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Cerebral effects of nicotine during cognition in smokers and non-smokers

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Abstract For the smoker, nicotine has a positive effect on attention, cognition and mood. Conversely, nicotine abstinence is characterized by uncomfortable psychological effects such as impaired attention, but also irritability. We postulated that nicotine exerts an effect on cerebral areas important for attention and mood. Regional cerebral blood flow (rCBF), as an index for cerebral activity, was measured in both smokers and non-smokers. They were scanned during performance of a psychometric task with and without IV infusion of nicotine (1-methyl-2-[3-pyridyl1] pyrrolidine). Nicotine induced rCBF decreases in the anterior cingulate cortex and the cerebellum, and concomitant increases in the occipital cortex. The changes were similar in nature and magnitude in smokers and non-smokers. Thus, specific changes were induced in areas pertaining to the anterior attention system and to higher order visual cortex. We conclude that these effects on cerebral activity provide insights into the desired positive effects of nicotine on cognition as well as the negative effects experienced during nicotine abstinence.

Key words Nicotine · Positron emission tomography · Regional cerebral blood flow · Brain activation · Human · Cognition

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Introduction

The tertiary amine nicotine is one of the most widely used psycho-stimulating drugs today (Corrigall 1991; Murray 1991). The urge for nicotine intake is often explained by both the positive psychological effects of intake as well as the negative effects of abstinence. Nicotine, when ingested or injected, has been shown to improve cognitive performance in several psychological tests in which attention is of importance (Warburton 1992; Warburton and Arnall 1994). Attention is impaired by abstinence, and a smoker in abstinence is less tolerant to stress and is more easily distracted (Grenhoff and Svensson 1989; Nil 1991). Nicotine effects on mood have often been described, but these effects are difficult to quantify, since they are subtle. The cerebral effects of nicotine have been attributed to its action in the "mesolimbic reward system", a metaphor denoting the structures involved in the emotional evaluation of cognitive processes (Papez 1937; Koob and Bloom 1988; Clarke 1994). The medial prefrontal cortex, including the anterior cingulate cortex (ACC), is one of the major projection areas for this reward system. Converging evidence suggests a crucial role for the ACC in the regulation of attention. In tasks containing conflicting information, such as the Stroop color-word interference test (Pardo et al. 1990; Bench et al. 1993b; Paus et al. 1993), activation of the ACC has been found to be positively correlated with the amount of inherent conflict in the task. Other neuropsychological tests, such as the Wisconsin Card Sorting test or tasks designed for specific testing of selective and sustained attention, also activate this region (Corbetta et al. 1991; Daniel et al. 1991; Ghatan et al. 1995).

We studied the specific effects of nicotine (1-methyl-2-[3-pyridyl1] pyrrolidine) on cerebral activity with PET, using regional cerebral blood flow (rCBF) as an index, in both nicotine-naive subjects (non-smokers) and in habitual cigarette smokers (smokers). They were

studied while performing a computerized maze test, a neuropsychological test that requires constant attention to the task and is considered sensitive to general intelligence, visuospatial skill and visually guided motor planning (Elithorn and Mornington 1982; Ghatan et al. 1995). Based on the symptoms that smokers in abstinence display, we postulated that nicotine has region-specific effects on the cerebral activity in areas that are involved in willed attention (Pardo et al. 1990; Frith et al. 1991; Paus et al. 1993). We examined whether the drug effect and its anatomical representation were similar in smokers and non-smokers. We also evaluated the relationship between nicotine administration and the functional activations elicited by the maze test. Furthermore, we examined the relationship between the degree of cerebral activation and the plasma levels of nicotine. We also evaluated practice-related effects in the maze test (Ingvar et al. 1995). In a third group of subjects, we measured the global cerebral blood flow and oxygen consumption in order to verify that the global effects on CBF of the nicotine infusion were limited, also in our experimental design.

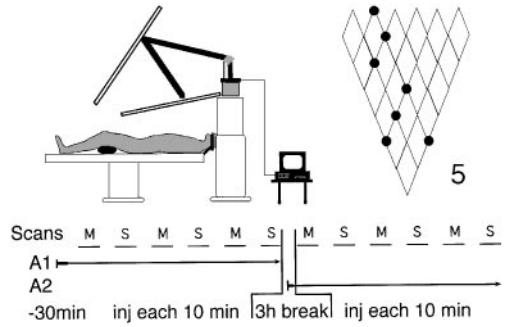

Fig. 1 Experimental setup and a maze grid from the computerized maze test. The maze contains a grid with superimposed dots and a digit in the lower right corner indicating the maximal number of dots that can be targeted in each maze. The subject obtains a visual feedback indicating the route chosen during advancement from bottom to the top. The Sham paradigm consists of the same grid but without dots or number. The infusion schedule for groups A1 and A2 have been changed indicated on bottom with approximate times. A 15-min bolus was started 30 min before the first scan in group A1 and before the seventh scan in group A2. *M* Denotes Maze scan and *S* Sham-task scan. Each scan is 1 min and scans are performed every 10 min (≈5 half-lives of the injected nuclide)

Materials and methods

Subjects

All procedures were approved by the local Ethics and Radiation Safety committees at the Karolinska Hospital. Informed consent was given by all subjects. Eighteen healthy subjects with no history of psychiatric, neurologic or other medical illness were included, 12 habitual smokers (smokers: > 20 cigarettes per day) and six nicotine-naive subjects (non-smokers). They were divided into three groups: group A consisted of eight smokers (age: 31–46 years), group B consisted of six non-smoking subjects (age 28–46 years) and group C of four smokers (age 25–31 years).

