased accident risk associated with their use [48]. Any impairment of these capabilities would therefore have a detrimental effect on the correct adaptation of patients receiving benzodiazepines to environmental requirements. Therefore, the present study targeted the effects of alprazolam on action monitoring including the stages of stimulus categorization,

* Corresponding author. Department of Neuropsychology, University of Magdeburg, Universitätsplatz 2, 39106 Magdeburg, Germany. Fax: +49 3916711947.
E-mail address: jordi.riba@nat.uni-magdeburg.de (J. Riba).

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conflict detection on correct trials, error detection, motor preparation and post-error adjustments by means of behavioral measures and event-related brain potentials (ERPs).

1.1. ERP indices of self-monitoring: the error-related negativity (ERN) and the N2

The peak of the error-(related) negativity (ERN or Ne[1]) is observed approximately 60–100 ms after the erroneous response in averages computed time-locked to the subject's response. It is followed by a positive component called the error positivity or Pe [14,17]. The ERN is maximal when accuracy is stressed [17] but, in some circumstances, is present even when errors are not consciously detected [33]. The ERN has been interpreted as a physiological correlate of the error detection process proper (that is, the more salient an error is, the more pronounced the ERN will be) (for a recent review, see [21]). Other authors have highlighted the role emotional and motivational aspects of the error in the generation of the ERN [4,27,28]. Furthermore, a recent theory views the ERN as a particular case of activation of a neural system responsible for detecting conflict [2,6]. This theory postulates that the system that generates the ERN is active in trials in which two competing responses are activated. Supporting this view, a second scalp potential, the N2, which is observed in the stimulus-locked averages, has been found to be enhanced in correct responses to high conflict trials, e.g., incongruent flanker stimuli (see below) [51]. The relationship between the ERN and corrective behavior has recently been addressed [43]. In this study, the increased ERN amplitude found for very fast-corrected errors as compared with slow corrections suggested an involvement of the process underlying the ERN in the correction and compensation of erroneous responses. Regarding the neuroanatomical substrates of the ERN, neural sources have been located in the rostral anterior cingulate cortex (ACC) and adjacent areas of the frontomedian wall, using event-related functional magnetic resonance imaging (fMRI) [5,16,25,50], intracerebral ERP recordings [3] and dipole source modeling [10,27,28].

1.2. ERP indices of motor preparation: the LRP

The LRP is a measure of the lateral asymmetry in the electrical potential over the motor cortex and has been used to detect the differential engagement of the left and right motor cortices in the preparation of action [7,11,18,46]. It can be computed from the ERP by a double subtraction procedure, i.e., subtracting activity at the right hemisphere lateral central electrode site from the corresponding left hemisphere activity and subtracting left from right hand responses. This way, the electrical activity related to differential activation of the contra- and ipsilateral motor cortex is isolated. The onset of the LRP has been shown to be a sensitive measure of response preparation, indexing the time at which central response activation becomes selective with respect to the response hand, the complexity of the movement [19] and the information related to response preparation [11,18]. The LRP has both a well-defined neuroanatomical source and a well-defined locus within the information processing sequence [31,49]. Using spatiotemporal dipole modeling, the neural generator of the LRP in voluntary movements has been located just anterior to the central sulcus (primary motor cortex), which accounts for most of the lateralized pre-movement activity [37,38,52].

1.3. Objectives

In the present study, the effects of two different doses of alprazolam on action monitoring and motor preparation were analyzed, while subjects performed a standard flanker task [13]. Stimulus evaluation and identification were evaluated by means of the P300, a centroparietal positivity that peaks between 200 and 600 ms after stimulus presentation, which is believed to reflect the categorization of task-relevant information [12,36,53]. Error detection was studied using the ERN/Pe components; and motor preparation was analyzed using stimulus- and response-locked LRPs. Previous studies with benzodiazepines have addressed the effects of single doses of oxazepam [23] and lorazepam [9] on the ERN, reporting amplitude decreases for this wave after drug administration. While the study by Johannes and coworkers [23] only assessed the ERN, the P300 and behavioral measures of error correction, De Bruijn and coworkers [9] extended their analyses to the Pe and to conflict on correct responses as measured by the N2. In this study, although lorazepam did not affect the incongruency effect at the behavioral level (i.e., increase of reaction time and error rate in incongruent trials relative to congruent trials), the authors reported a suppression of the N2 effect. However, an inspection of their data suggests that this effect may have been delayed rather than abolished, thus hinting at a differential effect of benzodiazepines on the ERN and the N2. Another recent study has also observed this dissociation for the α_2-adrenoceptor antagonist yohimbine, which selectively increased ERN amplitude but not the N2 [41].This is an important issue which we address in the present study. Because the conflict theory postulates the same neural substrates for the N2 and the ERN in the anterior cingulate cortex [2], which would lead one to expect both waves to be similarly affected by benzodiazepines or other drugs, evidence from fMRI studies suggests that error monitoring and conflict detection could have different neural substrates [50], making it possible for benzodiazepines to target one process while sparing the other. Thus, additional drug data can provide new insight into the interrelationships of the two processes. Furthermore, in the present study, in addition to behavioral measures of error correction, we provide a detailed analysis of the motor preparation processes occur-

[1] The acronyms ERN and Ne are used interchangeably in the literature.

ring prior and subsequent to the emission of erroneous responses and of the relationship in terms of timing between the corrective response and the ERN.

2. Materials and methods

The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans and was approved by the Hospital Ethics Committee and the Spanish Ministry of Health.

