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Transdermal Nicotine: Single Dose Effects on Mood, EEG, Performance, and Event-Related Potentials

VERNER KNOTT, MELISSA BOSMAN, COLLEN MAHONEY, VADIM ILIVITSKY AND KEVIN QUIRT

Department of Psychiatry, University of Ottawa/Royal, Ottawa Hospital and Institute of Mental Health Research, Ottawa, Ontario, Canada

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KNOTT, V., M. BOSMAN, C. MAHONEY, V. ILIVITSKY AND K. QUIRT. *Transdermal nicotine: Single dose effects on mood, EEG, performance, and event-related potentials.* PHARMACOL BIOCHEM BEHAV **63**(2) 253–261, 1999.—A 21-mg dose of nicotine was administered transdermally to 16 overnight smoking-deprived smokers in a double-blind, placebo-controlled design. Mood ratings, electroencephalography (EEG), behavioral performance and event-related potential (ERP: P300) indices of attention and information processing speed were assessed before and 4 h after placebo/nicotine treatment. Although nicotine, relative to placebo, failed to alter mood, it increased absolute and relative power indices of EEG arousal, shortened reaction times, and increased P300 amplitudes. The results are discussed in relation to nicotine's actions on cholinergic transmission and its role in smoking behavior. © 1999 Elsevier Science Inc.

Transdermal nicotine Cigarette smoking Electroencephalography Mood Performance Event-related potentials

THE attraction of cigarette smoking is believed to be based in part on the central actions of nicotine on neuroregulatory systems controlling arousal, mood, and cognition (67). Electroencephalographic (EEG) evidence of nicotine's putative cortical arousing properties has been consistently found in the psychostimulant-like EEG profile seen with the smoking of a single cigarette (5,11,40,41). Although the acute response profile has been shown to vary with dose, brain region, personality, and cognitive style (6,17,19,36–38,49), the bulk of evidence has indicated that smoke-inhaled nicotine via cigarettes produces a shift in scalp-recorded voltage from low (delta, theta, alpha$_1$) to high (alpha$_2$, beta) electrocerebral frequencies (7,8,69), a response profile not too dissimilar to that seen with other central stimulants such as amphetamine (41). The affect component of cigarette smoking has been well documented with respect to smoking abstinence, with increments in self-reported negative affect ratings (e.g., anger, irritability, drowsiness) being observed immediately after the discontinuation of tobacco use (25,26,33). Smoking-induced mood alterations, including the frequently associated calming effects (72) and the purported euphoric reactions (77), have, however, remained somewhat more elusive during laboratory assessments, and although increases in subjective alertness and arousal have been demonstrated with smoking (48), these effects have not been observed in any consistent manner. Although literature reviews pertaining to cognition have generally agreed that smoking/nicotine can improve performance on a variety of tasks (particularly tasks requiring sustained effortful capacity for demanding and complex stimulus processing) in (overnight) smoking abstinent smokers, they have dif-

Requests for reprints should be addressed to Dr. Verner J. Knott, Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario Canada, K1Z 7K7.

fered in their interpretive stance in that they view these findings as supporting either an absolute facilitative (i.e., smoking/nicotine produces "better than normal" performance) effect (70,71,80) or a normalization (i.e., smoking/nicotine simply reverses the performance deficits induced by temporary cigarette abstentian) effect (27). Despite this controversy, there is general agreement that further elucidation of the effects of smoking/nicotine requires the use of nicotine delivery systems other than tobacco cigarettes to control dosage more effectively. Findings of improved response accuracy and speed in vigilance/sustained attention performance paradigms have been partially reinforced with the concomitant utilization of scalp-recorded event-related potentials (ERPs) such as the late-positive P300, the amplitude and latency of which has been shown to be related to attention and processing speed, respectively (66). Although these so-called cognitive potentials have not always responded to acute smoking or have responded in a less than robust fashion, a number of positive reports have indicated, by way of increased P300 amplitudes and shorter P300 latencies, that cigarette smoking may improve performance either by a more efficient allocation of attentional resources to significant task events and/or by improving the speed of stimulus-related processes (12,31,32,50).

