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Effects of a low dose of transdermal nicotine on information processing

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The objective of this research was to assess the effect of a low dose of nicotine (7 mg/24 h), administered through a transdermal device, on the cognitive processes of subjects who were slightly dependent smokers. Sixteen smokers were chosen as subjects using a French version of Fagerström's Test of Nicotine Dependence. Under suboptimal alertness conditions the subjects were faced with a choice reaction time (CRT) task. Two conditions of signal quality (intact or degraded) and two conditions of fore period (FP) (short or long) were used during two different experimental sessions (nicotine or placebo). At the same time, the subjects filled in a mood questionnaire and took part in a critical flicker fusion (CFF) determination test. The results obtained suggest that nicotine improves the subjective state of alertness of the subjects and enables them, despite the suboptimal state, to maintain a constant performance level during a CRT task. Neither an effect of nicotine on the CFF nor any interaction between the nicotine, the signal quality or the duration of the FP were observed. The conclusion to be drawn from the results is that nicotine has an enabling effect, but the results do not allow the determination of the precise site of this effect among the different stages of information processing.

Introduction

The results to be found in the literature indicate that, in general, nicotine improves cognitive functions and changes mood. Whatever the method of administration, nicotine, by acting on the attentional system, seems not only to facilitate learning but also to improve performance in many different types of tasks. Nicotine seems to modify memory processes (Lindgren, Stenberg, & Rosen, 1999; Rusted & Eaton-Williams, 1991; Rusted, Graupner, & Warburton, 1995), to delay performance deterioration during a visual vigilance task (Wesnes & Warburton, 1983, 1984; Wesnes, Warburton, & Matz, 1983), to improve the intensity feature of attention (Mancuso, Warburton, Melen, Sherwood, & Tirelli, 1999), to limit the effects of fatigue induced by sleep deprivation (Parkin, Fairweather, Shamsi, Stanley, & Hindmarch, 1998), to shorten reaction time (RT; Bates, Pellett, Stough, & Mangan, 1994; Houlihan, Pritchard, Krieble, Robinson, & Duke, 1996a; Houlihan, Pritchard, & Robinson, 1996b; Knott, Bosman, Mahoney, Ilivitsky, & Quirt, 1999), to lessen the variability in performance and the number of errors, and to improve the detection of pertinent stimuli during visual or auditory tasks (Houlihan *et al.*, 1996a; Levin, Conners, Silva, Hinton, Meck, March, & Rose, 1998a). However, whereas the effects of nicotine on performance have been the subject of numerous investigations, the site of nicotine influence within the sequence of stages of information processing has yet to be determined. This work is carried out on a macrosopic level, and therefore the main objective of the current study is to locate the effect of nicotine within the information processing stages. Working on the basis of Sanders' cognitive-energetic model of stress and performance (1983) and the Additive Factors Method (AFM) of Sternberg (1969), this study also examines the effects of the administration of a low dose of nicotine on a four-choice reaction time (CRT) task. Even if continuous flow models are consistent with Sternberg's logic (McClelland, 1979), the four-stage serial discrete-stage

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models of Sanders (1983) appear to be a more appropriate inferential framework to highlight the peripheral and/or the central influence of nicotine. At this thought level, the use of continuous flow models does not give a more accurate prediction than the serial flow model related to the main hypothesis.

Sanders' (1983) model is organized on three levels: the first level being the computational stages of information processing, the second being the energetic resources allocated to these mental operations, and the third corresponding to the evaluation mechanism. The first, cognitive, level is composed of four information processing stages, functioning according to a discrete serial mode. These stages are stimulus preprocessing, feature extraction, response choice and motor adjustment. The second level corresponds to three energetic attention control mechanisms principally brought to light by the research in neurophysiology and neuropsychology: arousal, effort and activation (McGuinness & Pribram, 1980; Pribram & McGuinness, 1975). The mechanisms of arousal and activation are considered to be basal mechanisms; the first underlain by the noradrenergetic and serotoninergetic systems and the second by the dopaminergic and cholinergic systems. The effort mechanism, in conjunction with the peptidergic system, represents a superior mechanism that supervises and coordinates the level of the basal mechanisms. Each of these mechanisms supplies a specific information processing stage. The arousal mechanism receives energy by means of a stimulus preprocessing stage and supplies the feature extraction stage. The activation mechanism supplies the resources at the motor adjustment stage, and the effort mechanism supplies the response choice stage as well as the two base mechanisms in the case of a disturbance of the energetic equilibrium. The effort mechanism is informed about the state of the basal mechanisms by an evaluation mechanism representing the third level of this model. In order to construct the cognitive-energetic model of stress and performance, Sanders (1980, 1983) based his work on numerous experimental results obtained from Sternberg's AFM (1969).

