Biological Psychology/Pharmacopsychology

Neuropsychobiology

Original Paper

Neuropsychobiology 1998;38:42–49

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Effects of Nicotine in a Bimodal Attention Task

Key Words
Nicotine, oral snuff
P300
Electroencephalogram

Abstract
Fifteen male users of oral snuff participated in an experiment where we used an auditory-visual vigilance task to study nicotine effects on P300 and response parameters. Quantitative EEG was also studied. Fifteen male nonusers served as controls. We found some decrease of response times and a tendency towards improved signal detection. P300 parameters were not affected in this study. Quantitative EEG analysis indicated an expected increase of arousal, as the activity within the alpha band shifted towards higher frequencies.

Introduction

Although the alleged positive effects of nicotine have been much debated [see e.g., 1–3], previous research has shown fairly consistent nicotine effects on psychomotor performance in smokers, primarily in continuous performance tasks [for reviews see 4, 5]. The effects have mostly been described as a counteracting of performance decrements in the typically monotonous vigilance tasks used [5–9], with reports of performance improvements above baseline levels being comparatively rare [5]. The nicotinic antagonist mecamylamine has furthermore been shown to prolong reaction times in nonsmokers [10], albeit without concomitant decreases in response accuracy. Attempts to decompose reaction time into decision time and motor time have shown decreases in decision time with no effect on motor time [11, 12], as well as opposite results [13, 14]. Nicotine effects on simple motor responses have been demonstrated by findings of faster finger tapping [15–17]. Administration of nicotine to nonusers has met with mixed results, with reports of improved performance on some parameters [18, 19], contrasting against reports of no effects [13, 20].

Some studies have used a divided attention task where subjects have performed a continuous tracking test, while having to respond to intermittent stimuli unrelated to the tracking [13, 21]. Nicotine improved tracking in these studies, but left reaction time to unrelated stimuli unaffected [13, 21] which could indicate an attention-related effect. However, visuomotor tracking is likely to be sensitive to the sensorimotor nicotine effects, as pointed out by Hindmarch et al. [13]. A study with a related focus examined the effects of the cholinergic antagonist scopolamine on working memory [22]. Rusted et al. [22] partly applied the tripartite working memory model of Baddeley [23, 24]. This model separates working memory into a central executive mechanism, involved in the allocation of processing resources between concurrent tasks and a two-slave system, dedicated to phonological and visuospatial material, respectively. Rusted et al. [22] found that sco-

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0302–282X/98/0381–0042$15.00/0

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polamine impaired the central executive mechanism, while leaving the so-called phonological loop unaffected.

Event-related potentials have been rather extensively used in nicotine research. Of special interest to the present study, the P300 component has been the focus in several reports [18, 25–27]. This is a parietocentral, positive deflection, affected by a multitude of biological processes [28]. It is a reliable indicator of late-stage attentional processes [29], emerging only when subjects are actively engaged in information-processing tasks. If target probability and task difficulty are held constant, the P300 amplitude reflects attentional allocation. The P300 latency can then be regarded as a reasonably reliable index of stimulus evaluation time, to a large extent, although not completely, independent of response selection processes [29, 30]. This makes the P300 a valuable complement to response measures [31].

Edwards et al. [25] recorded event-related potentials while subjects performed the much-used vigilance task rapid visual information processing [32] and found a decreased P300 latency. Le Houezec et al. [18] studied P300 latency in tasks with different combinations of easy and hard stimulus evaluation and response selection. Their subjects, who did not normally use nicotine, showed rather complex effects, with a latency decrease in the combination of hard stimulus/hard response and the opposite result in the hard stimulus/easy response condition. In a study where both visual and auditory oddball tasks were used [27], decreased visual but unaffected auditory latencies were found. The authors noted that studies using visual tasks have been more succesful in demonstrating latency differences. Increased amplitudes were not found by Le Houezec et al. [18], but some evidence of dose-dependent amplitude effects was reported by Norton et al. [26].