Procedure

Group A

The smokers (group A) were instructed to abstain from nicotine for 24 h before the study. They underwent 12 PET scans each in a balanced design. In four subjects (group A.1), the first six scans were performed during abstinence and the subsequent six scans were obtained during IV nicotine infusion. In four other subjects (group A.2), the initial six scans were performed during nicotine administration and the subsequent six after a new nicotine-free period of 3 h to re-establish basal nicotine levels. This order of scans was chosen to balance the possible learning/habituation and improvement effects on the performance of the maze tests (see below). Nicotine administration was started by intravenous infusion at 2.0 μg/kg per minute for 30 min, followed by 0.5 μg/kg per minute during the remainder of the infusion (approximately 80 min). From laboratory experience, it was estimated that this procedure would yield constant plasma levels during the measurements. Plasma nicotine levels were determined before the set of abstinence scans and in all scans during nicotine infusion. The infusion dose was experimentally determined in separate subjects prior to inclusion in the study. A dose and speed of infusion was chosen that was projected not to induce nausea or discomfort.

Each subject was scanned 12 times, six performing a maze task and six during a sham condition. The task was alternated between the maze and a sham condition in every other scan. The perceptual maze test (PMT) is a computerized task consisting of sequential mazes where the subject must choose a route and try to hit a predetermined number of targets with a tracer (Fig. 1) (Ghatan et al. 1995). The performance of the maze test is automatically rated according to four parameters: *inspection time* (the time from the visual display of each maze grid to the start of solving the maze), *processing speed* (median number of processed nodes/s calculated from the total number of nodes divided by the total solution time), *maximum rows* (largest (rows) correctly solved maze-grid during the testing procedure) and *accuracy* (percentage of correctly solved mazes). A sham task was used as a control condition. It consists of maze grids without targets and the subjects were instructed to guide the tracer without choice of specific route. Hence the cognitive processing and visual feedback necessary to perform the test were minimal, while it contained the same amount of motor performance as in the maze test.

Group B

The non-smokers underwent 12 PET scans and nicotine was infused at a steady dose of 0.3 μg/kg per minute during the first six scans. The nicotine infusion was changed to physiological saline in the last six scans, without notifying the subjects. The same computerized maze test was used as in group A, but here they solved the maze task in all 12 scans. The design of the infusion allowed for calculation of orthogonal influences of the drug-effects and the time effects, the latter attributable to learning or habituation effects on rCBF. The plasma concentration was monitored and was added as a covariate (increased during the first scans and decreased during the last scans) and time was added as increment number for the number of runs. The subjects were screened with a simple questionnaire based on the visual analog scale for mood and possible aversive effects of nicotine. Plasma nicotine levels were determined for each scan and these values were later used as covariates when determining the dependence of rCBF on nicotine levels in plasma (Curvall et al. 1982).

Group C

Global CBF was determined in four smokers using the Kety-Schmidt method with [^{133}Xe] as the inert tracer (Kety and Schmidt 1948). Catheters were inserted percutaneously into a jugular vein with the catheter tip in the jugular bulb and into a brachial artery, under local anesthesia and fluoroscopic control. Blood was drawn simultaneously from the jugular vein and the artery for assessment of oxygen content. The subjects were allowed to breathe in a closed system with oxygen and [^{133}Xe] (140 MBq) for 6 min. They were then switched to room air and arterial and venous blood samples were collected at timed intervals for 12 min. [^{133}Xe] in blood was measured in a scintillation counter. The area between the arterial and jugular venous curves was determined and the blood flow was calculated using a partition coefficient of 0.83. Measurement was first made while the subject was in abstinence and then after 45 min of nicotine infusion according to the protocol above. On both occasions, the subjects were studied in a basal resting state. Cerebral oxygen uptake was calculated as the product of global CBF and the difference between arterial and jugular-venous oxygen content.

PET scanning

In group A, a 2D 10 cm field of view (FOV) camera (Scanditronix PC 2048-15, General Electric) was used, with a resolution of $5 \times 5 \times 6.5$ mm full width half maximum (FWHM) (Holte et al. 1989), and rCBF was measured after injection of 700 MBq [^{15}O]butanol. In group B, a 3D 15 cm FOV camera (Ecat Exact HR, Siemens CTI, Knoxville, USA) (Wienhard et al. 1994) was used and rCBF was measured after injection of 480 MBq [^{15}O]butanol. The use of [^{15}O]butanol as a flow-tracer with a radioactive half-life of 2 min permitted a protocol of 12 scans in one session. The uptake of [^{15}O]butanol, dissolved in a mixture of ethanol and physiological saline (≈3 ml, ratio 1:9), was measured for 100 s in 20-s time frames. More than 10 min (5 half-lives of ^{15}O) elapsed between the scans to allow for the decay of residual radioactivity and for re-establishing resting state levels of CBF. The respective tasks were started prior to the injection of the tracer. The compounded radiation dose gave an individual exposure estimated to be less than 5 mSv. A stereotactic fixation of the subject's head (Bergström et al. 1981) insured a constant position of the subject's head during the scanning procedure.

Data analysis

The data were analyzed with statistical parametric mapping (using software from the Wellcome Dept of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc. Sherborn, Mass., USA). Statistical parametric maps are spatially extended statistical processes that are used to characterize regionally specific effects in imaging data. Statistical parametric mapping combines the general linear model (to create the statistical map or SPM) and the theory of Gaussian fields to make statistical inferences about regional effects (Friston et al. 1990, 1991, 1994, 1995; Worsley et al. 1992).

