

In vivo Brain Imaging of Human Exposure to Nicotine and Tobacco

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Abstract While most cigarette smokers endorse a desire to quit smoking, only 14–49% will achieve abstinence after 6 months or more of treatment. A greater understanding of the effects of smoking on brain function may result in improved pharmacological and behavioral interventions for this condition. Research groups have examined the effects of acute and chronic nicotine/cigarette exposure on brain activity using functional imaging; the purpose of this chapter is to synthesize findings from such studies and present a coherent model of brain function in smokers. Responses to acute administration of nicotine/smoking include reduced global brain activity; activation of the prefrontal cortex, thalamus, and visual system; activation of the thalamus and visual cortex during visual cognitive tasks; and

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increased dopamine (DA) concentration in the ventral striatum/nucleus accumbens. Responses to chronic nicotine/cigarette exposure include decreased monoamine oxidase (MAO) A and B activity in the basal ganglia and a reduction in $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nAChR) availability in the thalamus and putamen (accompanied by an overall upregulation of these receptors). These findings indicate that smoking enhances neurotransmission through cortico–basal ganglia–thalamic circuits by direct stimulation of nAChRs, indirect stimulation via DA release or MAO inhibition, or a combination of these and possibly other factors. Activation of this circuitry may be responsible for the effects of smoking seen in tobacco-dependent smokers, such as improvements in attentional performance, mood, anxiety, and irritability.

1 Introduction

Smoking remains a major health issue in USA and quitting smoking continues to be a challenge. In a recent survey, approximately 23% of Americans were found to smoke cigarettes (Balluz et al. 2004). While most smokers endorse a desire to quit (Fiore et al. 2000), very few will quit smoking without treatment, and only about 14–49% will achieve abstinence after 6 months or more of effective treatment (Holmes et al. 2004; Hughes et al. 1999; Hurt et al. 1997; Jorenby et al. 1999; Killen et al. 2000, 1999). Because cigarette smoking carries both considerable health risks (Bartal 2001; Mokdad et al. 2004) and high societal costs (Leistikow et al. 2000a, b), there is an urgent need for improved treatments for this condition. Functional brain imaging (in conjunction with other lines of research) holds great promise for elucidating both brain circuits and molecular targets that mediate the acute effects of cigarette smoking and the chronic effects of tobacco dependence. A greater understanding of brain function associated with smoking may result in improved pharmacological (and behavioral) interventions.

Many functional brain imaging studies of tobacco use and dependence have been performed, using four primary imaging modalities: (i) functional magnetic resonance imaging (fMRI), (ii) positron emission tomography (PET), (iii) single photon emission computed tomography (SPECT), and (iv) autoradiography. These imaging modalities have been used to determine relationships between brain function and the effects of acute and chronic cigarette smoking and of smoking-related behaviors. For this chapter, the MEDLINE database was searched using keywords for the four imaging techniques mentioned above, cross-referenced with the words “nicotine”, “cigarette”, and “tobacco.” Only data-driven functional imaging studies were included in this review, and reference lists within papers found on MEDLINE were also examined and relevant studies included here. In order to maintain focus in this chapter, functional imaging techniques that provide measures of blood flow and metabolism (which are closely related under normal conditions; Paulson 2002) are combined under the general heading of brain activity (including fMRI and certain types of SPECT, PET, and autoradiography studies). Also, in order to build

a cohesive model of brain activity responses to acute and chronic smoking, nicotine and cigarette studies will be reviewed together while recognizing that cigarette smoke has many constituents other than nicotine (Baker et al. 2004; Fowles and Dybing 2003).

The purpose of this chapter is to synthesize findings from functional brain imaging studies of tobacco use and dependence, and present a coherent model of brain function in smokers. Acute brain responses to nicotine/smoking will be reviewed first, followed by chronic responses to nicotine/smoking, and concluding with a discussion of these imaging findings in the context of neuroanatomical work and the clinical effects of smoking in tobacco-dependent subjects.

2 Brain Function Responses to Acute Nicotine Administration and Cigarette Smoking

2.1 Brain Activity Responses to Nicotine/Cigarette Administration

Many functional brain imaging studies have been performed examining the effects of administration of nicotine or cigarette smoking compared with a placebo or control state (Table 1). Though a wide range of brain regions have been reported to have altered activity in response to nicotine or cigarette smoking, several global and regional findings have been replicated, leading to general conclusions about the acute effects of nicotine or smoking on brain activity.

One common finding is that nicotine administration (Domino et al. 2000b; Stapleton et al. 2003b) or cigarette smoking (Yamamoto et al. 2003) results in decreased global brain activity. Similarly, smokers who smoke ad lib prior to SPECT scanning (including the morning of the scan) have decreased global brain activity compared to former smokers and nonsmokers (Rourke et al. 1997). These findings are generally supported by studies using transcranial Doppler ultrasound or the Xe 133 inhalation method to measure responses to smoking, with some (Cruickshank et al. 1989; Kubota et al. 1983, 1987; Rogers et al. 1983), but not all (Kodaira et al. 1993; Terborg et al. 2002), studies showing diminished cerebral blood flow.

A large ($n = 86$), recent study (Fallon et al. 2004) further characterized this decreased global activity with nicotine administration. ^{18}F -fluorodeoxyglucose (FDG) PET was performed while smokers and exsmokers performed the Bushman aggression task (designed to elicit an aggressive state) and wearing either a 0, 3.5-, or 21-mg nicotine patch. Smokers who were rated high on the personality trait hostility had widespread cerebral metabolic decreases while wearing the 21-mg patch and performing the aggression task. Low-hostility smokers did not have these changes during PET, suggesting that personality profile may determine which smokers have global metabolic decreases in response to nicotine.