It has often been suggested that tobacco users manipulate their arousal with the aid of nicotine [see e.g., 33, 34] in an individually adapted way. A recent study [35] showed that the effects of nicotine on EEG dimensionality were dependent on initial complexity, with a 'normalizing' effect of nicotine. Studies aiming at the arousal effects of nicotine have often used the EEG at rest, and results have mostly included some combination of nicotine-related decreases of activity in the delta and theta bands and either an increased dominant alpha frequency or a decreased alpha power and increased beta acitivity [36, 37]. Although criticism has been directed at many EEG studies, where the EEG recordings have been made under nontask conditions [36], on the whole, these results seen valid, implicating increased arousal. A nicotine-related increase in arousal might to some extent explain the findings of improved vigilance mentioned above.

We attempted to combine auditory and visual event-related potentials (ERP) by means of a task where subjects were asked to alternate between a comparatively demanding visual monitoring task and a less demanding auditory discrimination task, with priority given to the visual task, if necessary. Our aim was to increase the working memory load from the typically easy discriminations used in standard oddball paradigms. As mentioned above, Rusted et al. [22] showed negative effects of scopolamine on central executive function. Nicotine might be hypothesized to instead increase capacity in tasks taxing this putative system. This would mean a parallel performance increase in both tasks after nicotine administration, with ERP an adjunct in trying to establish the locus of effects. As the task shares many characteristics with previously used vigilance tests, it is likely that the alleviation of abstinence would be reflected in decreased response time and increased sensitivity. EEG at rest, but in close temporal proximity to the attention task, should be recorded to monitor arousal. Oral snuff is a quite common medium of nicotine administration in Sweden [38], and previous studies have shown effects of oral snuff in cognitive tasks [e.g., 39], which make it seem worthwhile to study the effects of short periods of oral snuff deprivation.

Subjects and Methods

Subjects

Fifteen healthy young volunteers [age 27.6 ± (SD) 4.4, range 21.5–33.9 years] were paid for their participation in this study. They were all habitual users of oral snuff, with at least 2 years' duration of use. The stated average consumption was 25.0 ± 15.3 g/day. In addition 15 nonusers of nicotine served as a control group (age 24.7 ± 3.8, range 19.7–33.8 years). There was a trend difference in age between groups [$t(28) = 1.93$, $p = 0.06$]. The subjects were informed about procedure and task, and gave their written consent. The study was approved by the Ethics Committee of the Medical Faculty.

Procedure

The subjects came to the laboratory in the morning without having taken any nicotine, caffeine, or alcohol since the previous evening, as verified by their own statements. The subjects were comfortably seated in front of the computer display, and the use of the response switch-box was explained. After electrode application, the attention-switching test described below was demonstrated, and a baseline session (A) was run. This and subsequent sessions lasted about 30 min. After completing the baseline session, the subjects applied oral snuff throughout a 30-min break. It has been shown [40] that relatively little nicotine is absorbed from snuff after 30 min, with the blood level of nicotine remaining stable for about 45 min. After an overnight abstinence, snuff users reach average blood levels of

about 14.5 ng/ml after 30 min of absorption [41], a level that has been shown to produce EEG changes [42]. Immediately after the 30-min break, snuff was removed, and a second test session run (B). After a 90-min intermission, during which the subjects were allowed to walk around freely, a final session (C) took place. The subjects were not allowed any caffeine-containing beverages or any extra nicotine during the experiment. Water was allowed, if desired.

Attention-Switching Task

The task consisted of 864 trials and was presented using a Neuroscan® Stim system. The subjects were asked to perform a relatively demanding visual task, namely to monitor a series of digits, presented centrally on the display, and respond by pressing a designated button when they had seen two consecutive even numbers. The target probability was 0.17. In the less demanding auditory task, the subjects heard a series of tones through earphones. Two frequencies were used, either 3,200 or 800 Hz. The 800-Hz tone was presented in 24% of the trials. The subjects were asked to press a button whenever the rare tone was heard. A visual stimulus was always followed by an auditory stimulus, with an interstimulus interval of 2.048 s. The subjects were instructed to follow both tasks as well as they could, but give priority to the visual task, should they find it difficult to master both. Resting EEG (eyes closed) was collected in connection with each session. The order between the attention switching task and the collection of resting EEG was balanced among subjects.

