Changes in brain activation associated with reward processing in smokers and nonsmokers: a PET study

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Abstract

Tobacco smoking is the most frequent form of substance abuse. Several studies have shown that the addictive action of nicotine is mediated by the mesolimbic dopamine system. This system is implicated in reward processing. In order to better understand the relationship between nicotine addiction and reward in humans, we investigated differences between smokers and nonsmokers in the activation of brain regions involved in processing reward information.

Using [$H_2{}^{15}O$] positron emission tomography (PET), we measured regional cerebral blood flow (rCBF) in healthy smokers and nonsmokers while they performed a prelearned, pattern recognition task. We compared two conditions involving nonmonetary reinforcement or monetary reward with a baseline condition in which nonsense feedback was presented.

With monetary reward, we found activation in the frontal and orbitofrontal cortex, occipital cortex, cingulate gyrus, cerebellum and midbrain in both groups. Additionally, monetary reward activated typical dopaminergic regions like the striatum in nonsmokers but not in smokers. We found a similar pattern of activation associated with nonmonetary reinforcement in nonsmokers, whereas activation was found in smokers only in the cerebellum.

The different patterns of activation suggest that the brains of smokers react in a different way to reward than those of nonsmokers. This difference involves in particular the regions of the dopaminergic system including the striatum. In principle these observations could be interpreted either as a consequence of tobacco use or as a primitive condition of the brain that led people to smoke. Supported by related nonimaging studies, we interpret these differences as a consequence of tobacco smoking, even if a short-term efffect of smoking prior to the eperiment can not be excluded.

Key words: reward, striatum, positron emission tomography, human, smokers

Introduction

Tobacco smoking is considered a worldwide public health problem because of its serious health consequences and high prevalence. Tobacco smokers often underestimate the addictive effect of nicotine, but studies have presented evidence that nicotine and other drugs of abuse act similarly at the neurobiological and behavioral level (Picciotto, 1998; Stolerman, 1997). The reinforcing properties of nicotine have been demonstrated with the intravenous self-administration paradigm in rats (Corrigall & Coen, 1989), primates (Sannerud et al., 1994) and in human smokers (Henningfield et al., 1983). Furthermore, the effects of nicotine seem to be mediated by the mesolimbic dopamine system (Clarke et al, 1988; Corrigall et al., 1992), a crucial system for reward processing (Di Chiara, 1995; Berridge, 1998; Koepp et al, 1998, Schultz, 1997) and for mediation of the reinforcing effects of many addictive drugs (Wise, 1996; Koob & LeMoal, 1997; Picciotto, 1998).

Reward reinforces operant behavior, elicits approach behavior and also induces positive emotional feelings. Reward is thought to play an important motivational role in the explanation of addiction. Like cocaine, amphetamine, morphine and ethanol, nicotine increases dopamine transmission in the nucleus accumbens (Pontieri et al., 1996), a brain region essential to reward processing. Lesions of neurons in the mesolimbic dopamine system induce decreases of nicotine self-administration in rats (Corrigall, 1992) and of locomotor stimulation by administered nicotine (Clarke et al., 1988). Moreover, nicotine withdrawal reduces the reward function in the rat's brain as does withdrawal of other drugs of abuse (Epping-Jordan et al., 1998).

In order to better understand the relationship between nicotine addiction and reward in humans, the present study investigated differences between smokers and nonsmokers in the activation of brain regions involved in processing reward information using positron emission tomography (PET). We performed an experiment using a prelearned delayed pattern recognition task with different reinforcers. Assuming that regions of the meso-striatal and meso-corticolimbic dopaminergic pathways react specifically to reward, we postulated that brain regions associated with these systems are activated by reward processing in both groups, but

that the pattern of brain activation in smokers differs from that in nonsmokers, especially in dopaminergic regions.

Materials and methods

Subjects:

The study involved one group of 9 healthy male nonsmokers, age (mean ± SD) 24.7 ± 3.5 and a second of 10 healthy male smokers, age 29.4 ± 8.7. All subjects were right-handed. They were tested for psychiatric, neurological or medical disease. Memory performance and executive functions were tested prior to the experiment using a short neuropsychological screening test including verbal fluency testing and the Rey visual design learning test (Rey, 1968). Candidates with depression were excluded using the BDI (Beck Depression Inventory). The mean depression score was 3.5 ± 3.67 (Mean ± SD) for smokers and 1.5 ± 1.2 for nonsmokers. No drug dependence or abuse other than nicotine dependence was allowed. Drug dependence was assessed using the ICD-10 symptoms checklists (WHO, 1995). The smokers had a current consumption of about 1 pack of cigarettes per day. Subjects could smoke prior to the experiment. The experiment was approved by the Ethics Committee of the Department of Neurology of the University Hospital of Zurich. All subjects gave their informed written consent according to the Declaration of Helsinki.

