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ORIGINAL INVESTIGATION

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Electroencephalographic effects of intravenous nicotine – a dose-response study

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Abstract *Rationale*: It has often been demonstrated that both tobacco abstinence and nicotine have effects on the EEG power spectrum and components of the event-related potentials. In contrast, few attempts have been made to establish the dose-response relationship between nicotine and EEG parameters. *Objectives*: The aim of this study was to investigate the dose-response relationship for EEG and auditory oddball P300 parameters over a wide range of intravenously infused nicotine doses. *Method*: Fourteen regular smokers who had abstained from nicotine for at least 12 h were given intravenous infusions of 0, 3.5, 7, 14 and 28 µg/kg nicotine over 10 min in a single-blind randomised cross-over design. Parallel recordings of spontaneous EEG, auditory P300 and heart rate, as well as venous blood sampling were made before, during and after nicotine administration. *Results*: Linear dose-related decreases of delta and theta power were found, along with increases in alpha$_2$ power and alpha peak frequency. Alpha$_1$, beta and P300 parameters were unaffected. *Conclusion*: Our results are consistent with nicotine-dependent changes in EEG measures indicative of arousal.

Key words EEG · P300 · Intravenous · Nicotine · Dose-response

Introduction

Tobacco smoking persists in spite of well-known health risks (Clee and Clark 1984). The motives for smoking are complex (Pomerleau and Pomerleau 1984; Tate et al. 1994). The smokers' wish to avoid aversive withdrawal symptoms is one significant part of the motivation (Stitzer and Gross 1988). Smokers also frequently state that nicotine aids their mental performance, providing a "psychological tool" (Stepney 1979) that makes them more alert and concentrated when need be (Russell et al. 1974; Warburton and Wesnes 1978; Nil 1991). This is probably related to the arousing effects of nicotine, as evident in the EEG.

When deprived users smoke in non-task conditions (see Church 1989; Pickworth et al. 1995 for reviews), the most frequent finding is a decrease of power in the theta band and less frequently in the delta band, and an increase of alpha$_2$ power or the dominant alpha frequency (Herning et al. 1983; Knott 1988; Pickworth et al. 1989; Pritchard 1991; Domino et al. 1992; Kadoya et al. 1994; Knott et al. 1995a, expt 1). Decrease of alpha$_1$ power has also been shown, as well as increased beta activity (Kadoya et al. 1994; Knott et al. 1995a, expt 1).

Deprivation has, correspondingly, produced electrophysiological signs of sedation, with increased delta and theta power, and decreased peak alpha frequency (Herning et al. 1983; see also Church 1989; Pickworth et al. 1995).

To a large extent, studies of nicotine administration, as distinct from smoking, have yielded similar results. Foulds et al. (1994), in a study of nicotine effects in non-smokers, gave two subcutaneous nicotine injections (0.6 mg) separated by 40 min, producing peak plasma concentrations of 5.3 ng/ml and 8.5 ng/ml, respectively. They found a significant increase in the dominant alpha frequency, but did not report any other significant EEG findings.

Comparatively few attempts have been made to establish the dose-response relationship and fewer still the plasma concentration relationship between nicotine and EEG parameters. Knott (1989a) compared low (0.4 mg), medium (0.8 mg) and high (1.6 mg) nicotine delivery cigarettes with respect to power in theta and alpha bands. Although all nicotine doses reliably decreased

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theta power and increased alpha power, no significant differences between the nicotine doses were reported. No plasma concentrations were reported. Kadoya et al. (1994) studied the EEG effects of smoking one cigarette, and reported relationships between plasma nicotine levels and EEG parameters. They found a decrease in $alpha_1$ and an increase in beta in subjects with more than 10 ng/ml, and a decrease in delta for subjects with blood levels above 15 ng/ml. Results for theta and $alpha_2$ were inconsistent. This study causes interpretation problems with respect to dose-response relationships, as subjects did not serve as their own controls. Pickworth et al. (1989, expt 2) suggested that repeated hourly administration of 4-mg nicotine polacrilex gum (mean plasma level 23 ng/ml) affected the EEG more than corresponding administration of 2-mg polacrilex gum (mean plasma level 14 ng/ml), although no statistical comparisons were made. In general, they found decreased delta and theta power, and increased beta power when deprived smokers were given polacrilex gum; alpha power was unaffected. Pickworth et al. (1996) used nicotine patches (0, 10, 20, 30 mg nicotine; plasma levels approximately 2, 10, 17 and 25 ng/ml, respectively) in a study of smokers. Theta power was higher in the placebo condition, and dominant alpha frequency lower. The authors reported that all nicotine doses differed from placebo but no comparisons between nicotine doses were reported.