Investigative attempts to relate these smoking-induced mood, arousal, and cognitive alterations to the direct central actions of nicotine per se have utilized oral (i.e., gum or tablets) or subcutaneous routes of nicotine administration and have, more or less, observed smoking-like increments in electrocortical arousal in smokers and as well as performance/ERP changes suggestive of a cognitive enhancing effect in both smokers and nonsmokers (15,34,53). Nicotine administered transdermally has proven to be somewhat efficacious in abating the cigarette craving and mood disturbances accompanying smoking abstinence in cigarette smokers (14,60). Although transdermal nicotine has been shown to reduce self-reported dysphoria and concentration difficulties (13), empirical attempts to examine the arousing and/or cognitive affects of transdermally applied nicotine have been noticeably lacking in the literature. The present study sought to examine the effects of a single dose of transdermal nicotine in overnight smoking-deprived cigarette smokers. More specifically, mood ratings, EEG indices of cortical arousal, as well as performance and ERP indices of cognition were examined in response to the acute administration of 21 mg of transdermal nicotine, the recommended starting dose for smokers attempting to abstain from cigarettes.

METHOD

Experimental Subjects

Sixteen, right-handed, Caucasian male volunteers participated in this study after having signed an informed consent. Only male subjects were used, to reduce the possible variance associated with menstrual cycle fluctuations in females. All subjects were cigarette smokers with a mean age of 29.4 (±9.2) years, and had been smoking, on average, for 12.8 (±8.8) years. The subjects were smoking an average of 23.0 (±4.0) cigarettes per day, with their preferred brands having a mean nicotine yield of 1.1 (±.1) mg per cigarette. Each of the smokers reported beginning daily cigarette consumption within 1 h postawakening. All subjects were interviewed to rule out alcohol/drug and psychiatric/neurologic histories. Subjects also underwent a physical exam to ensure that there were no contraindications to transdermal nicotine treatment.

Study Design

Subjects attended the laboratory for one orientation session and two test sessions. The test sessions involved the randomized, double-blind administration of a placebo and nicotine skin patch. Study measures were collected before and 4 h after application of the patches. Half of the subjects, randomly selected, received the placebo patch in their first session and the nicotine patch in their second session. The remaining subjects received placebo and nicotine patches in the reverse order. Test sessions were separated by a 3–7-day interval.

Study Procedure

Smokers attended the laboratory for the two morning (0800 h) test sessions following overnight (beginning at 2400 h) abstinence from smoking, caffeine, alcohol, drugs, and food (with the exception of toast and juice as a "light" breakfast). All subjects reported compliance with these conditions. Subjects were directed to a sound-attenuated, electrically shielded chamber where study measures were collected before and 4 h after administration of a skin patch. The study measures were always collected in the same order at pre- and postpatch time points, and included mood ratings followed by EEG recordings and finally assessment of task performance with concomitant P300 recordings. Assessments at pre- and postpatch time points were generally completed within 20 min.

Nicotine Administration

The active nicotine treatment consisted of the Nicoderm (Marion Merrell Dow) patch that delivers a systemic dose of 21 mg/day over 24 h (recommended initial dose in smoking cessation programs). The Nicoderm patch covers an area of 22 cm^2, and has a total nicotine content of 114 mg. A maximum plasma nicotine concentration (^{C}max) of approximately 23 ng/ml is reached 4–5 h (^{t}max) after a single application (20). The placebo patch was similar in size and color, and both active and placebo patches were applied to an area on the upper back of the subjects (22). None of the subjects were able to distinguish active and placebo patches on questioning at the end of the two test sessions. During the 4-h absorption period subjects were allowed access to videos and magazines and were given light snacks (juice and cookies) at hourly intervals.

Mood Ratings

Subjective measures of mood states were based on the Profile of Mood States (POMS) questionnaire (55). Subjects rated themselves (using a five-point scale: not at all, a little, moderately, quite a bit, extremely) on 65 mood adjectives, the scores of which were converted to six bipolar mood dimensions: tension–anxiety, depression–dejection, anger–hostility, vigor–activity, and fatigue–inertia. The POMS questionnaire had demonstrated predictive and construct validity in controlled outpatient drug trials (55), and had been shown to be sensitive to mood alterations occurring during smoking cessation (25,26,62).

EEG Recordings

Subjects sat in a reclining chair, in a dimly lit, sound-attenuated, electrically shielded room for a 5-min eyes-closed rest period. Electrical activity was recorded from six scalp sites utilizing a monopolar (linked ears reference) montage with tin electrodes positioned on homologous left (F_3, C_3, P_3) and

right (F_4, C_4, P_4) hemisphere regions according to the 10–20 international system. Electrodes were placed on left and right hemispheres, as several studies had reported asymmetric EEG power shifts with acute smoking (17,19). Additional electrodes were placed on the orbital ridges and external canthus of the right eye to monitor vertical (VEOG) and horizonal (HEOG) electrooculographic activities. Electrode impedances were kept below 5 K Ohms, and all electrical signals were amplified with a bandpass of 0.1–40.0 Hz and were sampled at 256 Hz.