2.1. Subjects

Twelve right-handed male volunteers (mean age: 26 years, range: 20–43) gave their written informed consent. Medical history, laboratory tests, ECG and urinalysis were normal, and none of the subjects had a history of psychiatric or neurologic disorders. They did not take any medication or illicit drugs in the period from 2 weeks before the study until the end of the experimental sessions and abstained from alcohol, tobacco and caffeinated drinks in the 48 h prior to each experimental day.

2.2. Study design

The experiment was carried out according to a double-blind randomized cross-over placebo-controlled design. Oral doses of 0.25 and 1.0 mg alprazolam or placebo (lactose), packaged into identical capsules, were administered in a balanced order. Experimental days were separated by a 1-week washout period. Volunteers participated on three separate experimental days. Upon arrival in the laboratory under fasting conditions, a urine sample was obtained to test for illicit drug intake, electrodes were applied to the scalp and medication was given. ERP recordings were started 2 h after drug administration. During each recording session, volunteers remained in a quiet room and were asked to stay alert throughout the experiment.

2.3. Stimuli and procedure

The Eriksen flanker task [13] was used. Subjects were required to focus on the letter in the center of the array (H or S), designated as "target", and to respond with the assigned right or left hand. The flankers surrounding this target either favored the target response (congruent trials, HHHHH or SSSSS) or primed the other response (incongruent trials, HHSHH or SSHSS). To optimize the number of errors produced, 40% of congruent trials and 60% of incongruent trials were presented. Each stimulus array subtended about 2.5° of visual angle in width, and a fixation cross was presented in the middle of the computer monitor just below the target letter in the array. Duration of the stimuli was 100 ms. A random stimulus onset asynchrony between 900 ms and 1100 ms was used. Letter/hand assignments were counterbalanced between subjects and maintained in the three sessions. Prior to the first experimental session, subjects were trained with 200 trials to reach a reaction time (RT) baseline level, and they were given feedback about their performance. The goal of this procedure was to aim for a reaction time that would yield approximately 10–15% of errors. The experiment proper consisted of 12 blocks of 4 min and 200 stimuli each. A 30-s rest period was allowed between blocks. Subjects were required to respond to the stimuli as fast as possible and to correct their errors as fast as possible whenever they detected them.

2.4. Electrophysiological recording

The ERPs were recorded from the scalp using golden electrodes located at 29 standard positions (Fp1/2, F3/4, C3/4, T3/4, T5/6, P3/4, O1/2, F7/8, Fz, Cz, Pz, Fc3/4, FT7/8, Cp3/4, TP7/8, PO3/4). Biosignals were re-referenced off-line to the mean of the activity at the two mastoid leads. Vertical eye movements were monitored with an electrode at the infraorbital ridge of the left eye. Electrode impedances were kept below 5 kΩ. The electrophysiological signals were filtered with a bandpass of 0.1–50 Hz and digitized at a rate of 250 Hz. Trials were automatically rejected off-line if base-to-peak electro-oculogram (EOG) amplitude exceeded 50 μV, if amplifier saturation occurred or if the baseline shift exceeded 200 μV/s.

Stimulus-locked ERPs were averaged over epochs of 1024 ms starting 100 ms prior to the stimulus. Two types of trials were averaged separately: correct responses and errors that were corrected. Response-locked ERPs were averaged starting 400 ms before the subject's response until 624 ms after response onset. The baseline used for the response-locked ERN was between −400 and −200 ms. ERPs shown in the figures were filtered with a low pass filter (8 Hz half amplitude cutoff).

LRPs were calculated following standard procedures [7,18,46]. The resulting LRP component is negative if subjects produce correct responses and positive for error trials. For some analyses, the polarity of the error-LRP was inverted in order to perform statistics and to allow visual comparison in the figures. Onset latencies for the LRPs were determined via a stepwise series of one-tailed serial t tests (step size = 4 ms) [45]. For each test, data from a time window of 40 ms were averaged (i.e., point of measure ± 20 ms), from 200 ms to 1000 ms after picture onset. Onset latency was defined as the point at which 4 consecutive t tests showed a significant difference from zero ($P < 0.05$). Baseline used for LRPs was from −300 to −200 ms. LRP shown in the figures were filtered with a low pass filter (6 Hz half amplitude cutoff).

For all statistical effects involving two or more degrees of freedom in the numerator, the Greenhouse–Geisser epsilon was used to correct possible violations of the sphericity assumption [22]. P values after correction are reported. Tests involving electrode × condition interactions (e.g., factors as

hemisphere or anterior–posterior electrode location) were carried out on data corrected using the vector normalization procedure described by McCarthy and Wood [30].

3. Results

3.1. Behavior

Reaction time performance (see Table 1) was analyzed by means of a three-way ANOVA, with treatment (placebo, low dose and high dose), type of response (error vs. correct) and compatibility (congruent vs. incongruent trials) as within-subject factors. A main effect of treatment was found ($F(2,22) = 11.32$, $P < 0.001$, shown as increases in mean reaction time due to alprazolam administration; linear contrast $F(1,11) = 16.7$, $P < 0.01$). At the high dose, reaction time was significantly slower than following placebo ($t = -4.0$, $P < 0.01$) and the low alprazolam dose ($t = -2.96$, $P < 0.05$), but no significant differences were found between low dose and placebo ($t = -1.7$, $P > 0.1$). A main effect of type of response was also observed, with erroneous responses faster than correct responses ($F(1,11) = 86$, $P < 0.001$; mean reaction time was 337 ms for correct responses and 269 ms for errors). A main effect of compatibility was obtained ($F(1,11) = 70$, $P < 0.001$) which was modulated by the type of response (type × compatibility $F(1,11) = 15.32$, $P < 0.002$), reflecting the fact that the effect of conflict was only present for correct responses (see Table 1). Finally, a significant interaction was found between type of response and treatment ($F(2,22) = 8.51$, $P < 0.01$), showing that the delay observed in the reaction times for the high-dose condition was more pronounced in the correct trials. The interaction between treatment, type and compatibility was not significant ($F < 1$).