To complement the quantitative EEG, many researchers have used event-related potentials (ERPs) (see Knott 1989b), i.e. the average electrical measure of the brain's information processing. The P300 component of the ERP (Picton 1992; Polich and Kok 1995) has been the focus of several studies in the tobacco and nicotine field (Edwards et al. 1985; Herning and Pickworth 1985; Norton et al. 1991; Le Houezec et al. 1994; Knott et al. 1995b; Houlihan et al. 1996), as it is thought to reflect controlled attentional processing (Picton 1992; Kok 1997). Mostly, a simple task is used, where rare (oddball) stimuli are discriminated from frequent standards.

In the common oddball task, findings have been mixed. Knott et al. (1995b, expt 1), studying deprived users smoking a 1.1-mg nicotine yield cigarette (no plasma concentrations were given), reported shorter auditory latencies after smoking, but unaffected amplitudes. Houlihan et al. (1996, expt 2) found decreased visual, but not auditory latencies after smoking a 1.1 mg nicotine yield cigarette. In a subset of their subjects, deep inhalers, visual amplitudes increased, but auditory amplitudes were stable. Nicotine concentrations were not measured. Norton et al. (1991) analysed the residual nicotine in cigarette butts, claiming that the nicotine dose is positively related to residual nicotine, and found that the high residual group had lower auditory P300 amplitude than the low residual group. P300 latencies and nicotine concentrations were not reported.

Some studies have used more complex designs. Edwards et al. (1985) studied the P300 in the rapid visual information processing (RVIP) task, and found decreased visual P300 latencies after cigarettes with 1.5 mg nicotine yield, but not after cigarettes with 0.9 mg nicotine yield.

Herning and Pickworth (1985) used a simple auditory discrimination task in low- and high-noise conditions, and found that 8 mg nicotine, but not 4 mg nicotine, administered by polacrilex gum, prevented a latency increase in high noise conditions. No plasma concentrations were given. Le Houezec et al. (1994) gave subcutaneous nicotine (0.8 mg, 2.9 ng/ml) to non-smokers. They obtained complex effects, and reported increases and decreases of visual P300 latencies, depending on task requirements. They reported no change in amplitudes.

This study aimed to establish the dose-response relationship between intravenously administered nicotine and quantitative EEG measures, and the parameters of the auditory oddball P300.

Materials and methods

Study design

The experiment was designed as a single-blind randomised, placebo-controlled crossover study. It was approved by the Ethics Committee of the University of Lund, and was conducted in accordance with the Declaration of Helsinki. All subjects gave their written informed consent prior to the study.

Subjects

Sixteen subjects participated, recruited from a local panel of volunteers. All were regular smokers, smoking an average of 19 (SD 3.9) cigarettes per day. Cigarettes had an average nicotine yield of 1.1 mg (SD 0.23), tar 12.5 mg (SD 2.8) and CO 11.2 mg (SD 2.4). Clinical interview, physical examination and routine laboratory screening gave no evidence of disease. Subjects were asked to abstain from nicotine for at least 12 h prior to each treatment session. Compliance was defined as a baseline plasma nicotine level below 4.0 ng/ml. Subjects were instructed to take normal meals, but exclude caffeine-containing beverages.

Procedure

Sessions were run twice a day, at 9.00 a.m. and 2.00 p.m. with one subject per session. Session time was kept constant for every subject, except for the highest dose, which was always run at 9 a.m. Treatments were separated by at least 1 week. The data collection schedule is described in Table 1.

Nicotine administration and blood sampling

Single intravenous infusions of 0.9% NaCl, or 3.5, 7.0, 14.0, and 28.0 μg/kg body weight nicotine were given to all subjects. Infusions were given in an antecubital vein of the dominant arm at a constant rate in 10 min by means of a motor syringe. Doses were chosen to correspond to the amount of nicotine reaching systemic circulation when smoking high- or low-nicotine cigarettes. Venous blood samples (5 ml) were collected in sodium heparinised glass tubes from an antecubital vein via an indwelling catheter in the contralateral arm. Blood samples were cooled and centrifuged at 4 C within 60 min, and transferred to cryotubes and frozen. Blood sampling followed the study plan in Table 1.

Table 1 Study plan

Minutes	Injection	Blood sample	EEG	Oddball	Heart rate
Prior		*	*	*	*
0					
5		*			*
12		*			*
15		*		*	*
20		*			*
25		*	*		*
30				*	
40		*	*		*
45				*	
55		*	*		*
60				*	
70		*	*		*
90				*	
100		*	*		*
120				*	
130		*	*		*

Bioanalytical method

Nicotine was assayed using capillary gas chromatography after a single-step liquid-liquid extraction of the plasma sample (Olsson et al. 1995). Nicotine was detected by means of a nitrogen sensitive detector. Normally, samples were analysed twice. However, if the results differed by more than 10%, and the absolute difference was greater than 1 ng/ml, a third analysis was performed. The median was used for all calculations. The quantitation limit for nicotine was estimated at 0.5 ng/ml.

Heart rate measurement

A Nihon Kohden Cardiofax was used. Ag/AgCl electrodes were attached at chest leads V_1 and left V_5, with a ground electrode placed at right V_5.