In studies examining regional activity responses to nicotine or smoking, the most common findings are relative increases in activity in the prefrontal cortex (including the dorsolateral prefrontal cortex, and inferior frontal, medial frontal, and

Table 1 Functional brain imaging studies of nicotine or cigarette administration

Authors	Subjects	Method	Intervention	Results
<i>Animal studies</i>				
London et al. (1988a, b)	Rats	2-Deoxy-D- $[1-^{14}C]$ glucose autoradiography	SC nic (0.1–1.75 mg kg ⁻¹)	↑ Nicotine rich regions, including thal, cereb, visual system, others
Marenco et al. (2000)	Rats – chronically nic exposed vs. nic naive	2-Deoxy-D- $[1-^{14}C]$ glucose autoradiography	SC nic (0.4 mg kg ⁻¹) vs. saline	↑ Thal, superior colliculus in chronically exposed; ↑ thal, superior colliculus, medial habenula, and dorsal lateral geniculate in nic naive
<i>Human studies</i>				
Rourke et al. (1997)	8 Smokers; 8 former smokers; 17 nonsmokers	Iodine-123 iodosamphetamine (IMP) SPECT	Smokers smoked the morning of the scan; other groups did not	↓ Cortical uptake of IMP (a measure of blood flow) in current smokers compared to other groups
Stein et al. (1998)	16 Smokers	fMRI	IV nic (0.75–2.25 mg/70 kg wt) vs. placebo	↑ R NAc and bilateral amyg, cingulate, frontal lobes, thal, others
Domino et al. (2000a)	18 Smokers	¹⁵ O-PET	Nic nasal spray vs. pepper spray	↑ Thal, pons, visual cortex, cereb
Domino et al. (2000b)	11 Smokers	FDG-PET	Nic nasal spray vs. pepper spray	Small ↓ global; ↑ L IFG, L PC, R thal, visual cortex; ↓ normalized L ins and R inf occ ctx

Zubieta et al. (2001)	18 Smokers	¹⁵ O-PET	Nic nasal spray vs. pepper spray	↑ Anterior thal; ↓ L ant temp and R amygd
Rose et al. (2003)	34 Smokers	¹⁵ O-PET	Cigarette vs. no nic control conditions	↑ L frontal factor (incl. prefrontal and ACC), ↓ L amygd rCBF
Yamamoto et al. (2003)	10 Smokers	^{99m} Tc-ECD SPECT	Cigarette vs. abstinence	↓ Global blood flow
Stapleton et al. (2003a)	4 Smokers; two nonsmokers	2 FDG-PETs (fully quantified)	IV nic (1.5 mg) vs. placebo	↓ Global and most regions studied
Zubieta et al. (2005)	19 smokers	¹⁵ O-PET	Nicotine containing vs. denicotinized cigarettes	↓ Global blood flow
Staley et al. (2006)	16 Smokers; 16 nonsmokers	5 IA-SPECT	Recent abstinence	↑ Striatum, parietal cortex, frontal cortex, anterior cingulate, temporal cortex, occipital cortex, cerebellum

All regional changes represent normalized activity, unless otherwise stated. SC subcutaneous, nic nicotine, thal thalamus, cereb cerebellum, SPECT single photon emission computed tomography, fMRI functional magnetic resonance imaging, IV intravenous, R right, L left, NAc nucleus accumbens, amygdala, FDG ¹⁸F-fluorodeoxyglucose, PET positron emission tomography, IFG inferior frontal gyrus, PC posterior cingulate, ins insula, inf occ ctx inferior occipital cortex, ant anterior, temp temporal lobe, ACC anterior cingulate cortex

orbitofrontal gyri) (Domino et al. 2000b; Rose et al. 2003; Stein et al. 1998), thalamus (Domino et al. 2000a, b; London et al. 1988a, b; Stein et al. 1998; Zubieta et al. 2001), and visual system (Domino et al. 2000a, b; London et al. 1988a, b). Additionally, a Xe 133 inhalation study reported increases in frontal lobe and thalamic blood flow in smokers who smoked a cigarette (Nakamura et al. 2000). The human studies here examined cigarette smokers, while the animal studies here used non-dependent rats, with strong concordance of findings between these sets of studies. Functional brain imaging studies of nicotine or cigarette administration to human nonsmokers have not yet been reported, and would be important for a more complete understanding of the effects of tobacco on brain activity. While this group of studies demonstrates specific regional activation with nicotine or smoking, they also imply activation of cortico–basal ganglia–thalamic brain circuits (Alexander et al. 1990) that mediate the subjective effects of smoking (see Sect. 4). Zubieta et al. (2005) have conducted a ^{15}O -PET study in 19 smokers using nicotine and denicotinized cigarettes, who were abstinent of smoking for 12 h before PET. In this study, increases in the regional cerebral blood flow (rCBF) in visual cortex and cerebellum, and reductions in rCBF in the anterior cingulate, the right hippocampus, and ventral striatum were found. Cigarette craving in chronic smokers also was correlated with rCBF in the right hippocampus, which is a region involved in associating environmental cues with drugs, and in the left dorsal anterior cingulate, an area implicated in drug craving and relapse to drug-seeking behavior.

Since regional activity was normalized to whole brain activity in at least some of these studies, and whole brain activity has been found to decrease with nicotine or cigarette administration, the regional findings presented here may represent either increased regional activity or, possibly, less of a decrease in regional activity than in other brain areas. Regional decreases in activity are generally not seen with nicotine or cigarette administration, though at least two studies found relatively decreased activity in the amygdala, left (Rose et al. 2003) and right (Zubieta et al. 2001)).