No differences between treatments were found for the overall percentage of errors committed ($F(2,22) = 1.28$, $P > 0.3$; see Table 1). In the incompatible condition, the percentage of errors was higher (~14 vs. ~25%, $F(1,11) = 49$, $P < 0.0001$). No interaction between treatment and compatibility was found ($F(2,22) = 1.59$, $P > 0.230$).

With regard to the percentage of corrected errors, both a trend towards a main effect of treatment ($F(2,22) = 2.89$, $P < 0.08$) and a significant interaction between treatment and compatibility ($F(2,22) = 5.65$, $P < 0.05$) indicated an effect of alprazolam on correction rate. Indeed, post hoc pairwise comparisons showed a significant reduction of the percentage of corrected errors in the high-dose relative to the placebo condition ($P < 0.05$).

Finally, the time needed to correct a response was also significantly prolonged in the high-dose condition ($F(2,22) = 3.7$, $P < 0.05$; placebo, 194 ± 47 ms; low dose, 193 ± 42 and high dose 212 ± 36).

In order to assess whether alprazolam affected the implementation of post-error adjustments, post-error slowing was investigated. Reaction times to correct trials immediately following a correct or an incorrect response, respectively, are shown in Table 1. The analysis of the data by means of a two-way ANOVA with treatment and type of preceding response (correct vs. incorrect) showed main effects of treatment ($F(2,22) = 13.44$, $P < 0.001$) and type of preceding response ($F(1,11) = 9.67$, $P < 0.01$), but not their interaction ($F(2,22) < 1$). Thus, alprazolam did not significantly modify post-error slowing.

3.2. ERP analysis

The percentage of EEG epochs rejected due to artifacts did not differ between treatments ($F(2,22) < 1$; 21% for placebo; 24% for low dose; and 26% for high dose). The mean number of corrected errors entered into the average after artifact rejection was 366 for placebo, 300 for low dose and 254 for high dose. A significant linear tendency was found ($F(1,11) = 6.5$, $P < 0.05$), showing a reduction in the number of trials with increasing doses of alprazolam.

3.2.1. Response-locked ERPs

The response-locked averages for correct and erroneous trials are shown in Fig. 1. Only those erroneous trials that were later corrected were included in the average. The error trials show a typical error-related negativity peaking at

Table 1
Behavioral measures in each treatment condition

	Placebo		Low dose		High dose	
	Compatible	Incompatible	Compatible	Incompatible	Compatible	Incompatible
RT correct	307 (36)	332 (36)	318 (29)	341 (36)	349 (40)	376 (48)
RT errors	255 (40)	261 (39)	260 (37)	269 (33)	279 (39)	292 (39)
% Errors	16.8 (9.9)	25.7 (10)	13.8 (8.2)	25.4 (10.2)	13.5 (7.2)	24.5 (9.1)
% Corrections	85.5 (11)	88.3 (9.6)	79.1 (15.5)	84.7 (14.9)	73.0 (19.9)	80.9 (19.7)
	Post-error slowing data					
	Placebo	Low dose	High dose			
RT after correct	336 (30)	343 (40)	372 (46)			
RT after error	341 (27)	355 (40)	386 (44)			

Data as group means (SD). Reaction time expressed in milliseconds.

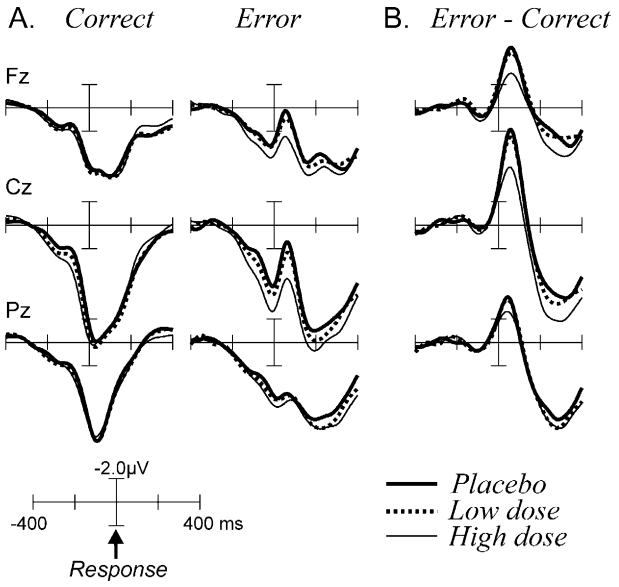

Fig. 1. (A) Response-locked grand average ERPs for midline electrode locations for correct and erroneous trials superimposed for the different treatment conditions. Note that immediately after the commission of an erroneous response, the error-related negativity (ERN) appears in all treatment conditions. (B) The amplitude of the difference waveforms (error-correct trials) shows a marked reduction at frontocentral locations after the high alprazolam dose.