Electrophysiological recordings

Subjects were supine during the recordings. EEG was recorded at 250 Hz using a NeuroScan system (NeuroScan Inc., Sterling, Va., USA), with amplifier bandpass settings of 0.3 Hz and 50 Hz. Separate Ag electrodes were placed according to the 10-20 system, including Oz. EEG was referred to earlobes, with a ground lead placed at Fpz. An electrooculogram was recorded from electrodes placed below the right eye and at the outer left canthus. For both the quantitative EEG and ERP data files, oculomotor artefacts were corrected offline using the dedicated EOG software of the Neuroscan system. EEG was converted into epochs, bandpass filtered at 0.3 and 31.5 Hz with 24-dB roll-off. Epochs where EEG voltages exceeded ±100 μV after EOG correction were excluded from further processing.

Oddball task

Two hundred 70-dB tones (3200 or 800 Hz, duration 100 ms) were presented binaurally through earphones by the Neuroscan Stim system. The 800 Hz tone was presented in 25% of the trials. Average inter-stimulus interval was 1.65 s (range 1.5–1.8 s), and the total task duration was 5.5 min. The subjects were asked to press a button on a response-pad when the rare tone was heard.

Data analysis

For the quantitative EEG analysis, EEG (eyes closed) was recorded continuously throughout the infusion period and until 2 min after the infusion. These continuous EEG files were broken down into six 2-min segments. The following EEG samples were 4 min long, excluding epochs when blood samples were drawn. To counteract arousal decreases, 100 ms tones were presented with a 12.2-s interval, and subjects were asked to respond by pressing a button. EEG data were converted into epochs from –1024 to 1024 ms, and epochs encompassing the auditory stimulation were excluded. EEG spectra were formed using a cosine window. Absolute power values were summed into the frequency bands delta (0.5–4.0 Hz), theta (4.1–8.0 Hz), $alpha_1$ (8.1–10.5 Hz), $alpha_2$ (10.6–13.0 Hz), and beta (13.1–26.5 Hz). To get a more stable estimate, power values were aggregated into quadrants, comprising AL (F7, F3, T7, C3), AR (F8, F4, T8, C4), PL (P3, P7, O1), and PR (P4, P8, O2). To facilitate comparisons between experimental sessions and frequency bands, quantitative EEG data from each band, quadrant and sample were divided by the corresponding individual baseline values for each nicotine level. This yields a power index that was the dependent variable of subsequent analyses. Because of non-normal distributions, the index was log-transformed before statistical analysis.

For the analysis of event-related potentials, continuous EEG (eyes open) from the oddball task was converted to epochs starting 200 ms before stimulus presentation, and ending 1024 ms post-stimulus. The prestimulus segment was used for baseline correction. Averages were formed for all target stimuli. The P300 was defined as the maximal positive peak in the interval 275–425 ms post-stimulus, and scored at the Fz, Cz and Pz leads. Average reaction times for correct responses and accuracy (percent correct responses) were calculated in the oddball task.

Statistics

Analyses were based on repeated measures ANOVA (5 nicotine doses×11 time points×4 quadrants for quantitative EEG, 5 nicotine doses×7 time points for data from the oddball task and 5 nicotine doses×11 time points for plasma nicotine and heart rate). Significant nicotine dose×time point EEG interactions were further explored by analysing the first five time points (from the infusion-period) and the six following in two separate ANOVAs. Greenhouse-Geisser corrections were applied where appropriate. As the main interest of the experiment was the investigation of dose-response relations, a linear polynomial contrast, adjusted for unequal spacing of nicotine doses, was used as a planned comparison.

Results

One subject was withdrawn because of non-compliance with the abstinence requirements (baseline nicotine plasma levels ranging between 8.4 and 19.2 ng/ml). One sub-