Behavioral Task

During the PET-measurement the subjects performed a pattern recognition task with delayed response (Figure 1). The subjects faced a 30x23 cm black-and-white computer screen mounted a distance of 80 cm in front of their head. Responses were made with the right index finger by pressing on a mouse button. Feedback comprised no reinforcement, a nonmonetary reinforcement or a monetary reward (Figure 2). The tasks were exactly identical except for the reinforcer used. In the baseline condition (XY), the subjects received a nonsense feedback for every response. In the reinforcement conditions, no reinforcement appeared if the response was wrong. Subjects were instructed before the scans that they would receive the sum shown at the end of the experiment. The maximum which could be won was 320 sFr. The baseline as well as the two reinforcement conditions consisted of 20 trials with the tasks presented in randomized order. Each condition was repeated once in random order yielding 6 scans for each subject. The three different conditions (XY, OK, MO) were also presented in randomized order. The subjects were thoroughly instructed before the experiment and they performed the task once under all three conditions during a training phase.

PET-Scanning

We measured regional blood flow (rCBF) using positron emission tomography (PET) with the tracer $H_2{}^{15}O$. Subjects were informed of the condition before each intravenous bolus of 500-600 MBq of $H_2{}^{15}O$, which they received immediately after the task began. Counts were recorded during the 90 seconds after the bolus arrived in the brain. An interval of 12 minutes was interposed between scans in order to permit sufficient decay of radioactivity. The measurements were made with an Advance tomograph (GE Medical Systems, Waukesha, WI) acquiring in three-dimensional mode. The emission scans were preceded by 10 minute transmission scans to permit correction for attenuation. Images of raw counts were reconstructed into 35 image planes of dimension 128x128 using filtered backprojection with a Hanning filter of FWHM 4 mm in the transaxial plane and a ramp filter of 8.5 mm in the axial direction. The pixel sizes were 2.34 mm in the transaxial plane and 4.25 mm in the axial direction.

Data analysis

The images were controlled for alignment and mapped into the stereotactic space described by Talairach and Tournoux (Talairach & Tournoux, 1988) using the standard spatial transformation of SPM96. After spatial standardisation the scans were smoothed with a Gaussian filter of 10 mm FWMH. Proportional scaling preceded comparison of conditions within a group using the design: multisubject with repetitions. The resulting voxel maps of t-statistics were then transformed into maps of normally distributed z-statistics (Grafton et al, 1991; Friston et al. 1991, Friston et al., 1995).

Psychological measures

Mood rating

The subject evaluated his mood after each condition by positioning a mobile cursor on a wooden visual analog scale. On the front, two faces appeared: an unhappy face (☹) at the right end and a happy face (☺) at the left end. On the back was a scale ranging from -5 to +5. The front of the scale was presented to the subjects while they reclined motionless in the scanner, and they instructed the experimenter to move the cursor to the position corresponding to their mood.

Monetary value

In a questionnaire filled out before the beginning of the experiment, the subjects rated the subjective value of different amounts of money (10.-, 100.-, 300.-, 500.- and 1000.- SFr) on a visual analog scale. After the experiment, the subjects rated the value of the amount of money they had won on the same scale.

Results

Behavioral performance:

The differences in correct responses between OK and MO reinforcements were significant in neither group using the Wilcoxon signed rank test: p=0.46 for nonsmokers and p=0.17 for smokers. Nor were there significant differences according to Mann Whitney U test between smokers and nonsmokers with OK reinforcement (p=0.07) or MO reinforcement (p=0.07), although these results indicated a trend. These results are displayed in figure 3.

Cerebral blood flow:

Regions revealed by the contrasts MO-XY, OK-XY and MO-OK indicate increased activation due to reinforcement and reward for both groups of subjects as summarized in Table 1. The contrast MO-XY in nonsmokers (figure 4A) shows rCBF increases in the left precentral gyrus, the right dorsolateral prefrontal cortex, right and left orbitofrontal cortex, the left cingulate gyrus, right cingulum, right medial temporal gyrus, left occipital cortex, cuneus, right midbrain, right putamen, right caudate nucleus and right and left cerebellum. Of these, the left precentral gyrus, one region of the right dorsolateral prefrontal cortex, the left cingulate gyrus, the left occipital cortex, one region of the temporal cortex, the right caudate nucleus, and two regions of the right cerebellum occur only in this contrast; plots of the activity show an increasing activation with condition: XY < OK < MO as illustrated in Figure 5A. A second region of the right dorsolateral prefrontal cortex, the right and left orbitofrontal cortex, the right cingulum, right midbrain and right cerebellum occur also in the contrast OK-XY, with reduced significance in some cases. Finally, regions belonging to the right medial temporal gyrus, the cuneus, right putamen, and cerebellum appeared also in the contrast MO-OK. Regions occurring exclusively in the contrast MO-OK include areas belonging to the right inferior parietal lobule, the right cuneus, the left inferior occipital cortex, the right putamen, right thalamus, right caudate nucleus, and right cerebellum. Plots revealed in all cases the pattern of relatively reduced activity in the condition of nonmonetary reinforcement illustrated in Figure 5B. Regions occurring exclusively in the contrast OK-XY include one belonging to the left orbitofrontal cortex, one belonging to the left superior temporal cortex, one in the left gyrus cinguli and two in the cerebellum.

Contrast MO-XY in smokers (figure 4B) evidences rCBF increases only in the right cingulate gyrus and right and left cerebellum. Of these regions, those in the right cingulate gyrus appeared also in the contrast MO-OK as did three regions in the right cerebellum and four in the left. Plots confirmed that these regions all exhibited increases with condition. Three regions in the cerebellum appeared in both contrasts MO-XY and OK-XY. Regions appearing only in the contrast MO-OK were in the left dorsolateral and orbitofrontal cortex, in the left midbrain, three in the right cerebellum and two in the left cerebellum; all showed a pattern of reduced rCBF increase in nonmonetary reinforcement. There were no regions appearing only in the contrast OK-XY.

Psychological measures:

After translation to a scale ranging from 0 to 11 points in order to eliminate negative values, the mean scores of mood in nonsmokers were 9.1 ± 2.0 points (mean ± SD) for XY, 9.7 ± 1.7 for OK and 9.2 ± 1.0 for MO. The mean scores in smokers were 7.3 ± 1.7 points for XY, 7.5 ± 1.7 for OK and 7.6 ± 1.1 for MO. A Friedman test found no significant differences in mood between conditions for the nonsmokers ($p <= 0.3$) or smokers ($p <= 0.4$). The Mann Whitney U test indicated a significant difference in mood between smokers and nonsmokers in trials with monetary reward ($p <= 0.01$) and with nonmonetary reinforcement ($p <= 0.05$), but not in trials with no reinforcement ($p = 0.7$).

In the evaluation of the value of money, we were particularly interested in differences between groups of subjects in rating the value of earnings. The mean amount of money earned by the nonsmokers was 301 ± 12 SFr and by the smokers 290 ± 13 SFr. These sums yielded mean rated values on the visual analog scale of 6.2 ± 1.2 points for the nonsmokers and 6.6 ± 2.9 points for the smokers. The Mann Whitney U test revealed significant differences between nonsmokers and smokers neither in the rated value of earnings ($p = 0.54$) nor in the amount ($p = 0.11$).

Discussion

We confirmed in the nonsmokers that a limited number of brain regions responded to reward stimuli. Many belonged to the meso-striatal and meso-corticolimbic system, but additional regions not associated with this system also responded to reinforcement and reward. We also found differences between the monetary and nonmonetary reinforcing conditions. No striatal activation was found in response to the nonmonetary reinforcement. In smokers rCBF increases were found in few regions of the mesolimbic dopaminergic system, but not in the striatum, whereas increases in the cerebellum remained an invariable feature.

The meso-striatal and meso-corticolimbic regions included the midbrain, the dorsolateral and orbitofrontal cortex, the dorsal striatum, the caudate nucleus, the thalamus and the cingulate gyrus. The observations of rCBF increases in the midbrain, thalamus and the Brodmann's areas of the frontal cortex confirm a previous PET study (Thut et al.,1997) that found increases in these regions in a contrast of monetary reward with nonmonetary reinforcement. These observations confirm the role of the midbrain in processing motivational stimuli, since Ljunberg et al. (1991) demonstrated that monkey midbrain dopamine neurons respond to salient attentional and motivating stimuli. A role of the orbitofrontal cortex in the processing of rewarding stimuli has been shown in other studies. For example, the neurons of the primate orbitofrontal cortex were shown to increase activity in reaction to signals predicting reward, during the anticipation and after the receipt of reward (Tremblay & Schultz, 1999). A PET study in humans found rCBF increases in the right inferior and orbital prefrontal cortex in a risk-taking task involving choice between small and large rewards (Rogers et al., 1999). The rCBF increases in the striatum agree with our expectations, since the striatum is one of the regions most investigated in relation to reward. The occurrence of the activation on the right, i.e. the ipsilateral, side contradicts its association with motor response. The increased activation of the striatum occurred primarily in the contrast of monetary reward with nonmonetary reinforcement, suggesting a specific role of the striatum in reward processing. Koepp et al. (1998) showed in a recent PET study that dopaminergic transmission was increased in the ventral and dorsal striatum in humans during a goal-directed motor task rewarded with money. Furthermore, activation of the caudate nucleus was found in a PET