The AFM is based on the discrete serial information-processing model, i.e., composed of a set of stages that are serially organized and non-overlapping. This method considers RT as the sum of the duration of each of the processing stages that occur between the moment of response signal (RS) and the initiation of a response produced by the subject. For each stage, at least one computational factor exists that directly and selectively affects its duration without modifying processing quality (assumption of selective influence). Some experimental factors that affect the stages of stimulus preprocessing, feature extraction, response choice and motor adjustment are stimuli intensity, signal quality, stimulus-response compatibility, and time uncertainty, respectively. These experimental factors act in a specific manner on certain stages of information processing, and therefore the use of the AFM makes it possible to determine the number and nature of the stage(s) affected by nicotine. According to Sternberg (1969), if a main effect between the actions of two factors is observed, then it can be hypothesized that these affect different stages; however, if an interaction between the two is observed, the variables are likely to affect at least one common processing stage. A certain number of results observed in the literature argue in favor of an effect of nicotine on the stages of feature extraction and motor adjustment via energetic mechanisms. Nicotine seems to affect the cholinergic (Callaway, Halliday, & Naylor, 1992), noradrenergic (Svensson, Grenhoff, & Engberg, 1990), and dopaminergic systems of the central nervous system (e.g., Rose & Corrigall, 1997). However, research carried out in neuropsychiatry has brought to light the therapeutic effects of nicotine during processing of cognitive deficits characterized by dysfunctioning of monoaminergic and cholinergic neurotransmitter systems. The effects of nicotine on patients with Parkinson's or Alzheimer's disease, schizophrenia, Gilles de la Tourette syndrome and Attentional Deficit Hyperactivity Disorder (ADHD) have been observed.

According to Humphreys and Revelle (1984), RT, vigilance, simple arithmetic and letter cancellation can be characterized as information transfer tasks. Performance on these tasks is assumed to be a monotonically increasing function of the number of resources applied. The region where performance increases with added resources is referred to as the resource-limited region. There is a point, however, where extra investment does not lead to an increase in performance. At this point, the region is referred to as the data-limited region, and performance is limited by the quality of the external data and the sensitivity of the subject. Wickens (1984) specifies that a task might be data-limited either because the measurement scale could go higher (the maximal performance is reached with little effort) or because the quality of the data is poor (performance cannot be improved despite increased effort). The distinction between data and resource limitation facilitates understanding of controversial findings in studies interested in the effects of stimulant drugs on RT. Using a CRT task, there is a risk of a ceiling effect problem linked to resource limitation, which could mask all modification of performance induced by drug administration. In such a case, bringing to light an improvement in performance due to any stimulant drugs and other arousers (i.e.. caffeine, nicotine, amphetamine) is impossible (for details see Humphreys & Revelle, 1984). In order to overcome this problem, Humphreys and Revelle (1984) suggest using tasks requiring many resources, or placing subjects at a low level of arousal, or both. In order to observe improvement in RT performance, we chose to place our subjects in suboptimal alertness conditions, so that they were in a resource-limited zone for all the experimental sessions. According to the research of Mavjee and Horne (1994), such a suboptimal state can be obtained by asking subjects to carry out a CRT task just after lunch and then asking them to watch, throughout

the afternoon, calm, 20-min-long documentaries in a darkened room heated to a comfortable 26°C.

For this study, the nicotine supply was controlled by the use of 7-mg transdermal nicotine patches. Such devices enable non-smoking subjects to be used, which avoids all controversy linked to the withdrawal state induced by nicotine deprivation. However, in agreement with studies that argue against a simple restoration of performance to the baseline explanations, we decided not to select non-smoker subjects (Parkin *et al.*, 1998; Warburton & Arnall, 1994; Wesnes & Warburton, 1983, 1984; Wesnes *et al.*, 1983). We preferred to opt for a compromise by retaining subjects who were 'light smokers'. Previous studies using 'light smoker' strategy to investigate the effects of nicotine on human performance can already be found in the nicotine literature (Wesnes *et al.*, 1983; West & Hack, 1990). The risks of abusive interpretations were thus limited, but we were nonetheless working with subjects who had relatively sensitive nicotine receptors. We also chose to administer only a low dose of nicotine to the subjects (7 mg/24 h) in order to minimize the undesirable effects that could occur during the administration of too high a dose (Gore & Chien, 1998).

The main objective of this study was to assess the effect of administering a low dose of nicotine to slightly dependent smokers, through a transdermal device, on the cognitive processes. First, we expected to observe a reduction in the subjects' RT without modification of the decision error rates, an effect of nicotine on the mood of the subjects, and an increase in the sensitivity of the subjects in determining a critical flicker fusion (CFF) test. As a measure of overall central nervous system activity, this test appears to be a simple and reliable way of assessing changes in arousal. The last change, which is related to the retino-cortical system, can be considered as relating to the arousal mechanism. Therefore, the CFF test produced an additional dependent variable to be inferred from an effect of nicotine on the input-processing stage. Second, we expected to localize the influence of nicotine within the information processing chain at the level of the feature extraction stage and that of motor adjustment by bringing to light an over-additive interaction between the effects of nicotine and signal quality and between the effects of nicotine and fore period (FP) duration.

Material and methods

Participants

A total of 16 subjects (2 men and 14 women), ranging from 19 to 32 years old (average age 25.17±2.78 years), who were slightly dependent smokers, provided informed consent and participated voluntarily in the experiment. They were not remunerated for participation. A number of smokers (n = 50) were recruited using advertisements. From these 50 volunteers, the final participants were chosen based on smoking consumption and nicotine dependence. Their nicotine dependence level was determined by a French version (Etter, Vu Duc, & Perneger, 1999) of Fagerström's Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). To be included in the study, subjects were required to have a low nicotine dependence (score 0 or 1) and no contraindications to nicotine administration. They smoked on average eight cigarettes per day. The participants were informed of the procedure and of the possible adverse effects and unpleasant symptoms, and they gave their written consent.