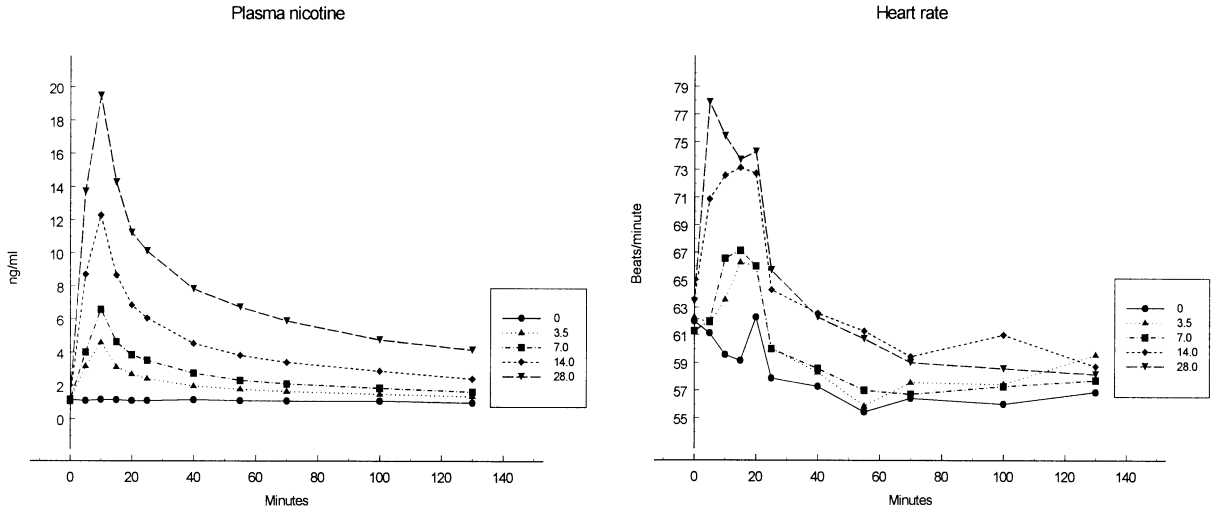

Fig. 1 Mean plasma nicotine (ng/ml) and heart rate (beats/min). ● 0, ▲ 3.5, ■ 7.0, ◆ 14.0, ▼ 28.0 ng/ml nicotine

ject completed only four sessions because of arrhythmia prior to nicotine administration in the last session. Results are based on the remaining 14 subjects (eight males, six females), age 20–48 years.

Plasma nicotine

Mean values are shown in the left panel of Fig. 1. As would be expected, plasma nicotine increased with higher nicotine doses [$F(4,52)=184.1$, $P<0.001$], and varied between time points [$F(10,130)=109.4$, $P<0.001$], with a highly significant interaction between nicotine dose and time point [$F(40,520)=39.1$, $P<0.001$], as plasma nicotine increased markedly during the infusion.

Heart rate

Mean values are shown in the right panel of Fig. 1. Nicotine infusion increased heart rate [$F(4,52)=11.2$, $P<0.001$], with a highly significant linear trend contrast [$F(1,13)=27.7$, $P<0.001$]. The nicotine×time point interaction was significant [$F(40,520)=7.2$, $P=0.01$], with pronounced heart rate acceleration after infusion of the 14.0 and 28.0 µg/kg nicotine dose.

Quantitative EEG

Diagrams of power change can be found in Fig. 2. Results are presented collapsed over quadrants as no significant interactions between nicotine doses and quadrants were found. Gender did not affect the results, and the following analyses refer to the entire group of subjects. Baseline values were similar over all measurements [$F(4,52)>2.9$, $P>0.07$ in all cases], and can be found in Table 2.

Delta

Nicotine decreased power in the delta band (see Fig. 2) [$F(4,52)=2.9$, $P=0.04$], with a highly significant linear trend [$F(1,13)=11.8$, $P=0.004$], giving evidence for a dose-response relation. The nicotine×time point interaction was not significant [$F(40,520)=1.4$, $P=0.21$].

Theta

Nicotine had a significant effect on the power index [$F(4,52)=4.7$, $P=0.008$], with higher doses decreasing theta power (Fig. 2). A dose-response relation was evident from the highly significant linear trend [$F(1,13)=9.4$, $P=0.009$]. The nicotine×time point interaction was significant [$F(40,520)=3.1$, $P=0.006$], due to

Table 2 Mean and SD baseline absolute power (μV^2) for all nicotine doses

Dose (µg/kg)	0		3.5		7.0		14.0		28.0	
	M	SD	M	SD	M	SD	M	SD	M	SD
Delta	13.6	3.0	13.6	2.7	14.5	3.6	13.4	3.1	13.1	2.7
Theta	9.3	3.0	9.2	2.9	9.4	3.2	9.4	2.9	8.8	2.7
$Alpha_1$	11.7	6.7	10.9	5.9	11.1	5.9	11.9	6.8	9.9	5.5
$Alpha_2$	6.3	2.2	6.0	2.2	6.2	2.2	6.4	2.3	5.7	2.3
Beta	16.2	4.4	15.8	3.6	16.0	3.9	16.4	4.2	15.5	4.2