Data Collection

Continuous EEG was sampled at 200 Hz using a Neuroscan® system and recorded on harddisk. On-line filters were set at 0.3 and 40 Hz with 12 dB roll-off. The A-D converter precision was 12 bits. EEG derivations were made at the Fz, Cz, Pz, Oz, F3, F4, C3, C4, P3, and P4 sites, with earlobes as references. In addition, electrodes were placed below the right eye and at the outer left canthus to monitor oculomotor artefacts. Impedances were kept below 5 kΩ. Response data from the subjects were recorded during the attention task.

Analysis

Average reaction times were computed for correct responses. Response times shorter than 100 ms were deemed spurious and excluded from further analysis. The signal detection index d_L [43] was computed according to the formula $d_L = LN[H \cdot (1 - FA)/FA \cdot (1 - H)]$ where H designates hit rate, and FA the false-alarm rate.

Continuous EEG from the attention task was converted into epochs, starting 200 ms before stimulus presentation and ending 800 ms after the stimulus. The prestimulus segment was used to correct the baseline of each epoch. Epoch data were digitally band pass filtered, using high- and low-pass setting of 0.3 and 20 Hz, respectively, and the roll off was 24 dB/octave. The epochs were subsequently corrected for oculomotor artefacts, using software from the Neuroscan system. Epochs where amplitudes following artefact correction still exceeded 100 μV were excluded. Averages were then formed for the two target classes (visual and auditory), and the Fz, Cz, and Pz channels were analyzed for the P3 component. This was defined as the maximum amplitude during the interval 250–550 ms. All averages contained a minimum of 40 sweeps, and sweeps with incorrect responses were excluded.

EEG data from the resting condition were digitally band pass filtered, using high- and low-pass settings of 0.5 and 30 Hz, respectively, with 24 dB roll off. Data were then subjected to a fast Fourier transform, yielding the root mean square power of the four frequency bands delta, theta, alpha, and beta. The alpha band was subdivided into alpha 1 (8–10.0 Hz) and alpha 2 (10.1–12 Hz). Only data from the derivations F3, F4, P3, and P4 were included in the statistical analysis of the EEG data.

Statistics

EEG data were analyzed by three-factor analyses of variance encompassing 2 groups · 3 sessions · 4 electrodes, with sessions and electrodes entered as repeated-measures factors. For the analysis of the alpha band, alpha 1 and 2 were entered as the two levels of a separate within-subject factor. ERP data were analyzed by four-factor analyses of variance (2 groups · 2 tasks · 3 sessions · 3 electrodes) and performance measures by 2 groups · 2 tasks · 3 sessions analyses. Arguably, the critical test of nicotine effects in the present design is a difference in patterns over sessions between the two groups. In statistical terms, this can be construed as the interaction between the group factor and a quadratic trend contrast over sessions, where relevant averaged over electrodes. In essence, this trend contrast compares the second session to the average of the others, thus attenuating linear statistical trends, due to, e.g., fatigue or training. A derived variable [B – (A + C)/2] expressing this contrast can be found in table 1, along with the confidence interval. Where relevant, separate analyses for the two tasks are reported.

Results

Quantitative EEG

EEG data are shown in figure 1. The alpha band was entered into the overall analysis with alpha 1/alpha 2 as a within-subject factor. The interaction between group, band, and quadratic contrast over sessions was highly significant [$F(1,28) = 10.2$, $p = 0.003$]. Further analysis of data from the nicotine group showed a strong interaction between subband and quadratic contrast over session [$F(1,14) = 14.7$, $p = 0.002$], with a decrease of alpha 1 power in the nicotine session and an increase of alpha 2 power from baseline to nicotine session. The corresponding test for the control group was no significant [$F(1,14) < 1$, NS]. No significant results were found in the other frequency bands [$F(1,28) < 1$, NS]. There were no significant interactions with electrodes in any frequency band [$F(6,168) < 2.3$, $p > 0.09$ for all comparisons].