2.2 Effect of Nicotine on Brain Activation During Cognitive Tasks

There is evidence that nicotine administration improves performance on tasks that require vigilant attention in nicotine-dependent smokers (Newhouse et al. 2004). Nicotine administration also has been reported to improve reaction time, regardless of smoking status (Ernst et al. 2001a). Consistent with these findings are studies that demonstrate that acute abstinence from smoking (within 12 h) results in slowed response times (Bell et al. 1999; Gross et al. 1993; Thompson et al. 2002).

In examining brain mediation of the cognitive effects of smoking, several groups have performed functional imaging studies in subjects performing cognitive tasks during administration of nicotine (compared to a control condition) (Table 2). For most of these studies, subjects performed a cognitive task that involved visual recognition and working memory, such as the n-back task. Results of these studies have been somewhat mixed, showing both decreased (Ernst et al. 2001b;

Table 2 Functional brain imaging studies of nicotine or cigarette administration during cognitive tasks/stimulation

Authors	Subjects	Method/task	Intervention	Effect of nicotine during task
Ghatan et al. (1998)	12 Smokers; 6 nonsmokers	¹⁵ O-butanol PET/computerized maze	IV nic infusion versus abstinence	↓ ACC and cerebellum; ↑ occ ctx
Ernst et al. (2001b)	11 Smokers; 11 former smokers	¹⁵ O-PET/2-back	Two pieces of 2-mg nic gum vs. placebo gum	↓ ACC and PFC activation in smokers
Jacobsen et al. (2002)	9 Smokers	fMRI/photoc stimulation	IV nic 10 mcg kg ⁻¹ vs. saline	No effect on visual cortex
Lawrence et al. (2002)	15 Smokers	fMRI/rapid visual information-processing	21-mg nic vs. placebo patch	↑ Parietal and occipital ctx., thal, caudate
Kumari et al. (2003)	11 Nonsmoking men	fMRI/n-back	SC nic (1 mg) vs. saline	↑ ACC, superior frontal ctx, superior pari- etal ctx
Jacobsen et al. (2004)	13 Schizophrenic smokers; 13 smokers	fMRI/n-back	28- or 35-mg nic vs. placebo patch	↑ ACC and bilateral thal activation (schizophrenic, nonschizophrenic)

PET positron emission tomography, *IV* intravenous, *nic* nicotine, *ACC* anterior cingulate cortex, *occ ctx* occipital cortex, *PFC* prefrontal cortex, *thal* thalamus, *fMRI* functional magnetic resonance imaging

Ghatan et al. 1998) and increased (Jacobsen et al. 2004; Kumari et al. 2003) anterior cingulate cortex (ACC) activation in response to nicotine administration while performing the task. Brain activation responses to nicotine during cognitive tasks have been more consistent in other brain areas such as the thalamus (Jacobsen et al. 2004; Lawrence et al. 2002) and visual cortex (Ghatan et al. 1998; Lawrence et al. 2002), while nicotine had no effect on the visual cortex during photic stimulation (Jacobsen et al. 2002). This last finding indicates that nicotine activates the visual cortex only during demanding visual tasks, rather than on simple stimulation.

2.3 Brain Dopamine Responses to Nicotine and Smoking

A common pathway for the positive reinforcement associated with most, if not all, addictive drugs is the brain dopamine (DA) reward pathway (Koob 1992; Leshner and Koob 1999). Laboratory animal studies demonstrate that DA release in the ventral striatum (VST)/nucleus accumbens (NAc) underlies the reinforcing properties of nicotine (Koob 1992; Leshner and Koob 1999). Microdialysis (Damsma et al. 1989; Di Chiara and Imperato 1988; Pontieri et al. 1996; Sziraki et al. 2001) and lesion (Corrigall et al. 1992) studies in rats indicate that nicotine-induced DA release is strongest in this region, and is more robust than the DA release found in associated structures receiving dopaminergic input, such as the dorsal striatum (Di Chiara and Imperato 1988). These studies generally used nicotine dosages that simulated human cigarette smoking. Acute exposure to cigarette smoke and nicotine has been found to upregulate dopamine transporter mRNA in the ventral tegmental area (VTA) and substantia nigra (Li et al. 2004), and chronic exposure to cigarette smoke, more so than chronic nicotine alone, has also been found to upregulate D₁ and D₂ receptor mRNA in the VST (Bahk et al. 2002). Additionally, many in vitro studies of the VST have reported DA release in response to nicotine administration (Connelly and Littleton 1983; Marien et al. 1983; Rowell et al. 1987; Sakurai et al. 1982; Westfall et al. 1983).

Functional brain imaging studies of the DA system (Table 3) corroborate and expand upon these laboratory findings. Striatal DA release in response to a nicotine or cigarette challenge has been demonstrated repeatedly in both nonhuman primates and humans (Brody et al. 2004b, 2006; Dewey et al. 1999; Marenco et al. 2004; Tsukada et al. 2002), with most of these studies using PET and the radiotracer ¹¹C-raclopride (a specific D₂/D₃ DA receptor binder) to demonstrate DA release through radiotracer displacement. These studies have reported a wide range of DA concentration change. In two studies that examined the question directly (Marenco et al. 2004; Tsukada et al. 2002), nicotine was found to result in less radiotracer displacement than amphetamine, while it has also been reported that nicotine-induced DA release is comparable in magnitude to that induced by other addictive drugs (Pontieri et al. 1996). Also, an association between ¹¹C-raclopride displacement and the hedonic effects of smoking (defined as elation and euphoria) has been demonstrated (Barrett et al. 2004), though this study did not find an overall difference between the