The scans from each subject were realigned using the first as a reference. The six parameters of this transformation were estimated using a least squares approach (Friston et al. 1995). Following realignment, all images were transformed into a standard space (Talairach and Tournoux 1988) and subsequently normalized to give a global uptake of 50 nCi/ml. As a final pre-processing step, the images were smoothed using an isotropic (16 mm FWHM) Gaussian kernel.

Statistical analysis

Subject and covariate effects were estimated according to the general linear model at each voxel (Friston et al. 1995). To test hypotheses about regionally specific condition (or covariate) effects, the estimates were compared using linear compounds or contrasts. The resulting set of voxel values for each contrast constitutes a statistical parametric map (SPM) of the t statistic, SPM{t}.

In group A, the conditions were abstinence/sham, abstinence/maze, nicotine/sham and nicotine/maze. The order of each scan was entered as a nuisance covariate. Determinations of contrasts were performed for nicotine/abstinence and also for maze/sham as well as for the interaction.

In group B, plasma levels of nicotine and scan order were entered as covariates of interest and the effects attributable to each of these were determined as well as the interaction between the two.

Data in the text, tables and figures are given as mean ± SD.

Statistical inference

The SPM{t} data sets were transformed to the unit normal distribution (SPM{Z}) with a threshold at 3.09 (or $P = 0.001$ uncorrected). The resulting foci were then characterized in terms of spatial extent (k) and peak height (u). The significance of each region was estimated using distributional approximations from the theory of Gaussian fields. This characterization is in terms of the probability that a region of the observed number of voxels K (or larger) could have occurred by chance P (nmax > k), or that the peak height observed (or higher) could have occurred by chance P (Zmax > u) over the entire volume analyzed (i.e. a corrected P-value).

A principal component analysis was then performed in order to obtain a relative estimate of the variance attributable to the main effect within the statistical model.

Following this analysis, the data are presented in the CBA anatomical space with its three-dimensional database (Greitz et al. 1991). Tabulated data are given the anatomical designation in this anatomical space with the corresponding spatial co-ordinates in the Talairach space according to the SPM standard (Talairach and Tournoux 1988; Friston et al. 1995).

Statistical differences for other results were calculated by means of analysis of variance (ANOVA, Abacus Concepts, Superanova), except where noted.

Results

All subjects included in the study withstood the infusion of nicotine well. None reported nausea or general mood changes when they were interviewed for this, nor did any became overtly euphoric or sad. Some of the smokers in abstinence reported feelings of restlessness and an urge to smoke prior to receiving the nicotine infusion.

Plasma nicotine levels and maze test scores

All subjects in group A and C (smokers) had a plasma nicotine level of 6 ± 2 ng/ml (mean ± SD) on the day of study. The plasma nicotine levels achieved in group A during infusion were comparable for the subgroups with the last scans during nicotine (A1) and the first scans during nicotine (A2) (25 ± 5 ng/ml and

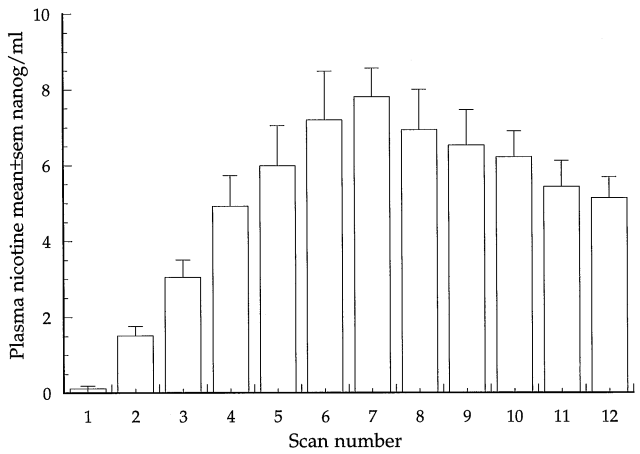

Fig. 2 Plasma nicotine levels in non-smokers (group B) during nicotine infusion (first six scans)

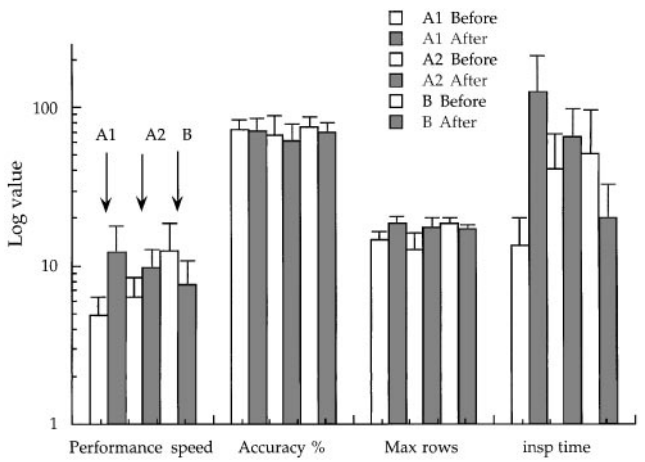

Fig. 3 Maze test score in smokers (group A1; first six scans during abstinence, group A2; last six scans during abstinence) and in non-smokers (group B). Test results were similar for the groups. Mean ± SD in the first and last solved maze task. Performance speed is given as median number of processed nodes/second calculated from the total number of nodes divided by the total solution time (= total time − inspection time). *Accuracy %* Is the number of correctly solved mazes/total number × 100. *Max rows* Is the maximally reached size of the maze. This is measured since the level of difficulty is automatically regulated according to previous success. *Insp time* Is the time from the visual display of each maze grid till the start of solving the maze

28 ± 6 ng/ml, respectively). In subgroup A2, nicotine concentrations had returned to basal levels during the last six PET scans. In group B, there were no detectable levels of nicotine at the start of the experiment and peak levels during the nicotine infusion were about one-third of the values seen in group A (Fig. 2).

