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ORIGINAL INVESTIGATION

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Effects of oxazepam on event-related brain potentials, EEG frequency bands, and vigilance performance

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Abstract Eighteen males performed two vigilance tasks with static and dynamic stimuli under the influence of oxazepam (20 and 40 mg) in a placebo-controlled, double blind, crossover design. Oxazepam dose-dependently impaired overall level of performance and aggravated the decrement with time in measures of accuracy and sensitivity relative to placebo. The drug reduced the amplitudes of the P1, N1, P2N2, and P3 (dose-dependently) waves of event-related potentials (ERPs). Oxazepam aggravated the linear decline with time of the P3 amplitude only. Oxazepam impaired accuracy was related to deterioration of central processing involved in stimulus discrimination (P2N2). Impairment of response-related performance measures (RT and RI) was associated with processing manifest in the P1, N1, and P3 waves. Oxazepam effects on the amplitudes of N1 and P3 correlated with drug effects on power in alpha 1 (8–10 Hz). Drug effects on overall performance and alpha were also related; the drug effect on response speed correlated only with the drug effect on beta 1 (12.5–21 Hz). Effects of time-on-task on performance and EEG were unrelated, but oxazepam induced performance declines with time may have been caused by declines in resource allocation, as manifest in the amplitude of P3. Time effects on EEG power bands and ERP amplitudes were not significantly related to the time course of oxazepam activity. A curious dissociation emerged: both oxazepam and time-on-task impaired performance, but the drug induced a decrease of theta and alpha 1 power, whereas time-on-task increased power. Various processes play a role in performance decrements with time, and various aspects of processing may be involved in signal-detection measures which makes terms such as sensitivity quite meaningless. So-called computational processing was indistinguishable from energetic processes, which questions the validity of the distinction between these two domains. Explanations of EEG activity in terms of a unidimensional theory of arousal are untenable.

Key words Vigilance performance · Electroencephalogram · Event-related potentials · Benzodiazepines · Arousal · Signal detection measures

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Introduction

Investigations into the relationship between overt performance and covert central processes may clarify which covert processes are involved in overt measures of performance. For example, several studies have focussed on the relationship between vigilance performance and event-related brain potentials (ERPs; for a review, see Koelega and Verbaten 1991). The use of ERPs allows us to assess which aspects of stimulus processing are affected by drugs, such as benzodiazepines (BZs), and how these effects relate to the impairing effects of the drugs on performance (Koelega 1989). In an earlier study (Van Leeuwen et al. 1992), in which this ERP approach was followed, significant correlations were obtained between the mean amplitudes of the N1 and P2N2 and mean level of sensitivity (A'), a measure from Signal Detection Theory (SDT). The N1 amplitude has been interpreted as reflecting processes involved in stimulus detection, whereas the visual P2N2 has been associated with the detection of stimulus-mismatch, so it is still not clear, if one is interested in the brain processes involved in these behavioral measures,

what sensitivity (or other SDT measures such as beta or cautiousness, for that matter) precisely stands for, because both the N1 and P2N2 correlated with sensitivity. A major issue in the present study, therefore, concerns the question of which aspects of stimulus processing, as manifested in ERPs, are involved in overt measures of performance, i.e., which ERP waves are related to measures such as sensitivity and response bias? In addition, can measures of electrocortical brain activity elucidate and explain changes in overt performance with time and after the ingestion of BZs?

The relationship between tonic, rather than event-related, electric brain activity (EEG) and vigilance performance has been subject of research for more than 30 years. Most of the early research has been reviewed by Davies and Parasuraman (1982), who stated that all these studies have interpreted their findings in terms of an arousal framework (p. 182). In particular, the power in the (upper) alpha and beta bands of the background EEG has been considered as an index of energetic processes in the brain (cortical arousal). It has frequently been found that a decline in performance with time concurred with an increase of power in the lower frequency bands (theta), whereas power in the higher frequencies (beta) declined (O'Hanlon and Beatty 1977; Milosevic 1978; Floru et al. 1985). At the end of a vigil there is usually a predominance of theta in the EEG record. Because a similar slowing in EEG frequencies is also found in states of drowsiness and light sleep, it is not surprising that the changes during vigilance performance have been interpreted as an indication of lowered electrocortical arousal (Davies and Parasuraman 1982).

The second aim of this study pertains to the relation between performance declines as a function of Drug and/or time-on-task (Period) and the concurrently measured changes in EEG power. In several studies both changes in performance and changes in EEG activity, especially delta and theta, have been reported (e.g. Horvath et al. 1975; O'Hanlon and Beatty 1977). A striking feature of these studies is that no attempt has been made to determine whether such behavioral changes and EEG changes were (statistically) (cor)related. There are some recent studies concerning background EEG and performance (e.g., Ogilvie et al. 1991; Makeig and Inlow 1993; Valentino et al. 1993), but some of them were aimed at validating quantitative EEG for clinical purposes, rather than attempting to assess relationships between performance and EEG. Concurrent measurement of EEG and performance was either restricted to limited periods only during task performance (Valentino et al. 1993), tasks were employed that could not be classified as vigilance tasks, because stimulus discrimination was not involved (Ogilvie et al. 1991), or target probability was too high (Makeig and Inlow 1993).

The same two factors inducing changes in ERPs and/or background EEG are time-on-task (Period) and the administration of drugs. This leads to another research question of this study, namely whether changes in ERP-waves under the influence of these two factors are related to changes in EEG background activity. The relationship between ERP waves are background EEG activity has been studied several times (e.g., Jasiukaitis and Hakerem 1988; Başar–Eroglu et al. 1992; Intriligator and Polich 1994). It has, however, never been the subject of investigation in vigilance tasks, possibly because in such tasks inter-stimulus intervals are usually short (from 1 to 4 s), and within the epoch used for the determination of EEG power, a stimulus (signal or non-signal) is always presented. Therefore, in the present study the non-event related spontaneous background EEG activity will be estimated by removing (possibly confounding) stimulus-locked EEG activity (i.e., ERPs) before assessment of the power in frequency bands.

In the present study, relationships between classes of dependent variables, i.e., between concurrently measured performance, ERPs, and EEG during task performance, will be estimated by means of analysis of covariance.

A special case in this approach is theta activity. The mere occurrence of (frontal-midline) theta has been reported in situations requiring continuous attention (Mizuki et al. 1980; Bruneau et al. 1993), and has been conceived of as related to focussed attention and signal detection (Başar-Eroglu et al. 1992). Increases in theta have been reported to occur in vigilance situations where performance ("attention") decreased (Beatty et al. 1974; O'Hanlon and Beatty 1977), but *reductions* in theta power were noted after the intake of benzodiazepines for example, Bond et al. (1983) and Manmaru and Matsuura (1989); so, because BZs also impair performance (see Koelega 1989, for a review), both increases and decreases of theta have been reported to go together with poorer performance. These effects are difficult to fit into one-dimensional theories of arousal. In the present study it will be investigated whether oxazepam induces a decrease, and time-on-task induces an increase, in theta power and how these effects relate to performance.

A third research issue concerns the seemingly paradoxical effect of benzodiazepines on beta activity. In several studies, a dissociation between behavioral and cortical arousal has been reported after ingestion of benzodiazepines. BZs usually lead to a decline in behavioral efficiency (e.g. Van Leeuwen et al. 1992, 1994a), but BZs also lead to an increase in beta activity concurrent with a decrease of power in the alpha range (Bond et al. 1983; Higgit et al. 1986; Saletu et al. 1986; Coppola 1987; Patat et al. 1990). This seems paradoxical because increasing beta activity is usually interpreted in terms of increasing cortical arousal. Some studies have been concerned with quantifying the relations between BZ blood concentrations and their effect of the EEG, i.e., in terms of pharmacokinetics

(Greenblatt et al. 1989; Breimer et al. 1990; Mandema et al. 1991). However, the level of performance has usually not been controlled for in these studies, or has not been inferred from (objective) measures of performance obtained in the same study. This means that the *behavioral* significance of the BZ-induced changes in background EEG activity has not yet been determined, which holds in particular for the paradoxical increase in beta activity after BZ ingestion. The third aim of the present paper is therefore to determine the behavioral significance of the BZ-induced changes in beta power by measuring EEG and performance concurrently and to investigate in which way they are related.

A final issue is concerned with the relationship between background EEG, ERPs, and pharmacokinetics. Analysis of these pharmacokinetic data might shed light on the question of whether changes in ERP waves and EEG bands as a function of time-on-task are related to the speed with which oxazepam is metabolized. In fact, several pharmacokinetic studies suggest that changes with time in beta power develop parallel to changes in BZ-binding equivalents (Dorow 1984; Ott 1984; Greenblatt et al. 1989; Breimer et al. 1990; Mandema 1991). Therefore, the time course in activity of the benzodiazepine oxazepam (i.e., oxazepam-equivalents) will be studied in relation to the behavioral, background EEG, and ERP effects of this drug.

The performance results of the present study have been reported elsewhere (Van Leeuwen et al. 1994a), but, because in the present study ERPs were determined only when subjects had their eyes open, a similar restriction to the data set will be implemented for performance in the present paper. ERP results of the present study pertinent to a manipulation of static and dynamic stimuli, inducing differences in eye movements, are reported elsewhere (Van Leeuwen et al. 1994b). In the present paper, results are collapsed across the static and dynamic conditions, because there were interaction effects of this factor only; there were no main effects, either on behavior, or on ERPs or background EEG.

Two major topics are addressed in the present paper. One concerns event-related brain potentials (ERPs), the other deals with ongoing background EEG. Results from both domains will be integrated and discussed in relation to overt performance in a visual vigilance task with concurrent benzodiazepine (BZ) administration.

Materials and methods

Subjects

Subjects were 18 males, aged 19–24 years (mean 21.1). All subjects were in good physical health, taking no medication. An initial screening session included physical and psychiatric examination and revealed that none of the selected participants had a history of drug use, and important medical or psychiatric disease. All subjects performed short-duration (15 min) versions of both the static and dynamic vigilance task (see below) during the screening session, and all performed within selection criteria, i.e., at least 50% correct detections and fewer than ten false alarms during the first 5 min of each task. Subjects wearing glasses or corrective lenses were not excluded from the experiment. The study protocol was approved by the Ethics Committee of the Academic Hospital, Utrecht. All subjects received oral and written information concerning theexperiment and experimental procedures and all gave informedconsent prior to the start of the study. The subjects were instructed to refrain from smoking, taking alcohol, coffee, tea, cola, or any otherdrug-containing liquids, starting at least 24 h prior to the test days. For safety reasons subjects were transported from the laboratory by taxi, and they were paid for their participation in the experiment.