Table 3 Functional imaging studies of the effects of nicotine or cigarette smoking on the dopamine (DA) system

Authors	Subjects	Method	Intervention	Results/conclusions
Dewey et al. (1999)	16 Baboons	¹¹ C-Raclopride PET (double bolus)	IV nic (0.3 mg)	↓ DV tracer (indicating ↑ DA concentration) in NAC
Dagher et al. (2001)	11 Smokers; 18 nonsmokers	¹¹ C-SCH 23390 PET		↓ BP in smokers (indicating ↓ D1 receptor density) in ventral striatum
Tsukada et al. (2002)	4 Macaca mulatto monkeys	¹¹ C-Raclopride PET (B/I)	IV nic (B/I)	Slight ↓ BP (indicating ↑ DA concentration) in anesthetized, but not conscious monkeys, in dorsal striatum
Salokangas et al. (2000)	9 Smokers; 10 nonsmokers	¹⁸ F-DOPA PET		↑ Uptake (indicating ↑ DA activity) in cd and Put of smokers
Krause et al. (2002)	11 Smokers w/ADHD; 11 nonsmokers w/ADHD	[^{99m} Tc]TRODAT SPECT		↓ DAT (striatal) in smokers
Staley et al. (2001)	21 Smokers; 21 nonsmokers	[¹²³ I] β-CIT SPECT		No overall binding difference between smokers and nonsmokers; ↑ brainstem 5-HT transporters in male smokers
Marenco et al. (2004)	5 Rhesus monkeys	¹¹ C-Raclopride PET (double bolus and B/I)	IV nic (0.01–0.06 mg kg ⁻¹)	↓ BP (indicating ↑ DA concentration) in basal ganglia with nic administration
Brody et al. (2004b)	20 Smokers	¹¹ C-Raclopride PET (B/I)	Single cigarette vs. no smoking	↓ BP (indicating ↑ DA concentration) in smoking, but not no smoking, condition in L ventral cd and put
Barrett et al. (2004)	10 Smokers	¹¹ C-Raclopride PET (double bolus)	Smoking every 12 min vs. no smoking	↓ BP correlated with hedonic response to smoking in cd and posterior put

PET positron emission tomography, IV intravenous, nic: nicotine, DV volume of distribution, DA dopamine, BP binding potential, B/I bolus-plus-infusion, cd caudate, put putamen, SPECT single photon emission computed tomography, DAT dopamine transporter, ADHD attention deficit hyperactivity disorder, β-CIT 2 β-carbomethoxy-3 β-(4-iodophenyl)-tropane, 5-HT serotonin

smoking and nonsmoking conditions. Thus, while most studies do provide evidence for nicotine/smoking-induced DA release, there are disparities between studies in the extent of human smoking-induced DA release, leaving this issue currently unresolved. Disparities between these studies may be due to differences in methodology (e.g., nicotine administration vs. cigarette smoking) and/or technical complexities in performing such studies. (As an aside, effects of smoking on dopamine projections to the prefrontal cortex (Goldman-Rakic et al. 1989) have not yet been reported with functional brain imaging.)

Nicotine-induced DA release in the NAc has been reported to be mediated by stimulation of nicotinic acetylcholine receptors (nAChRs) on cells of the VTA that project to the NAc rather than by nicotinic receptors within the NAc itself (Nisell et al. 1994). Lesioning of mesolimbic VTA neurons projecting to the NAc leads to decreased nicotine self-administration (Corrigall et al. 1992; Lanca et al. 2000). Additionally, the effects of nicotine on the dopaminergic system appear to be modulated by glutamatergic and GABAergic neurons (Picciotto and Corrigall 2002), with nicotine stimulation of glutamatergic tracts from the prefrontal cortex to the VTA leading to increased DA neuron firing (Kenny and Markou 2001) and GABA agonism leading to a dampening of DA neuron responses (Cousins et al. 2002). Recent work indicates that nicotine administration causes prolonged depression of GABAergic firing, leading to relatively large excitatory (glutamatergic) input into the mesolimbic DA system and increased DA neuron firing (Mansvelder et al. 2002).

Other functional imaging studies of the DA system have reported decreased D₁ receptor density (Dagher et al. 2001), increased ¹⁸F-DOPA uptake (a marker for increased DA turnover) (Salokangas et al. 2000), and both decreased (Krause et al. 2002) and no alterations (Staley et al. 2001) in dopamine transporter binding in smokers.

To summarize these studies of the DA system, there is extensive evidence that nicotine administration and smoking result in activation of the brain DA mesolimbic pathway, resulting in increased DA release and turnover in the VST/NAc. Because dopaminergic input to the NAc modulates neurotransmission through cortico-basal ganglia-thalamic circuitry (Haber and Fudge 1997), smoking-induced increases in DA concentration may explain some of the clinical effects of smoking, as discussed in Sect. 4.

2.4 Functional Imaging of Nicotinic Acetylcholine Receptors (nAChRs)

Because stimulation of nAChRs is intimately linked with the effects of smoking, a longstanding and still developing area of research is the labeling of nAChRs using functional brain imaging. Nicotinic acetylcholine receptors are ligand-gated ion channels consisting of α and β subunits (Court et al. 2000; Hogg et al. 2003). Many nAChRs have been identified, with the heteromeric $\alpha_4\beta_2$ being the most common subtype in the brain and the homomeric α_7 being the next most common.