Thirty artifact-free 2-s duration epochs of EEG were selected from each recording and subjected to Fast Fourier Transform (FFT) analysis for computation of absolute and relative power estimates in six frequency bands: delta (1–3.5 Hz), theta (4–7.5 Hz), $alpha_1$ (8–10.5 Hz), $alpha_2$ (11–13.5 Hz), $beta_1$, (14–21.5 Hz), and $beta_2$ (22–29.5 Hz). Relative power was calculated by expressing absolute power in each band as a percentage of total power across the six band (e.g., relative delta = [delta/(delta + theta + $alpha_1$ + $alpha_2$ + $beta_1$ + $beta_2$)] × 100). As recommended (16), EEG values were changed to adhere to Gaussian distribution using natural logarithm transformation log [x/(1−x)] for relative values, where x is the relative amplitude of a frequency band, and log (x) for absolute amplitude values, where x is the corresponding absolute value.

Performance Task

A choice reaction time paradigm, the Stimulus Evaluation-Response Selection (SERS) task, was employed, as it had been previously shown to be sensitive to the acute administration of cholinergic, dopominergic, and noradrenergic drugs (4,21,58), as well as to the subcutaneous administration of single doses of nicotine (53). The SERS task, which independently manipulated two levels of stimulus complexity and two levels of response complexity, was developed to evaluate, with the aid of ERPs (P300), two processing stages—stimulus evaluation, and response selection.

The SERS procedure was similar to that reported by Le Houezec et al. (53). The task was carried out in the same recording chamber as the EEG, with the subject seated in a comfortable chair. Two levels (easy and hard) of stimulus and response complexity trials were involved in the SERS task. Prior to each trial a 1000-ms fixation display—a checkerboard pattern filling the four possible horizontally arranged positions where stimuli may be displayed—appeared on the monitor. On each trial the target "X" appeared in one of the four possible positions, with target position varying randomly from trial to trial. In the easy stimulus condition the X appeared embedded with single dots in the three other positions. The letter X appeared embedded with three asterisks in the hard stimulus condition. Subjects responded to the trial stimuli with a four-key keypad with the response keys horizontally arrayed in a manner similar to the stimulus display. In the easy response condition, subjects pressed the far right key if the target appeared to the right of the center of the stimulus display, and pressed the far left key if the stimulus target appeared to the left of the stimulus display. In the hard response condition, subjects pressed the key matching the exact spatial position of the target in the horizontal stimulus array. The white-on-black stimulus displays (luminance 0.7 log FL) covered a 6.0 × 1.2-cm area on the video monitor positioned 36 inches from the test subjects.

The test consisted of eight blocks of 32 trials with response complexity alternating from block to block beginning with the easy response condition. Stimulus condition varied randomly within each block. These manipulations resulted in 64 trials for each of the four conditions [easy stimulus/easy response (EE), easy stimulus/hard response (EH), hard stimulus/easy response (HE), and hard stimulus/hard response (HH)]. For each of the 256 trials the stimulus remained on the monitor until the subject responded, to a maximum of 2000 ms, at which time the fixation display reappeared. After each block there was a brief pause while the subject was instructed to switch to the alternate response condition. The entire test time was 12–15 min. for each test. The number of correct (i.e., hits) and incorrect responses (i.e., false alarms) were calculated for each of the four conditions as was mean reaction time, which was the time measured (in ms) from the onset of the stimulus to the onset of the response. Hits and false alarms were expressed as a percentage score. Instructions placed equivalent emphasis on speed and accuracy.