Response Data

Mean values for the response parameters are given in table 1. The response time pattern differed between groups, with a significant interaction between group and quadratic trend [$F(1,28) = 6.6$, $p = 0.02$]. Separating the tasks, a marginally significant interaction was found for the visual task [$F(1,28) = 3.9$, $p = 0.06$], whereas there was no effect for the auditory task [$F(1,28) < 1$, NS], in spite of significantly decreased auditory reaction times in the

Table 1. Mean values of the ERP and performance parameters for the sessions A, B, and C

	A	B	C	$B - \frac{A+C}{2}$	CI low	CI high
N2 amp aud, μV						
Nic	−0.07	−1.38	−0.87	−0.92	−1.44	−0.39
Con	−1.43	1.08	1.91	0.84	0.22	1.45
N2 amp vis, μV						
Nic	−0.83	−0.72	−0.28	−0.16	−0.68	0.36
Con	−0.80	−0.67	−1.07	0.27	−0.06	0.60
N2 lat aud, ms						
Nic	259.71	251.00	252.97	−5.34	−12.74	2.06
Con	248.71	243.28	231.38	3.23	−1.48	7.95
N2 lat vis, ms						
Nic	259.53	266.33	276.57	−1.72	−16.68	13.25
Con	266.32	254.80	216.22	13.52	5.33	21.70
P3 amp aud, μV						
Nic	7.52	7.37	7.83	−0.30	−1.13	0.53
Con	9.06	8.82	8.72	−0.07	−1.25	1.11
P3 amp vis, μV						
Nic	5.61	6.48	6.07	0.64	−0.13	1.41
Con	7.63	7.31	6.91	0.04	−0.79	0.87
P3 lat aud, ms						
Nic	366.00	379.78	370.33	11.61	1.15	22.05
Con	363.11	373.96	380.98	1.91	−14.94	18.77
P3 lat vis, ms						
Nic	376.78	396.11	397.44	9.0	−10.00	28.02
Con	395.20	405.33	406.76	4.36	−10.12	18.83
Aud rt, ms						
Nic	663.56	632.26	626.15	−12.60	−23.17	−2.03
Con	707.27	673.7	681.95	−20.91	−57.83	16.01
Vis rt, ms						
Nic	605.22	583.71	574.48	−6.15	−26.32	14.02
Con	667.73	712.08	660.64	47.89	−7.61	103.40
Aud d_L						
Nic	8.62	9.42	8.60	0.81	−0.11	1.73
Con	8.45	7.98	7.57	−0.03	−0.51	0.45
Vis d_L						
Nic	8.36	8.65	8.46	0.25	−0.21	0.70
Con	8.15	7.86	7.73	−0.08	−0.41	0.25

The mean of the contrast variable comparing session B to the mean of sessions A and C is given with confidence interval limits.

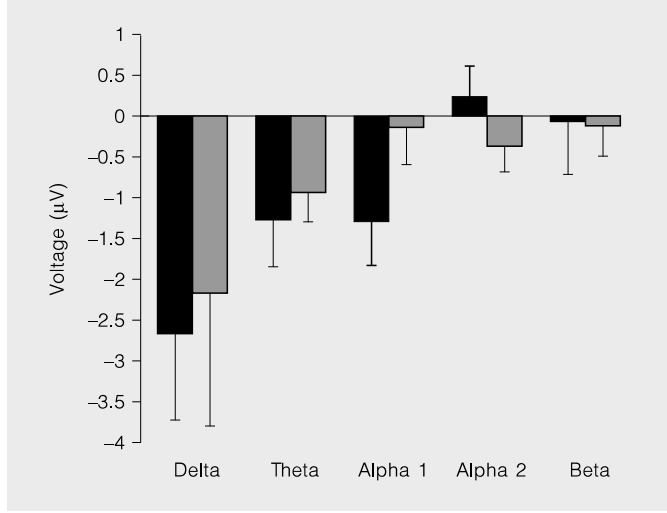

Fig. 1. RMS power change, expressed as the difference between power in the second session and the average power of the remaining sessions. Results are collapsed over electrodes. Black columns denotate the nicotine group and open columns the controls.

nicotine group (see table 1). The data shown in table 1 suggest that the nicotine group generally decreased their reaction time after the alleviation of the overnight abstinence, while controls tended to have longer visual reaction times during the second session.

