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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 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

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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 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;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 D_1 and D_2 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 ^{11}C-raclopride (a specific D_2/D_3 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 ^{11}C-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 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 gluatamatergic 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 D_1 receptor density (Dagher et al. 2001), increased ^{18}F-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; Corrigall 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*)-azetidinylmethoxy 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-[^{18}F]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.

[^{123} I]5-IA or simply 5-I-A is a SPECT radioligand that binds to β_2nAChRs. In a recent study, Staley et al. (2006) hypothesized that an abnormally high number of β_2nAChRs 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_2nAChRs.

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 mecamylamine (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 mecamy-lamine, 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 [^{11}C]clorgyline (Fowler et al. 1996b) and [^{11}C]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 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 (Mansvelder 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.

References

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. Prog Brain Res 1990;85:119–146. [PubMed: 2094891]

Bahk JY, Li SP, Park MS, Kim MO. Dopamine D-1 and D-2 receptor mRNA up-regulation in the caudate-putamen and nucleus accumbens of rat brains by smoking. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:1095–1104. [PubMed: 12452531]

Baker RR, Massey ED, Smith G. An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. Food Chem Toxicol 2004;42(Suppl):S53–S83. [PubMed: 15072838]

Balluz L, Ahluwalia IB, Murphy W, Mokdad A, Giles W, Harris VB. Surveillance for certain health behaviors among selected local areas–United States, Behavioral Risk Factor Surveillance System, 2002. MMWR Surveill Summ 2004;53:1–100. [PubMed: 15269697]

Barrett SP, Boileau I, Okker J, Pihl RO, Dagher A. The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [^{11}C]raclopride. Synapse 2004;54:65–71. [PubMed: 15352131]

Bartal M. Health effects of tobacco use and exposure. Monaldi Arch Chest Dis 2001;56:545–554. [PubMed: 11980288]

Bell SL, Taylor RC, Singleton EG, Henningfield JE, Heishman SJ. Smoking after nicotine deprivation enhances cognitive performance and decreases tobacco craving in drug abusers. Nicotine Tob Res 1999;1:45–52. [PubMed: 11072387]

Benwell ME, Balfour DJK, Anderson JM. Evidence that tobacco smoking increases the density of (−)-[^{3}H]nicotine binding sites in human brain. J Neurochem 1988;50:1243–1247. [PubMed: 3346676]

Berlin I, Anthenelli RM. Monoamine oxidases and tobacco smoking. Int J Neuropsychopharmacol 2001;4:33–42. [PubMed: 11343627]

Blaha CD, Allen LF, Das S, Inglis WL, Latimer MP, Vincent SR, Winn P. Modulation of dopamine efflux in the nucleus accumbens after cholinergic stimulation of the ventral tegmental area in intact, pedunculopontine tegmental nucleus-lesioned, and laterodorsal tegmental nucleus-lesioned rats. J Neurosci 1996;16:714–722. [PubMed: 8551354]

Breese CR, Marks MJ, Logel J, Adams CE, Sullivan B, Collins AC, Leonard S. Effect of smoking history on [^{3}H]nicotine binding in human postmortem brain. J Pharmacol Exp Ther 1997;282:7–13. [PubMed: 9223534]

Brody AL, Mandelkern MA, London ED, Childress AR, Bota RG, Ho ML, Lee GS, Saxena S, Baxter LR, Madsen D, Jarvik ME. Brain metabolic changes during cigarette craving. Arch Gen Psychiatry 2002;59:1162–1172. [PubMed: 12470133]

Brody AL, Mandelkern MA, Lee G, Smith E, Sadeghi M, Saxena S, Jarvik ME, London ED. Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: a preliminary study. Psych Res Neuroimaging 2004a;130:269–281.