Study design

The experiment involved a repeated-measures design. After a practice session, each subject completed two experimental sessions on two different days, separated by a minimum of 72 h and a maximum of 120 h. Three types of tests were used in the study: an information processing system test, a mood assessment questionnaire and a CFF determination test. The study tests were presented in a fixed order to the participants: first the mood questionnaire, then the CRT and finally the CFF.

In one experimental session, the subjects' performances were tested with a nicotinic transdermal system on their shoulders. The subjects arrived in the morning after having abstained from smoking for at least 10 h prior to testing. Cigarettes continued to be prohibited until the end of the experiment. In another experimental session, the conditions were the same but a placebo patch was applied. The administration of either nicotine or placebo patches was carried out double-blind. A cross-over design was used in order to counterbalance the two experimental sessions for the subjects.

Drug administration

For the study, the nicotine session consisted of the application of the Nicopatch (Laboratoire Pierre Fabre) transdermal system. The active patch delivered 7 mg of nicotine per 24 h. The placebo patch used for the non-nicotine session was similar in size (10 cm^2) and color. Both nicotine and placebo sessions were carried out double-blind and randomly administered. During both sessions, the patch was applied to the same skin area (the deltoid muscle).

Cognitive task

The sensorimotor reaction to a stimulus was measured by using a CRT task. Subjects were seated in front of a computer screen. The task consisted of hand-operating two levers in response to a visual stimulus lasting for 200 ms. Resistance was controlled by a constant intensity electromagnetic brake (3 volts). Four numbers (2, 3, 4 and 5) were randomly presented in the center of the display. Each number corresponded to a specific response, namely a flexing or a stretching of the right or left wrist. Each subject carried out four series of 32 trials,

making 128 trials in all. Two experimental factors were manipulated: the signal quality and the FP duration. Each factor was crossed with the manipulation of the other. The signal quality could be either degraded or intact, and the FP duration, which began with an auditory warning signal (WS), could be either short (500 ms) or long (5000 ms). The WS presented via speakers was 200 ms duration at a comfortable auditory intensity. The inter-trial duration depended on the subject's swiftness to get back into the starting position. Finally, a new trial began only after a 200-ms stabilization period in the starting position. The manipulation of experimental factors resulted in 32 trials each of the four possible conditions: intact signal/short FP, intact signal/long FP, degraded signal/short FP and degraded signal/long FP. The order of presentation of the different series in the block was randomized across the subjects. For any one subject, the same counterbalanced order was maintained for the two test days. The response signal was composed of a rectangular frame made up of small black squares, in which a figure, itself made up of a pattern of small black squares, was placed. In order to degrade the signal, some of the small black squares of the external frame were relocated randomly within the frame, in places not occupied by the figure. Each stimulus image could be degraded in four different ways, and the order of appearance of these was randomized to minimize perceptive learning. The subject was instructed to respond correctly in the shortest possible time. RT was measured from the onset of the stimulus to the onset of the response. The results were given to the subject at the end of each test (1500 ms after the subject's response). These results concerned the response speed or the type of error: anticipation (RT<150 ms), extremely slow response (RT>2000 ms), and decision error (side or direction error). Accuracy and response time were measured. Only the RTs of the correct responses were examined.

CFF test

The CFF test (Leeds Psychomotor-tester, 10200) is a means of measuring the ability to distinguish discrete sensory data. It is used as an index of overall central nervous system activity and as a measure of cortical arousal (Parkin *et al.*, 1998; Smith & Misiak, 1976). This CFF system has already been used to investigate the effects of nicotine on humans (Hindmarch, Kerr, & Sherwood, 1990; Kerr, Sherwood, & Hindmarch, 1991). The subject was seated 1 m from a display screen, which presented a set of light-emitting diodes at the center. The flicker frequency changed in two ways: it either increased or decreased. The subject was required to respond by pressing a button when he discriminated, after a foveal fixation, flicker from fusion (and vice versa). The subject performed three ascending and three descending tests alternately. The average of the six values, in Hertz, was used as an overall response.

Mood ratings

Subjects were asked to complete a self-evaluation questionnaire: the visual analog scale 16–100 mm devised by Bond and Lader (1974).

The questionnaire consisted of a 16-item subjective questionnaire. Responses were given on a visual analog scale of 100 mm. The subjects placed a mark on a horizontal line equivalent to the strength of a particular feeling at that time. For example, the line might represent a continuum from 'calm' to 'excited.' The 16 mood scales assessed three main factors: alertness, happiness and calmness.

Study procedure

Whatever the nature of the session, the subjects came to the laboratory between 07.00 and 08.00 h. The experiment lasted until 17.00 h. The subjects always came to the laboratory after a 10-h period of abstinence from stimulating substances. Statistical analysis on RT was carried out on the data, taking into account baseline performances in order to minimize the effect of intra-individual variability resulting from the possible non-respect of drug abstinence on the part of the subjects. Drug abstinence was also controlled through an interview administered as soon as the subject arrived. We decided not to use carbon monoxide measurements, because participants were slightly dependent on nicotine and because this way of controlling abstention from stimulant use, which is sensitive to many endogenous and environmental factors (i.e., traffic, heating and cooking emissions), is not reliable for discriminating between non-smokers and light smokers (Benowitz *et al.*, 2002).

The subjects were instructed to abstain from drinking any caffeinated beverages and alcohol from 22.00 h the night before the test and throughout the test day.