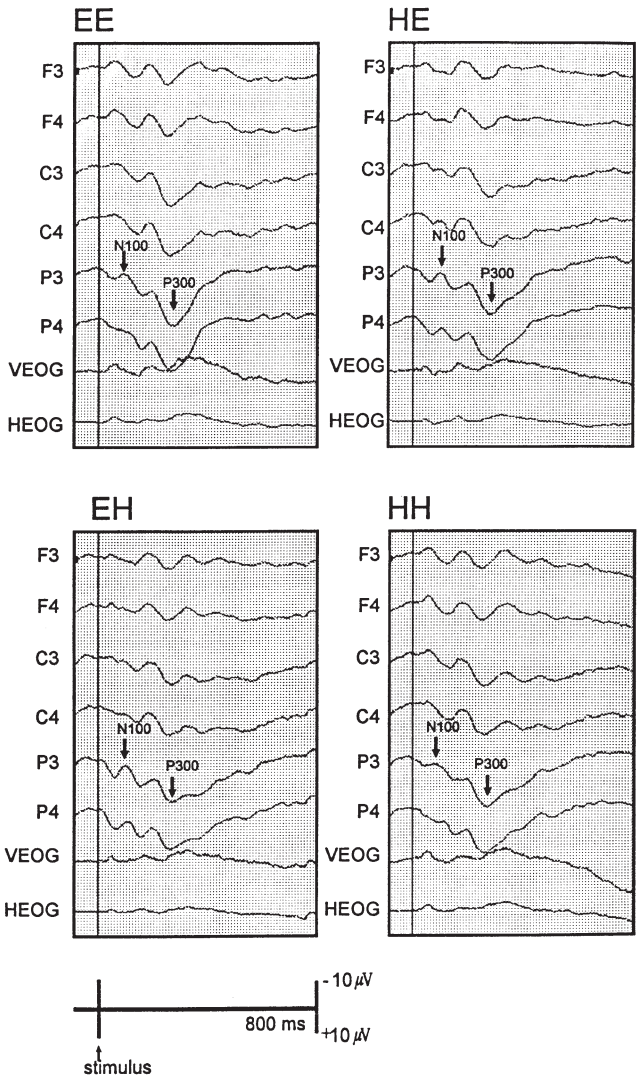

FIG. 1. Event-related potential (ERP) waveforms from six scalp-sites typical N100 and P300 components elicited in a single subject (baseline condition) during each of the four SERS task conditions.

ERP Recordings

ERPs were recorded with the same electrode montage, amplifier filter settings, and digitization sampling rates as used with the EEG recordings. The sampling period was 800 ms, beginning 80 ms prior to stimulus (target) onset. Off-line analysis excluded incorrect trials and trials with EEG/EOG exceeding ±50 μV from the final averaging process, which was carried out separately for each of the recording sites in each of the four task conditions. Placebo and nicotine recordings did not differ in the number of EEG or EOG related trial rejections. Example ERP waveforms are shown on Fig. 1. The primary ERP measures for each average were the amplitude and latency of the P300. Amplitude was defined as the maximum positive voltage between 250–600 ms poststimulus onset measured in relation to the average prestimulus baseline voltage. Latency was defined as the time to reach maximum (peak) voltage from stimulus onset. The amplitude and latency of the N100 component, an earlier negative component with a peak latency of approximately 200 ms poststimulus onset, were also measured to determine the specificity of any nicotine-induced P300 amplitude and/or latency changes.

Data Analysis

Statistical analysis was carried out on "difference" scores whereby pre-placebo/nicotine values were subtracted from post-placebo/nicotine values in order to arrive at "net affect" change score data. Change scores for each of the six mood dimensions were subjected to separate one-way (placebo vs. nicotine) analysis of variance (ANOVA) procedures. Change scores for the three performance measures (hits, false alarms, and reaction times) were analyzed by separate 2 (drug–placebo and nicotine) × 2 (stimulus: easy and hard) × 2 (response: easy and hard) repeated-measures ANOVAS. Absolute and relative power change scores for each of the EEG bands were subjected to separate 2 (drug) × 2 (hemisphere: left and right) × 3 (region: parietal, central and frontal) repeated-measures ANOVAS. N100 and P300 amplitude/latency change scores were subjected to separate 2 (drug) × 2 (stimulus) × 2 (response) × 2 (hemisphere) × 3 (region) repeated-measures ANOVAS. To reduce the occurrence of type I errors resulting from excessive statistical tests, Greenhouse-Geisser corrected *p*-values were utilized where appropriate and follow-up tests of significant interactions were to be carried out by *t*-tests.

For the statistics, one subject was not included in the performance or ERP analysis due to a computer problem with the SERS task, and two additional subjects were not included in the ERP analysis due to excessive movement artifact.

RESULTS

None of the subjects spontaneously reported any of the adverse CNS effects (headache, dizziness, fatigue), gastric disturbances (nausea, vomiting), or any signs of sweating, muscle/limb pain, parasthesia, coughing, or palpitations, which are known to occasionally accompany the use of transdermal nicotine patches (60).

Mood Ratings

Mean (±SD) placebo- and nicotine-induced mood dimension changes are shown in Fig. 2.

Although there was some indication that nicotine and placebo patches differentially affected the vigor-activity dimension, there was marked variability in all six dimensions change scores, and no significant effects were observed.