There were no significant differences in the maze test score between the nicotine-free condition or during nicotine infusion in group A and B (Fig. 3).

Table 1 Changes in rCBF related to nicotine effects in group B calculated in a factor analysis where time effects were separated (see Table 2). Significant maxima located stereotactically in the space of Talairach (X, Y, Z mm) within volumes of significant correlation of rCBF with nicotine. Hence each confluent volume of pixels (Size k) may have several maxima. The Z-max and derived *P* value represents the level of significance (corrected for multiple comparisons according to the theories of Gaussian random fields). Data represent 72 scans, all performed during the solving of the maze task and infusion of nicotine (nicotine infusion scan 1–6 and falling levels of nicotine scans 7–12), respectively. Data is presented as separate contrasts for correlations with nicotine in plasma and simple time dependent changes (Table 2), respectively. *P* values are corrected for multiple comparisons at $P < 0.05$ level [Initial threshold $Z > 3.09$, volume (S) 74026, FWHM = (18.3 21.1 24.2 mm)]. Nomenclature according to Talairach and Tournoux atlas (Talairach and Tournoux 1988) and Brodmann area designations according to the 3-D database of Greitz et al. 1991 (volumes are given in number of pixels (1 pixel = 8mm^3). *cx* cortex, *gy* gyrus

Region	Size {k}	P(nmax > k)	Zp(Zmax > U)		{X,Y,Z mm}		
Positive correlations between rCBF and plasma nicotine							
Superior occipital gy (BA19si)	191	0.086	4.57	0.009	−14	−78	36
Superior occipital gy (BA18si)	284	0.04	4.45	0.010	−10	−102	−16
Middle frontal gy (BA45si)	166	0.10	4.37	0.019	−54	22	8
Middle frontal gy (BA46si)			4.12	0.049	−50	36	8
Negative correlations between rCBF and plasma nicotine							
Anterior cingulate cx (BA24dx]	2008	0.000	5.56	0.000	6	16	32
Superior frontal gy (BA6dx)			4.40	0.018	30	8	56
Posterior cingulate gy (BA31dx)			4.35	0.021	2	−36	40
Middle frontal gy (BA9dx)			4.13	0.048	44	4	36
Middle frontal gy (BA6si)			3.93	0.097	−24	4	56
Middle frontal gy (BA9dx)			3.80	0.000	8	38	20
Middle frontal gy (BA6dx)			3.79	0.000	16	−2	64
Anterior cingulate cx (BA24dx)			3.72	0.18	2	−12	40
Operculum (BA44dx)			3.59	0.25	48	4	24
Operculum (BA44dx)			3.56	0.27	46	20	24
Middle frontal gy (BA6dx)			3.40	0.40	40	6	48
Amygdala dx	185	0.091	4.22	0.034	32	6	−16
Inferior parietal cx [BA40dx]	147	0.127	4.80	0.003	52	−30	36
Cerebellum, quadrangular lobe dx	215	0.070	4.44	0.015	20	−76	−24