Postmortem (Benwell et al. 1988; Breese et al. 1997) and laboratory (Yates et al. 1995) studies demonstrate that smokers have widespread upregulation of nAChRs, likely related to desensitization of these receptors from nicotine exposure. Many animal studies also demonstrate upregulation of nAChRs in response to chronic nicotine administration (e.g., Pauly et al. 1996; Shoaib et al. 1997; Zhang et al. 2002). Thus, nAChRs are a natural target for tracer development in the pursuit of a greater understanding of tobacco dependence and other illnesses with abnormal nAChR levels.

Animal research demonstrates that nicotine binds to nAChRs in the brain to mediate a variety of behavioral states (Lukas 1998), such as heightened arousal and improved reaction time and psychomotor function (Paterson and Nordberg 2000). Nicotine administration also produces reward through DA release in the NAC, at least in part through stimulation of nAChRs in the VTA (Blaha et al. 1996; Corrigan et al. 1994; Nisell et al. 1994; Yeomans and Baptista 1997; Yoshida et al. 1993). Nicotinic acetylcholine receptors are widespread throughout the brain, with a rank order distribution of nAChR density being thalamus > basal ganglia > cerebral cortex > hippocampus > cerebellum (Broussolle et al. 1989; Cimino et al. 1992; Clarke et al. 1984; Davila-Garcia et al. 1999, 1997; London et al. 1985, 1995; Pabreza et al. 1991; Pauly et al. 1989; Perry and Kellar 1995; Valette et al. 1998; Villemagne et al. 1997).

Radiotracers for the nAChR have been developed in recent years, with labeled A-85380 (3-(2(*S*)-azetidylmethoxy pyridine) (Koren et al. 1998) compounds having the most widespread use. Radiolabeling of A-85380 was a major advance in imaging nAChRs, because administration of radiolabeled nicotine (used for previous imaging studies) resulted in high nonspecific binding and short drug-receptor interaction times (Sihver et al. 2000). 2-[¹⁸F]F-A-85380 or simply 2-FA and related compounds (Chefer et al. 1999; Horti et al. 1998; Koren et al. 1998) are being used for PET imaging, and 5-[^{123/125}I]iodo-A85380 is being used for SPECT imaging (Chefer et al. 1998; Horti et al. 1999; Mukhin et al. 2000) of $\alpha_4\beta_2$ nAChRs.

Studies of nonhuman primates and humans have examined distributions of nAChRs with these new radiotracers, and found regional densities of these receptors similar to those in the animal work cited above (Chefer et al. 2003, 1999; Fujita et al. 2002, 2003; Kimes et al. 2003; Valette et al. 1999). Two recent studies on baboons examined effects of nicotine or tobacco smoke on nAChR availability. In a 2-FA PET study (Valette et al. 2003), IV nicotine (0.6 mg), inhalation of tobacco smoke from one cigarette (0.9 mg nicotine), and IV nornicotine were all found to reduce the volume of distribution of the tracer by roughly 30–60% in the thalamus and putamen at 80 min, and this reduction of 2-FA binding was relatively long lived (up to 6 h). Similarly, a 50% reduction in nAChR availability was found with IV nicotine administration to baboons using an epibatidine analog and PET scanning (Ding et al. 2000). Taken together, these studies demonstrate that radiotracers for nAChRs can be administered safely to measure nAChR densities, and that nicotine and smoking substantially decrease $\alpha_4\beta_2$ nAChR availability.

In a recent study (Brody et al. 2006), human cigarette smokers were studied using 2-FA and PET scanning. In this study, only one to two puffs of a cigarette resulted in

50% occupancy of brain $\alpha_4\beta_2$ nAChRs, and this occupancy lasted for at least 3.1 h after smoking. Smoking a full cigarette resulted in 88% occupancy, and was accompanied by a reduction in cigarette craving. Binding of nicotine to $\alpha_4\beta_2$ nAChR causes desensitization of these receptors, and this 2-FA PET study indicated that smoking may lead to withdrawal alleviation by maintaining nAChRs in the desensitized state.

[¹²³I]5-I-A or simply 5-I-A is a SPECT radioligand that binds to β_2 nAChRs. In a recent study, Staley et al. (2006) hypothesized that an abnormally high number of β_2 nAChRs in early abstinence may be responsible for continued tobacco usage. In this study, 16 smokers and 16 nonsmokers underwent 5-I-A SPECT scanning. Smokers were imaged in the abstinent phase, 7 days after their last cigarette. Each group consisted of seven men and nine women who were matched for age. Women smokers and nonsmokers were also matched by phase of menstrual cycle. Smokers quit cigarettes with brief behavioral counseling, and no medication was used for smoking cessation. In this study, recently abstinent smokers were found to have significantly higher 5-I-A uptake in the striatum, parietal cortex, frontal cortex, anterior cingulate, temporal cortex, occipital cortex, and cerebellum, which suggests that smoking upregulates the number of β_2 nAChRs.

2.5 Glutamatergic (and Other) Effects of Nicotine/Cigarette Smoking

Recent autoradiography studies of rodents have examined the effects of nicotine/smoking in other neurotransmitter systems that may be activated by nAChR stimulation. For example, in response to nicotine, glutamate release has been demonstrated in the prelimbic prefrontal cortex (Gioanni et al. 1999), and glutamate and aspartate release have been demonstrated in the VTA (Schilstrom et al. 2000). The finding of nAChR-induced glutamate release in the prefrontal cortex has also been demonstrated by measuring spontaneous excitatory postsynaptic currents (Lambe et al. 2003). Importantly, one of these studies (Gioanni et al. 1999) also demonstrated that nicotine administration facilitates thalamo-cortical neurotransmission through stimulation of nAChRs on glutamatergic neurons.