Brody AL, Olmstead RE, London ED, Farahi J, Meyer JH, Grossman P, Lee GS, Huang J, Hahn EL, Mandelkern MA. Smoking-induced ventral striatum dopamine release. Am J Psychiatry 2004b; 161:1211–1218. [PubMed: 15229053]

Brody AL, Mandelkern MA, London ED, Olmstead RE, Farahi J, Scheibal D, Jou J, Allen V, Tiongson E, Chefer SI, Koren AO, Mukhin AG. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. Arch Gen Psychiatry 2006;63:907–915. [PubMed: 16894067]

Brody AL, Mandelkern MA, Olmstead RE, Jou J, Tiongson E, Allen V, Scheibal D, London ED, Monterosso JR, Tiffany ST, Korb A, Gan JJ, Cohen MS. Neural substrates of resisting craving during cigarette cue exposure. Biol Psychiatry 2007;62:642–651. [PubMed: 17217932]

Broussolle EP, Wong D, Fanelli RJ, London ED. *In vivo* specific binding of [^{3}H]-nicotine in the mouse brain. Life Sci 1989;44:1123–1132. [PubMed: 2704294]

Carter BL, Tiffany ST. Meta-analysis of cue-reactivity in addiction research. Addiction 1999;94:327–340. [PubMed: 10605857]

Carter CS, Botvinick MM, Cohen JD. The contribution of the anterior cingulate cortex to executive processes in cognition. Rev Neurosci 1999;10:49–57. [PubMed: 10356991]

Chefer SI, Horti AG, Lee K, Koren A, Jones DW, Gorey J, Links JM, Mukhin AG, Weinberger DR, London ED. *In vivo* imaging of brain nicotinic receptors with 5-[^{123}I]iodo-A-85380 using single photon emission computed tomography. Life Sci 1998;63:PL355–PL360. [PubMed: 9870715]

Chefer SI, Horti AG, Koren AO, Gündrisch D, Links JM, Kurian V, Dannals RF, Mukhin AG, London ED. 2-[^{18}F]F-A-83580: a PET radioligand for α4β2 nicotinic acetylcholine receptors. Neuroreport 1999;10:2715–2721. [PubMed: 10511429]

Chefer SI, London ED, Koren AO, Pavlova OA, Kurian V, Kimes AS, Horti AG, Mukhin AG. Graphical analysis of 2-[F-18]FA binding to nicotinic acetylcholine receptors in rhesus monkey brain. Synapse 2003;48:25–34. [PubMed: 12557269]

Chua P, Krams M, Toni I, Passingham R, Dolan R. A functional anatomy of anticipatory anxiety. Neuroimage 1999;9:563–571. [PubMed: 10334900]

Cimino M, Marini P, Fornasari D, Cattabeni F, Clementi F. Distribution of nicotinic receptors in cynomolgus monkey brain and ganglia: localization of alpha 3 subunit mRNA, alpha-bungarotoxin and nicotine binding sites. Neuroscience 1992;51:77–86. [PubMed: 1465189]

Clarke PBS. Nicotinic modulation of thalamocortical neurotransmission. Acetylcholine in the cerebral cortex. Prog Brain Res 2004;145:253–260. [PubMed: 14650920]

Clarke PBS, Pert C, Pert A. Autoradiographic distribution of nicotine receptors in rat brain. Brain Res 1984;323:390–395. [PubMed: 6098346]

Cohen C, Pickworth WB, Henningfield JE. Cigarette smoking and addiction. Clin Chest Med 1991;12:701–710. [PubMed: 1747988]

Connelly MS, Littleton JM. Lack of stereoselectivity in ability of nicotine to release dopamine from rat synaptosomal preparations. J Neurochem 1983;41:1297–1302. [PubMed: 6619866]

Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology 1992;107:285–289. [PubMed: 1615127]

Corrigall WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res 1994;653:278–284. [PubMed: 7982062]

Court JA, Martin-Ruiz C, Graham A, Perry E. Nicotinic receptors in human brain: topography and pathology. J Chem Neuroanat 2000;20:281–298. [PubMed: 11207426]

Cousins MS, Roberts DC, de Wit H. GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. Drug Alcohol Depend 2002;65:209–220. [PubMed: 11841892]

Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuroimage 2001;13:S392.

Cruickshank JM, Neildwyer G, Dorrance DE, Hayes Y, Patel S. Acute effects of smoking on blood-pressure and cerebral blood-flow. J Hum Hypertension 1989;3:443–449.