around 60 ms and having a frontocentral maximum. The ERN was also clearly present in the error minus correct difference waveforms, shown in the right column of Fig. 1. The ERN component was reduced at the high alprazolam dose compared to low dose or placebo. The ERN was quantified by a mean amplitude measure (0–100 ms) and subjected to an ANOVA introducing type of response, treatment and electrode site (Fz, Cz and Pz) as within-subject factors. A main effect of type of response was found ($F(1,11) = 27.6$, $P < 0.0001$), reflecting the significant increase in negativity for erroneous trials. While the main effect of treatment was not significant ($F(2,22) = 2.24$, $P > 0.13$), the interaction between type of response and treatment was ($F(2,22) = 8.6$, $P < 0.01$). This interaction reflected the reduced negativity for the erroneous trials in the high-dose condition (correct trials, placebo 7.4 μV ± 4.6, low dose 7.7 μV ± 4.6, high dose 7.5 μV ± 4.5; erroneous trials, 2.9 μV ± 3.8, 3.33 μV ± 4.3, 4.6 μV ± 3.8, respectively). In order to address a possible drug effect on the baseline affecting the results obtained for the ERN, the difference waveform of error-correct trials was also tested for the effect of treatment between 0 and 100 ms. This effect was significant at Fz ($F(2,22) = 6.2$, $P < 0.01$) and Cz ($F(2,22) = 9.31$, $P < 0.01$). Mean amplitudes at Cz were: placebo −6.5 μV ± 4.7, low dose −6.2 μV ± 3.8, high dose −4.0 μV ± 2.7). Three additional analyses were performed in order to confirm the effects of the alprazolam high dose on ERN amplitude. These analyses were performed at Fz, where there was the least overlap with slow activity. The first analysis used as dependent variable the ERN peak value, defined as the most negative value of the signal in the window 0–150 ms following the response. A significant amplitude decrease was found ($t = -4.02$, $P < 0.002$). The second analysis used a baseline-to-peak measure. The peak value was defined as before and the baseline was computed as the average value of the signal in the time windows preceding the response (−100, 0). The difference value of peak–baseline was introduced in the statistical analysis, which showed again a significant difference ($t = -3.0$, $P < 0.012$). Thirdly, a trough-to-peak measure was used. The ERN peak value was defined as before, and subsequently a backward search for the preceding positive through was conducted. The peak–trough difference was calculated and used for the statistical analysis. Again, a statistically significant difference was found ($t = 3.1$, $P < 0.010$).

Isovoltage and current source density maps show the typical frontocentral distribution of the ERN component (Fig. 2). No differences are seen for the distribution of the ERN between the three treatment conditions.

An increase in the error positivity (Pe) is also evident in Fig. 1B in the high-dose condition between 200 and 400 ms in the difference waveforms, especially at the Cz recording site. A mean amplitude measure for this time window showed

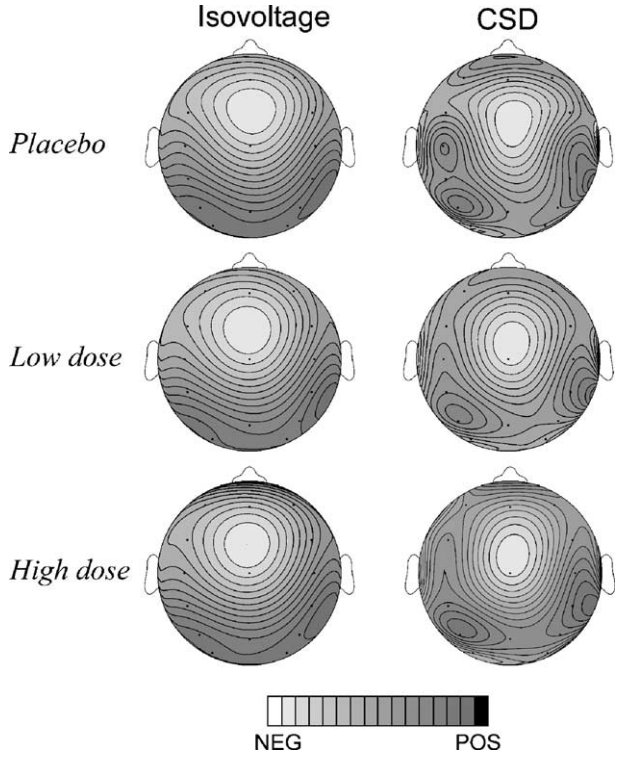

Fig. 2. Topographical maps for the ERN component (corrected errors) obtained using isovoltage spline interpolation and current source density (CSD) for the 30–80 ms interval. Maps were generated for erroneous responses after each of the three administered treatments. Note that relative scaling was used. Maximum and minimum values in μV for each isovoltage map (from top to bottom) are: −3.2/1.5, −3.0/1.3, −2.4/0.8. Averages used for the maps were high pass filtered (1 Hz) in order to compensate for the positive trend on which they are superimposed.

a significant effect for treatment ($F(2,22) = 3.68$, $P < 0.05$; placebo 6.2 μV ± 2.3, low dose 6.7 μV ± 2.5, high dose 7.9 μV ± 4.01).

To test whether the observed effects on the ERN and the Pe are independent or are representing a general positive shift of the waveforms in the high-dose condition, high-dose minus placebo difference waves were computed. Fig. 3 shows the isovoltage maps derived from these difference waves in the ERN (0–100 ms) and Pe (300–400 ms) latency ranges. In the ERN time range, a centrally distributed effect is seen, which has a topography similar to the ERN proper (cf. Fig. 2), whereas in the Pe time range the difference between high dose and placebo has a parietal distribution similar to that reported for the Pe. The following statistical analysis was performed to test for the independence of drug effects on each of the two components: we computed the mean amplitude of the high-dose minus placebo difference wave in the ERN (0–100 ms) and Pe (300–400 ms) time windows. These measures were subjected to the normalization procedure suggested by McCarthy and Wood [30], and the normalized values were analyzed by means of a two-way ANOVA with time window (2 levels) and lead (29 electrode locations). A significant interaction was encountered between time window and lead ($F(28,308) = 3.64$, $P < 0.0130$), suggesting that both ERN and Pe are independently modulated by alprazolam.