3 Brain Function Responses to Chronic Nicotine Administration and Cigarette Smoking

3.1 Functional Brain Imaging of Cigarette Craving

As for brain imaging studies of chronic tobacco/nicotine dependence, cigarette smokers experience craving for cigarettes (urge to smoke) within minutes after the last cigarette, and the intensity of craving rises over the next 3–6 h (Jarvik et al.

2000; Schuh and Stitzer 1995). Cigarette-related cues have been shown to reliably enhance craving during this period, compared to neutral cues (Carter and Tiffany 1999).

Two studies used a cigarette versus neutral cue paradigm paired with functional imaging to evaluate brain mediation of cigarette craving. In one study (Due et al. 2002), six smokers and six nonsmokers underwent event-related fMRI when presented with smoking-related images (color photographs) compared with neutral images, for 4 s each. For the smoker group, craving increased during the testing session and exposure to smoking-related images resulted in activation of mesolimbic (right posterior amygdala, posterior hippocampus, VTA, and medial thalamus) and visuospatial cortical attention (bilateral prefrontal and parietal cortex and right fusiform gyrus) circuitry, whereas the nonsmoker group did not have these changes. In the second study (Brody et al. 2002), 20 smokers and 20 nonsmokers underwent two FDG-PET sessions. For one PET session, subjects held a cigarette and watched a cigarette-related video, while for the other, subjects held a pen and watched a nature video (randomized order) during the 30-min uptake period of FDG. When presented with smoking-related (compared to neutral) cues, smokers had higher regional metabolism in bilateral (ACC), left orbitofrontal cortex (OFC), and left anterior temporal lobe. Change in craving scores was also positively correlated with change in metabolism in the OFC, dorsolateral prefrontal cortex, and anterior insula bilaterally.

Taken together, these studies of cigarette craving indicate that immediate responses to visual smoking-related cues (fMRI study) activate the brain reward system, limbic regions, and the visual processing system, while longer exposure to cues (FDG-PET study) leads to activation of the ACC, which mediates anxiety, alertness, and arousal (Chua et al. 1999; Critchley et al. 2001; Kimbrell et al. 1999; Naito et al. 2000; Rauch et al. 1999) and the OFC, which functions in part as a secondary processing center for sensory information (Rolls et al. 1998; Rolls and Baylis 1994).

In a related preliminary study, 17 smokers underwent the same FDG-PET craving versus neutral cue protocol as in the second study of craving listed above (Brody et al. 2002) after treatment with a standard course of bupropion HCl (tapered up to 150 mg orally twice a day for a mean of 5.6 weeks). This group of treated subjects had a significant reduction in smoking levels from pre- to post-treatment (mean 27.1 down to 3.7 cigarettes per day). These treated smokers also had reduced cigarette cue-induced craving and diminished ACC activation when presented with cigarette-related cues, compared to untreated smokers (Brody et al. 2004a). This diminished ACC activation was due to elevated baseline-normalized ACC activity in treated smokers, giving an indication that bupropion treatment of smokers increases resting ACC metabolism.

A more recent study examined (Brody et al. 2007) brain activation during resistance of the urge to smoke when smokers were presented with cigarette-related cues. In this study, activation was found in the cigarette cue resist condition compared with the cigarette cue crave condition in the left dorsal ACC, posterior cingulate cortex (PCC), and precuneus. Other findings of this study include lower magnetic resonance signal for the cigarette cue resist in the cuneus bilaterally, left lateral occipital

gyrus, and right postcentral gyrus. These activations and deactivations were stronger when the cigarette cue resist condition was compared with the neutral cue condition. The urge to smoke scale (craving) score had positive correlations with MR signal in the medial aspect of superior frontal gyrus, supramarginal gyrus, precuneus, inferior frontal gyrus/anterior insula, bilateral corpus callosum, left precentral gyrus, putamen, and middle frontal gyrus, and right lingual gyrus extending to the fusiform gyrus. Negative correlations were found for the cuneus, left occipital gyrus, anterior temporal lobe, postcentral gyrus, insula, and right angular gyrus. This study concludes that active suppression of craving during cigarette cue exposure is associated with activation of limbic and related brain regions and deactivation of primary sensory and motor cortices.

3.2 Functional Brain Imaging of Cigarette Withdrawal

Abstinence-induced changes have also been studied (McClernon et al. 2005) in 13 dependent smokers using event-related fMRI. FMRI images were taken after usual smoking and following overnight abstinence. Self-reported craving measures were also conducted before, during, and after scanning. Results revealed larger hemodynamic responses to smoking compared to control cues in ventral anterior cingulate gyrus and superior frontal gyrus. Results show that brain responses to smoking cues, while relatively stable at the group level following short-term abstinence, may be modulated by individual differences in craving in response to abstinence, particularly in regions subserving attention and motivation.

Rose et al. (2007) also studied smokers ($n = 15$) with functional brain imaging following treatment for nicotine dependence. In this study, subjects were given nicotine patches and denicotinized cigarettes. PET scans were obtained at baseline, after 2 weeks of nicotine patch and denicotinized cigarettes, and 2 weeks after patients returned back to smoking. Craving of cigarettes was lower at the second session compared to the other two. After 2 weeks' exposure to nicotine patches and denicotinized cigarettes, the authors found decreased brain metabolic activity in the right hemisphere anterior cingulate cortex.