Dagher A, Bleicher C, Aston JAD, Gunn RN, Clarke PBS, Cumming P. Reduced dopamine D1 receptor binding in the ventral striatum of cigarette smokers. Synapse 2001;42:48–53. [PubMed: 11668590]

Damsma G, Day J, Fibiger HC. Lack of tolerance to nicotine-induced dopamine release in the nucleus accumbens. Eur J Pharmacol 1989;168:363–368. [PubMed: 2479574]

Dávila-García MI, Musachio J, Perry D, Xiao Y, Horti A, London E, Dannals RF, Kellar K. [^{125}I]IPH, an epibatidine analog, binds with high affinity to neuronal nicotinic cholinergic receptors. J Pharmacol Exp Ther 1997;282:445–451. [PubMed: 9223586]

Davila-Garcia MI, Houghtling RA, Qasba SS, Kellar KJ. Nicotinic receptor binding sites in rat primary neuronal cells in culture: characterization and their regulation by chronic nicotine. Mol Brain Res 1999;66:14–23. [PubMed: 10095073]

Dewey SL, Brodie JD, Gerasimov M, Horan B, Gardner EL, Ashby CRJ. A pharmacologic strategy for the treatment of nicotine addiction. Synapse 1999;31:76–86. [PubMed: 10025686]

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 1988;85:5274–5278. [PubMed: 2899326]

Ding YS, Volkow ND, Logan J, Garza V, Pappas N, King P, Fowler JS. Occupancy of brain nicotinic acetylcholine receptors by nicotine doses equivalent to those obtained when smoking a cigarette. Synapse 2000;35:234–237. [PubMed: 10657031]

Domino EF, Minoshima S, Guthrie S, Ohl L, Ni L, Koeppe RA, Zubieta JK. Nicotine effects on regional cerebral blood flow in awake, resting tobacco smokers. Synapse 2000a;38:313–321. [PubMed: 11020234]

Domino EF, Minoshima S, Guthrie SK, Ohl L, Ni L, Koeppe RA, Cross DJ, Zubieta J. Effects of nicotine on regional cerebral glucose metabolism in awake resting tobacco smokers. Neuroscience 2000b; 101:277–282. [PubMed: 11074150]

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824–827. [PubMed: 9126739]

Due DL, Huettel SA, Hall WG, Rubin DC. Activation in mesolimbic and visuospatial neural circuits elicited by smoking cues: evidence from functional magnetic resonance imaging. Am J Psychiatry 2002;159:954–960. [PubMed: 12042183]

Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci 2000;23:475–483. [PubMed: 11006464]

Ernst M, Heishman SJ, Spurgeon L, London ED. Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 2001a;25:313–319. [PubMed: 11522460]

Ernst M, Matochik JA, Heishman SJ, Van Horn JD, Jons PH, Henningfield JE, London ED. Effect of nicotine on brain activation during performance of a working memory task. Proc Natl Acad Sci USA 2001b;98:4728–4733. [PubMed: 11274349]

Fallon JH, Keator DB, Mbogori J, Turner J, Potkin SG. Hostility differentiates the brain metabolic effects of nicotine. Brain Res Cogn Brain Res 2004;18:142–148. [PubMed: 14736573]

Fiore, MC.; Bailey, WC.; Cohen, SJ.; Dorfman, SF.; Goldstein, MG.; Gritz, ER.; Heyman, RB.; Jaen, CR.; Kottke, TE.; Lando, HA.; Mecklenburg, RE.; Mullen, PD.; Nett, LM.; Robinson, L.; Stitzer, ML.; Tommasello, AC.; Villejo, L.; Wewers, ME. Clinical Practice Guideline. U.S. Department of Health and Human Services. Public Health Service; Rockville, MD: 2000. Treating tobacco use and dependence.