Study design and drug treatment

This is a within-subjects, double blind, placebo controlled study. Subjects performed both a static and a dynamic vigilance task on three separate occasions, maintaining a wash-out period of 1 week. Order of drug treatment and task were balanced in a pseudo-Latin Square. Time of day was balanced between subjects; there were test sessions in the morning, the afternoon, and in the evening. Subjects were randomly assigned to task order, drug order, and time of day. Drug capsules containing placebo, 20 mg, or 40 mg oxazepam were taken with 200 ml orange juice. Vigilance tasks were performed 1 h after capsule administration.

Apparatus

Electroencephalogram (EEG) and electrooculogram (EOG)

Electroencephalographic activity was recorded by tin electrodes, by means of an electrocap. Scalp locations were at F3, Fz, F4, C3′ (1 cm anterior to C3), Cz, C4′ (1 cm anterior to C4), P3, Pz, P4, O1, Oz, and O2, according to the 10–20 system. Linked earlobe electrodes were used as references, and were connected with a 15 kohm resistor to prevent distortion of hemispherical asymmetries (Katznelson 1981). Horizontal EOG was recorded using tin electrodes in plastic cups attached to the outer canthus of each eye by means of adhesive rings. Similarly, vertical EOG was recorded from infra-orbital and supra-orbital electrodes in line with the pupil of the left eye. A ground electrode was attached to Fpz. For both EEG and EOG, ECI (electro-gel) EEG paste was used. The EOG signals and EEG signals were amplified and filtered with time constants of 5 s in conjunction with a low-pass filter setting of 30 Hz. To suppress 50 Hz frequency and harmonics, amplifier output was first sent through a 45-Hz passive low-pass network, followed by a 50-Hz notch filter (bandwidth of 4–5 Hz). Subsequently, the signals were sent to analog inputs of a PDP 11/23 computer for on-line analog-digital conversion. Sampling, at a rate of 250 Hz, started 100 ms before stimulus onset, and lasted 1024 ms.

Eye view behavior

Eye view behavior was measured by a Whittaker Eye View Monitor system (model 1998S) which is based on an infrared corneal reflection technique. Sample rate of the digital output of this system was 50 Hz, lasted 1000 ms, and was started concurrently with EEG/EOG sampling. Presentation of stimuli and data acquisition was controlled by the PDP 11/23.

Tasks and stimuli

Stimuli were oblique gratings, alternating black and white bars, equal in orientation (45° to the upper right), size (15 mm in vertical direction, 10 mm in horizontal direction), brightness (0.6 Lux), and duration (60 ms). The occasionally presented signals differed from non-signals in spatial frequency only (0.6 and 0.85 cycles per degree of arc, respectively). Stimuli were successively presented during the 45-min vigilance tasks. The event-rate (or stimulus presentation rate) was 48 per minute. Four signals were pseudo-randomly distributed over every 5-min period (signal probability 0.0167). The duration of the interval between stimulus offset and (next) stimulus onset (stimulus onset asynchrony; SOA) was fixed (1.25 s). The stimulus configuration on the TV screen was equal for both the static and the dynamic vigilance task, and consisted of a permanently displayed matrix of 9×9 open rectangles (15 mm by 20 mm). In the static version of the task, all stimuli were presented in the central rectangle of this matrix. In the dynamic task, each following stimulus, whether non-signal or signal, was presented at a rectangle to the right, by skipping one position. End of a line of rectangles (or end of the complete matrix, i.e., lower right) forced the next stimulus to be presented at the next line (or upper left again), as in reading. Subjects had to cover approximately 5° of arc by anticipatory eye movements prior to most signals presented. However, for each 5-min period of the task, one signal was (or should have been) preceded by eye movements covering approximately 15° of arc, i.e., at the end of a line. In both the static and dynamic task the same signal and non-signal stimuli were used, with the same pseudo-random signal presentation schedule. Thus the static and dynamic task only differed in location of stimulus presentation.

Stimulus conditions

The experiment took place in an acoustically and electrically shielded room (ambient illumination approximately 1 Lux). The subjects were seated in a dentist's chair which was adjustable, so that the subject's head could be adjusted to a position roughly parallel to a TV monitor (black-white, 67 cm screen), which was positioned above and in front of the subject at a distance of 60 cm from the subject's eyes. A vacuum cushion was attached to the top of the chair in order to fix the subject's head in such a way that the centre of the TV screen, where the stimuli were to be presented, was in the centre of the visual field. Eye movements from the centre of the TV screen to any of the four corners were 28° of arc.

Procedure

On arrival in the laboratory the subjects underwent a short medical examination. An indwelling butterfly cannula (1.2 mm diameter, 45 mm length) was placed on top of the non-responding forearm for the blood sampling procedure (for purpose and results see Van Leeuwen et al. 1994a). Subjects were then taken to the experimental room and were seated in a dentist's chair. The first baseline blood sample was taken after 5 min. Subsequently, subjects left the experimental room and were allowed to consume a standard meal consisting of orange juice and some currant buns. Thereafter, the drug capsule was administered, and the subjects were further prepared for the experiment. Watches or other time pieces were collected, and the subject was again seated in the dentist's chair. Calibration of the EVM followed: a grid consisting of the digits 1–9 was presented on the TV screen, and the subject was instructed to fixate these digits in a sequential order at the experimenter's request. This procedure was repeated until all digits were satisfactorily calibrated. Subjects performed both a static and a dynamic task on each test session, immediately after the second blood sample was taken. Tasks were separated by a 10-min pause during which the third blood sample was taken. After completion of both tasks, the fourth blood sample was taken. All blood samples were taken while subjects were seated in the dentist's chair, and the interval between sampling was 70 min.

Subjects were instructed to press a button, attached to the forefinger of their preferred hand, whenever they detected the signal. This button push induced a 1.5-V pulse in an analogue input channel (sample rate 250 Hz) of the PDP 11/23.

On each test session, and in both type of tasks, subjects were shown the stimuli, and were allowed a 5-min practice period prior to task performance (employing the same schedule of stimulus presentation as in the experimental task) with knowledge of results. Subjects were instructed to respond to a signal as accurately and as quickly as possible.

Eye movement correction and ERP estimation

After completion of the vigilance task, the subject was presented with 36 additional stimuli. These consisted of either the digit "2" or "5" and were delivered at various locations on the screen for 1 s. Subjects were required to count the occasions on which a "5" was presented. The aim of this task was to evoke large saccadic eye movements. Horizontal and vertical EOGs, as well as EEGs, were measured in the same way as during presentation of the vigilance stimuli. Using these additional data, the regression technique for removing eye movements and blinks from the ERPs (Woestenburg et al. 1983a) could be applied more powerfully. Subsequently, single-trial ERPs were estimated with an orthogonal polynomial trend analysis in the frequency domain (OPTA; Woestenburg et al. 1983b).

ERP scoring

Single-trial ERPs were determined separately for hits, misses, and for the non-signals immediately preceding the signals. Non-signals that induced a response (i.e., false alarms) rarely occurred and were excluded from the ERP analysis, so only correct rejections remained. For each 5-min period of the task, one mean ERP was determined for signals (the average ERP of the number of hit- and miss-ERPs in that period), and one mean ERP for the non-signals. Amplitudes and latencies of four different peaks were scored in the ERPs, always after stimulus onset and relative to the 100-ms pre-stimulus level. The P1 was scored as the largest positive deflection between 28 and 100 ms, occurring before the N1. The N1 was scored as the largest negative peak occurring between 48 and 152 ms. The P2N2 was scored as the largest positive-negative going complex occurring after N1, in the latency range from 188 to 460 ms, but occurring before P3, which was scored as the largest positive peak occurring in the latency window between 444 and 924 ms. Grand average ERPs are shown in Fig. 1.

Scoring of the EEG

Non-signal epochs, or rather, epochs yielding correct rejections, were used for estimation of power in the ongoing background EEG, because these epochs are more likely to be free from activity involved in the preparation or execution of motor responses, or from other activity related to task performance. However, non-signal stimuli were still presented in these epochs and subjects had to make a decision not to respond, thus precluding the estimation of electrocortical power in silent (stimulus-free) epochs. In order to solve this problem an extension of the OPTA procedure was implemented in such a way that event-related brain activity was subtracted from these epochs prior to power estimation.

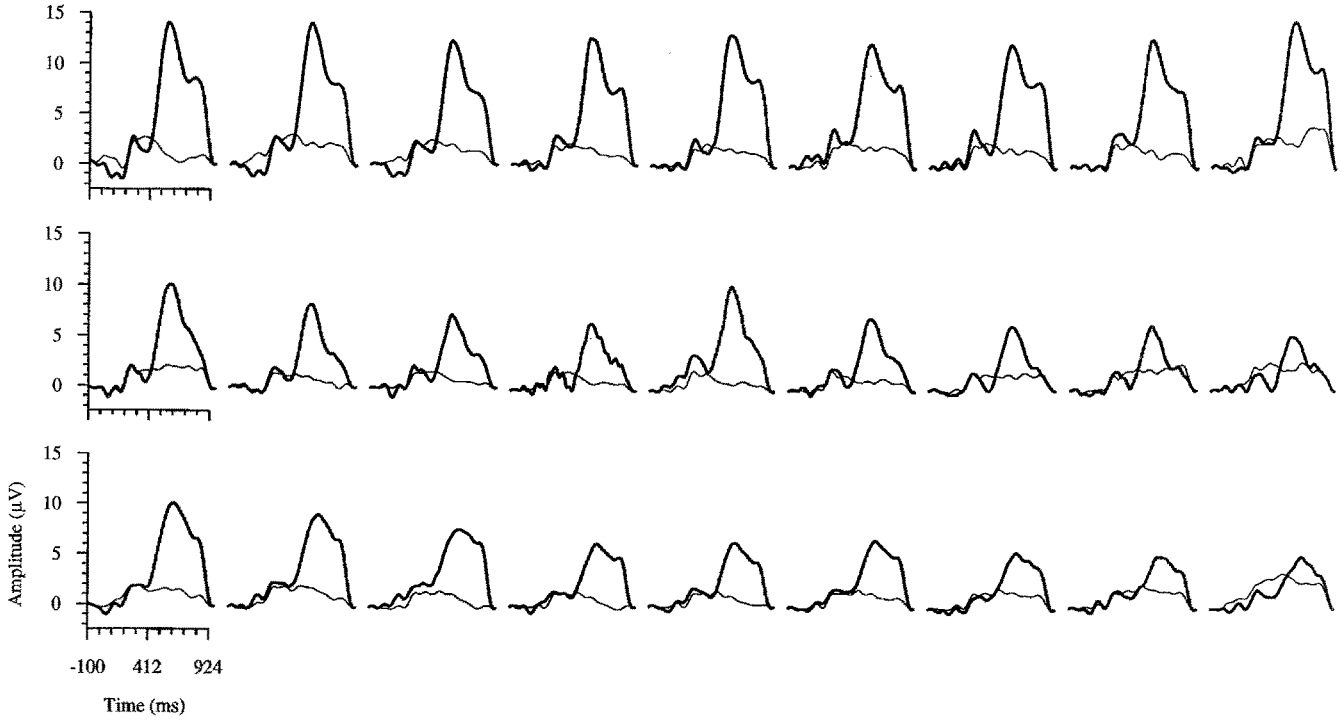

Fig. 1 Grand average ERPs as a function of time-on-task (subsequent 5-min periods) for signals (*bold lines*) and non-signals (*thin lines*); placebo (*upper panel*), 20 mg (*middle panel*), and 40 mg (*lower panel*) oxazepam. Data collapsed across leads. $n = 18$

The absolute power was estimated for the residual, non event-related, brain activity by applying Fast Fourier Transformation (FFT). For each 5-min period of the task, the mean power was determined for frequencies in the delta range from 0.5 to 3.5 Hz; for theta from 4 to 7.5 Hz; for (lower) alpha 1 from 8 to 10 Hz; for (higher) alpha 2 from 10.5 to 12 Hz; for (lower) beta 1 from 12.5 Hz to 21 Hz, and for (higher) beta 2 from 21.5 to 30 Hz.