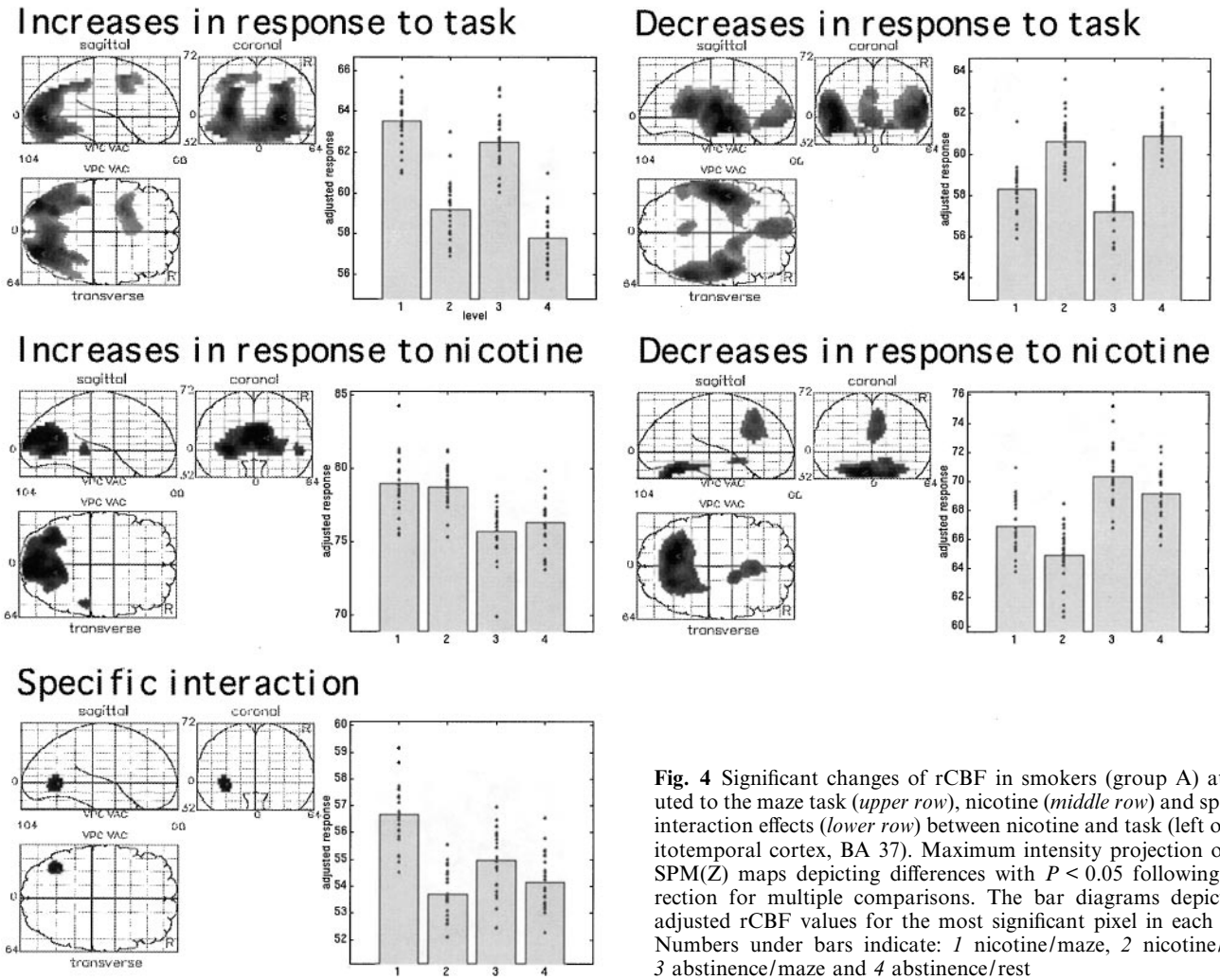

Fig. 4 Significant changes of rCBF in smokers (group A) attributed to the maze task (*upper row*), nicotine (*middle row*) and specific interaction effects (*lower row*) between nicotine and task (left occipitotemporal cortex, BA 37). Maximum intensity projection of the SPM(Z) maps depicting differences with $P < 0.05$ following correction for multiple comparisons. The bar diagrams depict the adjusted rCBF values for the most significant pixel in each case. Numbers under bars indicate: *1* nicotine/maze, *2* nicotine/rest, *3* abstinence/maze and *4* abstinence/rest

Nicotine effects on cerebral blood flow

There were no changes in global CBF as measured with the Kety-Schmidt method (group C) or in cerebral oxygen uptake that could be attributed to the infusion of nicotine. Global CBF before and after infusion of nicotine was 36.2 ± 2.8 (SD) ml/100 g per minute and 35.0 ± 3.2, respectively, and cerebral oxygen uptake was 2.28 ± 0.17 before and 2.34 ± 0.48 ml/100 g per minute during nicotine infusion.

In smokers (group A) changes in the activation pattern related to the maze-task were analyzed separately from changes related to nicotine as well as the interaction between these factors (Fig. 4). The differences in rCBF between the maze test and the sham were very similar to the changes reported in a previous study using the maze test (Ghatan et al. 1995). Marked bilateral increases were found in the occipito-temporo-parietal cortices and in the superior prefrontal cortex, and decreases in the medial temporal cortex and the lower medial frontal cortex. Nicotine infusion led to bilateral increases in the parieto-occipital region and decreases in the ACC and cerebellum. An interaction between the factors of nicotine/abstinence and maze/sham was found in the left occipito-temporal region (Brodmann area 37), indicating an rCBF increase during nicotine/task that was not seen during abstinence/task.

In non-smokers (group B) a separate correlation analysis was performed of plasma nicotine levels and time. The changes related to plasma nicotine levels are depicted in Fig. 5 and Table 1. Increases were found in the occipito-temporal regions, with more widespread changes on the right side. Decreases were noted in the ACC, the thalamus and the basal ganglia. The changes related to monotonous time effects are presented in Fig. 6 and Table 2. Bilateral increases were found in basal parts of the medial prefrontal and medial temporal cortices and bilateral decreases in the occipital cortex extending into the right temporal cortex.

Discussion

We observed no changes in global CBF or metabolic rate caused by the administration of nicotine