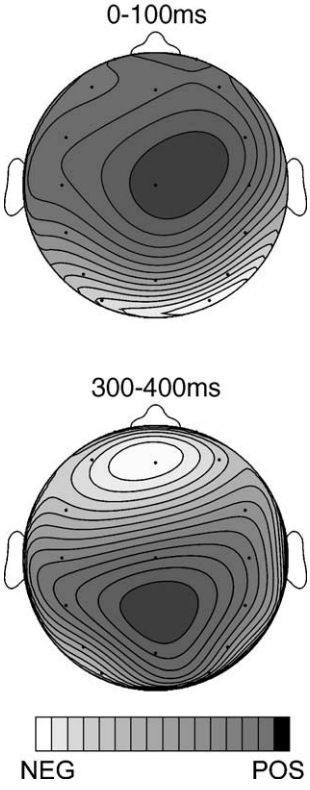

Fig. 3. Isovoltage maps of the difference between high-dose alprazolam and placebo (response-locked averages). The distribution of the drug effect is shown for the ERN (upper panel) and Pe (lower panel).

3.2.2. Stimulus-locked ERPs

The grand average ERPs for the correct and incorrect trials as well as the respective difference waveforms are shown in Fig. 4. Both types of trials were characterized by an initial small negativity followed by a positive deflection (P2) peaking at 150 ms. A negativity (N2) was observed at 250 ms, which was considerably broader in the error trials. Furthermore, the subsequent late positivity was less pronounced and broader in the error trial. These differences in N2 and late positive morphology between error and correct trials are reflected in the difference waves: a frontocentral negativity starting at about 200 ms and peaking at about 350 ms was followed by a centroparietal positivity with a peak latency of about 600 ms.

With regard to treatment effects, the difference waveforms obtained for the placebo and low-dose sessions were virtually identical. Inspection of the original waveforms suggests, however, that the N2 component was reduced at the low dose for both error and correct trials. At the high dose, a marked positive shift was seen especially for the error trials, such that the late positivity is of equal amplitude for the error and correct trials.

The N2 was quantified as mean amplitude (time window 250–450 ms, Fz, Cz, Pz). Errors showed an increased negativity when compared to correct responses ($F(1,11) = 10.8$, $P < 0.01$). There was no main effect of treatment ($F < 1$), but the interaction between type of response and treatment was significant ($F(2,22) = 13.8$, $P < 0.001$). This interaction reflects the fact that the negativity distinguishing erroneous and correct responses was smaller for the high alprazolam dose. Mean amplitude values for correct responses were 6.4 μV ± 3.2 for placebo, 6.7 μV ± 3.8 for the low dose and 5.9 μV ± 3.7 for the high dose. Mean amplitude values for the erroneous responses were 4.7 μV ± 3.4 for placebo, 5.1 μV ± 4.1 for the low dose and 5.5 μV ± 3.3 for the high dose.

ERP averages for incongruent and congruent trials in the different treatment conditions are shown in Fig. 5. In order to explore the effects of alprazolam on neural correlates of response conflict on correct trials, the N2 component of the stimulus-locked averages was evaluated in congruent vs. incongruent trials. This analysis was conducted on the correct trials only and yielded a main effect of compatibility ($F(1,11) = 12.8$, $P < 0.01$) but no interaction between compatibility and treatment ($F(2,22) = 1.34$, $P < 0.3$). The N2 was also analyzed by a trough-to-peak measure (the amplitude difference between the P2 component and the N2 component) for which main effects of compatibility ($F(1,11) = 8.7$, $P < 0.015$) and treatment ($F(2,22) = 2.2$, $P < 0.021$) were observed. However, the interaction between both factors was not significant ($F < 1$).

The P300 component in the stimulus-locked averages was only assessed for correct responses in order to avoid the distorting effect of the response-locked error-related components on the stimulus-locked averages. Peak amplitudes at the Cz and Pz electrodes were measured in the 200–600 ms

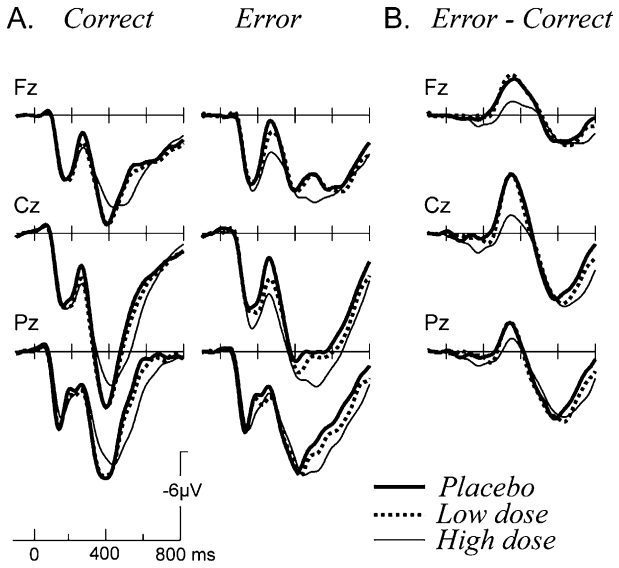

Fig. 4. (A) Stimulus-locked grand average ERPs. In the erroneous trials, a more negative response was observed in the placebo and low-dose conditions. (B) The difference waveforms (error-correct trials) show a negative deflection in frontocentral locations which is clearly reduced in the high-dose condition.

time window. This analysis yielded no main effect of treatment at Cz ($F(2,22) = 1.99$, $P < 0.1776$) but a significant decrease in amplitude after alprazolam at Pz ($F = 3.92$, $P < 0.05$; placebo 10.2 μV ± 4.5, low dose 10.1 ± 4.9, high dose 8.9 ± 4.2).