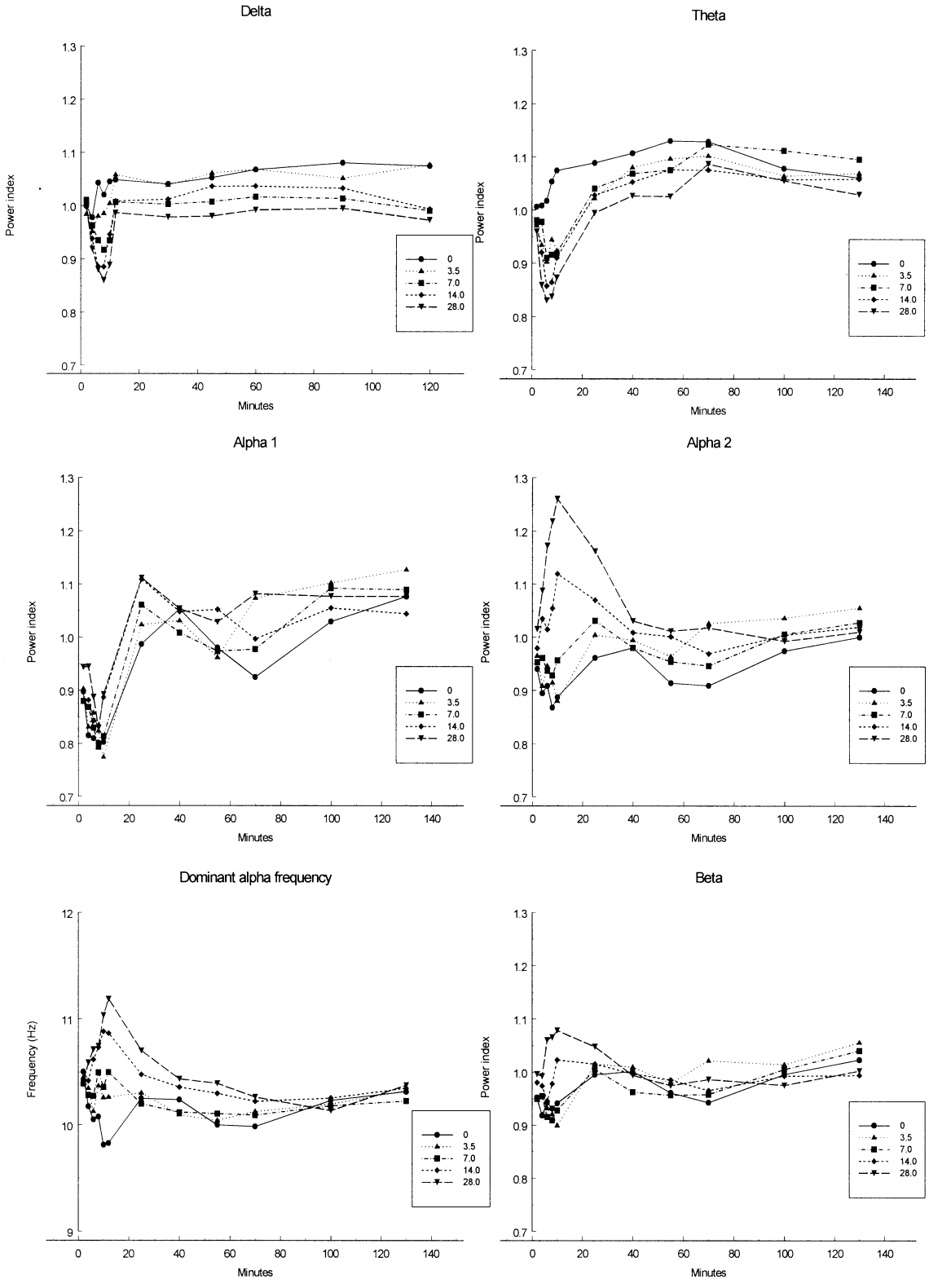

Fig. 2 Mean power and alpha peak change, referred to baseline. Data shown collapsed over quadrants. ● 0, ▲ 3.5, ■ 7.0, ◆ 14.0, ▼ 28.0 ng/ml nicotine

pronounced power decreases during infusion of the higher doses of nicotine (Fig. 2). The linear trend for the measurements during infusion was highly significant [$F(1,13)=12.3$, $P=0.004$], whereas there was no such trend in the later time points [$F(1,13)=3.4$, $P=0.09$].