Statistical analysis

A multivariate analysis of variance (using the program MULTIVARIANCE; Finn 1978) was performed on the ERP-data. Within-subject factors were Drug (0, 20, and 40 mg oxazepam), the difference between signals and non-signals (S-NS), and period (P). For P, linear and quadratic orthogonal polynomial trend-scores were determined: P(lin) and P(qua). Topographical differences are reported only when in interaction with Drug and/or period, and were tested with the factor anterior-posterior (AP), i.e. electrode locations from frontal, through central and parietal, to occipital. Further, a factor laterality (LAT) tested differences between electrodes at the left and right hemisphere and midline. The same within factors, except for the ones pertinent to topography and the difference between signals and non-signals, were maintained for the briefly discussed overt performance measures. As to the application of analyses of covariance, only in those cases where the initial analysis shows significant reductions of variance, that is, when effects adjusted for covariance cease to reach significance levels, will a reverse analysis be carried out in order to assess the robustness of the adjustment. For all tests, a 5% (two-tailed) level was adopted as level of significance.

Table 1 *F*-values of major effects (of oxazepam and time-on-task) on measures of performance pertinent to the complete (*Com*) data set (i.e., eyes open and eyes closed at stimulus presentation), and restricted (*Res*) data set (eyes open at stimulus presentation). Effects shown are significant at 5% two-tailed level of significance

	Drug $F(2,16)$		Period (lin) $F(1,17)$		Drug × Period (lin) $F(2,16)$		SD × Drug × Period (lin) $F(2,16)$	
	Com	Res	Com	Res	Com	Res	Com	Res
Hits	21.04	19.75	70.40	66.51	4.34	4.96	4.16	3.00*
FAs	7.45	7.25	ns	ns	ns	ns	ns	ns
A′	13.29	11.40	76.33	73.37	11.06	11.45	ns	ns
SI	13.96	11.96	83.88	82.94	9.41	9.66	ns	ns
RI	11.23	10.51	48.71	43.83	ns	ns	ns	ns
RT	4.42	4.42	38.58	38.58	ns	ns	ns	ns

*Significant at 10% two-tailed level of significance
ns non-significant

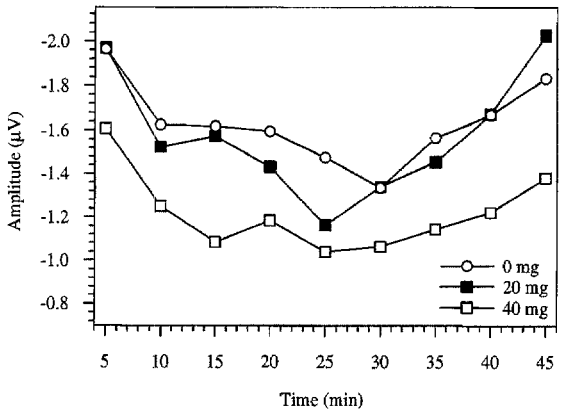

Fig. 2 The amplitude of the N1 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open squares*) oxazepam. Data collapsed across signals and non-signals and leads. $n = 18$

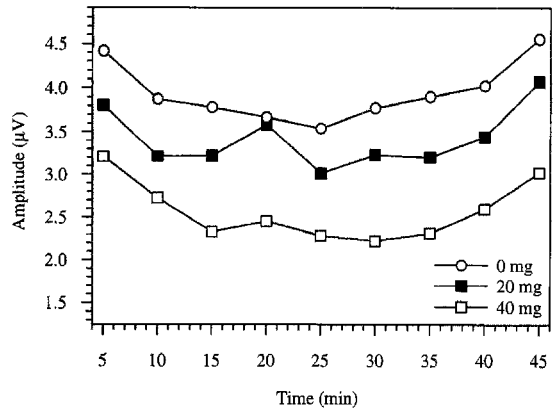

Fig. 4 The amplitude of the P2N2 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open squares*) oxazepam. Data collapsed across signals and non-signals and leads. $n = 18$

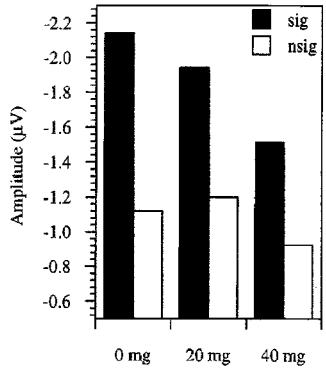

Fig. 3 Amplitudes of the N1 for signals and non-signals after placebo, 20 mg, and 40 mg oxazepam. Data collapsed across leads. $n = 18$

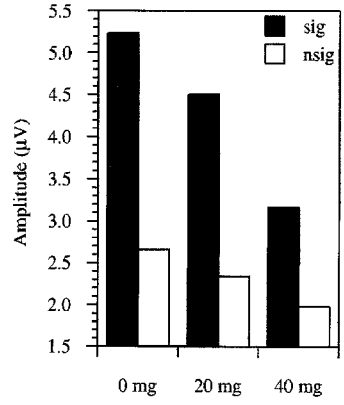

Fig. 5 Amplitudes of the P2N2 for signals and non-signals after placebo, 20 mg, and 40 mg oxazepam. Data collapsed across leads. $n = 18$

Results

Performance

Vigilance performance

The main results of the earlier study (Van Leeuwen et al. 1994a) were also observed in the present, more restricted, data set, where trials with eye closures during stimulus presentation were excluded. Table 1 presents a summary of the major results of the complete and restricted data.

There were Drug effects on overall level of hits, false alarms (FA), two sensitivity measures (A′ and SI) responsivity (RI), and response latency to hits (RT); in all cases, performance after placebo was superior to performance after administration of 20 and 40 mg oxazepam, respectively. As in the original data set, vigilance performance declined significantly with time-on-task, as reflected in hits, sensitivity, responsivity, and RT (the latter measure displaying an increase). Note, that effects on RT were equal in both the complete and restricted data sets, which indicates that all responses to detected stimuli were generated when the eyes were open at stimulus presentation. Further, a differential decline with time after oxazepam emerged for hits and sensitivity: the declines were steeper than after placebo.

Event related potentials

P1. A main Drug effect, implying lower amplitudes after the intake of oxazepam, was noted for the amplitude of P1 [$F(2, 16) = 14.86$]. Further analyses showed that placebo differed from 40 mg, and 20 mg differed from 40 mg [$F(1, 17) = 7.84$ and 7.88, respectively; mean amplitudes for placebo, 20 and 40 mg oxazepam were 1.11, 0.92, and 0.71 mV, respectively]. The amplitude of P1 declined quadratically with time-on-task [$F(1, 17) = 27.60$]. Signal amplitudes were larger than non-signal amplitudes [$F(1, 17) = 54.78$]. There were no significant interactions.

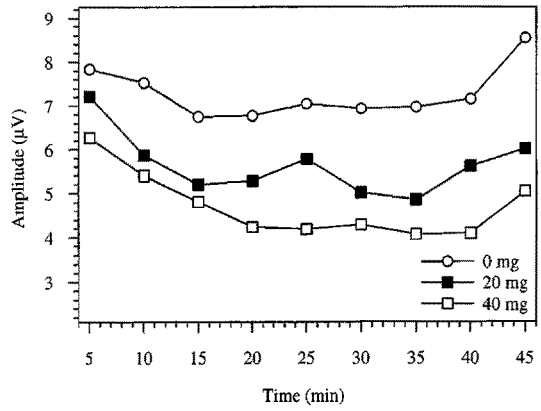

Fig. 6 The amplitude of the P3 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open squares*) oxazepam. Data collapsed across signals and non-signals and leads. $n = 18$

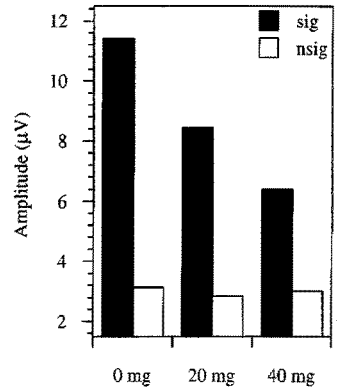

Fig. 7 Amplitudes of the P3 for signals and non-signals after placebo, 20 mg, and 40 mg oxazepam. Data collapsed across leads. $n = 18$

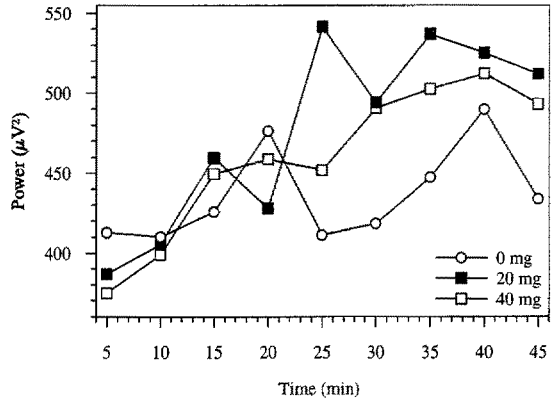

Fig. 8 Mean power in delta as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open circles*) oxazepam. Data collapsed across leads. $n = 18$

N1. A main Drug effect, implying lower amplitudes after oxazepam ingestion, was also noted for the amplitude of NI [$F(2, 16) = 6.18$]. Pairwise analyses showed that placebo differed from 40 mg [$F(1, 17) = 7.84$], and that the difference between 20 and 40 mg was also significant [$F(1, 17) = 7.88$] (0 > 40, 20 > 40). The amplitude of N1 decreased quadratically with time-on-task [$F(1, 17) = 32.05$]. Signal amplitudes were larger than non-signal amplitudes [$F(1, 17) = 38.20$; mean N1 amplitudes were −1.86 and −1.08 mV for signals and non-signals, respectively; see Figs 2 and 3].