Signal detection was generally high, with near perfect performance in the auditory task. When d_L was collapsed over tasks, the pattern over sessions was marginally different between the groups [$F(1,28) = 3.3$, $p = 0.08$]. Some tendency of a difference between groups in auditory sensitivity was found [$F(1,28) = 3.0$, $p = 0.10$], with no effects in the visual task [$F(1,28) = 1.5$, $p = 0.23$] (see table 1).

Event-Related Potentials

Visual and auditory grand averages for the Fz, Cz, and Pz derivations are shown in figures 2 and 3, respectively. Mean amplitudes, latencies and contrast values are given in table 1.

When collapsed over tasks, the quadratic-pattern interaction was not significant for either P300 amplitudes [$F(1,28) < 1$, NS] or latencies [$F(1,28) < 1$, NS]. Separate analyses for tasks gave no further information concerning either amplitudes or latencies [$F(1,28) < 1.1$, $p > 0.31$]. There were no interactions involving electrodes [$F(4,112) < 1.3$, $p > 0.26$]. As can be seen from table 1, there is, however, an increase of auditory P300 latency in the nicotine group, but when compared to the control group this was not significant.

Curve inspection suggested a possible effect on the auditory N2 amplitude, and the minimum amplitude in the interval 175–300 ms was identified for the midline leads. The contrast for amplitudes was highly significant [$F(1,28) = 18.1$, $p = 0.0002$], suggesting significantly different patterns in the two groups. Separate analyses showed that amplitudes were higher during the second