EEG Measures

Analysis of absolute and relative power change scores resulted in significant drug effects but no interaction effects. Figure 3 displays the mean (±SD) placebo- and nicotine-induced changes in absolute and relative EEG power. As shown in Fig. 3, nicotine, relative to placebo, decreased absolute power in the delta, $F(1, 15) = 9.40$, $p = 0.01$, and theta, $F(1, 15) = 8.91$, $p = 0.01$, bands and increased power in the alpha$_2$ band, $F(1, 15) = 7.60$, $p = 0.01$. With respect to the effect of nicotine on relative power indices, compared to placebo, nicotine decreased theta power, $F(1, 15) = 15.37$, $p = 0.001$, and increased both alpha$_2$, $F(1, 15) = 26.9$, $p = 0.001$, and beta$_2$, $F(1, 15) = 7.40$, $p = 0.02$, power.

Performance Measures

Mean (±SD) difference scores for each of the three performance measures are shown in Fig. 4.

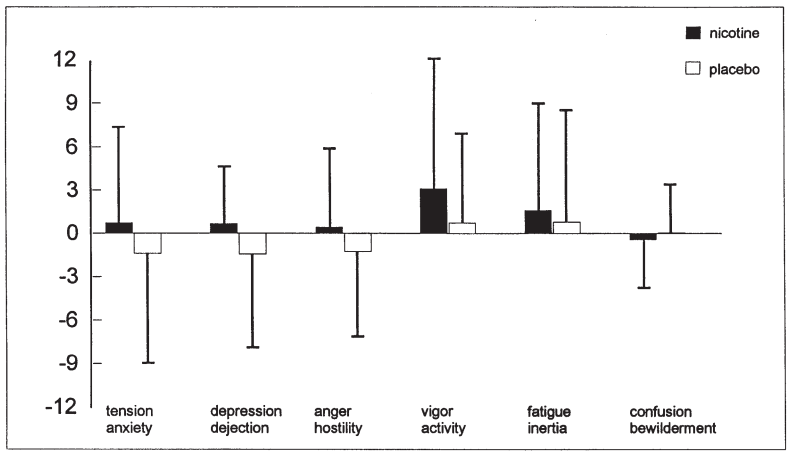

FIG. 2. Mean (±SD) difference (post-placebo/nicotine values minus pre-placebo/nicotine values) scores for the six dimensions extracted from the profile of mood states (POMS).

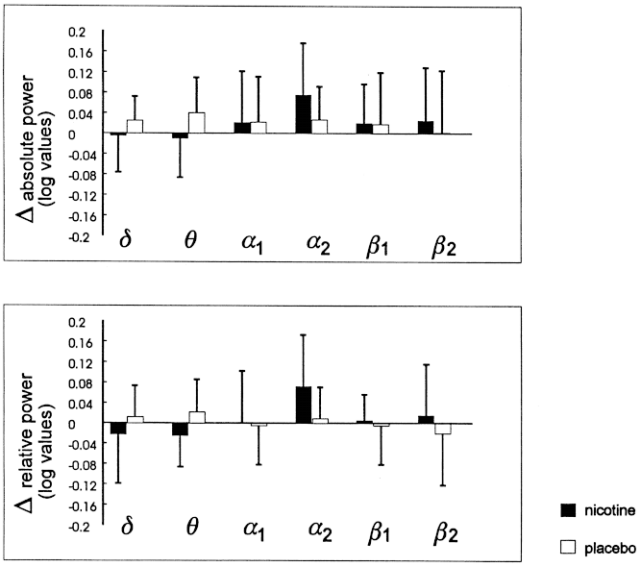

FIG. 3. Mean (±SD) absolute and relative power difference scores (post-placebo/nicotine values minus pre-placebo/nicotine values) for delta (δ), theta (ϑ), alpha1 (α_1), alpha2 (α_2); beta (β_1) and beta2 (β_2) EEG frequency bands (averaged across the F3, F4, C3, C4, P3, and P4 scalp sites).