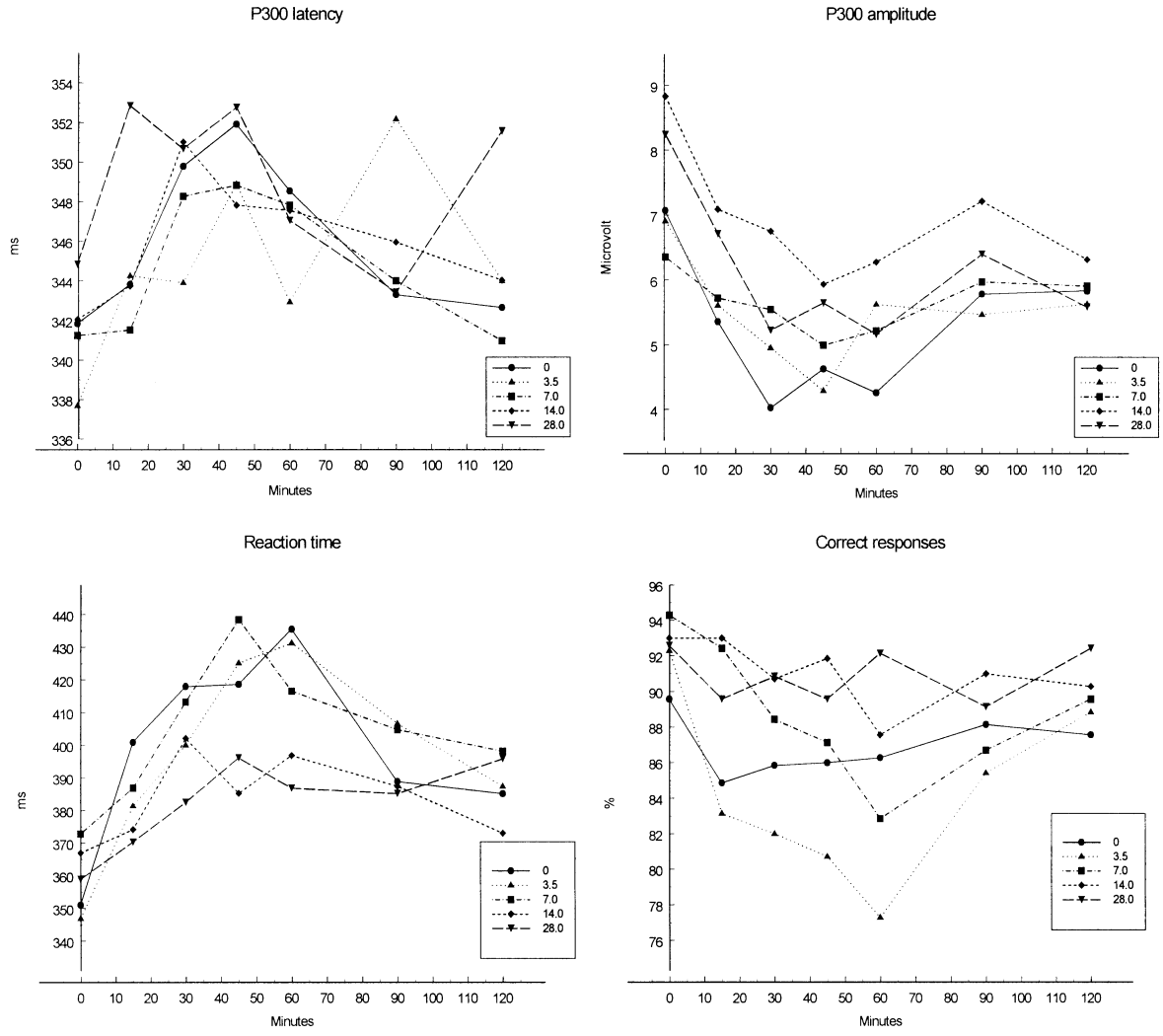

Fig. 3 P300 and response parameters from the oddball task. P300 parameters are shown collapsed over Fz, Cz and Pz. ● 0, ▲ 3.5, ■ 7.0, ◆ 14.0, ▼ 28.0 ng/ml nicotine

Alpha$_1$

Nicotine had no consistent effect on the power index [$F(4,52)<1$, n.s.], and the linear trend was not significant [$F(1,13)<1$, n.s.], suggesting no dose-response effect. There was no differential nicotine effect over time points, as the nicotine×time point interaction was non-significant [$F(40,520)<1$, n.s.].

Alpha$_2$

Nicotine increased alpha*2* power [$F(4,52)=4.3$, $P=0.02$], according to a significant linear dose-response pattern [$F(1,13)=6.3$, $P=0.03$] (Fig. 2). The nicotine×time point interaction was significant [$F(40,520)=3.4$, $P=0.01$], with more pronounced power increases during infusion of the higher nicotine doses (Fig. 2). The initial phase conformed to the linear trend [$F(1,13)=6.6$, $P=0.02$], whereas the effect was attenuated in the later phase [$F(1,13)=3.6$, $P=0.08$].

Alpha peak frequency

Nicotine increased the dominant alpha frequency [$F(4,52)=7.8$, $P=0.001$], well described by a linear trend over nicotine levels [$F(1,13)=17.7$, $P=0.001$] (Fig. 2). The nicotine×time point interaction was significant [$F(44,572)=7.8$, $P=0.001$], with markedly differential effects in the early measurements (Fig. 2).

Beta

Nicotine had no effect on the power index [$F(4,52 =1.0$, $P=0.38$], and the linear trend was not significant [$F(1,13)=1.7$, $P=0.21$]. However, the nicotine×time point interaction was significant [$F(40,520)=2.4$, $P=0.02$], as beta activity seemingly increased initially at the highest dose (Fig. 2). The linear trend for the infusion phase approached significance [$F(1,13)=3.9$, $P=0.07$], with no effects in the later phase [$F(1,13)<1$, n.s.].