Fowler JS, Volkow ND, Logan J, Wang GJ, MacGregor RR, Schyler D, Wolf AP, Pappas N, Alexoff D, Shea C. Slow recovery of human brain MAO B after L-deprenyl (Selege-line) withdrawal. Synapse 1994;18:86–93. [PubMed: 7839316]

Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, MacGregor R, Alexoff D, Shea C, Schlyer D, Wolf AP, Warner D, Zezulkova I, Cilento R. Inhibition of monoamine oxidase B in the brains of smokers. Nature 1996a;379:733–736. [PubMed: 8602220]

Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, Shea C, Alexoff D, MacGregor RR, Schlyer DJ, Zezulkova I, Wolf AP. Brain monoamine oxidase A inhibition in cigarette smokers. Proc Natl Acad Sci USA 1996b;93:14065–14069. [PubMed: 8943061]

Fowler JS, Volkow ND, Logan J, Pappas N, King P, MacGregor R, Shea C, Garza V, Gatley SJ. An acute dose of nicotine does not inhibit MAO B in baboon brain in vivo. Life Sci 1998a;63:L19–L23.

Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, MacGregor R, Alexoff D, Wolf AP, Warner D, Cilento R, Zezulkova I. Neuropharmacological actions of cigarette smoke: brain monoamine oxidase B (MAO B) inhibition. J Addict Dis 1998b;17:23–34. [PubMed: 9549600]

Fowler JS, Wang GJ, Volkow ND, Franceschi D, Logan J, Pappas N, Shea C, MacGregor RR, Garza V. Smoking a single cigarette does not produce a measurable reduction in brain MAO B in non-smokers. Nicotine Tob Res 1999;1:325–329. [PubMed: 11072429]

Fowler JS, Wang GJ, Volkow ND, Franceschi D, Logan J, Pappas N, Shea C, MacGregor RR, Garza V. Maintenance of brain monoamine oxidase B inhibition in smokers after overnight cigarette abstinence. Am J Psychiatry 2000;157:1864–1866. [PubMed: 11058487]

Fowler JS, Logan J, Wang GJ, Volkow ND. Monoamine oxidase and cigarette smoking. Neurotoxicology 2003a;24:75–82. [PubMed: 12564384]

Fowler JS, Logan J, Wang GJ, Volkow ND, Telang F, Zhu W, Franceschi D, Pappas N, Ferrieri R, Shea C, Garza V, Xu YW, Schlyer D, Gatley SJ, Ding YS, Alexoff D, Warner D, Netusil N, Carter P, Jayne M, King P, Vaska P. Low monoamine oxidase B in peripheral organs in smokers. Proc Natl Acad Sci USA 2003b;100:11600–11605. [PubMed: 12972641]

Fowler JS, Logan J, Wang GJ, Volkow ND, Telang F, Zhu W, Franceschi D, Shea C, Garza V, Xu Y, Ding YS, Alexoff D, Warner D, Netusil N, Carter P, Jayne M, King P, Vaska P. Comparison of monoamine oxidase a in peripheral organs in nonsmokers and smokers. J Nucl Med 2005;46:1414–1420. [PubMed: 16157522]

Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control 2003;12:424–430. [PubMed: 14660781]

Fujita M, Seibyl JP, Vaupel DB, Tamagnan G, Early M, Zoghbi SS, Baldwin RM, Horti AG, Koren AO, Mukhin AG, Khan S, Bozkurt A, Kimes AS, London ED, Innis RB. Whole-body biodistribution, radiation absorbed dose, and brain SPET imaging with [^{123}I]5-I-A-85380 in healthy human subjects. Eur J Nucl Med Mol Imaging 2002;29:183–190. [PubMed: 11926380]

Fujita M, Ichise M, van Dyck CH, Zoghbi SS, Tamagnan G, Mukhin AG, Bozkurt A, Seneca N, Tipre D, DeNucci CC, Iida H, Vaupel DB, Horti AG, Koren AO, Kimes AS, London ED, Seibyl JP, Baldwin RM, Innis RB. Quantification of nicotinic acetylcholine receptors in human brain using [I-123]5-I-A-85380 SPET. Eur J Nucl Med Mol Imaging 2003;30:1620–1629. [PubMed: 14523584]

Ghatan PH, Ingvar M, Eriksson L, Stone-Elander S, Serrander M, Ekberg K, Wahren J. Cerebral effects of nicotine during cognition in smokers and non-smokers. Psychopharmacology 1998;136:179–189. [PubMed: 9551775]