Prior to the test sessions, the subjects familiarized themselves with the self-evaluation mood questionnaire and the CFF test and learned the CRT task. This learning session minimized the possibility that practice or strategy effects would interfere with the assessment of the effects of nicotine administration. This session stopped when subjects were able to carry out the CRT task with a variability below 15% and an error rate below 5% (Sanders, 1980, 1990).

In both experimental sessions, four tests were carried out in which subjects performed four blocks of 128 trials (four series of 32 trials), completed a self-evaluation subjective mood questionnaire and carried out a CFF test. The first test was performed at 08.00 h, as soon as the subject came to the laboratory, just before patch application. This was a control test, and the data recorded were considered as reference data for the day. The three other tests were performed in the afternoon after 6, 7 and 8 h of patch application. Half the subjects began with the nicotine session and half with the placebo session.

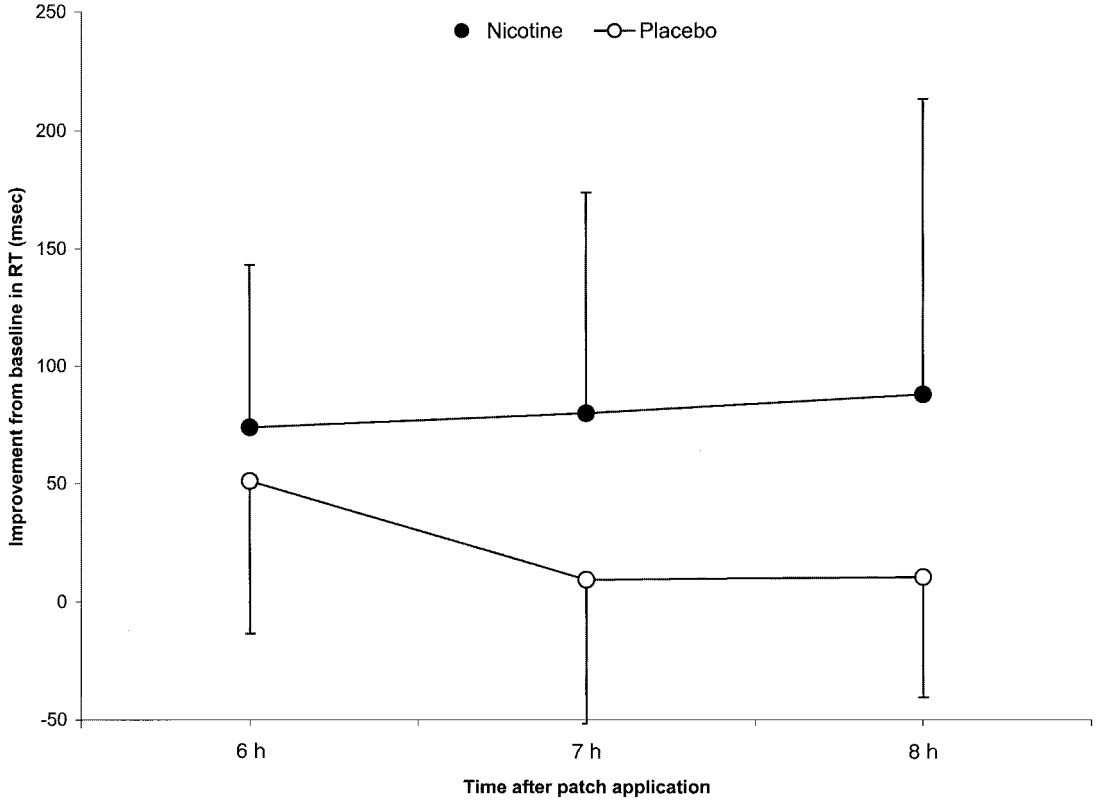

Figure 1. Improvement from baseline in mean reaction time (ms) as a function of time after transdermal nicotine or placebo system application.

Statistical analysis

For the visual analog scale 16–100 mm, the item score analysis was based on the results from the principal component factor analysis made by Bond and Lader (1974). The 16-item mood scale assessed three main factors: alertness, happiness and calmness, pooling nine, five and two items, respectively. The individual scores on each scale were multiplied by the scale-loading factor (regression weights) and totaled within the three factors.

All the data were analyzed using a univariate analysis of variance (ANOVA). In contrast, when repeated-measures factors had more than two levels a repeated-measures multivariate analysis of variance (MANOVA) was selected to study the main effects and interactions.

Post-hoc analyses using the Newman–Keuls test were conducted on all significant interaction findings. Alpha was established at 0.05 for all analyses.

Results

RTs

ANOVA plans, carried out on the average RT values and on the variance of each distribution of RT, were composed of four repeated-measures factors: the nature of the transdermal device (two levels), the series (four levels), the signal quality (two levels) and the FP duration (two levels). Irrespective of the form of transdermal device applied, the ANOVA carried out on the average RT values revealed an improvement in average RT according to the series: $F(3,45) = 32.92$. Significant effects of signal quality and of FP lengthening were observed on average RT values. The stimulus degradation caused an average increase in RT of 88 ms, $F(1,15) = 60.19$, and the lengthening of the FP brought about an average RT increase of 51 ms, $F(1,15) = 29.59$. Significant effects of signal quality and of FP lengthening were also observed on average variance of RT. Stimulus degradation caused an average increase in variance of 7156 ms^2, $F(1,15) = 20.38$, and the FP duration caused an average increase in variance of 4020 ms^2, $F(1,15) = 21.13$. The interaction between the signal quality and FP duration was not significant either on the average RT, $F(1,15) = 0.05$, or on the RT variance ($F(1,15) = 0.85$).