With respect to the peak latency of the P300 component at Cz, a significant effect of treatment was encountered ($F(2,22) = 9.4$, $P < 0.0011$), showing a delayed peak latency for the high-dose compared to the low-dose alprazolam and placebo conditions (high-dose vs. placebo: $P < 0.001$; high-dose vs. low-dose: $P < 0.05$ and low-dose vs. placebo: $P > 0.09$).

3.3. Motor preparation and time course of corrective responses

3.3.1. Stimulus-locked LRPs (s-LRPs)

s-LRPs are shown in Fig. 6 for correct and erroneous responses. The onset latency (determined by serial t tests) for correct responses was 124 ms for placebo, 180 ms for low dose and 180 ms for high dose. No significant differences were found between the low dose and placebo at any point. However, both treatments differed significantly from the high dose. Placebo and the high dose differed between 152 and 360 ms (in all cases $P < 0.05$), reflecting the reduced amplitude of the high-dose LRP. The low dose and high dose differed between 192 and 352 ms.

The LRPs to erroneous responses showed significant ($P < 0.05$) values above 0 between the following time points: placebo 128–280 ms, low dose 144–296 ms, and high dose 136–256 ms. The low-dose and placebo waveforms did not differ significantly at any point in time. The placebo and high-dose error-LRPs showed a significant difference between 180 and 256 ms and again between 380 and 432 ms. This second phase reflected the preparation of the corrective response. The same pattern was observed for the comparison between low dose and high dose ($P < 0.05$ between 188 and 268 ms, and between 360 and 512 ms).

3.3.2. Response-locked r-LRPs

r-LRPs show the typical lateralization before the onset of the response (Fig. 6). The r-LRPs have steeper slopes and higher amplitudes than the s-LRPs because they are computed time-locked to the response. No differences were found for the onset latencies and the period of significant lateralization above zero of the r-LRPs to correct responses ($P < 0.05$; placebo: −120 ms to 112 ms, low dose −112 ms to 116 ms, high dose −120 to 48 ms). As is evident from the figure, the amplitude of the r-LRP for the high-dose condition is reduced, which was reflected in significant differences between high dose and placebo (between −68 ms and 32 ms, paired t test, all $t > -2.24$, $P < 0.05$) and between high-dose and low-dose (between −60 ms and 0 ms, all $t > 2.26$, $P < 0.05$).

Error r-LRPs show a biphasic morphology with an initial positive phase indexing the preparation of the error followed by a negative phase indicating the preparation of the corrective response. The onset/offset latencies as determined by the t test method for the first phase were: placebo −112/24 ms, low dose −104/20 ms, high dose −132/−12 ms. The

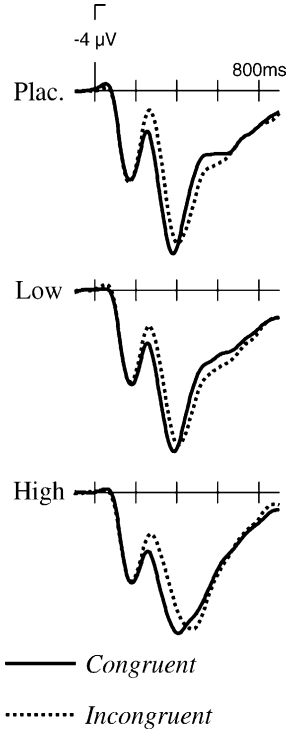

Fig. 5. Stimulus-locked grand averages for correct responses in the three treatment conditions separated for congruent and incongruent stimuli. ERPs after correct responses to incongruent stimuli show an amplitude increase on the N2 component. This effect is of similar magnitude in the three treatment conditions.

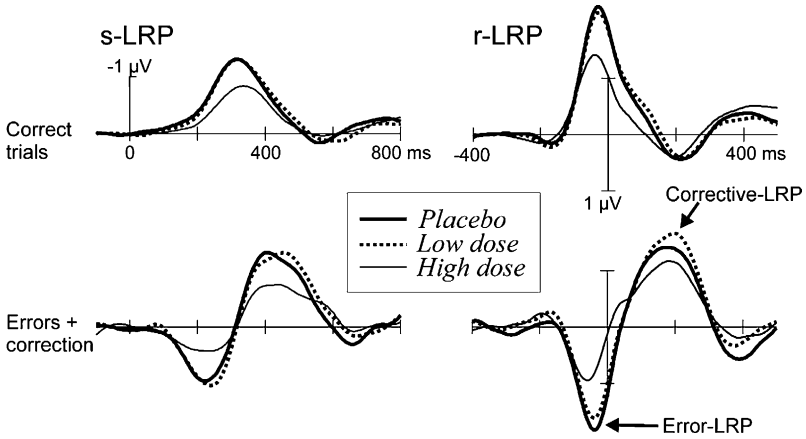

Fig. 6. Stimulus-locked (left column) and response-locked (right column) lateralized readiness potentials computed for the C3 and C4 channels. Note that errors are first lateralized in the wrong direction (positive amplitude) and after 200 ms begin to lateralize in the correct direction due to the implementation of the corrective response.

onset/offset latencies for the second phase were: placebo 60/288 ms, low dose 68/280 ms and high dose 84/268 ms. Low dose and high dose differed significantly between −60 and 36 ms (preparation of error response) and between 156 and 252 ms (corrective response), while placebo and high dose showed differences between −56 and 28 ms ($P < 0.05$) and between 100 and 160 ms ($P < 0.07$). Low dose and placebo were not different.