Gioanni Y, Rougeot C, Clarke PB, Lepouse C, Thierry AM, Vidal C. Nicotinic receptors in the rat prefrontal cortex: increase in glutamate release and facilitation of mediodorsal thalamo-cortical transmission. Eur J Neurosci 1999;11:18–30. [PubMed: 9987008]

Goldman-Rakic PS, Leranth C, Williams SM, Mons N, Geffard M. Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. Proc Natl Acad Sci USA 1989;86:9015–9019. [PubMed: 2573073]

Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 2002;159:1642–1652. [PubMed: 12359667]

Groenewegen HJ, Galisde Graaf Y, Smeets WJAJ. Integration and segregation of limbic cortico-striatal loops at the thalamic level: an experimental tracing study in rats. J Chem Neuroanat 1999;16:167–185. [PubMed: 10422737]

Gross TM, Jarvik ME, Rosenblatt MR. Nicotine abstinence produces content-specific Stroop interference. Psychopharmacology 1993;110:333–336. [PubMed: 7831427]

Haber SN, Fudge JL. The primate substantia nigra and VTA: integrative circuitry and function. Crit Rev Neurobiol 1997;11:323–342. [PubMed: 9336716]

Hatsukami D, Fletcher L, Morgan S, Keenan R, Amble P. The effects of varying cigarette deprivation duration on cognitive and performance tasks. J Subst Abuse 1989;1:407–416. [PubMed: 2485288]

Herrero MT, Barcia C, Navarro JM. Functional anatomy of thalamus and basal ganglia. Childs Nervous Syst 2002;18:386–404.

Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol 2003;147:1–46. [PubMed: 12783266]

Holmes S, Zwar N, Jimenez-Ruiz CA, Ryan PJ, Browning D, Bergmann L, Johnston JA. Bupropion as an aid to smoking cessation: a review of real-life effectiveness. Int J Clin Pract 2004;58:285–291. [PubMed: 15117097]

Horti AG, Scheffel U, Koren AO, Ravert HT, Mathews WB, Musachio JL, Finley PA, London ED, Dannals RF. 2-[F-18]fluoro-A-85380, an in vivo tracer for the nicotinic acetylcholine receptors. Nucl Med Biol 1998;25:599–603. [PubMed: 9804040]

Horti AG, Koren AO, Lee KS, Mukhin AG, Vaupel DB, Kimes AS, Stratton M, London ED. Radiosynthesis and preliminary evaluation of 5-[$^{123/125}$I]iodo-3-(2(S)-azetidinylmethoxy)pyridine: a radioligand for nicotinic acetylcholine receptors. Nucl Med Biol 1999;26:175–182. [PubMed: 10100216]

Horti AG, Villemagne VL. The quest for Eldorado: development of radioligands for in vivo imaging of nicotinic acetylcholine receptors in human brain. Curr Pharm Des 2006;12:3877–3900. [PubMed: 17073685]

Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE, Broughton JO, Fortmann SP, Leischow SJ, McKenna JP, et al. Are higher doses of nicotine replacement more effective for smoking cessation? Nic Tobacco Res 1999;1:169–174.

Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM. A comparison of sustained-release bupropion and placebo for smoking cessation. NEJM 1997;337:1195–1202. [PubMed: 9337378]

Jacobsen LK, Gore JC, Skudlarski P, Lacadie CM, Jatlow P, Krystal JH. Impact of intravenous nicotine on BOLD signal response to photic stimulation. Magn Reson Imaging 2002;20:141–145. [PubMed: 12034334]

Jacobsen LK, D'Souza DC, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. Nicotine effects on brain function and functional connectivity in schizophrenia. Biol Psychiatry 2004;55:850–858. [PubMed: 15050867]

Jarvik ME, Madsen DC, Olmstead RE, Iwamoto-Schaap PN, Elins JL, Benowitz NL. Nicotine blood levels and subjective craving for cigarettes. Pharmacol Biochem Behav 2000;66:553–558. [PubMed: 10899369]

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. NEJM 1999;340:685–691. [PubMed: 10053177]

Kenny PJ, Markou A. Neurobiology of the nicotine withdrawal syndrome. Pharmacol Biochem Behav 2001;70:531–549. [PubMed: 11796152]

Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy? Exp Clin Psychopharm 1999;7:226–233.