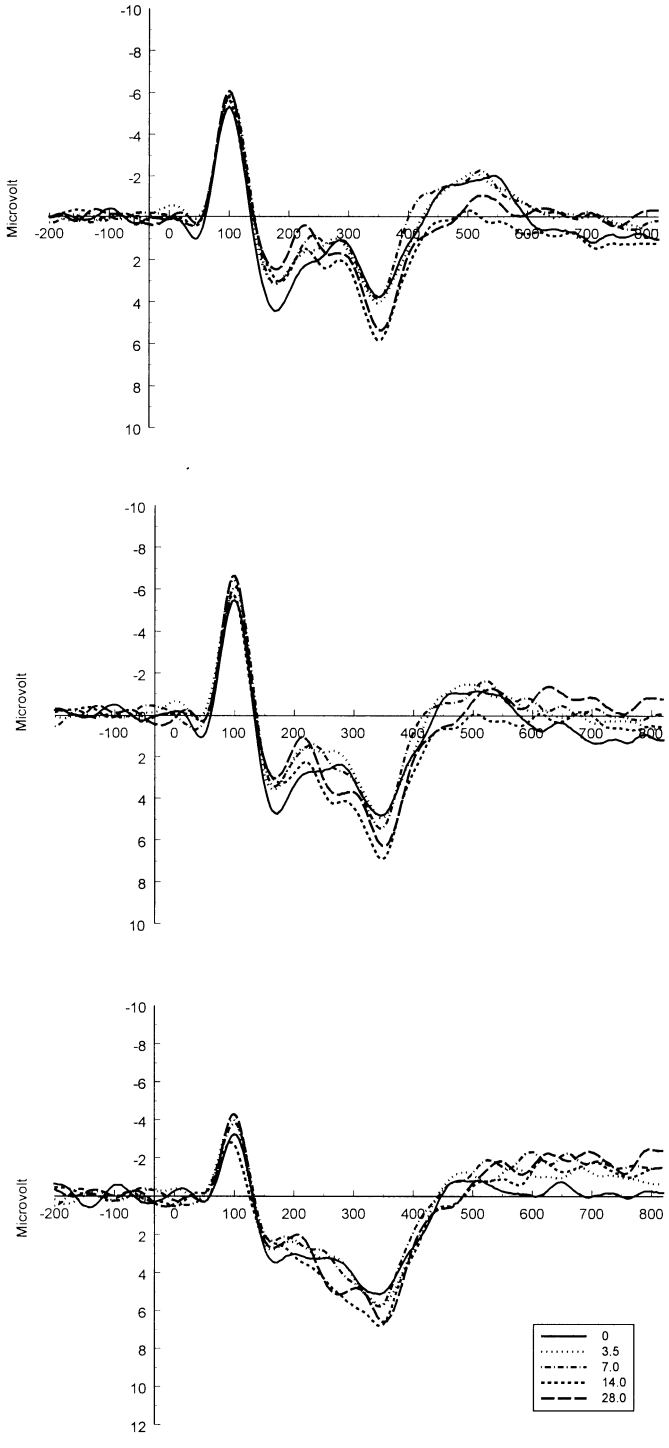

Fig. 4 Grand averages from the first post-infusion measurement at the Fz (*top*), Cz (*middle*) and Pz (*bottom*) derivation. _____ 0, ... 3.5, ._._._._._ 7.0, ---------- 14.0, - - - - - 28.0 ng/ml nicotine

Oddball task

Diagrams depicting P300 parameters and performance in the oddball task can be found in Fig. 3, and grand averages from the measurement following infusion are shown in Fig. 4. Due to technical problems, ERP data were missing from one task presentation each for two subjects. In the statistical analysis, these missing values were replaced by the average from that nicotine condition for each individual.

P300 amplitude

There was no significant effect of nicotine [$F(4,52)=2.5$, $P=0.09$], and no nicotine×time point interaction [$F(24,312)=1.1$, $P=0.36$], giving no evidence for any differential nicotine effects over time points. P300 amplitude differed between the midline electrodes [$F(2,26)=16.4$, $P=0.001$], with largest amplitudes over the parietal lead (Fz mean 4.8, SD 2.9; Cz mean 6.1, SD 4.0; Pz mean 6.7, SD 3.8 μV).

There was no interaction between nicotine dose and electrode [$F(24,312)<1$, n.s.], nor between nicotine, time point and electrode [$F(48,624)=1.1$, $P=0.38$]. Measurement 2, following nicotine infusion, was separately analysed but no nicotine effect could be demonstrated [$F(4,52)=1.8$, $P=0.15$], nor any nicotine×electrode interaction [$F(8,104)<1$, n.s.] (Fig. 4).