P2N2. A main Drug effect, implying lower amplitudes in the oxazepam conditions, was noted [$F(2, 16) = 13.99$]. Pairwise analyses revealed significant differences between placebo and 40 mg and between 20 and 40 mg [$F(1, 17) = 9.26$ and 7.02, respectively] (0 > 40, 20 > 40). Further, a Drug × S-NS interaction was noted [$F(2, 16) = 14.38$]. It appeared that the magnitude of the S-NS difference decreased from placebo to 40 mg (values for the comparison between placebo and 40 mg, and between 20 and 40 mg were $F(1, 17) = 29.54$ and 6.20, respectively). Analysis per stimulus type showed a significant Drug effect for both signals [$F(2, 16) = 18.47$] and non-signals [$F(2, 16) = 5.31$]. Pairwise analysis of the Drug effect for signals showed that differences between placebo and 40 mg and between 20 and 40 mg reached signi ficance [$F(1, 17) = 28.91$ and 15.59, respectively]. For non-signals the only difference was that between placebo and 40 mg [$F(1, 17) = 11.09$]. The ampli tude of P2N2 declined quadratically with time-on-task [$F(1, 17) = 23.94$]. There was a significant difference between non-signals and signals [$F(1, 17) = 70.14$], signals were larger in amplitude (see Figs 4 and 5).

P3. A main Drug effect was found for the amplitude of P3 [$F(2, 16) = 10.66$], indicating that amplitudes were lower after the two drug doses. Paired analysis revealed dose-dependent differences [$F(1, 17) = 11.38$, 22.34 and 7.67, respectively caused by 0 > 20, 0 > 40, and 20 > 40]. Further, a Drug × S-NS interaction emerged [$F(2, 16) = 14.03$]. Separate analysis showed a Drug effect for signal P3s only [$F(2,16) = 14.14$]. When analysed pairwise, dose-dependency emerged [$F(1, 17) = 14.19$, 28.44 and 15.90, for placebo versus 20 mg, placebo versus 40 mg, and 20 versus 40 mg, respectively]. Although there was a significant linear and quadratic decline with time-on-task, collapsed across the drug conditions [$F(1, 17) = 7.30$ and 43.70, respectively], a Drug × P(lin) effect for the P3 [$F(2$ $16) = 5.88$] showed significant linear decrements in amplitude for 20 and 40 mg only, not for placebo [$F(1, 17) = 6.67$ and 7.91, for 20 and 40 mg, respectively]. Signals induced larger P3 amplitudes than non-signals [$F(1, 17) = 39.13$]. An S-NS × P(lin) interaction [$F(1, 17) = 24.90$] implied that only signal P3s showed a linear decline in amplitude [$F(1, 17) = 20.90$; see Figs 6 and 7].

Summarizing, the main findings were that there were Drug effects on all ERP waves; however, the Drug effect

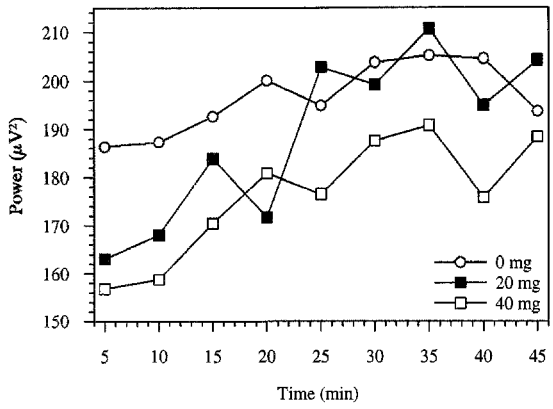

Fig. 9 Mean power in theta as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open circles*) oxazepam. Data collapsed across leads. $n = 18$

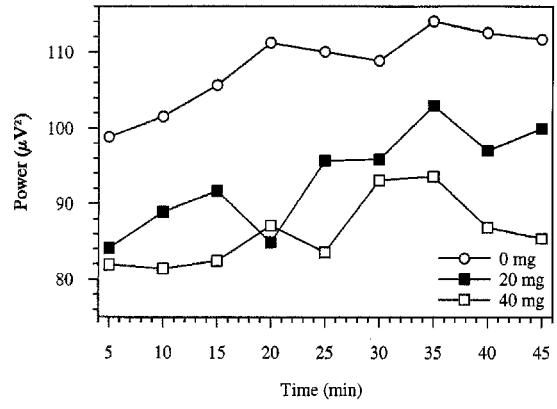

Fig. 10 Mean power in alpha 1 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open circles*) oxazepam. Data collapsed across leads. $n = 18$

was dose-dependent for the P3 only. The S-NS main effect (larger amplitudes to signals) was significant for all ERP-waves. Drug × S-NS interactions, however, were only significant for the P2N2 and the P3. Although all ERP-waves showed a decrease in amplitude as a function of time (either linear or quadratic), only the P3 showed a Drug × P (lin) interaction, reflecting that only in the 20 and 40 mg oxazepam conditions but not after placebo a linear decrease of the amplitude over time occurred.

EEG

Delta. There was no main Drug effect, but there was a main linear increase in delta power with time-on-task [$F(1, 17) = 30.57$]; see Fig. 8. No other significant effects were noted.

Theta. There was no main Drug effect, but there was a significant Drug × LAT interaction[$F(4, 14) = 12.93$]. Subsequent analysis per LAT level showed Drug effects

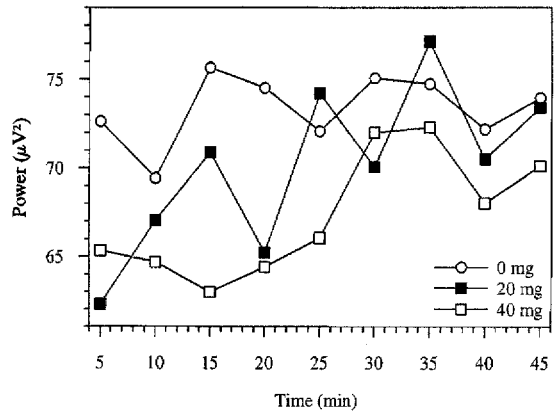

Fig. 11 Mean power in alpha 2 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open circles*) of oxazepam. Data collapsed across leads $n = 18$

at the left side as well as at midline positions [$F(2, 16) = 6.52$ and 10.39, respectively], but there were no drug effects on the right hemisphere. Differences at the left electrode positions only reached significance between placebo and 40 mg [$F(1, 17) = 12.91$], with lower power in the 40 mg condition. At midline positions, power was higher in the placebo condition than in the 20 mg [$F(1, 17) = 10.36$], and the 40 mg [$F(1, 17) = 21.66$] condition. There was both a linear and quadratical increase with time-on-task [$F(1, 17) = 22.14$ and 6.04, respectively], but no significant interactions involving the factors Drug and Period; see Fig. 9.

Alpha 1. There was a main Drug effect on alpha 1 [$F(2, 16) = 7.91$], although this was not dose-dependent; see Fig. 10. A paired analysis showed significantly more power after placebo than after 20 or 40 mg [$F(1, 17) = 5.96$ and 16.20, for placebo versus 20 and placebo versus 40 mg, respectively]. A Drug × LAT interaction was also found [$F(4, 14) = 10.56$], and subsequent analysis per LAT level showed a Drug effect at the left and midline positions only [$F(2, 16) = 11.86$ and 10.87, respectively]. At the left hemisphere, drug effects were dose-dependent; placebo versus 20 mg, placebo versus 40 mg, and 20 versus 40 mg comparisons all reached significance [$F(1, 17) = 7.18$, 21.98, and 5.69, respectively]. There were both linear and quadratic increases in power with time-on-task [$F(1, 17) = 22.27$ and 4.67, respectively], but no significant interactions with any of the other factors.

Alpha 2. There was no significant Drug main effect, but a Drug × LAT interaction was noted [$F(4, 14) = 3.38$]. Analysis per LAT level showed Drug effects at the left side as well as at midline positions [$F(2, 16) = 4.49$ and 5.96, respectively], but there were no drug effects on the right hemisphere. Further analyses for the left hemisphere showed a significant difference between placebo and both 20 and 40 mg [$F(1, 17) = 4.52$ and 8.75, respectively, with the highest power in the placebo

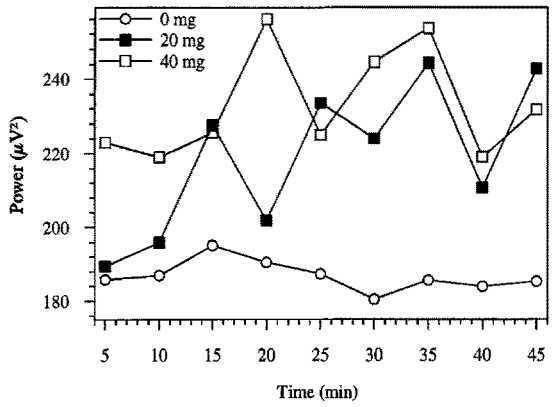

Fig. 12 Mean power in beta 1 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open circles*) oxazepam. Data collapsed across leads. $n = 18$

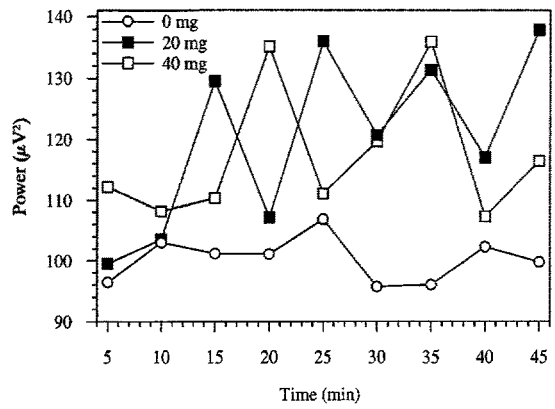

Fig. 13 Mean power in beta 2 as a function of time-on-task for placebo (*circles*), 20 mg (*filled squares*), and 40 mg (*open circles*) oxazepam. Data collapsed across leads. $n = 18$

and the lowest in the 40 mg condition. The same picture emerged at the midline positions, where again differences between placebo and both 20 and 40 mg reached significance [$F(1, 17) = 11.57$ and 6.57, respectively. A Drug × AP interaction was also found [$F(6, 12) = 4.19$]. A subsequent analysis showed that a significant drug effect was noted at the frontal line only [$F(2, 16) = 5.09$], where placebo power level was higher than in the 40 mg condition [$F(1, 17) = 10.82$]. The only significant effect relating to the factor Period was a significant linear increase with time-on-task [$F(1, 17) = 7.83$]; see Fig. 11.