Killen JD, Fortmann SP, Schatzberg AF, Hayward C, Sussman L, Rothman M, Strausberg L, Varady A. Nicotine patch and paroxetine for smoking cessation. J Consult Clin Psych 2000;68:883–889.

Kimbrell TA, George MS, Parekh PI, Ketter TA, Podell DM, Danielson AL, Repella JD, Benson BE, Willis MW, Herscovitch P, Post RM. Regional brain activity during transient self-induced anxiety and anger in healthy adults. Biol Psychiatry 1999;46:454–465. [PubMed: 10459394]

Kimes AS, Horti AG, London ED, Chefer SI, Contoreggi C, Ernst M, Friello P, Koren AO, Kurian V, Matochik JA, Pavlova O, Vaupel DB, Mukhin AG. 2-[18F]F-A-85380: PET imaging of brain nicotinic acetylcholine receptors and whole body distribution in humans. FASEB J 2003;17:1331–1333. [PubMed: 12759330]

Klimek V, Zhu MY, Dilley G, Konick L, Overholser JC, Meltzer HY, May WL, Stockmeier CA, Ordway GA. Effects of long-term cigarette smoking on the human locus coeruleus. Arch Gen Psychiatry 2001;58:821–827. [PubMed: 11545664]

Kodaira K, Fujishiro K, Wada T, Maie K, Satoi T, Tsukiyama E, Fukumoto T, Uchida T, Yamazaki S, Okamura T. A study on cerebral nicotine receptor distribution, blood flow, oxygen consumption, and other metabolic activities–a study on the effects of smoking on carotid and cerebral artery blood flow. Yakubutsu Seishin Kodo 1993;13:157–165. [PubMed: 8237131]

Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharm Sci 1992;13:177–184. [PubMed: 1604710]

Koren AO, Horti AG, Mukhin AG, Gundisch D, Kimes AS, Dannals RF, London ED. 2-, 5-, and 6-halo-3-(2(S)-azetidinylmethoxy)pyridines: synthesis, affinity for nicotinic acetylcholine receptors, and molecular modeling. J Med Chem 1998;41:3690–3698. [PubMed: 9733494]

Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K, Ackenheil M. Stimulant-like action of nicotine on striatal dopamine transporter in the brain of adults with attention deficit hyper-activity disorder. Int J Neuropsychopharmacol 2002;5:111–113. [PubMed: 12135534]

Kubota K, Yamaguchi T, Abe Y, Fujiwara T, Hatazawa J, Matsuzawa T. Effects of smoking on regional cerebral blood-flow in neurologically normal subjects. Stroke 1983;14:720–724. [PubMed: 6658956]

Kubota K, Yamaguchi T, Fujiwara T, Matsuzawa T. Effects of smoking on regional cerebral blood-flow in cerebral vascular-disease patients and normal subjects. Tohoku J Exp Med 1987;151:261–268. [PubMed: 3590173]

Kumari V, Gray JA, Ffytche DH, Mitterschiffthaler MT, Das M, Zachariah E, Vythelingum GN, Williams SCR, Simmons A, Sharma T. Cognitive effects of nicotine in humans: an fMRI study. Neuroimage 2003;19:1002–1013. [PubMed: 12880828]

Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology 2003;28:216–225. [PubMed: 12589374]

Lanca AJ, Adamson KL, Coen KM, Chow BL, Corrigall WA. The pedunculopontine tegmental nucleus and the role of cholinergic neurons in nicotine self-administration in the rat: a correlative neuroanatomical and behavioral study. Neuroscience 2000;96:735–742. [PubMed: 10727791]

Lawrence NS, Ross TJ, Stein EA. Cognitive mechanisms of nicotine on visual attention. Neuron 2002;36:539–548. [PubMed: 12408855]

Leistikow BN, Martin DC, Milano CE. Estimates of smoking-attributable deaths at ages 15–54, motherless or fatherless youths, and resulting Social Security costs in the United States in 1994. Prev Med 2000a;30:353–360. [PubMed: 10845743]