A statistical analysis was carried out on score differences calculated between different RT series and the baseline values recorded each testing day before placebo or nicotine patch application[1] to assess the effects of nicotine on cognitive performance. This data treatment minimized the intra-individual variability resulting from the experimental protocol nature and was not incompatible with the AFM. The ANOVA plan was composed of four repeated-measures factors: the nature of the transdermal device (two levels), the series (three levels), the image quality (two levels) and the FP duration (two levels). This analysis revealed an effect of nicotine on the improvement of RT performances, $F(1,15) = 14.84$. The transdermal administration of nicotine caused an increase

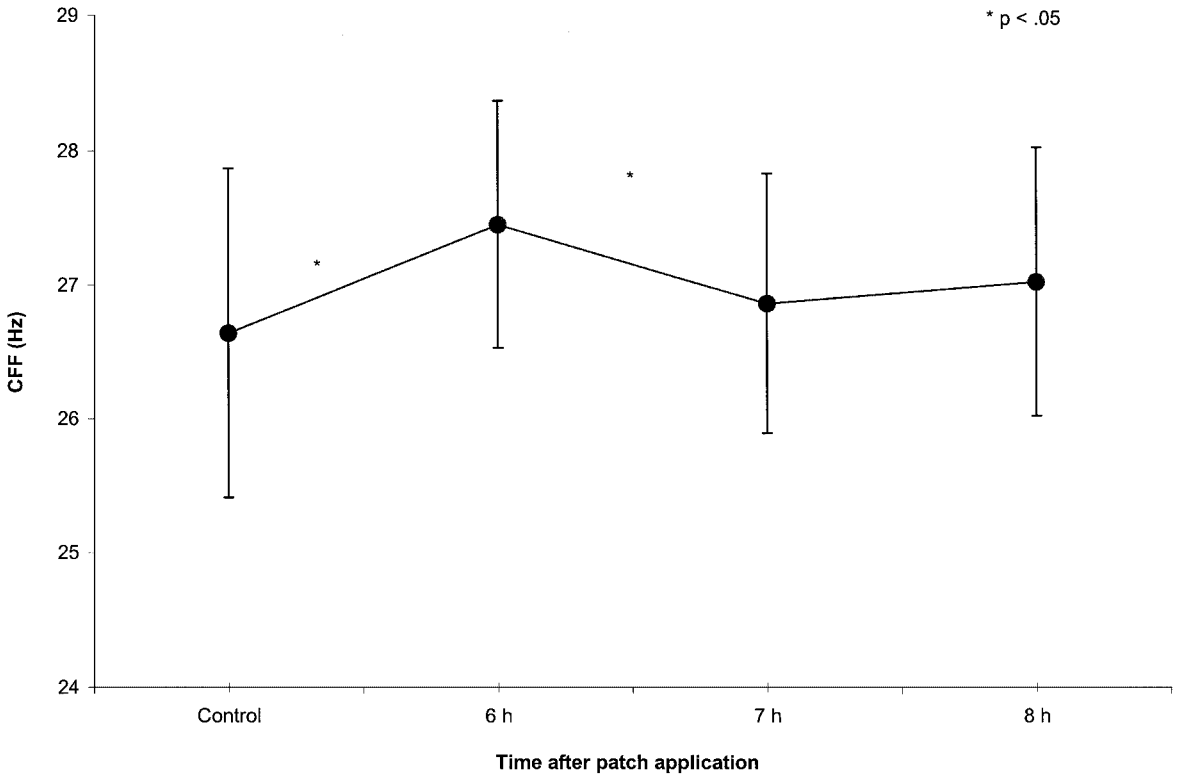

Figure 2. Change of Critical Flicker Fusion (Hertz) as a function of time after transdermal system application.

in the improvement of average RT across all conditions of 57 ms. An interaction between the nicotine and the different series carried out by the subject was also found: $V(2,14) = 3.63$; Figure 1.

After 6 h of patch application, no significant difference appeared as a function of the nature of transdermal device. The effect of nicotine only appeared 7 h after patch application. When subjects did not receive nicotine, a significant reduction in the improvement of cognitive performance appeared between 6 and 7 h, following by a stagnation of performance between 7 and 8 h after patch application. On the contrary, when subjects received nicotine regularly through a nicotine transdermal device, the improvement in RT with regard to the reference values remained constant. No significant interaction could be observed either between nicotine and signal quality, $F(1,15) = 0.95$, $p = 0.34$, or between nicotine and FP duration, $F(1,15) = 0.19$, $p = 0.66$.

The same ANOVA as above carried out on the RT variance values did not reveal any principal effect of the nicotine factor, $F(1,15) = 1.8$. But a significant reduction in performance variability could be observed as a function of the number of series carried out by the subjects: $V(3,13) = 9.96$.

CFF test

The ANOVA plan, carried out on values recorded during the CFF determination test, was composed of four repeated-measures factors: the nature of the transdermal device (two levels) and the series (four levels). This statistical analysis revealed no effect of nicotine: $F(1,13) = 0.20$.