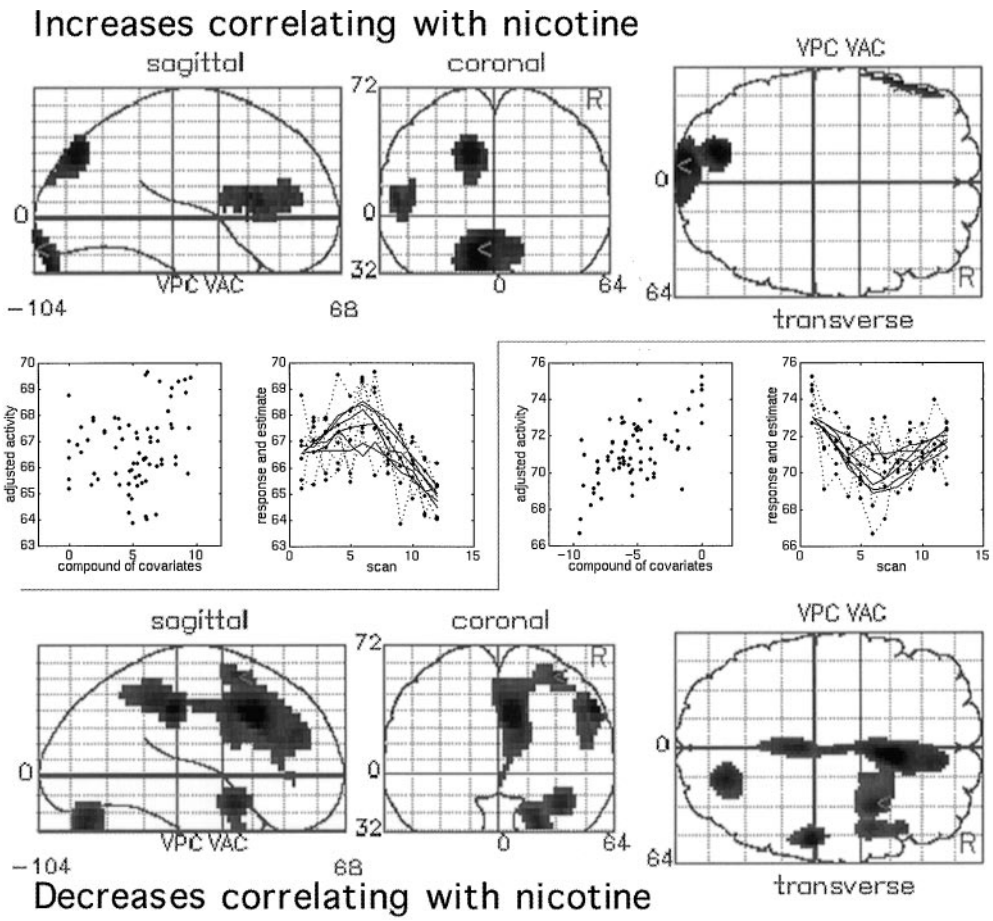

Fig. 5 Nicotine effects on rCBF in non-smoking subjects (group B) Maximum intensity projection of the SPM(Z) maps depicting significant positive (*upper row*) and negative (*lower row*) correlations with plasma nicotine levels and rCBF ($P < 0.05$ following correction for multiple comparisons). For details see Table 1

(McNamara et al. 1990). Meyer et al. (1995) have reported that the longer the time of abstinence, the more expressed the global effect of nicotine will be, and that for short periods of abstinence, the global effects of nicotine are minimal. The abstinence period in this study was short and of similar duration for groups A and C. The prestudy nicotine concentrations in group A were somewhat higher than expected for a 24-h abstinence period indicating that either there was a methodological problem in quantitating these low levels of nicotine or that their compliance with the instruction of 24-h abstinence was not complete. However, it should be emphasized that the measured levels were low; all were therefore considered to be abstinent, albeit, in some cases, not for the full 24-h period. The possible lack of full compliance does not influence the conclusions of this study. Results from group C support the use of global normalization for the PET procedure when measuring regional changes in CBF. The design of the present experiments performed with and without nicotine allows us to conclude that the regional changes found pertain specifically to the difference between states. Nicotine elicited rCBF changes that were similar in both smokers and non-smokers (Figs. 4 and 5) in spite of the different doses used (non-smokers do not tolerate nicotine to the same extent as smokers). The design of the experiment in group A (smokers) allowed for an analysis of the interaction between nicotine effects and the cognitive test, whereas the design in group B (non-smokers) allowed for an analysis of interaction between nicotine effects and monotonous time-effects.

Both smokers and non-smokers showed a decrease in the medial part of the prefrontal cortex (right ACC). A general reduction in metabolic activity in the cerebral cortex, particularly in frontal regions, has been suggested to reflect the desired euphoriant effects of drugs like nicotine (London et al. 1990a, b, 1991). For example, amphetamine has been shown to decrease the global cerebral blood flow (Daniel et al. 1991). Such a decrease in metabolic activity may not reflect the specific site of action for the ingested drug, but rather a metabolic response to a general decrease in concern and anxiety level with regard to external or internal cognitive events.

The ACC has strong reciprocal connections with the dorsolateral prefrontal cortex (DLPFC) (Vogt and Pandya 1987). Together, they constitute the anterior attention system (Posner 1990). In studies addressing mood disorders, decreased activity in the DLPFC has been described (Bench et al. 1992, 1993a; Dolan et al. 1992, 1993; Mayberg et al. 1994). These rCBF changes