Beta 1. A main Drug effect was found [$F(2, 16) = 6.57$], but this was not dose-dependent; see Fig. 12. Subsequent analyses revealed that the lowest beta 1 powder levels were found in the placebo condition, which differed significantly from 40 mg only [$F(1, 17) = 13.96$]. A Drug × LAT interaction was also found [$F(4, 14) = 4.53$]. Drug effects were significant at the left and midline electrodes only [$F(2, 16) = 4.38$ and 9.92, respectively]. Pairwise comparisons at the left hemisphere revealed that the highest levels were found in the 40 mg condition and the lowest levels in the placebo condition. Significant differences were found between placebo and both 20 and 40 mg [$F(2, 16) = 5.65$ and 8.91, respectively]. At the midline locations, dose-dependency emerged because placebo differed from both 20 and 40 mg, and the latter two differed also [$F(2, 16) = 8.70$, 21.07, and 13.44, for placebo versus 20 and 40, and 20 versus 40 mg, respectively]. A Drug × AP interaction was found [$F(6, 12) = 3.77$]. Further analysis showed that a Drug effect was noted at central, parietal, and occipital lines [$F(2, 16) = 5.98$, 8.10, and 5.71, respectively], but not at the frontal line. Paired analysis at the central line showed a difference between placebo and 40 mg only [$F(1, 17) = 12.70$]. Similar analyses at the parietal line revealed differences between placebo and both 20 and 40 mg [$F(1, 17) = 5.62$ and 17.10, respectively]. At the occipital line, placebo differed only significantly from 40 mg [$F(1, 17) = 11.74$]. No further interactions involving the factor Drug were found. The linear Period effect just failed to reach significance [$F(1, 17) = 3.78$, $P = 0.06$], but a quadratic trend emerged [$F(1, 17) = 4.67$], the latter indicating that the speed of the increase decreased over time.

Beta 2. The Drug effect was not significant, but a Drug × AP interaction [$F(6, 12) = 4.31$] indicated that a Drug effect was present at the parietal line [$F(2, 16) = 3.63$]. Paired analyses at this line showed that power levels were lowest in the placebo condition, but also that only the difference between placebo and 40 mg reached significance [$F(1, 17) = 6.18$]. Neither main linear, nor main quadratic trends with time-on-task could be noted, nor were there any interactions involving the factor Period, see Fig. 13.

Summarizing, the main findings were that there were Drug effects on power in theta, alpha 1 at left and midline (dose-dependently) electrode positions, alpha 2 at left and midline positions, beta 1 at left and midline (dose-dependently) positions. Increases in power with time-on-task (either linear or quadratic) were noted for theta, alpha 1, and beta 1. Significant interactions involving the factors Drug and Period were not obtained.

Analyses of covariance

Analyses of covariance (Finn 1978) was used in this study for the determination of relationships between classes of dependent variables. It was decided that only in those cases where initially a univariate or multivariate analysis of variance had shown a significant (main) effect of Drug and/or time-on-task which became insignificant after the analysis of covariance, a meaningful dependence between predictors and dependent variables may be inferred. It is acknowledged that this procedure may entail a certain limitation in the

investigation of the relationships between EEG/ERPs and behavior: lack of a Drug effect on EEG/ERPs and behavior does not imply that the these domains are unrelated. Likewise, the procedure followed with respect to the relationships between the effects of time-on-task on EEG/ERPs and behavior, i.e. to study the collapsed three drug conditions, may obscure placebo relationships as a result of the extra variance introduced by the 20 and 40 mg oxazepam conditions. Further, reversed order analyses of covariance will be carried out in those cases where the initial adjustment for common variance led to significant reductions in *F*-values, to probe the robustness of the relationships.

Relationship between ERPs and behavior

Drug. More details about the Drug effects on overall level of performance can be found elsewhere (Van Leeuwen et al. 1994a). Briefly, Drug effects were noted for percentage of hits and false alarms, the sensitivity measures A′ and SI, responsivity (RI), and response latencies to hits (RT), see also Table 2. The main Drug effects on performance measures (with the exception of false alarms) were adjusted for common variance with the main Drug effects observed for all ERP waves; see Table 2. For false alarms, several effects were noted (a drug effect and a quadratic increase with time-on-task), but single-trial false alarm ERPs could not be reliably determined, and, consequently, ANCOVA was not applied for this measure. Note, that *F*-values for performance measures are now given pertinent to eyes open conditions. Where a Drug × S-NS interaction was observed (for the P2N2 and the P3), and where the Drug effect appeared to be most pronounced for single-amplitudes, the analysis of covariance pertained to signal-amplitudes only. When adjusted for the drug effect on signal-P2N2 amplitudes, all drug effects on performance ceased to reach significance, albeit that the effects on RT still bordered on significance ($P < 0.058$). Use of the signal-P3 drug effect as predictor led to insignificant drug effects on RT and RI, but the effect on RI still bordered on significance ($P < 0.069$). Although the Drug effects on hits and both sensitivity measures (A′ and SI) decreased to some extent when the signal-P3 amplitude was used as a covariate, these effects remained significant.

In the absence of Drug × S-NS interactions (for the P1 and N1), signals and non-signals were collapsed and subsequently used as covariates for the Drug effect on performance measures. Although in all cases the *F*-values decreased, the Drug effect on hits remained significant. Significant drug effects remained also intact for A′, SI, and RI. However, the Drug effect on RT was significantly affected by these ERP waves, although adjustment for N1 resulted in a Drug effect bordering on significance ($P < 0.074$).

Period. Linear declines with time-on-task were found for hits, A′, SI, RI, RT (increase), and as indicated by an S-NS × P(lin) interaction, also for the P3 signal amplitudes. After adjusting the linear declines in hits, A′, SI, RI and RT for common variance with the P3 to signals, all respective *F*-values of the linear declines dropped to lower *F*-values [$F(1, 16) = 20.08$, 22.64, 26.51, 13.57, and 11.29, respectively], but remained significant. Because quadratic declines in overt performance were not as strong as their linear counterparts, additional analyses of covariance were not applied to these trends. For false alarms, however, only a quadratic trend (increase) with time-on-task emerged, but as already stated, individual single-trial false alarm ERPs could not be determined.

A further observation concerns the Drug × P(lin) effects, which were noted for hits, A′ SI, and P3 amplitude. Because the Drug effect on P3 amplitude was restricted to signals, it was first established whether the Drug × P(lin) effect was also significant for P3 signal amplitudes [$F(2, 16) = 5.02$]. In the subsequent analysis of covariance, percentage of hits was adjusted

Table 2 *F*-values for Drug effects on measures of performance and ERPs, before and after adjustment for common variance

	Before [$F(2,16)$]	After [$F(2,14)$]								
		Hits	A′	SI	RI	RT	P1	N1	P2N2 signals	P3 signals
Hits	19.75						6.32	8.42	2.10**	5.64
A′	11.40						4.96	5.40	1.26**	4.50
SI	11.96						5.11	5.48	1.18**	4.54
RI	10.51						3.85	4.54	0.50**	3.25*
RT	4.42						2.31**	3.15*	3.49*	0.22**
P1	14.86	3.98	7.15	6.88	6.41	10.18				
N1	6.18	0.88**	2.08**	1.86**	1.87**	4.60				
P2N2 signals	18.47	1.68**	4.30	3.83	3.76	15.36				
P3 signals	14.14	3.08*	6.16	5.79	5.29	5.87				

*Significant Drug effect remained after adjustment for common variance at 10% two-tailed level of significance
**Significant adjustment for common variance at 5% two-tailed level of significance

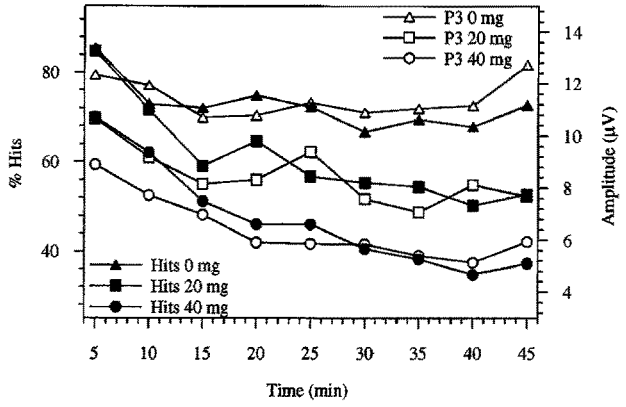

Fig. 14 The amplitude of the signal P3 (*open markers*) and hits (*filled markers*) as a function of time-on-task for placebo, 20 mg, and 40 mg oxazepam. P3 data collapsed across leads. $n = 18$

for common variance with P3 signal amplitudes. The Drug × P(lin) effect for hits disappeared when P3 amplitude was used as a predictor (the F-value dropped to a non-significant $F(2, 14) = 0.29$; and became 0.32 for the reversed order); see also Fig. 14.

The sensitivity measures behaved differently: in both cases the F-values were reduced after adjustment, but the Drug × P(lin) effect remained significant for A′ [$F(2, 14) = 3.81$], and became non-significant for SI [$F(2, 14) = 2.63$; 0.10 for the reversed order].

Finally, it was inspected to what extent the Drug effects found for the various ERP waves were related, see Table 3. The P3 Drug effect was significantly related to the Drug effect on the P2N2, while it was less affected by adjustment for common variance with the N1 or P1 (at a 10% two-tailed level of significance only). The P2N2 Drug effect remained unaffected by adjustment for common variance with the Drug effects on N1 or P1, but was marginally (again $P < 0.10$, two-tailed) affected by the Drug effect on P3. The Drug effect on N1 became insignificant after adjustment for common variance with the Drug effects on P1, P2N2, and P3. The P1 Drug effect appeared to be unaffected by adjustment for common variance with the other ERP waves.

Relationship between background EEG and ERP-waves

Drug effects. This analysis pertains to the question of whether Drug effects on ERP waves in response to signals are related to Drug effects on power in frequency bands. Although in some cases (the P1 and N1 waves) there were no differences between the effects of Drug (and/or Period) on signal and non-signal waves, in other cases (the P2N2 and P3), these effects were largest at waves in response to signals. Therefore, and also not to complicate further the analysis of covariance, only the dependence between background EEG and signal ERP waves was considered. The underlying assumption here was that background EEG activity might be taken as an index of the state of cortical activation, forming the energetical (Sanders 1986) base for the computational processes (which were allegedly stronger in the case of signals) as reflected in the ERP waves. The main Drug effects found on alpha 1 and beta 1 (see above) were used as predictors of main Drug effects on the signal amplitudes of the P1, N1, P2N2, and P3 [the latter F-values being $F(2, 16) = 9.13$, 4.77, 18.47, and 14.14, respectively]. After analysis of covariance with the alpha 1 band as covariate, the F-values for the Drug effects on the ERP waves were all reduced, but only in the case of the N1 and the P3 the Drug effects became insignificant [$F(2, 14) = 0.91$, and 3.61, respectively; with 2.85 ($P < 0.10$) and 0.62 for the analyses of covariance in the reversed order, respectively, i.e., the significant drug effects on alpha 1 also disappeared when adjusted for common variance with N1 and P3]. All F-values were reduced after analysis of covariance with beta 1 as covariate, but they remained significant. So, the effect of oxazepam on alpha 1 significantly related to the effect of the drug on the amplitudes of the N1 and P3.