study (Elliott et al., 1997) in association with the processing of performance feedback under different task conditions. The emergence of the thalamus in the contrast of monetary reward with nonmonetary reinforcement which we observed might follow from its connections with the frontal cortex and amygdala. A relation between the emotional meaning of visual stimuli and activation of the thalamus has been demonstrated recently (Teasdale et al., 1999). rCBF increases with conditions in the cingulate gyrus suggest its role in general reinforcement mechanisms. A study in rats reported that the anterior and posterior cingulate gyrus played a role in stimulus-reward learning and stimulus-response learning (Bussey et al., 1997). A PET study found activation associated with the processing of pleasant relative to neutral stimuli in the cingulate gyrus (Paradiso et al., 1999).

Additional regions not associated with the meso-striatal and meso-corticolimbic system which also responded to reinforcement and reward in nonsmokers include the primary motor cortex, the visual cortex, the inferior temporal gyrus, the parietal inferior lobule, and the cerebellum. The increasing activation of the left primary motor cortex is certainly related to the motor response of the right hand. rCBF increases in the Brodmann's areas 17 and 19 of the visual cortex could be explained by differences in the words presented as feedback in the three conditions. Previous PET studies reported increases in the striate and extrastriate visual cortex while reading words in comparison with viewing a fixation point, and in the left medial extrastriate visual cortex while reading words and pseudowords but not letter strings (Petersen et al., 1988; 1990). Activations of the parietal and temporal cortex are situated in typical association areas for the treatment of visual information, and could also be involved in reading. An occipitotemporal activation has been found in several studies of the processing and encoding of single words (Henke et al., 1999; Hagoort et al, 1999). On the other hand, activation of the visual cortex and precuneus were found in previous neuroimaging studies in response to visually presented pleasant and unpleasant stimuli, suggesting that these regions may also be involved in processing the emotional value of visual stimuli (Paradiso et al., 1999; Teasdale et al., 1999). The parietal cortex in primates has also been associated with assessing the value of reward (Platt & Glimcher, 1999). Finally, activation in the cerebellum was found in all the contrasts, which suggests a basic role of the cerebellum in processing reinforcement.

The increases could have multiple interpretations. They could confirm the role of the cerebellum in reading the different verbal feedbacks presented, since many studies investigating word processing and reading found cerebellar activation (Jernigan et al., 1998; Brunswick, N., 1999); or could reflect higher arousal related to the reward condition associated with additional effort in planning and executing the motor response. That the cerebellum is involved in attentional processes and could participate in coordinating the direction of selective attention has been shown (Allen et al., 1997; Akshoomoff et al.,1997).

rCBF increases recorded in the cerebellum were the most apparent feature in smokers. Remarkable in the contrasts of the smokers is the absence of thalamus and striatal regions and of occipital, temporal or parietal regions; the only areas of the dopaminergic system evidencing increases, mainly in the contrast of monetary reward with nonmonetary reinforcement, were the left orbitofrontal cortex, right cingulate gyrus and left midbrain. The lack of striatal activation could indicate that chronic tobacco use induces changes in the meso-striatal dopaminergic system. However, a short-term pharmacological effect in our subjects cannot be excluded, since we have no direct measure of dopaminergic changes in the brain after smoking.

Supporting the hypothesis of change in the meso-striatal dopaminergic system is a recent ^{18}F-Fluorodopa PET-study (Salokangas et al. 2000) reporting greater dopamine activity in the striatum of smokers than of non-smokers, suggesting that nicotine dependence is associated with changes in dopamine activity in the brain. Another study showed that cigarette smokers are more impulsive than nonsmokers (Mitchell, 1999) and prefer immediate rewards. Another study reported that delayed outcomes very quickly lose their subjective value for smokers in comparison with nonsmokers (Bickel et al., 1999). Thus, the effect of the monetary gain presented on the screen could be weaker in smokers than nonsmokers, because it involved a delayed outcome. Additional evidence was the significant mood difference between the smokers and nonsmokers during nonmonetary reinforcement and monetary reward, suggesting that the nonsmokers were in a better mood than the smokers during the two conditions. This observation can be interpreted according to the salience hypothesis (Berridge, 1998) in which striatal dopaminergic regions are implicated in attributing salience to incentive stimuli. The

criterion for salience in nonsmokers was fulfilled by the presented amount of money, but this was not the case for smokers.