Onset latency of the s- and r-LRPs in correct trials was also estimated by a proportional peak latency measure [47]. This method estimates the LRP onset by determining the point in time at which a certain proportion (in this case 30%) of the peak amplitude of the LRP is reached. Table 2 shows the onset latency, the peak amplitude and the peak amplitude latency for the s- and r-LRPs. For the s-LRPs, a clear difference in peak amplitude was observed reflecting the lower amplitude in the high-dose condition. In addition, a significant difference was found in the onset latency as a function of treatment. The same pattern was observed for the r-LRPs.

3.4. Onset of motor corrective-commands

The moment in time when the LRP for correct responses differs from the LRP for error responses can be taken as an index of the onset of the corrective command [43]. To determine this time point, the polarity of the error-LRPs was inverted, and the two waveforms were compared using serial t tests (Fig. 7) (placebo −40 ms, low dose −52 ms, high dose −68 ms). In Fig. 7, in order to illustrate the temporal relation between the onset of the preparation of the corrective response and the ERN, the ERN (difference wave between error and correct waves at the Cz site, see Fig. 1) has been superimposed (with a different μV scale) on the r-LRPs (see Fig. 6). The onset of the ERN determined by the t test method was relatively stable in all treatment conditions (placebo −32 ms, low-dose −36 ms, high-dose −20 ms) and in each case was later than the measure for the onset of the preparation of the corrective response (corrective LRP).

4. Discussion

The main findings in the present study can be summarized as follows: alprazolam induced a behavioral impairment consisting in an increase in reaction time and a decrease in the number of erroneous responses corrected. At the neurophysiological level, the high 1.0 mg dose

Table 2
Characterization of stimulus- and response-locked LRPs in the correct trials

	Placebo (PL)	Low dose (LD)	High dose (HD)	Treatment	PL-LD	PL-HD	LD-HD
s-LRP							
Onset latency (ms)[a]	197 (38)	227 (52)	240 (36)	*	n.s.	**	n.s.
Peak latency (ms)	318 (36)	334 (44)	317 (38)	n.s.	n.s.	n.s.	n.s.
Peak amplitude (μV)	−1.66 (0.8)	−1.61 (0.7)	−1.21 (0.6)	**	n.s.	*	*
r-LRP							
Onset latency (ms)	−86 (19)	−86 (23)	−106 (28)	*	n.s.	*	*
Peak latency (ms)	−27.3 (17)	−29.3 (19)	−35.3 (43)	n.s.	n.s.	n.s.	n.s.
Peak amplitude (μV)	−2.79 (1.4)	−2.74 (1.4)	−1.99 (1.1)	***	n.s.	***	**

Notes. Degrees of freedom in the treatment and pairwise comparison are in all cases: $F(2,22)$ and $t(11)$; n.s.= nonsignificant; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a] Determined using a proportional peak latency measure.

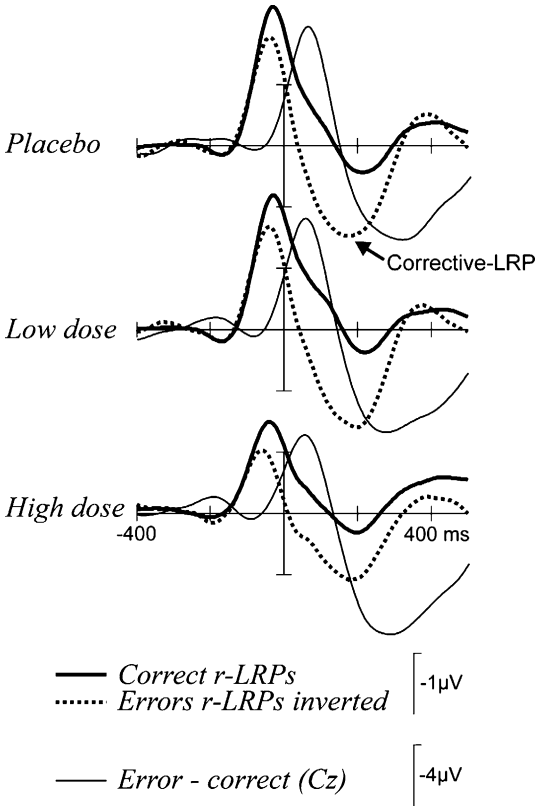

Fig. 7. Inverse-polarity response-locked lateralized readiness potential (r-LRPs; C3 and C4 derivations) for erroneous responses compared with r-LRPs for correct responses. Note the point in time at which correct and erroneous responses begin to diverge due to the preparation of the corrective command. For comparison, the time course of error detection (indexed by the ERN; error-correct waveform at Cz) is superimposed. Note that the LRPs and ERN are drawn at a different voltage scale.

decreased the amplitude of the ERN as was evidenced in the response-locked as well as stimulus-locked averages. On the other hand, the amplitude difference of the N2 component in the stimulus-locked averages between correct-congruent and correct-incongruent trials was not modified by the drug. Furthermore, alprazolam did not significantly modify post-error slowing. Regarding motor preparation measures, alprazolam reduced the amplitudes and increased the latencies of the LRPs.