Period effects. There were no Drug × Period interactions for EEG power bands, but several main linear Period effects were found. Delta, theta, alpha 1, alpha 2, and beta 1 all increased as a function of time-on-task (the increase in beta 1 approached significance). In addition, quadratic Period effects were found for theta, alpha 1 and beta 1. The only ERP-wave which showed a linear change over time (a decrease) was the P3. Removing the common variance in the respective EEG bands from the (linear) Period effect on the P3 did not render the Period effect on the P3 insignificant, however. The same holds for the removal of the common variance in the EEG power bands from the quadratic Period effect on the P1, N1, P2N2, and P3 waves.

Table 3 F-values for Drug effects on ERP waves before and after adjustment for common variance

	Before $F(2,16)$	After $F(2,14)$			
		P1	N1	P2N2	P3
P1	14.86		5.72	4.22	5.11
N1	6.18	0.89**		0.21**	0.86**
P2N2	13.99	3.80	4.19		3.51*
P3	10.66	2.88*	3.34*	1.92**	

*Significant Drug effect remained after adjustment for common variance at 10% two-tailed level of significance

**Significant adjustment for common variance at 5% two-tailed level of significance

So, the effect of time-on-task on the frequency bands are not related to the effect of time on the P3 wave to signals.

Relationship between background EEG and performance

Drug effects. Drug effects on performance (see also Table 2) were all adjusted for common variance with the main Drug effects on alpha 1 and beta 1 power, the only bands showing a significant effect of oxazepam. It appeared that the Drug effects on false alarms. A′, RI, and RT became insignificant when corrected for common variance with alpha 1 power (the *F*-values after analysis of covariance were $F(2, 14) = 2.00$, 3.64, 3.18 and 1.87, respectively, with 2.25, 0.95, 1.42, and 4.37 ($P < 0.05$) for the respective reversed order analyses, i.e., the effect of alpha 1 became insignificant when corrected for false alarms, A′, and RI, but not when corrected for RT). Moreover, the Drug effects on hits and SI were greatly reduced, but remained significant. After correcting performance data for common variance with beta 1 power, only the Drug effect on RT became insignificant [$F(2, 14) = 2.00$, with 3.55 ($P < 0.10$) for the reversed order, so, the effects on beta 1 also became insignificant]. So, the effect of oxazepam on alpha 1 was significantly related to the effect of the drug on overall level of performance, and the effect on beta 1 was related to the effect on the measure of speed only.

Period effects. There were linear Period effects on hits, A′, SI, RI, and RT (see Table 1). After removal of the common variance of the linear Period effect on delta, theta, alpha 1, alpha 2, and beta 1, none of the significant Period effects on the performance measures became insignificant, although delta activity in particular explained much of the variance of the declines in performance [the *F*-values of the linear effects in performance were reduced to $F(1, 16) = 24.23$, 24.34, 26.44, 14.49, and 14.17, for hits, A′, SI, RI, and RT, respectively. So, the effects of time-on-task on the frequency bands are largely unrelated to the effects of time on performance.

Relationship between oxazepam equivalents, background EEG, and ERPs

Drug effects. All Drug effects on EEG power bands and ERPs were rendered insignificant after adjustment for common variance with the Drug effect noted in oxazepam equivalents.

It was further determined to what extent the Drug × P(lin) effect on P3 to both non-signals and signals was affected by the Drug × P(lin) effect on oxazepam equivalents [$F(2, 16) = 54.88$], i.e., whether the P3 effect with time was related to time changes in the activity of the drug. It appeared that the Drug × P(lin) effect on the P3 was somewhat decreased after adjustment for the Drug × P(lin) effect noted for oxazepam equivalents: $F(2, 16) = 5.88$ before adjustment, and an *F*-value of 3.56 ($P < 0.056$) thereafter, which bordered on significance.

Period effects. This analysis of covariance pertained to relationships between pharmacokinetics, as indicated by changes in oxazepam equivalents, and time effects on power in the frequency bands. Because the magnitude of the quadratic trends with time in both EEG power and equivalents were not as high as their linear counterparts (i.e., the latter *F*-values were higher), only the latter trends were subjected to analyses of covariance. It was established whether the linear increase in oxazepam equivalents [$F(1, 17) = 93.03$] could predict the linear increases noted for delta, theta, alpha 1, alpha 2, and beta 1. Only the linear effect on alpha 2 was significantly affected by the removal of the common variance with oxazepam equivalents. The *F*-value of the linear decrease in alpha 2 power dropped from $F(1, 17) = 7.83$ to $F(1, 16) = 2.59$ after correction for common variance with the linear change in oxazepam equivalents. Time effects on beta 1 also became insignificant, but the linear increase in this band bordered only on significance to begin with $F(1, 17) = 3.78$ ($P < 0.68$) and $F(1, 16) = 1.57$ after adjustment). *F*-values for the other EEG bands became lower, but remained significant [for delta, theta, and alpha 1 these *F*-values were $F(1, 16) = 5.34$, 6.84, and 5.73, respectively].

An additional analysis of covariance was performed with the linear increase in oxazepam equivalents as a predictor for the linear decline in the amplitude of the signal-P3, when (in both cases) drug conditions were collapsed. The latter effect was affected by adjustment of common variance with the increase in oxazepam equivalents [the *F*-value decreased from $F(1, 17) = 20.90$ to $F(1, 16) = 14.14$], but remained significant. Because there also was a significant quadratic increase of oxazepam-equivalents over time [$F(1, 17) = 27.57$], a similar adjustment of common variance was performed for the quadratic trends noted for all ERP waves. The latter effects, although reduced in comparison with their unadjusted *F*-values, remained significant; *F*-values were $F(1, 16) = 21.14$, 32.72, 51.95, and 28.12, for P1, N1, P2N2, and P3, respectively.

Discussion

Drug effects on ERPs

The effects of oxazepam were already apparent on the early P1 wave, and were propagated through all subsequent aspects of (covert) information processing as

manifested by the N1, P2N2, and P3 waves. Except for the P1, a wave not measured by Van Leeuwen et al. (1992), the present results confirm the effects of bromazepam on ERPs in the vigilance task reported by these authors. All amplitudes were reduced after BZ ingestion, so BZs appear to dampen all aspects of processing manifest in the various ERP waves, which suggests a state of general sedation. Because the P1 may to some extent be exogeneous, its reduced amplitude under the influence of oxazepam might reflect deteriorated visual input pertinent to subsequent stimulus processing rather than a central effect. However, the Drug effect on P1 was not affected by adjustment for common variance with the Drug effect on fixation accuracy [$F(2, 16) = 5.85$], noted by Van Leeuwen et al. (1994a); the F-value dropped from $F(2, 16) = 14.86$ to $F(2, 14) = 12.69$ only. So, the effect of oxazepam on the P1 cannot be "explained" by peripheral factors, e.g. deteriorated fixation accuracy (an additional analysis of covariance learned that fixation accuracy did not effect the other ERP waves either). The present results also show that the P1, and the N1 as well, cannot be considered as exogeneous waves: there were already effects of task manipulation and attention (differences between signals and non-signals) in the time window between 28 and 100 ms. The Drug effect on the N1 confirms the results earlier reported in the study by Van Leeuwen et al. (1992).

The Drug effect on the P2N2 is more difficult to evaluate because two different processes might be manifested in this wave: stimulus mismatch and processing negativity (PN), the latter being a negative going wave in reaction to target stimuli, so sensitive to task relevance (Courchesne et al. 1975; Näätänen and Gaillard 1983; Kenemans et al. 1989). Stimulus mismatch, on the other hand, has been found to be insensitive to manipulations of task-relevance (Näätänen and Gaillard 1983; Kenemans et al. 1992). Because there was no "ignore" (non-task-relevant) condition in the present study, the two processes could not be disentangled, but the presence of attention effects on the visual P2N2 implies that in vigilance or oddball tasks this wave cannot merely be considered to be the visual analogue of the auditory stimulus mismatch, as has been suggested by Kenemans et al. (1989).

The *interpretation* of positive-negative going electrocortical activity in the time domain encompassing P2N2 might be facilitated by its occurrence in different response classes, in particular false alarms. Van Leeuwen et al. (1992) showed grand mean ERPs determined for false alarms that displayed clear P2N2-like activity, in addition to large P3s. This was a somewhat curious result because, under the assumption that the P2N2-like activity indeed signifies stimulus mismatch, there was no deviant stimulus. The large P3 in the false alarm ERP in the same study may be easier to explain, because P3 activity relates to the further processing of the misperceived non-signal, and may signify allocation of resources pertinent to this further processing. False alarm rates were quite substantial in the earlier study, so subjects had often taken non-signals for signals. In the present study, false alarm rates were much lower, and there was much less ambiguity as to the recognition of the signals. In Fig. 15, grand average ERPs are presented for the four different response classes (including false alarms[1]) in order to throw more light on the meaning of the ERP effects.

Figure 15 shows, with respect to the false alarm ERP, that P2N2-like activity is present, despite the absence of physical stimulus differences. This result rejects the interpretation of this positive-negative going activity solely in terms of mismatch negativity. Note that the grand mean ERP for "misses" (and for hits, of course) also displays similar activity in the P2N2-range; but now physical stimulus differences were actually present. In the case of "misses" even some P3-like activity is noticeable, although this activity probably does not signify further processing of the stimulus, as it does in the case of "hits".

The presently reported P2N2 results further show that the S-NS difference decreased from placebo to 20 mg and from 20 to 40 mg: under the influence of 40 mg oxazepam the differential brain reactions to signals and non-signals in this latency window were significantly smaller than after placebo and 20 mg. The drug effect on the P2N2 may therefore be interpreted as indicating a reduced ability to discriminate, as an impaired ability to detect a difference between stimuli, after oxazepam ingestion. It is important to note that although there were both Drug and S-NS main effects on the P1 and the N1, neither wave showed a Drug × NS interaction. It can, therefore, be concluded that no sooner than in the P2N2 domain, the differential brain reactivity to signals and non-signals was deteriorated by oxazepam ingestion. For the Drug effect on the amplitudes in the P3-range, assuming that waves in this latency range indicate resource allocation (Wickens 1984), the results may be taken to indicate that BZ-ingestion decreased resource allocation, thus confirming a similar conclusion reached earlier (Van Leeuwen et al. 1994b).