A repeated-measures MANOVA carried out on the CFF values enabled us to observe a change in CFF according to the series: $V(3,13) = 8.65$. The CFF values increased between the baseline values and the values recorded in the beginning of the afternoon. However, during the afternoon a decrease in CFF values was observed (Figure 2).

Mood ratings

A MANOVA was also carried out from the scores of the three principal factors of the mood test. The statistical analysis plan was composed of four repeated-measures factors: the nature of the transdermal device (two levels), the series (four levels), and the principal factors (three levels). The results of this analysis revealed an effect of the nicotine factor: $V(3,13) = 3.42$. In order to identify precisely the influence of nicotine, a repeated-measures MANOVA was carried out on each of the three main factors.

The MANOVA carried out on the alertness factor revealed an interaction between nicotine and the different series: $V(3,13) = 4.22$. The Newman–Keuls test revealed a difference in the alertness of the subjects, depending on the nature of the transdermal device. Six hours after application of the transdermal device, an increase in the alertness level of the subjects with regard to the reference level was noted. This increase was only significant when the patch diffused nicotine (Figure 3).

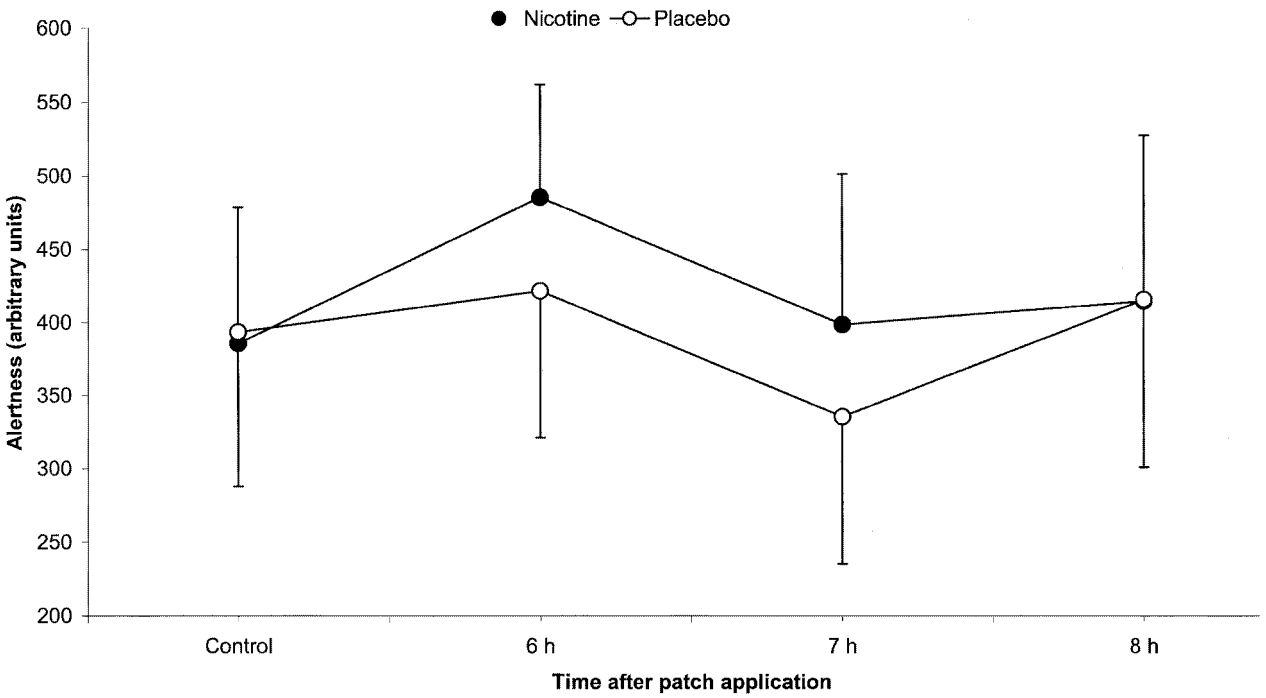

Figure 3. Subjects' alertness (arbitrary units) as a function of time after transdermal nicotine or placebo system.

Six hours after application of the transdermal device, the subjects who had received an active substance were more alert than those who had received a placebo. Between 6 and 7 h after application, the level of alertness of the subjects diminished, regardless of the nature of the device. Seven hours after application, those subjects with nicotine in their systems were always more alert than those without. After 7 h, a significant increase in the state of alertness of the subjects with a placebo patch was noted, as well as a retention of the previously acquired level for the subjects with nicotine. Another repeated-measures MANOVA carried out on the calmness factor also revealed an effect of the series factor on the calm state: $V(3,13) = 7.41$. After *a posteriori* analysis, it seems that the subjects were significantly calmer when they arrived in the morning than when they returned to the laboratory at the beginning of the afternoon. The analyses carried out on the 'happiness' and 'calmness' factors respectively revealed no significant interaction.

Percentage of errors

In order to detect potential changes in strategy, two different ANOVAs were used. A first analysis was carried out on the percentage of decision errors and a second on the arcsinus-transformed values (Winer, 1962). Neither analysis revealed a significant difference. Therefore, any increase in error rates accompanied by a reduction in RT can be interpreted as a modification of the subject's performance on the speed–accuracy trade-off functions (Pachella, 1974). Thus, to testify to a true facilitating action of nicotine, the error rate must remain constant. According to this analysis, no significant increase in the number of errors appeared. Therefore, the results of this study can be easily interpreted, given that the subjects improved their performance in terms of speed with no modification in the precision of their response.