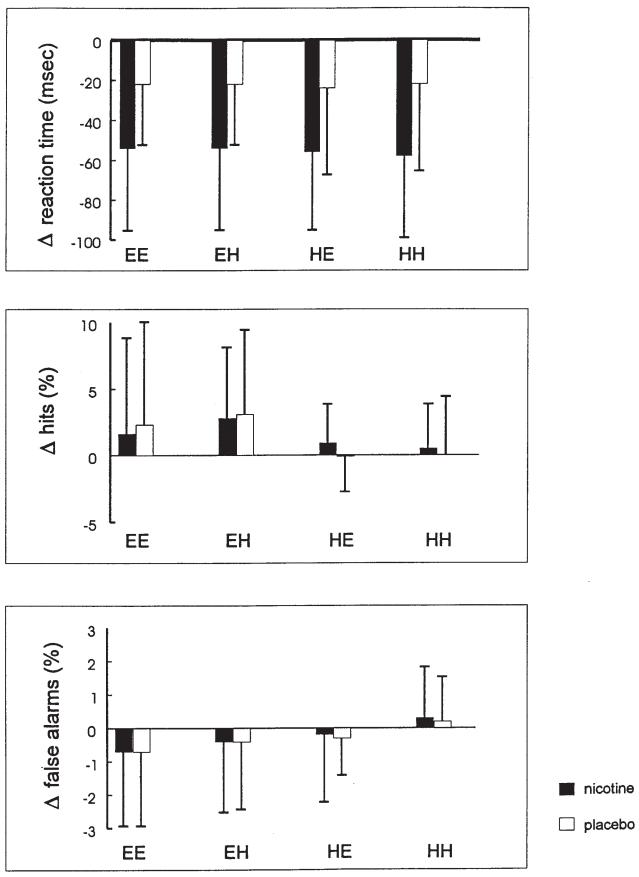

FIG. 4. Mean (±SD) difference scores (post-placebo/nicotine values minus pre-placebo/nicotine values) for reaction time, hits, and false alarm performance indices derived from the SERS task.

Of the three behavioral measures, a significant drug effect was evident only with reaction time, $F(1, 14) = 7.50$, $p = 0.016$. As shown in the figure, nicotine administration resulted in faster reaction times compared to the administration of a placebo.

ERP Measures

Mean (±SD) P300 amplitude and latency difference scores are shown pre- and post-placebo-nicotine in Fig. 5, and an average of waveforms of six subjects are shown in Fig. 6. Although no significant drug effects were observed for N100 amplitude and latency measures, a significant drug effect was observed with P300 amplitude, $F(1, 12) = 9.72$, $p = 0.009$. As shown in Figs. 5 and 6, post-nicotine waveforms exhibited a greater positivity compared to pre-nicotine waveforms, and in general, P300 amplitudes were found to be significantly increased by nicotine relative to placebo. Although the positivity appeared more evident at frontal–central scalp sites, drug effects did not interact with electrode position or stimulus/response task levels. There was a trend for nicotine to shorten P300 latency relative to placebo, but no significant drug effects were observed for this P300 index.

DISCUSSION

In this study 21 mg of transdermal nicotine exerted a significant impact on electrocerebral arousal as well as on behavioral and ERP indices of cognitive processing. This study had a number of limiting design features (e.g., limiting assessments to a single dose and time), and it did not attempt to differentiate whether nicotine was directly facilitating arousal/cognition functions (i.e., as might be evidenced by nicotine's

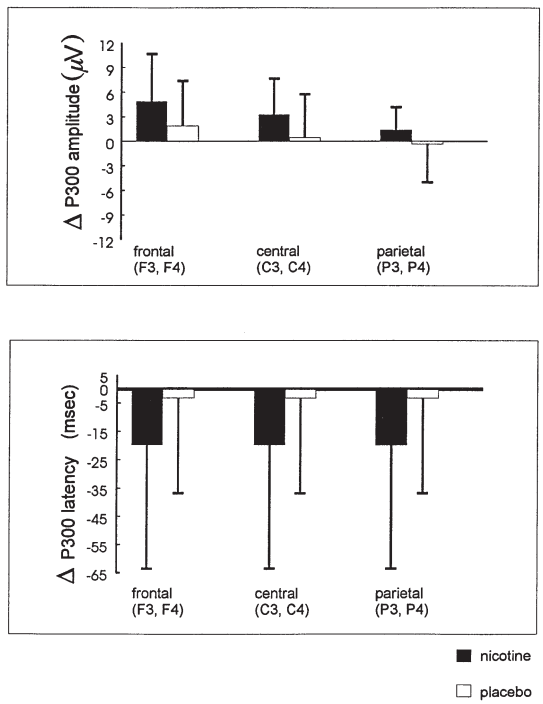

FIG. 5. Mean (±SD) P300 amplitude and latency difference scores (post-placebo/nicotine values minus pre-placebo/nicotine values) derived from averaged frontal (F3, F4), central (C3, C4), and parietal (P3, P4) scalp sites.