The decrease in amplitude of all ERP waves after BZ treatment raises the question of whether the various ERP waves are related. It seemed a logical step, therefore, to investigate whether Drug effects on ERP waves share common variance. It appeared that the common variability resulting from oxazepam intake was more or less limited to two ERP waves: the Drug effect on the P3 shared common variance only

[1] Grand averages were necessarily based upon unequal numbers, i.e., subjects may have differed in their total number of hits, correct rejections, misses, and false alarms. Note, that a grand mean false alarm ERP cloud now be established, in contrast to the individually derived single trial false alarm ERPs, which require a minimum number of observations (see also Method section).

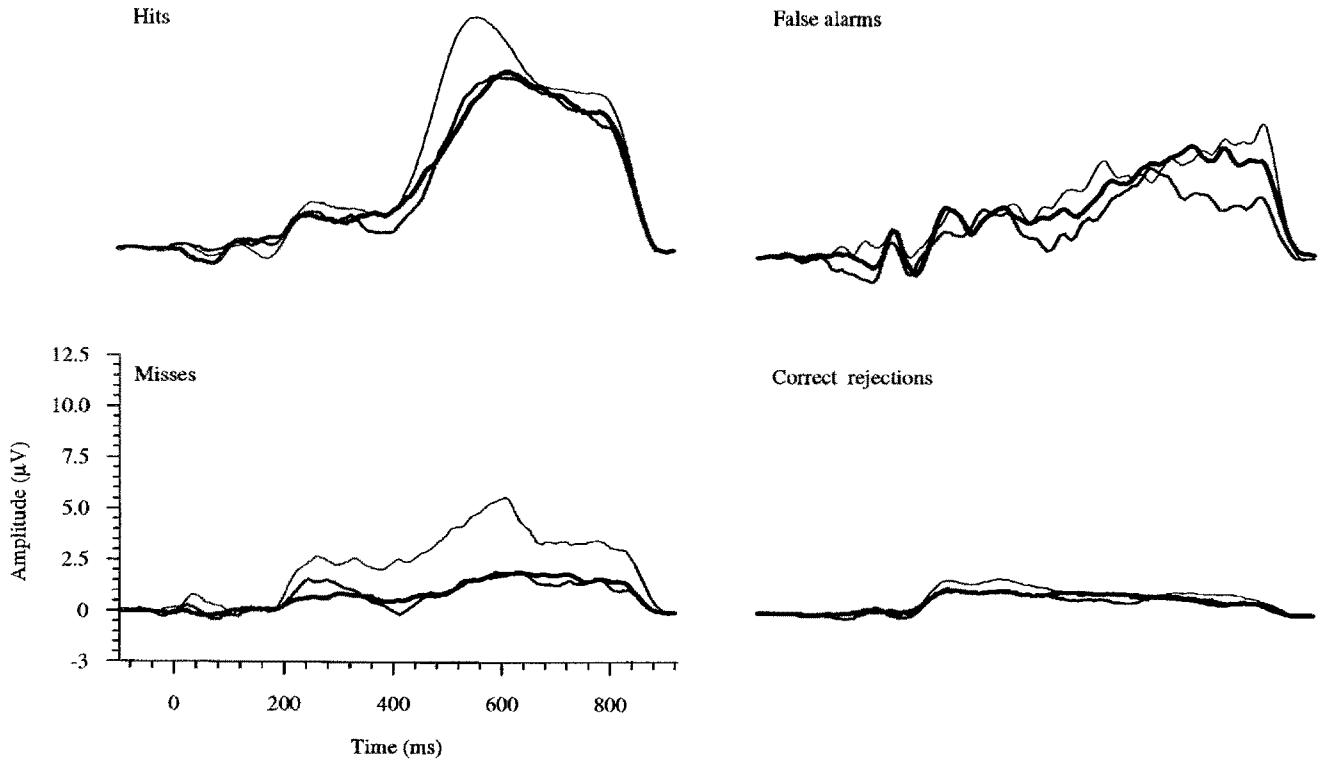

Fig. 15 Grand mean ERPs for separate response classes, i.e., hits (*upper left panel*), misses (*lower left panel*), false alarms (*upper right panel*) and correct rejections (*lower right panel*). Data collapsed across leads and periods. *Thin lines*: placebo, *medium lines*: 20 mg oxazepam, and *bold lines*: 40 mg oxazepam

with the Drug effect on the P2N2, and the Drug effect on the N1 significantly related to the Drug effects on the P1, P2N2 and P3. Of course, these results do not necessarily imply that the processes underlying these ERP waves are similar. They merely show the interdependence of the BZ effect on some waves.

Drug effects on ERPs and behavior

When Drug effects on performance were tested for their dependence on Drug effects on ERPs, it appeared that the effects of oxazepam on overall level of hits and sensitivity (both A′ and SI) were significantly related to the Drug effect on the P2N2. Adjustment of the Drug effects on measures of performance for the common variance with the Drug effect on the P2N2 amplitude, resulted in a non-significant oxazepam effect on all performance measures, except RT. It can, therefore, be concluded that the above noted decreased differential brain reactivity to signals and non-signals after oxazepam, observed for the P2N2 (not for earlier ERP-waves!) expressed itself at the behavioral level as reduced sensitivity to signal-non-signal differences.

For the measure of responsivity (RI), the same relationship with the P2N2 was noted, but in this case there also was a contribution of P3, indicating that lower responsivity concurred with attenuation of both the processes manifested in P2N2 and P3. Thus, it appears that oxazepam exerts its effect on absolute level of performance mainly by deteriorating early stimulus discrimination as indexed by the P2N2 and not by later controlled processes such as manifested in the P3, with the exception of the measure of responsivity.

As noted, even a process as early as manifest in the P1, displayed a signal-non-signal difference. This effect may partly have been caused by differences in spatial frequency between the two types of stimuli, because Ossenblok (1992) showed that the P1 varied with spatial frequency. It is, however, important to note that this S-NS difference was not affected by oxazepam treatment, and probably, therefore, was unrelated to the drug's effect on performance.

In the present study the N1, purportedly reflecting mere stimulus detection, rather than its content or significance (Näätänen and Picton 1987), also displayed a significant signal-non-signal difference, whereas this was not found in the study of Van Leeuwen et al. (1992), possibly because discrimination was extremely difficult in the latter study. Note that the S-NS difference on N1 was unaffected by the effects of BZ or time-on-task. Furthermore, use of the Drug effect on the N1 as a predictor of the Drug effect on hits and the sensitivity measures (A′ and SI), had no effect. Both results indicate that the N1 was involved in the detection of signal-non-signal differences but not

in the deterioration of this discrimination by drugs or time, as reflected in the effects on sensitivity and percentage of hits.

The signal/non-signal differences noted for the P3 would suggest that more resources were allocated to the processing of signals (Wickens 1984). The Drug × S-NS interaction for the P3, showing a Drug effect on signals only, indicates that under the influence of oxazepam less resources could be allocated to the processing of signals. It appeared, however, that the Drug × S-NS effect for the P3 disappeared after adjustment for common variance with the Drug × S-NS interaction for the P2N2 [the F-value dropped from $F(2, 16) = 14.03$ to $F(2, 14) = 2.62$, $P > 0.05$]. This result may be taken to mean that, under the influence of oxazepam, the S-NS difference was more difficult to detect (P2N2), and therefore further processing was abandoned.

Period effects on ERPs and behavior

A following issue concerns the decline in ERPs and performance with time over the collapsed Drug conditions. Vigilance performance declined with time-on-task, and could partially be explained in terms of an increase in eyelid closures and oxazepam equivalents as time progressed (see Van Leeuwen et al 1994a). An additional factor responsible for the decline in performance appeared to be the process manifest in the amplitude of the P3. The P3 was the only ERP-wave which displayed a significant linear decline with time -on-task. The F-values of the linear declines in performance were strongly reduced (although they remained significant) when adjusted for common variance with the P3. Because both the decline in performance and in the P3 were now independent of the P2N2 (which displayed no linear decline), the decrement reflected by P3 might reflect diminishing resource allocation as a function of time-on-task, contributing to the performance declines noted.

The significant relation between time trends in P3 amplitude to signals plus non-signals and RT to hits, reported by Koelega et al. (1992), was confirmed in the present study, that is when all drug treatments were collapsed, because the increase in RT was substantially affected by the decline in P3. However, when considering the placebo condition only, a more valid comparison to the study by Koelega et al., the increase in RT [$F(1, 17) = 27.15$] was not found to be associated with P3, because there was no significant linear decline in this wave in the placebo condition. Note, however, that the P3 in the present study peaked much later than the P3(1) scored by Koelega et al. and is more comparable to the latter authors' P3(2).

The decline in hits and sensitivity (A′ and SI) was steeper after oxazepam ingestion, and in this sense the present results differ from those reported by Van Leeuwen et al. (1992). This steeper decline could not be explained by either increases in eyelid closures during stimulus presentation or increases in plasma concentrations of oxazepam (i.e., in terms of pharmacokinetics). It is therefore proposed that aggravation of the decline in performance after BZ was caused by its effect on central factors. The amplitude of the P3 was the only ERP wave that displayed a Drug × P(lin) interaction. An analysis of covariance showed that the Drug × P(lin) effect on hits and P3 were significantly related. In addition, the Drug × P(lin) interaction for the P3 appeared to be partly related to the Drug × P(lin) effect in oxazepam equivalents, because this P3 effect almost disappeared when corrected for increasing amounts of oxazepam equivalents as a function of time. This demonstrates that the effect of oxazepam plasma concentration on hits was mediated through its effect on the process reflected by the P3.

The two sensitivity measures differed from hits in this respect: adjustment for common variance with the decline in P3 significantly affected the decline in SI, but not that in A′, two measures that usually correlate very highly. A difference between hits on the one hand and sensitivity (A′ or SI) on the other hand, may have been brought about by false alarms, i.e., reactions to non-signal stimuli, which are implicated in the formula for their determination (see Grier 1971; Frey and Colliver 1973). However, the number of false alarms generated at positions where non-signal ERPs were sampled, i.e., preceding the signals, was too small to warrant reliable single-trial ERP estimation. Therefore, the possible contribution of false alarms to the non-signal P3 amplitudes could not be determined in the present study, which might explain the difference that correction for common variance with the P3 has on sensitivity and hits, but cannot explain the difference between SI and A′.