Leistikow BN, Martin DC, Milano CE. Fire injuries, disasters, and costs from cigarettes and cigarette lights: a global overview. Prev Med 2000b;31:91–99. [PubMed: 10938207]

Leshner AI, Koob GF. Drugs of abuse and the brain. Proc Assoc Am Phys 1999;111:99–108. [PubMed: 10220804]

Li SP, Kim KY, Kim JH, Kim JH, Park MS, Bahk JY, Kim MO. Chronic nicotine and smoking treatment increases dopamine transporter mRNA expression in the rat midbrain. Neurosci Lett 2004;363:29–32. [PubMed: 15157990]

London ED, Waller SB, Wamsley JK. Autoradiographic localization of [^{3}H] nicotine binding sites in the rat brain. Neurosci Lett 1985;53:179–184. [PubMed: 3982705]

London ED, Connolly RJ, Szikszay M, Wamsley JK, Dam M. Effects of nicotine on local cerebral glucose-utilization in the rat. J Neurosci 1988a;8:3920–3928. [PubMed: 3193185]

London ED, Dam M, Fanelli RJ. Nicotine enhances cerebral glucose utilization in central components of the rat visual system. Brain Res Bull 1988b;20:381–385. [PubMed: 3365564]

London ED, Scheffel U, Kimes AS, Kellar KJ. *In vivo* labeling of nicotinic acetylcholine receptors in brain with [^{3}H]epibatidine. Eur J Pharmacol 1995;278:R1–R2. [PubMed: 7664806]

Lukas, RJ. Neuronal nicotinic acetylcholine receptors. In: Barrantes, FJ., editor. The nicotinic acetylcholine receptor: current views and future trends. R.G. Landes; Georgetown: 1998. p. 145-173.

Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 2002;33:905–919. [PubMed: 11906697]

Marenco T, Bernstein S, Cumming P, Clarke PBS. Effects of nicotine and chlorisondamine on cerebral glucose utilization in immobilized and freely-moving rats. Br J Pharmacol 2000;129:147–155. [PubMed: 10694214]

Marenco S, Carson RE, Berman KF, Herscovitch P, Weinberger DR. Nicotine-induced dopamine release in primates measured with [C-11]raclopride PET. Neuropsychopharmacology 2004;29:259–268. [PubMed: 14666115]

Marien M, Brien J, Jhamandas K. Regional release of [^{3}H]dopamine from rat brain in vitro: effects of opioids on release induced by potassium, nicotine, and L-glutamic acid. Can J Physiol Pharmacol 1983;61:43–60. [PubMed: 6132674]

McClernon FJ, Huettel SA, Rose JE. Abstinence-induced changes in self-report craving correlate with event-related fMRI responses to smoking cues. Neuropsychopharmacology 2005;301:940–1947.

Miller NS, Goldsmith RJ. Craving for alcohol and drugs in animals and humans: biology and behavior. J Addict Dis 2001;20:87–104. [PubMed: 11681596]

Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA 2004;291:1238–1245. [PubMed: 15010446]

Mukhin AG, Gundisch D, Horti AG, Koren AO, Tamagnan G, Kimes AS, Chambers J, Vaupel DB, King SL, Picciotto MR, Innis RB, London ED. 5-Iodo-A-85380, an alpha 4 beta 2 subtype-selective ligand for nicotinic acetylcholine receptors. Mol Pharmacol 2000;57:642–649. [PubMed: 10692507]

Naito E, Kinomura S, Geyer S, Kawashima R, Roland PE, Zilles K. Fast reaction to different sensory modalities activates common fields in the motor areas, but the anterior cingulate cortex is involved in the speed of reaction. J Neurophysiol 2000;83:1701–1709. [PubMed: 10712490]

Nakamura H, Tanaka A, Nomoto Y, Ueno Y, Nakayama Y. Activation of fronto-limbic system in the human brain by cigarette smoking: evaluated by a CBF measurement. Keio J Med 2000;49(Suppl 1):A122–A124. [PubMed: 10750360]

Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 2004;4:36–46. [PubMed: 15018837]

Nisell M, Nomikos GG, Svensson TH. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse 1994;16:36–44. [PubMed: 8134899]