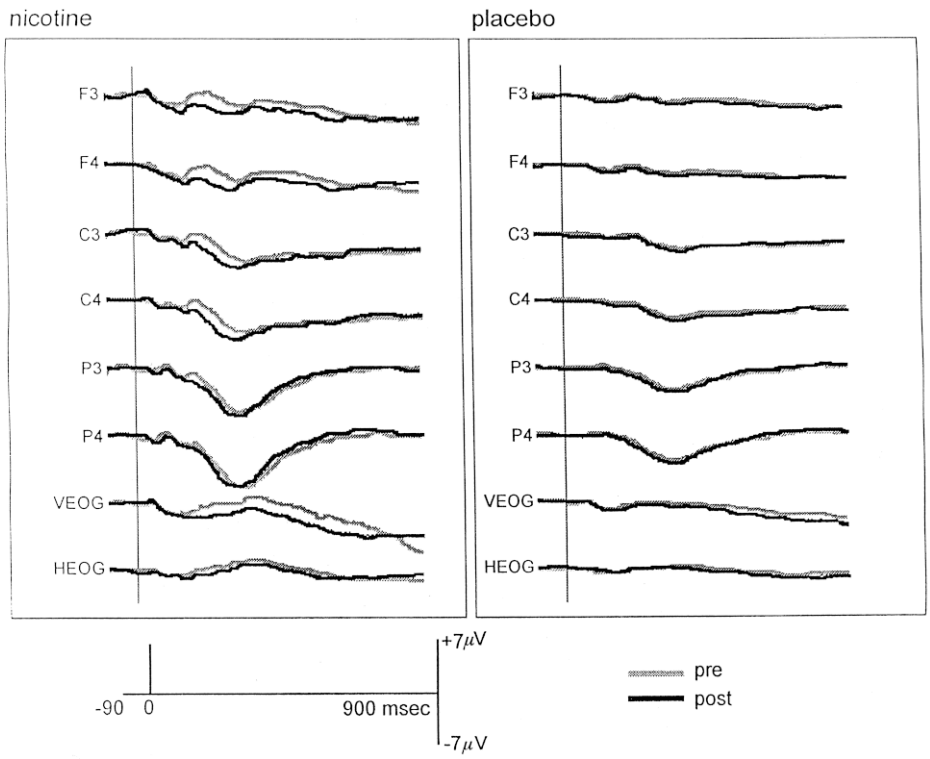

FIG. 6. Pre- and postplacebo and nicotine group averaged waveforms (averaged across the four SERS task conditions) based on six subjects (technical problems with the data files of the remaining 10 subjects prevented these subjects from being included in a group ERP average).

actions in nonsmokers) or alleviating arousal/cognitive impairments associated with smoking abstinence, but the observed findings do have particular relevance with respect to smoking motivation and the role of nicotine.

Transdermal nicotine failed to exert any significant effect on the six mood dimensions. Despite the frequent reports by smokers that the calming and alerting functions of smoking are key motivators reinforcing the maintenance of the habit (72), these current findings parallel previous failed attempts to objectively document these mood-related claims in laboratory settings. The mood-modulating effects of nicotine may, however, depend on the route of administration, and it may well be that the rapid lung-to-brain delivery time of nicotine boli from inhaled smoke may play a crucial role in impacting mood-related neuroregulatory systems and its perceived effect in smokers. Nicotine, however, is only one component of cigarette smoke, and, as argued elsewhere, more elaborate study designs encompassing state and trait factors may be required to tease out the specific emotional reactions that may accompany smoking behavior (18).

Absolute and relative EEG power indices were influenced by transdermal nicotine in a manner consistent with other psychostimulant agents (73). The resultant EEG profile, characterized by power reductions in slow-wave frequencies and power augmentation in fast-wave frequencies has been functionally described as "vigilance promoting" in contrast to "vigilance demoting" EEG profiles, which are characterized by power shifts from high to slow frequencies (29). As cigarette smoking has resulted in similar profiles, with power being increased in $alpha_2$ and beta bands (7,9,45,49), and as these smoking-induced EEG power profiles are evident only when plasma nicotine levels reach a threshold (i.e., >10.0 ng/ml) level (8), it is reasonable to conclude that smoking-related neuroelectric alterations are mediated by the central actions of nicotine. Nicotine gum has also been shown to be capable of exerting an EEG activating effect in cigarette-deprived smokers (64,65). To date, evidence is conflicting as to whether these physiologic alterations reflect normalization of abstinence-related slow wave power incrementation associated with smoking deprivation (28,76) or an actual enhancing effect of nicotine. Some studies have shown post-smoking EEG arousal levels to be similar to that of nonsmokers (51), while others have shown post-smoking EEG arousal levels of smokers to be greater than those of nonsmokers (43).