4.1. Error detection

The alprazolam-induced decrease in the amplitude of the ERN suggests a detrimental effect of alprazolam on error monitoring, which was confirmed by the performance results in the flanker task. Although participants did not commit more errors under medication, they corrected fewer erroneous responses in the high-dose condition when compared to placebo. These results corroborate and extend previous findings showing similar effects for the benzodiazepines oxazepam [23] and lorazepam [9], as well as alcohol [42]. The ERN has been shown to emanate from medial frontal cortex [10,27], and fMRI investigations have similarly pointed to the ACC and adjacent areas [25,50]. The ACC is an area that is particularly rich in GABAergic neurons [1,29,56], which form the target for benzodiazepines. Thus, the modulation of the ERN component in the high-dose condition in the present experiment would be compatible with a specific action of benzodiazepines on error monitoring.

With regard to the functional significance of the ERN, several theories have been advanced, viewing it either as a reflection of error detection proper [21], of response conflict [2] or of the emotional impact of an error [4]. It is noteworthy that the observed dissociation of alprazolam actions on the ERN and the N2 congruency effect would not be predicted by the conflict theory. This dissociation has also been observed in other drug studies. For example, the noradrenergic stimulant yohimbine selectively increased ERN amplitude but not the N2 [41]. Recent neuroimaging data [50] suggest that different areas within the frontomedial cortex mediate error processing and correct response conflict, which might explain the dissociation. Our findings are compatible with the view that the ERN reflects the affective evaluation of response outcomes [4]. Alprazolam might reduce the affective impact associated with errors as it acts as an anxiolytic and has been shown to modulate experimentally induced anxiety [40].

Importantly, previous findings suggest that the ERN is not necessarily an index of the initial internal error signal but rather might reflect a somewhat later process [43]. The onset latency of the ERN indicates that this component occurs in parallel or just after the onset of the motor corrective command (see also Fig. 7), i.e., at a time at which the error must have been already detected as such. Thus, the ERN component could be considered as reflecting a second stage of error monitoring, probably involved in the conscious perception of the error and in the implementation of remedial actions. These might include a slowing of response times on subsequent trials (post-error slowing). Post-error slowing was not modified by alprazolam in the present study, thus making it unlikely that the observed ERN decreases are related to an impaired compensatory post-error behavior.

4.2. Conflict on correct trials

The increased negativity for incongruent relative to congruent stimuli in stimulus-locked waveforms, sometimes called N2 component, has been interpreted as a reflection of response conflict [26,34,51]. The current data set showed this typical difference (cf. Fig. 5), which, as mentioned above, was not influenced by the drug administration, however. This is in contrast to the study of De Bruijn et al. [9], who report an absence of the N2 congruency effect in their lorazepam condition. Inspection of their Fig. 2 suggests, however, that the effect of conflict on correct trials might be delayed rather than abolished.

4.3. Motor preparation and error correction

As in previous studies, reaction times were delayed after benzodiazepine administration [20,32,40]. The LRP as a neurophysiological index of response preparation showed a reduction of amplitude in the response-locked and stimulus-locked averages (see Table 2). While it is tempting to interpret this amplitude reduction as a sign of impaired motor preparation under alprazolam, one has to bear in mind that the LRP is the result of a double subtraction procedure, and, therefore, a smaller amplitude merely indicates a decreased voltage difference between the contralateral and ipsilateral motor cortex. For response-locked LRPs, an earlier onset was observed for the high alprazolam dose relative to the placebo (−106 ms vs. −86 ms). This difference is in fact indicating that the time that it takes to prepare the motor response from its onset until its final emission is longer. Thus, this can be taken as evidence for impaired motor preparation under alprazolam.

We are reluctant to interpret the alprazolam effects on the ERN and LRP as a result of a general depressant effect of this drug on ERPs. For example, while the peak amplitude of the P300 component to the correct trials appeared reduced in the stimulus-locked averages under alprazolam, it was also considerably broader, suggesting a possible effect of latency jitter. Notice also that a significant delay in the mean reaction time (and a larger variation of RT) was encountered under the high-dose condition as well as a delayed P300 peak latency, but no increase in the percentage of erroneous responses. This behavioral pattern suggests an adjustment in the speed–accuracy trade-off in this condition and suggests that alprazolam has a clear effect on the performance [20,32,40,48,54]. Participants required more effort under the high-dose condition in order to perform as well as in the other two conditions. However, two results clearly argue against an unspecific drug-induced amplitude-reducing on the ERPs: (i) no effect was observed on the P300 for the correct trials in the response-locked ERPs and, more important, (ii) the amplitude of the Pe component in the error trials (response-locked averages) showed an increase after alprazolam.

The interpretation of the Pe amplitude increase after alprazolam is not straightforward. This component has been associated by different authors with later aspects of error processing such as conscious error monitoring, the adjustment of response strategies, the emotional significance of an error and conscious awareness of an error [8,15,33,51,55]. None of these theories seem to accommodate the present findings as an increased Pe would indicate for instance that subjects were more aware of errors being made or that error commission had a greater emotional impact on the volunteers under the drug. Increased awareness is not supported by the fact that after alprazolam subjects corrected less erroneous responses and also by the fact that post-error slowing was not significantly altered. Similarly, a greater emotional impact following drug administration would contradict the well-known effects of benzodiazepines on mood. A dissociated modulation of the ERN and the Pe, with a reduction of the former and an increase of the latter, has also been observed in a study involving the induction of transient functional lesions by means of transcranial magnetic stimulation to the frontomedial cortex [44]. An alternative explanation for the increase in the amplitude of the Pe after the high alprazolam dose could be the increased difficulty in performing an already demanding task involving the internal triggering of a new motor command and the adjustment of different motor parameters. This explanation would be supported by the fact that P300 amplitude has been shown to increase with task complexity [24].

In conclusion, alprazolam's detrimental effect on human performance was shown to be paralleled by a disruption of neurophysiological correlates of error monitoring (ERN) and motor preparation (LRPs).

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