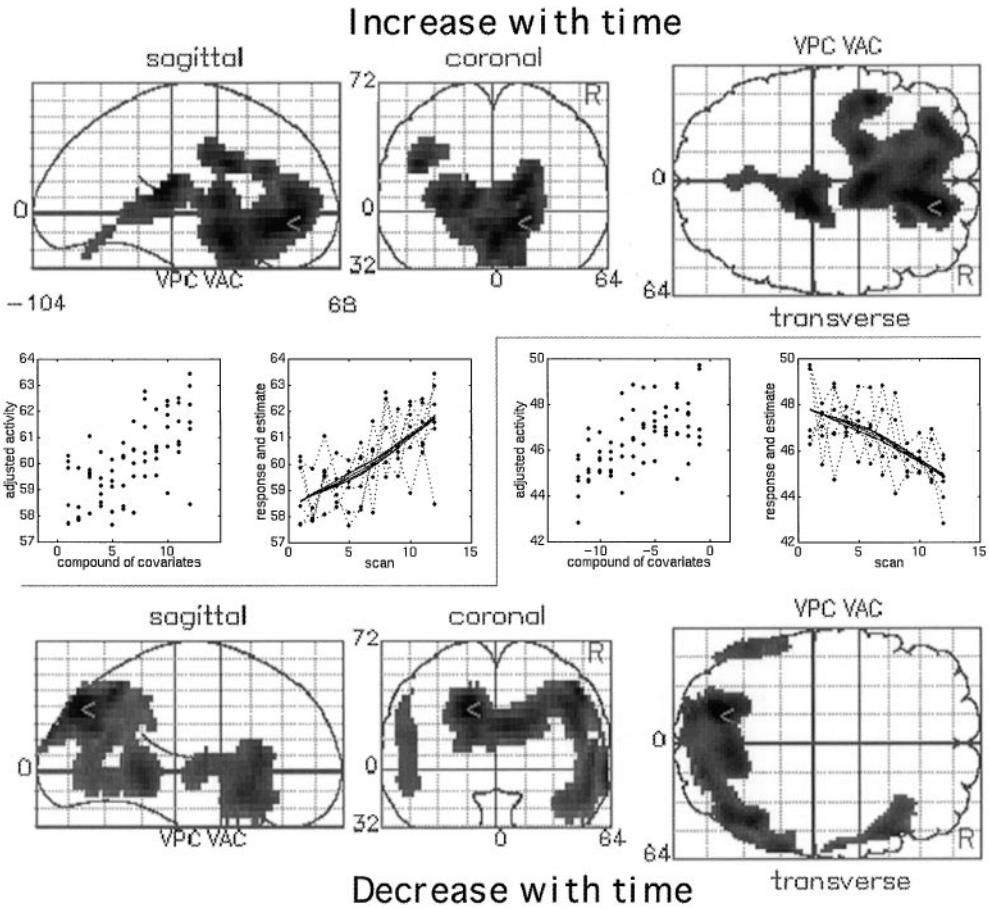

Fig. 6 Monotonous time effects in non-smoking subjects (group B) Maximum intensity projection of the SPM(Z) maps depicting significant positive (*upper row*) and negative (*lower row*) changes in rCBF attributed to time ($P < 0.05$ following correction for multiple comparisons). For details see Table 1

have been said to reflect the symptoms of mood disorders rather than the disease itself (Dolan et al. 1993). The decrease in activity in the ACC caused by drugs of abuse is compatible with decreasing demands for handling conflicting internal and external cognitive processes, which is probably part of the desired effect. An increase in the degree of conflict inherent in a cognitive task, such as the Stroop color-word interference test, activates the ACC (Pardo et al. 1990; Bench et al. 1993b). Nicotine has been shown in an electrophysiological study to reduce the Stroop effect (improved performance) (Hasenfratz and Bättig 1994). Our data suggest that symptoms of nicotine abstinence, such as dysphoria and subjectively experienced difficulty in maintaining willed attention, could be associated with a higher tone in the ACC.

The desired effects of nicotine may be due to its interaction with the cerebral reward systems such as the dopaminergic system (Nisell et al. 1994; Schultz et al. 1997). The mesolimbic part of the dopaminergic system has major projections to the ACC. Activity in such an internal reward system should be high whenever there is a discrepancy between the expected and the actual reward. Subjective reports of pleasure following nicotine ingestion could be an expression of a higher congruence between predicted and actual reward, thereby decreasing activity in the ACC. The reward prediction theory suggests that plasticity in response to phasic dopamine signals resets the system and this could represent one key to the induction of habitual nicotine use (Schultz et al. 1997). However, nicotine has many effects on the brain, and the dopaminergic system is only one of the neurotransmitter systems affected (Toth et al. 1992; Summers and Giacobini 1995).

Low doses of nicotine improve cognitive function in man and direct effects on attention have been described (Pritchard et al. 1992; Houezec et al. 1994). This has led to trials in which nicotine has been used to treat attention disorders (Levin et al. 1996). The finding in the present study of a nicotine-related decrease of rCBF in the ACC in both smokers' and non-smokers is consistent both with the smokers self-reported difficulties in maintaining attention and the effects on mood described during abstinence. The right-sided rCBF decrease in the ACC in both groups is enigmatic. In chronic pain, the aversive response is also right-sided, with increases in the caudal part of the ACC (Hsieh et al. 1995, 1996). Improvements in mood and attention may improve cognitive performance (Houezec et al. 1994), although the nicotine effects previously reported have been marginal. We did not observe nicotine-induced enhancement of cognition in this study (Fig. 3), although the number of studies is too small for us to be able completely to exclude such effects.

Table 2 Changes in rCBF related to monotonous time effects in group B. Significant maxima within areas of increased and decreased rCBF attributed monotonous time contrast (n = 1–12) for each subject. Data is presented as separate contrasts for correlations with time. For further details see Table 1