P300 latency

There was no significant effect of nicotine [$F(4,52)<1$, n.s.], and no nicotine×time point interaction [$F(24,312)=1.1$, $P=0.36$]. There was a trend difference in latency between the midline electrodes [$F(2,26)=3.6$, $P=0.06$], with longest latencies at the frontal lead (Fz mean 350.7, SD 20.3; Cz mean 346.1, SD 23.6; Pz mean 344.8, SD 25.1 ms). There was no interaction between nicotine dose and electrode [$F(24,312)=1.1$, $P=0.36$], nor between nicotine, time point and electrode [$F(48,624)=1.5$, $P=0.18$]. No latency difference was found between the immediate post-infusion measurements [$F(4,52)=1.1$, $P=0.36$], and no interaction between nicotine and electrode [$F(8,104)=1.6$, $P=0.19$].

Reaction time

There was no significant effect of nicotine [$F(4,52)=1.4$, $P=0.27$], but the nicotine×time point interaction approached significance [$F(24,312)=1.9$, $P=0.07$], as reaction time was seemingly more stable over sessions in the high nicotine conditions (Fig. 3).

Accuracy

There was no significant effect of nicotine [$F(4,52)=1.7$, $P=0.22$], and no nicotine×time point interaction [$F(24,312)<1$, n.s.].

Discussion

We found clear relations between nicotine dose and power in the delta, theta, and alpha$_2$ bands. Delta and theta power decreased with nicotine dose, consistent with increased arousal. Alpha$_2$ power increased markedly at the higher nicotine doses, 14.0 and 28.0 µg/kg, as did the dominant alpha frequency. These results are largely consistent with earlier findings, both after smoking (Kadoya et al. 1994; Knott et al. 1995a) and nicotine administration (Pickworth et al. 1989, expt 2, 1996). These changes had all reached their peaks by the end of the infusion period. Most signs of sedation were found throughout the placebo session, well in line with findings in deprived smokers (Church 1989; Pickworth et al. 1995). The alpha$_1$ band showed no consistent nicotine effects, in contrast to some (Kadoya et al. 1994; Knott et al. 1995a), but not all (Domino et al. 1992) earlier findings during smoking. Earlier studies have also found increased beta power after smoking (Domino et al. 1992; Kadoya et al. 1994; Knott et al. 1995a), and nicotine administration (Pickworth et al. 1989, expt 2). Inspection of Fig. 2 suggests a short-lasting power peak at the highest dose, but only marginally significant effects were found during infusion. Beta power is, however, sensitive to error sources such as the filtering properties of the cranium and dura, which might affect results.

The arousing effect was marked in the delta and theta bands. The relationship with alpha$_2$ was somewhat weaker. It might be noted that the monotonous study situation probably induces low frequency activity, such as delta and theta. It seems reasonable that an arousing agent like nicotine would primarily decrease activity associated with drowsiness, whereas the relatively activated state indicated by alpha$_2$ is less likely to occur under the present circumstances.

We failed to find any significant changes in auditory oddball P300 parameters. This contrasts with the findings by Knott et al. (1995b), but is in line with Houlihan et al. (1996), both studying smokers. Houlihan et al. (1996) suggested that auditory P300 is relatively insensitive to nicotine. The rationale behind their claim is probably the more imperative character of tone stimuli, when compared to the moderately intensive visual stimuli typically used in these tasks. Visual P300s are mostly longer in latency and less temporally defined than auditory. This is likely to give more leeway for latency decreases, but also for amplitude increase, as the amplitude of an average waveform is lower if the P300 onset varies significantly. If this latency jitter is reduced, P300 amplitudes will increase.

In the present study, the standard oddball task was chosen for practical reasons. While this facilitates comparisons with the large P300 literature (e.g. Picton 1992; Polich and Kok 1995), the very simplicity of the task might render it insensitive to subtle changes in cognitive performance. It might therefore be fruitful to study the P300 in more demanding situations, such as dual-task workload paradigms (e.g. Kramer and Spinks 1991; Humphrey and Kramer 1994).

Reaction time and accuracy did not show any dose-response effects. Although improvements of these parameters are frequent findings in the nicotine literature (Sherwood 1993; Heishman et al. 1994), one must note that our task was easy in comparison to the often-used RVIP, leaving little room for change.

The arousing effects of nicotine, as reflected in the EEG, are quite significant in this study, and it is very likely that these effects would seem desirable to many smokers. However, our findings were made in monotonous non-task conditions, and a fuller understanding of nicotine use as an arousing tool in everyday situations would require systematic mapping of individual nicotine use under varying task loads (Perkins 1995).

As no non-smoking controls were included in the present study, our results are ambiguous regarding whether the arousing effect is a reversal of abstinence-related sedation or an "absolute" arousal increase. Two points can nevertheless be made: the increase of alpha$_2$ power and the dominant alpha frequency might be a primary effect of nicotine (Foulds et al. 1994), and the central nicotinic antagonist mecamylamine accentuates sedative "abstinence effects" in the EEG (Pickworth et al. 1988). These two findings might then suggest that our result is a combination of primary or "absolute" effects and abstinence reversal.

In conclusion, clear signs of dose-related activation were found from the EEG measures. There was no support for a relation between nicotine dose and auditory P300.

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