With respect to the basic issue of where the SDT measures sensitivity (A′ or SI) responsivity (RI), and cautiousness (B″) stand for, it may be concluded that apparently various aspects of processing are involved in these measures (but note that with respect to cautiousness or B″, neither effects of time-on-task, nor effects of drug were noted; thus, this measure was not related to any electrophysiological data at all). Sensitivity suggests a reflection of neural efficiency, a process that is outside the person' s control, whereas cautiousness (or willingness to respond) or responsivity would depend on factors under control (motivation, adopted criteria etc.). It is clear from the literature, and from our data, that this distinction is invalid. For example, the statement that A′ or SI stand for sensitivity may be quite meaningless, in particular so because sensitivity has often been reported to correlate highly and positively with the P3 amplitude (e.g., Ruchkin et al. 1980). In the P3, various aspects of cognition (task relevance, expectancy, probability, memory, context undating, response selection, motor processes, resource

allocation) may be implicated. Further, Koelega and Verbaten (1991) reported that d′ and beta, two psychological contructs that should be independent, have often been shown to correlate with the same ERP waves.

Drug effects on EEG and ERPs

Main Drug effects were only found for the alpha 1 and beta 1 power bands. Power in alpha 1 decreased (not dose-dependently) after oxazepam administration, but beta 1 power increased (also non dose-dependently). These two effects have earlier been reported in the literature (e.g., Mandema 1991) but the behavioral significance of these changes has remained unclear.

The decrease of alpha 1 power has been interpreted as a decrease of cortical arousal (Pribram and McGuiness 1975). The present finding that the Drug effect on the N1 and P3 waves became insignificant after correction for common variance with power in the alpha 1 band, may therefore, if the interpretation of alpha 1 in terms of arousal would be correct, mean that the so-called computational processes reflected by the N1 (attention to and detection of stimuli) and the P3 (stimulus evaluation) are either related to energetical processes as indicated by alpha 1 power, or reflect in fact energetical processes (arousal), which questions the validity of the distinction of the two types of processes. This in contrast to the processes manifest in waves such as the P1 and P2N2 which were not significantly reduced by removal of the alpha 1 activity. The fact that the removal of the Drug effect on alpha 1 did not lead to a significant reduction of the Drug effect on the P2N2 is of interest here, given the fact that the N1 and the P3 have both been characterized as waves reflecting a voluntary controlled, process of limited capacity (Isreal et al. 1980; Parasuraman 1985), whereas the visual P2N2 allegedly stands for a capacity-free, automatic process (Kenemans et al. 1992), but see above where this view of the P2N2 is questioned in the case of vigilance tasks. These results are compatible with the notion of limited capacity (e.g., Isreal et al. 1980) and can be taken to mean that the pools of capacity are of a tonic nature, apparently manifest in power in the alpha 1 band. It can also be inferred that available capacity is under the influence of GAB Aergic neurons, for when these influences become stronger after ingestion of oxazepam, less capacity is available for stimulus detection and stimulus evaluation, but note that capacity is also affected by cholinergic, dopaminergic and noradrenergic influences (Koelega 1993).

As mentioned, other authors have characterized the power in the alpha frequency range as an index of (cortical) arousal. It is generally acknowledged that this concept is somewhat abused (cf. Koelega 1991). Some authors have suggested that arousal should be conceived of as indicating resource availability (Humphreys and Revelle 1984), but note that these authors consider arousal to be a conceptual dimension. The present results support this suggestion by showing that, after oxazepam ingestion, decrease of power in the alpha 1 band is significantly related to a decrease in strength and quality of so-called computational processes (reflected by the N1 and P3), but not to other processes (reflected by the P1 and P2N2). This result may be corroborated by findings reported by Intriligator and Polich (1994), who showed that, in particular under low target probability, alpha power contributed to the amplitude of P3. It should be emphasized, however, that the presently reported relationship between (the drug effects on) alpha and P3 were physically independent, that is, alpha was not a component of the evoked potential (P3), in the sense used by Başar (1994) because stimulus locked electrocortical activity was eliminated before power in the frequency bands was estimated. With respect to the present data, alpha 1 is not exclusively related to computational processes manifest in the P3, as shown by the linear Period effects: the P3 to signals became smaller as time progressed but this could *not* be explained by alpha 1 or any other band. Likewise, quadratic time trends in all ERP waves were unrelated to quadratic trends in EEG bands.

Drug and Period effects on EEG and performance

The second issue of interest concerned the relationship between the effects of both drug and time-on-task on performance and EEG bands. It appeared that removal of the common variance of the Drug effect on performance measures with alpha 1 power affected both response-related and sensitivity-related measures. The fact that significant Drug effects on some performance measures (A′, SI, FAs, and RT) disappeared after removing the common variance with alpha 1 power, fits into the conception developed here. In this conception the decrease in alpha 1 power under the influence of oxazepam reflects a reduction of limited processing capacity, leading to the deterioration of stimulus detection and evaluation as reflected by the (decreased) N1 and P3 waves. This conception leads again, but now more specifically, to an hypothesis about a probable cause for the performance decrease after oxazepam ingestion. At least one of the causes seems to be a reduction of central processing resources that function as basic energy sources for both stimulus detection and evaluation processes, and consequently fewer resources can be allocated, as reflected by the amplitude of P3 (see also Van Leeuwen et al 1994b). It seems logical that, when processes related to the detection and evaluation of stimuli decrease in efficiency, other (motor) functions which are to some extent dependent on such processes, such as motor preparation and execution (Sternberg 1969; Sanders

1986) are then also affected, as turned out to be the case with RI and RT.

In contrast to the above mentioned intricate relationships between the effects of drugs on both performance, ERPs, and power in EEG bands, these relationships were found to be either absent or much more loose in the case of the effects of time-on-task. Although there were (linear) changes with time both in performance measures and in all EEG power bands except beta 2, removal of the common variance in EEG power bands from the performance Period effects, did not result in statistical non-significance of the latter Period effects.

The conspicuous increase in power noted for all frequency bands in this study deserves some further comment, particularly because this phenomenon has been reported to occur immediately preceding errors of omission (Ogilvie et al. 1991). Although EEG sampling was not restricted to errors of this kind in the present study, but rather was measured pertinent to correct rejections, an increase in errors of omission was clearly present with time-on-task: the vigilance decrement. Further, it appeared that the increase in delta power with time-on-task considerably reduced the *F*-values of declines in measures of performance. A similar finding, but with respect to other frequencies as well, was interpreted by Ogilvie et al. (1991) to be induced by increasing amounts of micro-sleep bursts with the passage of time. Moreover, increased delta power in the latter half of the vigil after oxazepam is apparent from Fig. 8 (although this effect was not statistically significant), and may well fit the interpretation of (increases in) delta activity as signifying the hypnotic potency of these type of drugs (cf. Mandema 1991).

The results of the present study cannot be interpreted in terms of a single unidimensional theory of arousal because apparent dissociations emerged between the effects of Drug and time-on-task on performance and EEG power bands. Both Drug ingestion and time-on-task led to a decrease of performance, a decrease in the ability of the subject to perform efficiently during the vigil. But the effects of drug and time-on-task on EEG power bands are differential: for example, a decrease of power in theta (left and midline) and alpha 1 bands after Drug ingestion, and an increase in delta, theta, alpha 1, alpha 2 and beta 1 activity as a function of time-on-task. Increases of power in the lower bands as a function of time have been reported before (see Introduction), but the earlier reported decline in power of the higher frequencies (see O'Hanlon and Beatty 1977) could not be confirmed in the present study; beta 2 was the only band showing no increase as a function of time-on-task, which is not the same as a decrease. It is remarkable that there were no drug effects on these time trends, i.e., interactions Drug × Period were absent, although these interactions approached significance for delta and beta 1 [$F(2, 16) = 2.68$ and 2.82, respectively]. For those frequency bands an interaction of this kind might be expected to occur because the effects of time-on-task and effects of BZ, as reported in the literature, apparently dissociate. However, this also holds for power in theta, where a similar interaction not even approached significance. It is clear that such results cannot be explained by an identical (neurophysiological) single concept, such as general cortical arousal.

Another issue of interest concerned the, so-called paradoxical, effects of BZs on behavior and EEG beta activity, in particular beta 1 (there was no Drug effect on higher beta power). It appeared that the Drug effect on all performance measures except RT remained significant after removal of the common variance with beta 1. This indicates that the increase in beta 1 power after oxazepam is not related to the impairing effects of this drug on performance measures other than RT, and is not a reflection or an index of an increase in the central processing resources necessary for stimulus detection and evaluation. This suggestion concurs with the finding that correction for beta 1 variance does not influence the Drug effects on the N1 and P3. Removal of the common variance with beta 1 from the Drug effect on RT, resulted in an insignificant *F*-value, the same effect as was noted after removal of the common variance with alpha 1. So, the slowing of response speed (RT) after oxazepam ingestion is related to power in both bands. It has already been recognized that the interpretation of the latter effects of BZs in terms of a (paradoxical) increase in arousal or activation is questionable (Koelega 1991, p. 357). There are more examples of these so-called pharmacological dissociations, well known, for example, is the dissociation induced by atropine (sleep-EEG with concurrent alert-behavior). Ray and Cole (1985) have also stated that the traditional model of EEG alpha and beta, interpreted in terms of arousal, cannot account for the complexity of human behavior to which it has been applied. Alternatively, the interpretation of the relationship between increased RT and increased beta 1 after oxazepam may be speculatively understood in terms of BZ-induced inhibition of frontal cortical influences. The frontal cortex can selectively activate the inhibitory effect of the thalamic reticular formation (RF) on the thalamic-cortico-relay cells (TCR) (Skinner and Yingling 1977). Massive inhibition of frontal cortical activity, given the fact that this area is relatively densely populated with GABA receptors (on which BZs may act) may well lead to a general decrease of the inhibitory RF influences on TCR cells, thereby shifting the power dominance in brain waves in the direction of an increase in beta power (and a decrease in alpha 1 power). Suggested by the lack of a relationship between beta 1 power and performance *efficiency*, this phenomenon may best be interpreted as an increase in neuronal noise.

A final issue in this paper was related to the question of whether effects of time-on-task on EEG power and ERP amplitudes were related to the time course in activity of oxazepam. Main linear increases with time-on-task were noted for delta, theta, alpha 1, alpha 2 and beta 1 (bordering on significance). A linear decline was found for the amplitude of the signal-P3, and main quadratic declines could be noted for the amplitude of P1, N1, P2N2, and P3. Oxazepam equivalents, determined across Drug doses, placebo included (a rationale for placebo-inclusion can be found elsewhere, see Van Leeuwen et al 1994a) displayed a significant linear and quadratic increase with time-on-task. The linear increases with time-on-task noted in EEG power were all affected by increase in oxazepam activity, but this was not the only determinant because the respective linear trends remained significant after removing the common variance with oxazepam equivalents (except for power in the alpha 2 and beta 1 range, but the linear effect in these frequency ranges was not very strong to begin with). Similarly, the declines in ERP amplitudes were also affected by the increase in oxazepam equivalents, but remained significant. So, apart from the time course in activity of the drug, other factors must also have contributed to these increases in EEG power and declines in ERP amplitudes with the passage of time.

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