Distinction between transdermal devices

As was the case in previous studies using nicotine transdermal devices, the majority of the subjects were incapable of distinguishing between the active and the placebo patches (Levin *et al.*, 1998a).

Discussion

Many of the results observed in this study were consistent with classic results already observed in the literature. The stimulus degradation and the lengthening of FP duration caused an average increase in RT and an average increase in variance of RT (Karlin, 1959; Sanders, 1980). The interaction between signal quality and FP duration did not prove to be significant either on RT average or on RT variance. This absence of interaction confirms the prediction of Sanders' model (1983) and reinforces the idea according to which these two computational factors selectively affect two distinct information-processing stages. Moreover, according to the research of Mavjee and Horne (1994) the experimental conditions manipulated in our study appear to be efficient and favorable to the observation of a facilitating effect of nicotine on RT. The data containing the determination of the CFF and the 16–100 mm mood test enabled confirmation of the hypoalertness state of the subjects. The CFF values recorded at the beginning of the afternoon testified to an increase in the arousal level

of the subjects during the morning. During the afternoon, the sedative effect of the experimental protocol caused a reduction in the state of arousal of the subjects. As far as the scores recorded on the three main factors of the mood questionnaire (i.e., alertness, happiness and calmness) are concerned, statistical analysis also brought to light an effect of experiment manipulation on subjects' 'alertness.' The results concur with those concerning the CFF, confirming the sedative effect of the experimental protocol and supplying a supplementary argument in favor of the fact that subjects were in a data-limited zone at the start of the afternoon. However, it seems that 8 h after patch application, an increase in the subjective state of alertness of the subjects can again be observed. This last development, not observed on the dependent CFF variable, can certainly be explained by a phenomenon of habituation to experimental conditions as the protocol advanced and by a progressive distance from the postprandial period. An effect of experiment manipulation on subjects' 'calmness' was also obtained. This result concurs with those previously observed, i.e., an increase in the ability to determine the CFF and an improvement in the state of alertness. Once again, the evidence suggests that not until 15.00 h do the subjects reach a level of calmness representative of the suboptimal state desired. It is not until 6 h after application of the transdermal device that an increase and a stabilization of the state of calmness of the subjects can be observed. In sum, all the results presented in this section confirm the monotonous and calm character of the environmental conditions of the video projections. However, it seems that the state of alertness of the subjects only becomes favorable to the observation of a facilitating effect of nicotine after 15.00 h. At the beginning of the afternoon, the subjects are most probably in a data-limited zone. Then, progressively, the soporific effect of the experimental protocol leads the subjects to a resource-limited zone as suggested by Humphreys and Revelle (1984), and Wickens (1984) in order to observe the effects of stimulant drugs on information transfer tasks such as CRT tasks.

Irrespective of the nature of the transdermal device applied, some results suggest a learning effect induced by the repetition of the task and thus justify the counterbalanced order of the protocol. An improvement in CRT performance during experimental sessions was observed and a significant reduction in the performance variability appears as a function of the number of series carried out by the subjects.

Turning to the effect of nicotine on cognitive performance, an increase in the improvement of average RT induced by the transdermal administration of nicotine and an interaction between nicotine and the different series were observed. The small, specific, positive effects of nicotine on the central nervous system generally reported in the literature are apparent in these results (Sherwood, 1993). As far as the interaction between nicotine and the different series is concerned, no significant difference induced by nicotine appeared until 7 h after application. Several explanations could justify this delay. Given the method of administration it seems reasonable to assume that, in order to generate a significant difference in terms of cognitive performance, the nicotine supply only becomes sufficient after the 7th hour. An improvement of performance after the 7th and 8th hour can also be explained by a development of tolerance. This interpretation is consistent with earlier results from Warburton and Mancuso (1998), which suggest that a tolerance might occur with longer exposure. However, this explanation should be treated with caution because in the study, subjects were not placed in a suboptimal state as in our study, and there is a possibility of confusing effects between these two variables. In fact, according to the results already seen, it is likely that after a meal the subjects were in a data-limited zone (Wickens, 1984). In contrast, as soon as the subjects were placed in a sedative environment they progressively moved into a resource-limited zone. At this precise moment, when the subjects did not receive the nicotine dose, a significant reduction in the improvement of cognitive performance between hours 6 and 7 was observed, followed by stagnation between hours 7 and 8. Against this, when the subjects received nicotine regularly through an active transdermal device, the improvement in RT with regard to the reference values remained constant despite the effect of task monotony and the suboptimal state in which the subjects were placed. Progressive diffusion of nicotine in the organism thus seems to contribute to the maintenance of a constant performance despite the monotonous character of the task (Wesnes & Warburton, 1983). These results also coincide with those obtained by Parkin *et al.* (1998), bringing to light the lesser effect of sleep deprivation following nicotine administration. In this study, because the exposure duration to nicotine was crossed with a suboptimal alertness state, it is extremely difficult to separate the development of tolerance from the facilitating effect of the suboptimal state in order to observe the influence of stimulant drugs.