Brain activity changes (measured with fMRI) during cigarette withdrawal were recently reported for nicotine-dependent rats (Shoaib et al. 2004). In this study, subcutaneous mecamlamine (1 mg kg^{-1}), a nicotine receptor antagonist, was administered to precipitate withdrawal during scanning, and this state was compared to a control state after subcutaneous saline administration. After subcutaneous mecamlamine, nicotine-dependent rats had bilateral increases in NAc activity compared to the control state.

3.3 Monoamine Oxidase (MAO) Function in Smokers

Fowler and colleagues have performed a series of important studies demonstrating decreases in MAO A and B activity in cigarette smokers using the PET tracers

[¹¹C]clorgyline (Fowler et al. 1996b) and [¹¹C]L-deprenyl-D2 (Fowler et al. 1996a, 1998b), respectively. When compared to former smokers and nonsmokers, average reductions for current smokers are 30 and 40% for MAO A and B (Fowler et al. 2003a). These reductions were the result of chronic smoking behavior rather than a single administration of intravenous nicotine (Fowler et al. 1998a) or smoking a single cigarette (Fowler et al. 1999, 2000, 2005), and are less than those seen with antidepressant MAO inhibitors (Fowler et al. 1994, 1996b). MAO A levels were found to be reduced up to 50% in peripheral organs (heart, lungs, and kidneys) in smokers when compared to nonsmokers. Additionally, a human postmortem study of chronic smokers demonstrated a modest reduction in MAO A binding that did not reach statistical significance (Klimek et al. 2001). Peripheral MAO B is also reduced in cigarette smokers (Fowler et al. 2003b).

MAO participates in the catabolism of dopamine, norepinephrine, and serotonin (Berlin and Anthenelli 2001; Fowler et al. 2003a), and it has been postulated that some of the clinical effects of smoking are due to MAO inhibition, leading to decreases in monoamine breakdown with a subsequent increase in monoamine availability (Berlin and Anthenelli 2001). Thus, smoking may enhance DA availability and the rewarding properties of smoking both through DA release (as described above) and MAO inhibition. Smoking may also alter mood and anxiety through MAO inhibition effects on norepinephrine and serotonin availability and turnover. Comprehensive reviews of the role of MAO in tobacco dependence have recently been published (Berlin and Anthenelli 2001; Fowler et al. 2003a).

4 Discussion: Functional Neuroanatomy of Tobacco Use and Dependence

Both acute and chronic effects of nicotine/cigarette exposure have been elucidated with functional brain imaging. Replicated responses to acute administration of nicotine/smoking include a reduction in global brain activity (perhaps most prominently in smokers with high levels of hostility as a personality trait); activation of the prefrontal cortex, thalamus, and visual system; activation of the thalamus and visual cortex (and possibly ACC) during visual cognitive tasks; and increased DA concentration in the ventral striatum/NAc. Replicated responses to chronic nicotine/cigarette exposure include decreased MAO A and B activity and a substantial reduction in $\alpha_4\beta_2$ nAChR availability in the thalamus and putamen (accompanied by an overall upregulation of these receptors).

This group of findings demonstrates a number of ways in which smoking might enhance neurotransmission through cortico–basal ganglia–thalamic circuits (Alexander et al. 1990), in addition to demonstrating direct effects of chronic nicotine exposure on nAChR availability (Fig. 1). Given that the thalamus (Groenewegen et al. 1999; Herrero et al. 2002; Sommer 2003) and ventral striatum/NAc (Groenewegen et al. 1999; Herrero et al. 2002) function as relay

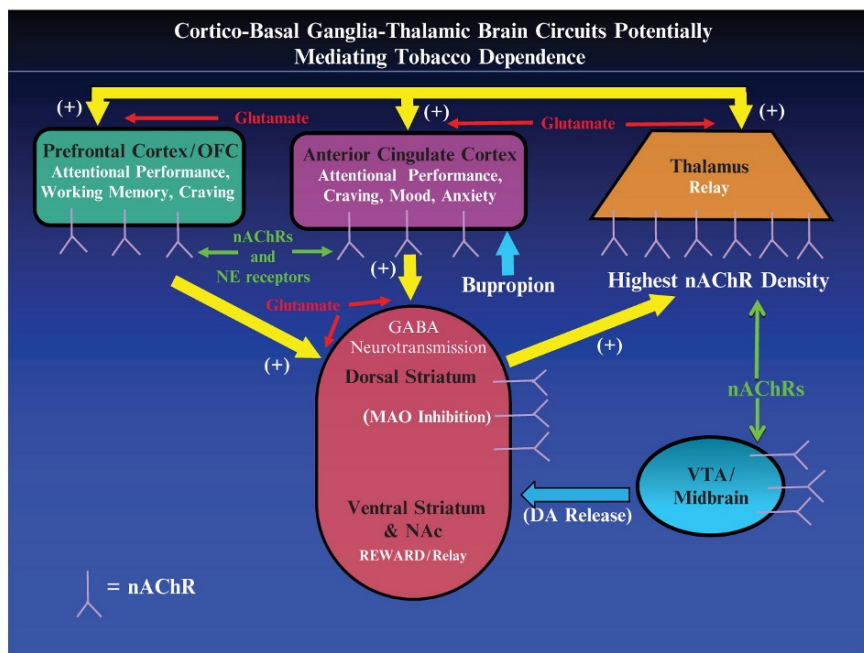


Fig. 1 Representation of the cortico–basal ganglia–thalamic brain circuitry that may mediate the effects of nicotine/smoking on attentional control, craving, mood, and anxiety. Potential targets for nicotine/smoking to enhance attention (and improve craving, mood, and anxiety) include (1) direct stimulation of nicotinic acetylcholine receptors (nAChRs) in cortex, (2) stimulation of the nAChR-rich thalamus and basal ganglia, (3) activation of dopaminergic mesolimbic reward pathways originating in the VTA and projecting to the striatum, and (4) monoamine oxidase (MAO) inhibition in the basal ganglia. *NAc* nucleus accumbens; *VTA* ventral tegmental area