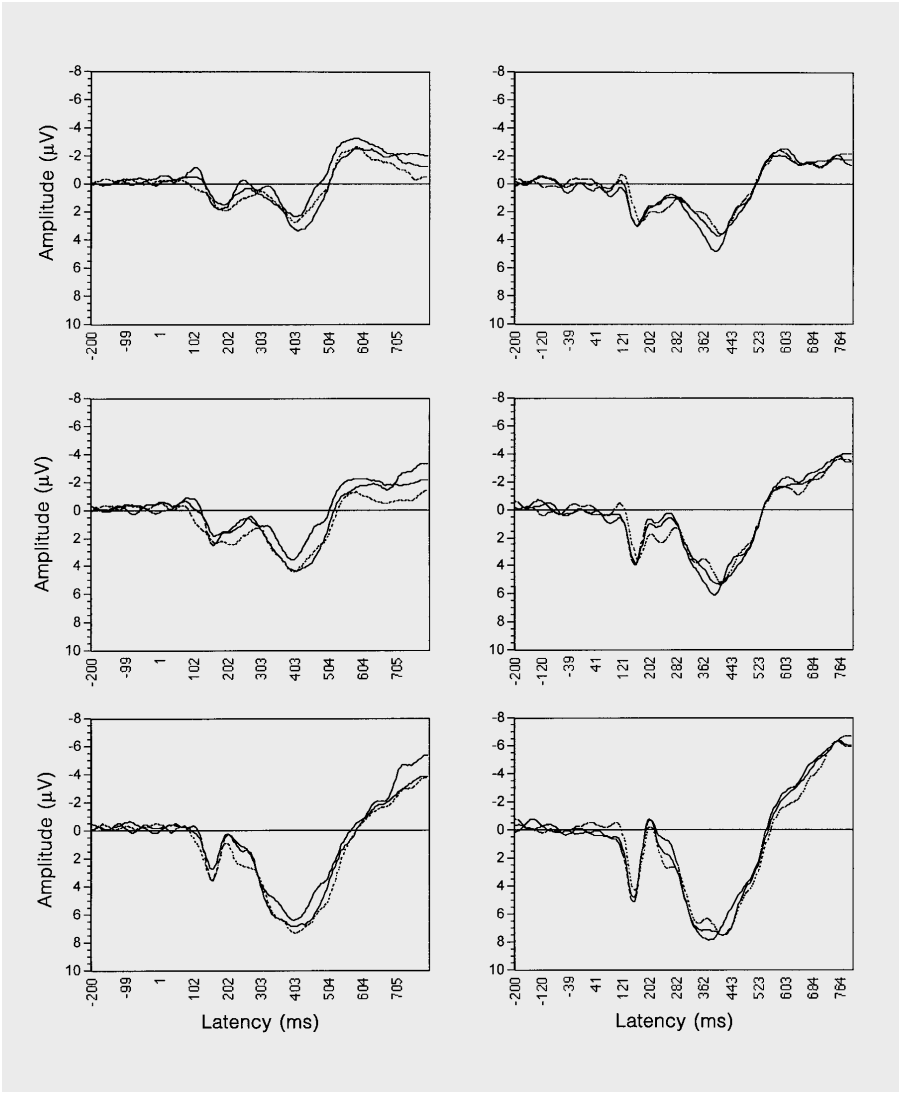

Fig. 2. Visual grand averages for the Fz (top), Cz (middle), and Pz (bootom) derivations in the first (– – –), second (——), and third (·····) sessions. The left column shows the nicotine group, the right column the controls. There was no significant nicotine effects on the P300.

session in the nicotine group [$F(1,14) = 11.8$, $p = 0.004$], while amplitudes decreased over sessions among controls. There was no interaction with electrodes [$F(4,112) = 2.3$, $p = 0.09$].

Discussion

After administration of oral snuff, we found signs of increased arousal in terms of a shift within the alpha band, in favor of larger alpha 2 power. The overall response time tended to decrease in the nicotine group, and there was some tendency towards positive effects on signal detection. P300 measures were unaffected when compared to controls, whereas an unexpected increase of auditory N2 amplitude was found after nicotine administration.

The reaction time decreased after nicotine administration, a finding well supported by earlier studies [4, 5]. The reaction time did not increase during the third session, possibly reflecting achieved task mastery. The moderate effect on signal detection rests mostly on decreased auditory task performance among controls during the second session. Speculatively, the controls might find the situation even more uneventful than the nicotine users did, and thus be less involved the second time around. Improved signal detection has been a common finding in nicotine studies using vigilance tasks [5]. Our task differs from the often-used rapid visual information processing task [32] by having a much lower stimulus rate due to soft-