Based on the CRT task data, no significant interaction could be observed either between nicotine and signal quality or between nicotine and FP duration. This result suggests that the facilitating effect of nicotine acts neither on the feature extraction stage nor on the motor adjustment stage. This suggestion concurs with the study of Houlihan, Pritchard, and Robinson (1999), who concluded in an action of nicotine on the response choice stage and the absence of effect on the feature extraction stage. Thus, the absence of interaction between nicotine and signal quality, as well as between nicotine and FP duration, seems relatively contradictory, with some studies bringing together nicotine with the cholinergic, dopaminergic and noradrenergic systems (Wesnes *et al.*, 1983). According to these different studies, the action of nicotine at the neurophysiological level is undeniable. However, if, as suggested by McGuinness and Pribram (1980), a close relationship exists between the arousal and activation

mechanisms and the different systems of noradrenergic, cholinergic and dopaminergic neurotransmitters, everything points to the existence of an interaction between nicotine, signal quality, and the FP duration. The administration of nicotine is known to act on different neurotransmitters (e.g., Watkins, Koob, & Markou, 2000), such as the noradrenergic system and the serotoninergic system, which underpin the arousal mechanism, and the dopaminergic system and the cholinergic system, which underpin the activation mechanism. Therefore, nicotine should modulate the arousal level and the activation level of the subjects. Studies carried out in psychopathology tend to support this prediction and lead us to remain extremely cautious in the interpretation of the absence of significant interaction between nicotine, FP and signal quality. According to Birtwistle and Hall (1996), it seems that by acting on the dopaminergic and cholinergic systems, nicotine plays a protective role against Parkinson's and Alzheimer's diseases and Gilles de la Tourette syndrome. Moreover, nicotine causes a reduction in the number of pathological symptoms in this type of patient and could possibly be used for therapeutic purposes (Heishman *et al.*, 1997). These results concur with those of Sahakian *et al.* (1989), Levin, Simon, and Conners (1998b), and White and Levin (1999), who also observed a reduction of symptoms in patients with Alzheimer's disease. Generally, these different studies argue in favor of a modulatory action of nicotine on the activation level: this modification may well intervene through the dopaminergic and cholinergic systems. In the same way, a certain number of studies have brought to light an increase in the ability for CFF determination following the administration of nicotine (Jones, Sahakian, Levy, Warburton, & Gray, 1992; Sherwood, Kerr, & Hindmarch, 1992; Warwick, & Eysenck, 1968). These latter studies suggest the existence of an influence of nicotine on the arousal mechanism. Taking into consideration all the results and according to the AFM of Sternberg (1969), the action of nicotine on the two energizing mechanisms should bring to light an interaction between nicotine and signal quality and between nicotine and FP duration. Our study has been unsuccessful in proving an indirect action of nicotine on certain stages of information processing using energizing mechanisms of arousal and activation. This absence of results appears to be linked essentially to the dose of nicotine administered to the subjects and to the mode of administration used. Thus, certain substances, such as nicotine, generate easily observed reactions at a biological level, but the repercussions of this same chemical substance are difficult to observe on a purely behavioral level for such low doses administered progressively.

Contrary to previous results presented in the literature, there was no significant difference on the CFF threshold between the placebo and nicotine condition (e.g., Jones *et al.*, 1992). The CFF is a dependent variable sensitive to the quantity and the method of administering the nicotine. As far as the experimental protocol is concerned, this absence of effect confirms that the nicotine dose was not sufficiently strong to induce a significant change in the level of arousal of the subjects. Moreover, it seems that the presence of a nicotine peak in the blood affects the observation of a change in the CFF following the administration of nicotine (Warwick & Eysenck, 1963). From the results of this study and from the results of experiments using low-dose transdermal devices (Levin *et al.*, 1998a), it seems that a relatively strong dose is necessary to observe the effects of nicotine on the cognitive procedures. Thus, transdermal devices diffusing 21 mg of nicotine over 24 h seem to be better adapted as they enable the effect of nicotine on the behavioral level to be observed without causing side effects that might prevent the experiment from being conducted successfully (Warburton & Mancuso, 1998). It is nonetheless important to note that these studies were carried out on subjects who were very dependent on nicotine and were used to having a high dose of nicotine. The tolerance to nicotine of the organism of a non-smoker or only slightly dependent subjects would perhaps not be as good when subjected to this kind of dose.

In contrast, the low dose of nicotine induced a difference in the alertness of the subjects. Six hours after application of the transdermal device, an increase in the alertness level of the subjects with regard to the reference level was noted, and this increase was only significant when the patch diffused nicotine. Those subjects who had received an active substance were more alert than those who had received a placebo. Between 6 and 7 h after application, following the first video projection, the level of alertness of the subjects diminished regardless of the nature of the device. Despite this fall, the subjects with nicotine were always more alert than those without. Following the second video projection, a significant increase in the state of alertness of the subjects with a placebo patch was noted as well as a retention of the previously acquired level for the subjects with nicotine. These results seem to agree with studies taken from the literature, notably those of Perkins *et al.* (1994) and Levin *et al.* (1998b). However, the heterogeneousness of the results observed in the literature reflects the complex character of the relationship between nicotine and mood. It seems that the influence of nicotine is a function of the method of administration and that a mode of diffusion which is continuous is not the most appropriate in order to observe this type of effect (Knott *et al.*, 1999). It is difficult to make comparisons between the different studies because of the multiplicity of populations tested and the variety of mood tests and cognitive tests used.

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Note

1. RT score difference series *i* = Baseline RT condition *n* – RT series *i* condition *n*.

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