centers for information and for paralimbic and motor processing in the brain, the net effect of smoking may be to enhance neurotransmission along cortico–basal ganglia–thalamic loops originating in the paralimbic cortex. Neurotransmission through these circuits may be stimulated directly by the interconnected (Sherman 2001; Sillito and Jones 2002) nAChR-rich thalamus and visual systems, and/or indirectly through effects on MAO inhibition and DA release in the ventral striatum/NAc, as well as through nicotine stimulation of excitatory glutamatergic input to the dopaminergic system (Mansvelter et al. 2002). In the thalamus, for example, nicotine has direct agonist action on excitatory thalamocortical projection neurons and local circuit neurons, although nicotine also stimulates GABAergic interneurons, so that the relationship between nicotine stimulation and thalamocortical stimulation may be complex (Clarke 2004). There is mixed evidence as to whether or not nicotine stimulates corticothalamic neurons (Clarke 2004).

Enhancement of neurotransmission through prefrontal and paralimbic cortico–basal ganglia–thalamic circuits may account for the most commonly reported

cognitive effect of cigarette smoking, namely, improved attentional performance (Newhouse et al. 2004), and also related effects, such as improvements in reaction times (Hatsukami et al. 1989; Pritchard et al. 1992; Shiffman et al. 1995), arousal (Parrott and Kaye 1999), motivation (Powell et al. 2002), and sustained attention (Rusted et al. 2000). Prefrontal (including both dorsolateral and ventrolateral) (Duncan and Owen 2000; Rees and Lavie 2001; Smith and Jonides 1999) and ACC (Carter et al. 1999; Duncan and Owen 2000; Peterson et al. 1999; Smith and Jonides 1999) cortices are reported to activate during attentional control tasks (especially visuospatial tasks) (Pessoa et al. 2003). Cigarette smoking may enhance attentional control through direct stimulation of nAChRs within these structures or perhaps through subcortical stimulation of nAChRs in the thalamus and via DA release and/or MAO inhibition in the basal ganglia.

In addition to improvement in attention, smoking improves withdrawal symptoms, such as depressed mood, anxiety, and irritability in tobacco-dependent smokers (Cohen et al. 1991; Parrott 2003), and all these effects depend (at least in part) on the expectations of the smoker (Perkins et al. 2003). Though nicotine administration generally results in increased activity along prefrontal and paralimbic brain circuits, it is interesting that both increased and decreased ACC activation during cognitive task performance has been reported (see Sect. 2.2). ACC activity has been associated with anxiety and mood, with increased activity being associated with greater anxiety (Chua et al. 1999; Kimbrell et al. 1999) and decreased activity being associated with depressed mood (Drevets et al. 1997). This combination of findings suggests a potential interaction between expectation of the effects of smoking (e.g., mood improvement, anxiety reduction, or decreased irritability) and direction of ACC activity change during cognitively demanding tasks. Perhaps smokers who expect to and do have anxiety alleviation from smoking have deactivation or decreased activation of the ACC while performing cognitive tasks, whereas those who expect to and do experience mood improvement from smoking have increased activation of the ACC.

In addition to these primary effects of nicotine and smoking, other functional imaging studies reviewed here focus on smoking-related states, such as cue-induced cigarette craving. Such studies are part of a large body of literature examining cue-induced craving for addictive drugs. Studies specific for cigarette cues/craving reveal that exposure to visual cigarette cues immediately activates mesolimbic (VTA, amygdala, and hippocampus) and visuospatial cortical attention areas of the brain, and acutely (over a 30-min period) activate paralimbic regions (ACC and OFC), and that this cue-induced activation may be diminished by a course of bupropion treatment. These results are similar to those of functional imaging studies for drugs other than tobacco (Goldstein and Volkow 2002; Miller and Goldsmith 2001), and it has been posited that at least some of the activations seen with cigarette-related cues (cortical attention areas and OFC) are associated with an expectation of smoking in the nontreatment-seeking subjects who participated in these studies (Wilson et al. 2004).

5 Future Directions

New radioligands are in development for nAChRs. Currently, 2-FA, 6-FA, and 5-I-A radiotracers are available, which have affinity to bind to the $\alpha_4\beta_2$ nAChR subtype. Other radiotracers are in development for this subtype, but there is need for radioligands for imaging of other subtypes of nicotinic receptors, including the α_7 subtype, which is abundant in humans. Future research is likely to focus on radioligands for imaging $\alpha_4\beta_2$ nAChR in the thalamus with faster kinetics than 2-FA, 6-FA, and 5-I-A. Radiolabeled antagonists for imaging of $\alpha_4\beta_2$ nAChR may prove very beneficial for greater understanding of receptor binding and ultimately in development of pharmacological agents to help with quitting smoking (Pomper et al. 2005; Horti et al. 2006).

New treatments are being discovered for smoking cessation, and the Food and Drug Administration has recently approved varenicline, which is a partial nAChR agonist and antagonist. The agonist effect is caused by binding to nicotinic receptors and stimulating receptor-mediated activity. The antagonist effect occurs when varenicline blocks the ability of nicotine to activate nicotinic receptors. Imaging studies with varenicline may tell us more about nicotine dependence and the role of the $\alpha_4\beta_2$ nicotine receptor.

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