Region	Size {k}	P(nmax > k)	Zp(Zmax > U)		{X,Y,Z mm}		
Areas with increases in rCBF with time							
Anterior cingulate gy (BA32dx)	3805	0.000	5.33	0.000	14	38	−4
Anterior cingulate gy (BA32dx)			5.22	0.000	10	30	−8
Septal area (BA 25 midline)			5.20	0.001	0	4	−16
Superior frontal gy (BA10si)			4.83	0.003	−8	38	−8
Putamen si			4.79	0.003	−16	0	8
Middle frontal gy			4.75	0.004	−30	40	8
Anterior cingulate gy (BA32dx)			4.46	0.014	20	24	24
Putamen si			4.24	0.032	−34	−10	8
Anterior cingulate gy (BA32si)			3.87	0.11	−22	26	−8
Hippocampal gy (dx)	608	0.005	5.45	0.000	16	−30	16
Hippocampal gy (dx)			3.90	0.104	4	−46	0
Areas with decreases in rCBF with time							
Superior occipital gy (BA19si)	2218	0.000	5.70	0.000	−16	−78	36
Inferior parietal lobule (BA40dx)			5.08	0.001	44	−60	−40
Precuneus (BA31si)			4.95	0.002	6	−72	−24
Superior occipital gy (BA19dx)			4.93	0.002	40	−74	36
Inferior parietal lobule (BA39dx)			4.88	0.002	42	−72	28
Middle temporal gy (BA21dx)			4.87	0.002	60	−44	−4
Superior occipital gy (BA18si)			4.62	0.007	−14	−96	20
Superior occipital gy (BA19dx)			4.57	0.009	18	−88	28
Superior occipital gy (BA19si			4.54	0.010	−18	−90	28
Superior occipital gy (BA19dx)			4.25	0.031	26	−82	36
Superior temporal gy (BA38dx)	577		4.84	0.003	48	14	−12
Operculum dx			4.81	0.003	52	20	8
Superior temporal gy (BA22dx)			4.76	0.004	50	16	−4
Inferior parietal lobule (BA39si)	337	0.027	4.11	0.051	−52	−62	20
Inferior occipital gy (BA37si)			3.69	0.196	−52	−74	0

Our findings corroborate previous reports that nicotine selectively increases rCBF in discrete areas of the visual system and subcortical areas (London et al. 1988; McNamara et al. 1990; Grünwald et al. 1991). The activation in the superior part of the occipital lobe (BA 18, 19) is localized in a region of the extrastriatal visual cortex that is functionally integrated with both the ventral and dorsal visual pathways (de Jong et al. 1994). It contains motion-sensitive neurons that contribute to information on the direction and layout of the visual environment and that form three-dimensional structures from motion (de Jong et al. 1994). Grasby, Friston and coworkers have reported that CBF can be increased in this region by buspirone (a 5 HT_{1A} partial agonist) (Friston et al. 1992; Grasby et al. 1992). This effect was attributed to secondary drug effects, rather than a direct receptor interaction. Nicotine has been shown to activate subcortical and cortical areas of the visual system in animals (McNamara et al. 1990). This interaction has been suggested as an explanation for the improvements in visual attention and processing reported in both non-smokers and smokers (Warburton 1992; Warburton and Arnall 1994). Therefore, the occipital rCBF increases could reflect both cortical and subcortical effects of nicotine.

The metabolic activity in the cerebellum in rats has been reported to increase in response to nicotine administration (McNamara et al. 1990). Our data suggest the opposite response in the cerebellum in both smokers and non-smokers. The reason for this discrepancy in results is unclear at present but could be due to differences in the experimental setup as well as the large doses of nicotine that were administered in the animal study. Nagata and coworkers have also reported an increase in the cerebellar blood flow (Nagata et al. 1995). However, the limited size of that dataset precludes a statistical handling with correction for multiple comparisons. The number of instructions in our study is larger, and therefore the statistical certainty of the findings is much higher.

The differences in rCBF between the maze test and the sham in smokers (Fig. 4) were consistent with those reported in previous communications (Ghatan et al. 1995; Ingvar et al. 1997). Activations were found in a network for visuoperceptual processing, attention, eye movements and motor performance. Regions outside this network, as for example the auditory system, the somatosensory system, and the frontobasal part of the limbic system, were deactivated (Ghatan et al. 1995). These rCBF decreases may reflect a filtering of information from these unrelated sensory modalities (Ghatan et al. 1995, 1997). The interaction analysis (Fig. 4, lowest panel) between nicotine

and the maze task revealed an activation of the left occipito-temporal region (BA 37) that was seen in the nicotine state during the maze task. The left occipito-temporal region is a higher order visual area involved in discriminative perception (object and face recognition) (Sergent et al. 1992; Moscovitch et al. 1995; Schacter et al. 1995) and attention-related mechanisms (Chelazzi et al. 1993; Corbetta et al. 1993; Frith et al. 1995). This interaction, in combination with the nicotine-induced decrease of rCBF in the ACC, could reflect a more perceptually based strategy in yielding a decreased demand on willed attention when nicotine is administered.

The monotonous time effects studied in group B (Fig. 6 and Table 2) revealed rCBF decreases in the occipital cortex overlapping the increases elicited by nicotine in both smokers and non-smokers. These time effects have been described in several studies and are attributed to practice, learning, time and habituation (Bench et al. 1993b; Friston et al. 1993). The time-related increases of rCBF were located in regions attributed to attention and learning (ACC and hippocampal regions), which supports the hypothesis that habituation is mediated by systems overlapping those regions (Bench et al. 1993b; Hugdahl et al. 1995). It could also reflect a time-related decrease in attention based inhibitory modulation, necessary for processing the task initially.

In conclusion, we found no effects of nicotine on the global cerebral blood flow. However, regional effects were shown in cortical areas pertaining to the regulation of mood and attention and also to higher order visual cortices, effects that were similar in smokers and non-smokers. These changes provide clues to the desired positive effects of nicotine on mood and attention and also the negative effects of nicotine abstinence.

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