Nicotine influences a range of neurotransmitter systems, but its primary action is on nicotinic cholinergic receptors (67). Although the altered EEG power profiles observed with nicotine in this current study stand in marked contrast to those exerted by nicotinic, but not muscarinic, antagonists (46,63), there is not sufficient evidence to conclude that the observed transdermal nicotine–EEG profiles are mediated solely by nicotinic systems. Given that EEG slow waves have been shown to be modulated in part by the cholinergically enriched basal forebrain (nucleus basalis) nuclei (2), and that nicotinic blockade abolishes only the smoking/nicotine-induced reductions in slow-wave power, but not smoking-induced increments in fast-wave power (47), it appears that one or more noncholinergic systems may act in concert with nicotinic systems to produce the smoking/nicotine-induced EEG arousal profile.

Behavioral performance alterations induced by transdermal nicotine were limited to reaction time, with no significant

effects being observed with respect to accuracy (i.e., number of correct or incorrect response) measures. Although the lack of an accuracy effect rules out the possibility of a speed/accuracy trade-off explanations for the improved reaction times seen with nicotine, the discrepancy in these two response measures would seem to impose restrictions on nicotine's putative cognitive-facilitating properties. Reviews of smoking-performance studies have shown reaction time improvements to be, with the exception of a few anomalies, a well-replicated effect with smoking (1,27,70,80), which has, with some exceptions (58), also been observed with nicotine gum in cigarette-deprived smokers (34,61,74,75) and nondeprived smokers (30), as well as with subcutaneous nicotine in cigarette-deprived smokers and nonsmokers (15,53). As observed with our transdermal nicotine, subcutaneous nicotine administration also failed to alter response accuracy in the SERS task paradigm (53), but both smoking in cigarette-deprived smokers and oral/subcutaneous nicotine administration in nonsmokers were found to improve target detections and reduce response errors in signal detection tasks, particularly in fast-paced tasks that impose a heavy burden on stimulus encoding (15,61, 81,83). The contention that these accuracy and reaction time effects may be mediated via nicotine's actions on cholinergic pathways controlling electrocortical arousal (54,78) is, in part, reinforced by the observation that oral nicotine administration effectively antagonizes scopolamine-induced performance decrements in these demanding tasks (79,82).

P300 amplitudes, but not P300 latencies, were significantly altered by transdermal nicotine, with larger amplitude increments being observed with nicotine relative to placebo. Increased amplitudes following smoking/nicotine have been observed by some (24,52,53,57), but not all, studies (12,31), and it appears that smoking-induced effects on P300 amplitude can vary as a function of task type (31,50), time after smoking (32), and degree of nicotine exposure (56,59). Although the increased P300 amplitudes may simply reflect nonspecific arousing effect of nicotine, a vast literature has associated P300 amplitudes with an array of cognitive processes (66), and has shown P300 amplitude to reflect the allocation of limited capacity attentional resources to task relevant stimuli (10,68). Although N100 was not influenced by nicotine, a number of previous studies have shown increased exogenous ERP amplitudes with smoking (39) and, combined with observations of increased P300 amplitudes, the smoking–ERP literature generally suggests that smoking increases the intensity of brain responsivity to sensory input as well as improves the attentional regulation of stimulus input (35). P300 amplitudes have been shown to be increased with smoking deprivation, and to be both increased and decreased with smoking resumption (52,59), so it is unclear as to whether the transdermal nicotine-induced increments only reflect a normalization/alleviation or absolute enhancement of attention-related neurophysiological processes. P300 amplitudes are also known to be diminished by cholinergic (scopolamine) blockers and to be augmented with an anticholinesterase (23), but the failure of mecamylamine and scopolamine to block smoking-induced P300 amplitude increments (44) suggests that the neurochemical basis of the nicotine-P300 amplitude effect is as yet unresolved.

P300 latencies, which have been found to be slower in cigarette deprived smokers compared to nonsmokers and nondeprived smokers (43), were not significantly altered by transdermal nicotine. The absence of a P300 latency effect in the presence of a significant shortening of reaction time indicates that smoking nicotine augmented reaction time by acting on response-related, not stimulus-related, processes. Although a number of studies have not observed smoking-induced P300 latency shifts (24,57), others have found faster latencies but in varying degrees depending on the nature of the task (31,32,53). Given that cholinergic agents tend to alter stimulus processing speed but not response processing speed, while aminergic drugs tend to have opposite effects (3,4,21,22,58), additional studies encompassing neurophysiologic, neurochemical, and behavioral probes in a range of cognitive tasks are required to elucidate nicotine's mechanism of action on arousal and information processing functions (42).

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