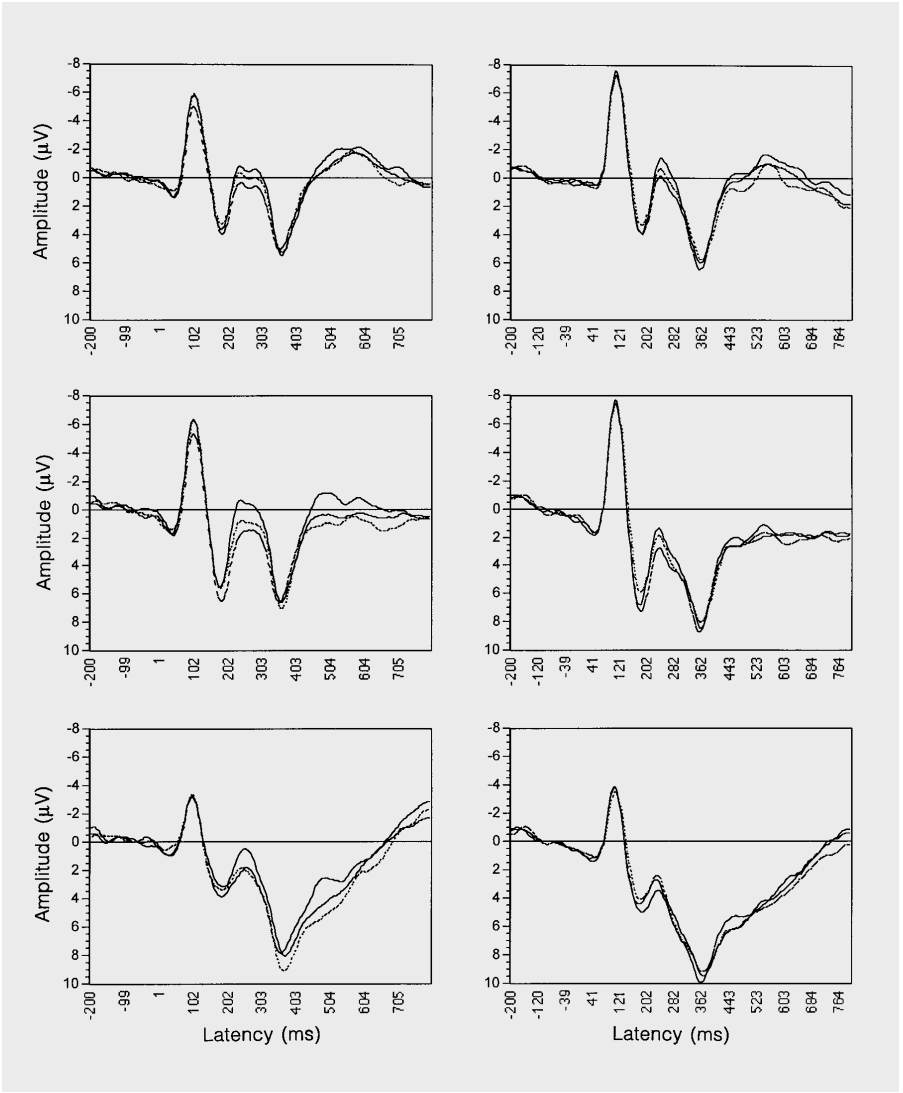

Fig. 3. Auditory grand averages for the Fz (top), Cz (middle), and Pz (bottom) derivations in the first (– – –), second (——), and third (·····) sessions. The left column shows the nicotine group, the right column the controls. The N2, at about 250 ms, was significantly affected by nicotine administration.

ware limitations. While making comparisons less straightforward, it might be argued that the low presentation rate will provoke boredom and decreased arousal to a considerable extent. However, the task was fairly easy, giving little room for improvement above baseline levels. It is very likely that a higher presentation rate would have increased the demands on a central executive function, because subjects now had ample time to consider the stimuli. This might rather have turned our task into a slow test of the phonological loop, as subjects probably verbally encoded relevant visual stimuli for comparison with the next trial. Further studies could use true dual-task paradigms to study possible effects on the central executive [24].

EEG measures indicated an increase in arousal, with the shift within the alpha band well in line with findings by Kadoya et al. [42] and the often reported increase of the dominant alpha frequency [36] which in our analysis most likely would yield a similar result. This pattern was strikingly different from that of the control group. The EEG changes were virtually reversed after a further short deprivation.

We found no effects on the P300 measures. It has been suggested [27] that P300 amplitudes are especially sensitive to the nicotine level. The long duration of our task and the imperfect pharmacological control might have attentuated possible effects on P300 parameters, as these seem generally less consistent than, e.g., findings of decreased response times. The finding of increased auditory

N2 amplitudes after nicotine administration was not a focus of our study and has to our knowledge not been reported before. Generally, the N2 is elicited when a deviant stimulus, in this case the target tone, is detected in attend conditions. It can be thought of as indexing a transient arousal response [44], something that might certainly be enhanced by nicotine.

When nonusers of nicotine serve as controls, some methodological problems might be expected. Firstly, one has the possibility than nicotine users differ from nonusers on relevant psychological traits [e.g., 45] which might affect performance in dearousing situations. Ideally, previous users should then be used as controls which for practical reasons was not possible in this case. Secondly, although an experimental situation such as the present will hardly be perceived as stimulating by either users or nonusers, the obvious incentive of tobacco in one of the sessions will naturally affect only the experimental group, thus possibly accentuating boredom in the control group.

The main weakness of the present study is certainly the inferred nicotine level. However, the effects in the alpha band give credence to our claim that a nicotine effect has been present. Future research might still profitably employ concurrent tasks to study nicotine effects under controlled circumstances.

In conclusion, the results of the present study indicate a generally arousing effect of nicotine, with no specific effects on attentional allocation.

Acknowledgements

This work was supported by the Swedish Tobacco Company (Grant Nos. 9320 and 9412) and the Medical Research Council (Grant No. B95-14J-00084-31B).

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