In conclusion, our results show that regions pertaining to a meso-striatal and meso-corticolimbic loop are activated by reward stimuli in nonsmokers. These results agree with our expectations. Additionally the rewarding condition induced activation in regions specific to the task performance. This activation could be interpreted as additional mental effort made in order to maximize the obtained results and as a direct effect of reward on goal-directed behavior. We also found differences between the monetary and nonmonetary reinforcing conditions. No striatal activation was found in response to the nonmonetary reinforcement, suggesting that this region reacts specifically to reward or to salient stimuli.

The patterns of activation in smokers differed from those in nonsmokers. Smokers also showed meso-corticolimbic activation, but specific to monetary reward. The nonmonetary reinforcer induced only cerebellar activation. There was neither striatal activation nor performance-specific activation in any of the contrasts. The lack of performance-specific activation could reflect a change in the effect of rewards on goal-directed behavior. We postulate that the differences in striatal activation indicate that a smoker’s brain interprets and reacts to reward in a different way than nonsmokers. This interpretation agrees with observations that smokers are more impulsive and sensation-seeking than nonsmokers. In principle these observations could be interpreted as either a consequence of tobacco use or as a primitive condition of the brain that led people to smoke. Since many studies have shown that nicotine administration has an effect on dopamine transmission in the striatum, we interpret the difference between smokers' and nonsmokers' brains to be a consequence of tobacco smoking. However, a short-term pharmacological effect due to cigarette smoking prior to the experiment can not be excluded, since we have no direct measure of dopaminergic changes in the brain after smoking in our subjects. A single study is not sufficient to provide evidence for one interpretation or the other, and further studies should be performed to clarify this point.

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Legends:

Fig. 1

Behavioral task. Three square fields were displayed simultaneously for 2500 msec on the screen: one at the top, the others at the bottom on the right and left side. In each square field were 5 black horizontal streaks, 50 mm long and 4 mm high; a 3 mm blank interrupted one of the streaks. This interruption was at a different position in each square field. The visual pattern had to be remembered by the subjects. After 3000 ms, during which the screen stayed blank, a square field was displayed at one of the initial three positions. The subjects were given 1500 ms to decide whether this pattern was identical to the one presented previously. If the pattern was identical and at the same position as the previous pattern, the correct response for the subjects was to press the computer mouse with the right index finger. Otherwise, no action was the correct response. No other movement was allowed during the test. After the response time had elapsed, the picture disappeared independently of the subject's response. With a further delay of 2500 ms, feedback appeared on the screen.

Fig. 2

Types of feedback. In the baseline condition, the letters "xy" were displayed on the bottom left side of the screen and the characters "az123" on the right side. Nonmonetary reinforcement consisted of the symbol "ok", and the monetary reward was 8 sFr for each correct response. For nonmonetary reinforcement (OK), the message following each correct answer consisted of the letters "ok" presented on the bottom left of the screen and the total number of correct responses displayed continuously on the bottom right. For monetary reward (MO), the message "8 sFr" appeared on the left bottom of the screen after each correct response, indicating a reward of 8 Swiss francs (sFr). The total amount of money earned was displayed constantly on the bottom right of the screen.

Fig. 3

Results obtained by smokers and non-smokers during the behavioral task in the different conditions. The mean percentage of correct responses with nonmonetary reinforcement (OK)

was 94.4 ± 3.7 for the nonsmokers and 90.7 ± 4.8 for the smokers. The mean percentage of correct responses with monetary reward (MO) was 93.0 ± 3.4 for the nonsmokers and 86.2 ± 7.6 for the smokers. There were no significant differences in the number of correct responses either between the two groups of subjects or between conditions.

Fig. 4

SPM projections of significantly activated brain areas in the comparisons between baseline and the monetary reward with an uncorrect search threshold of $p < 0.001$.

A. in nonsmokers B. in smokers.

Fig. 5

Plots of typical patterns of rCBF activation with respect to the conditions for smokers and nonsmokers.

A. Increasing activation with condition B. Suppressed nonmonetary activation

Table 1

Talairach coordinates of regions of activation in nonsmokers and smokers. Z-values are indicated in the significant contrasts. The number of resels in the search volumes for the nonsmokers was 1391 and for smokers 1344.