Pabreza LA, Dhawan S, Kellar KJ. [^{3}H]Cytisine binding to nicotinic cholinergic receptors in brain. Mol Pharmacol 1991;39:9–12. [PubMed: 1987453]

Parrott AC. Cigarette-derived nicotine is not a medicine. World J Biol Psychiatry 2003;4:49–55. [PubMed: 12692774]

Parrott AC, Kaye FJ. Daily uplifts, hassles, stresses and cognitive failures: in cigarette smokers, abstaining smokers, and non-smokers. Behav Pharmacol 1999;10:639–646. [PubMed: 10780505]

Paterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. Prog Neurobiol 2000;61:75–111. [PubMed: 10759066]

Paulson OB. Blood-brain barrier, brain metabolism and cerebral blood flow. Eur Neuropsychopharmacol 2002;12:495–501. [PubMed: 12468012]

Pauly JR, Stitzel JA, Marks MJ, Collins AC. An autoradiographic analysis of cholinergic receptors in mouse brain. Brain Res Bull 1989;22:453–459. [PubMed: 2706548]

Pauly JR, Marks MJ, Robinson SF, van de Kamp JL, Collins AC. Chronic nicotine and mecamylamine treatment increase brain nicotinic receptor binding without changing alpha 4 or beta 2 mRNA levels. J Pharmacol Exp Ther 1996;278:361–369. [PubMed: 8764371]

Perkins K, Sayette M, Conklin C, Caggiula A. Placebo effects of tobacco smoking and other nicotine intake. Nicotine Tob Res 2003;5:695–709. [PubMed: 14577986]

Perry DC, Kellar KJ. [^{3}H]Epibatidine labels nicotinic receptors in rat brain: an autoradiographic study. J Pharmacol Exp Ther 1995;285:1030–1034. [PubMed: 7473129]

Pessoa L, Kastner S, Ungerleider LG. Neuroimaging studies of attention: from modulation of sensory processing to top-down control. J Neurosci 2003;23:3990–3998. [PubMed: 12764083]

Peterson BS, Skudlarski P, Gatenby JC, Zhang HP, Anderson AW, Gore JC. An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. Biol Psychiatry 1999;45:1237–1258. [PubMed: 10349031]

Picciotto MR, Corrigall WA. Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. J Neurosci 2002;22:3338–3341. [PubMed: 11978809]

Pomper MG, Phillips E, Fan H, McCarthy DJ, Keith RA, Gordon JC, Scheffel U, Dannals RF, Musachio JL. Synthesis and biodistribution of radiolabeled alpha 7 nicotinic acetylcholine receptor ligands. J Nucl Med 2005;46:326–334. [PubMed: 15695794]

Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 1996;382:255–257. [PubMed: 8717040]

Powell J, Dawkins L, Davis RE. Smoking, reward responsiveness, and response inhibition: tests of an incentive motivational model. Biol Psychiatry 2002;51:151–163. [PubMed: 11822994]

Pritchard WS, Robinson JH, Guy TD. Enhancement of continuous performance task reaction-time by smoking in nondeprived smokers. Psychopharmacology 1992;108:437–442. [PubMed: 1410155]

Rauch SL, Shin LM, Dougherty DD, Alpert NM, Orr SP, Lasko M, Macklin ML, Fischman AJ, Pitman RK. Neural activation during sexual and competitive arousal in healthy men. Psychiatry Res Neuroimaging 1999;91:1–10.

Rees G, Lavie N. What can functional imaging reveal about the role of attention in visual awareness? Neuropsychologia 2001;39:1343–1353. [PubMed: 11566316]

Rogers RL, Meyer JS, Shaw TG, Mortel KF, Hardenberg JP, Zaid RR. Cigarette-smoking decreases cerebral blood-flow suggesting increased risk for stroke. JAMA 1983;250:2796–2800. [PubMed: 6644957]

Rolls ET, Baylis LL. Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J Neurosci 1994;14:5437–5452. [PubMed: 8083747]

Rolls ET, Critchley HD, Browning A, Hernadi I. The neurophysiology of taste and olfaction in primates, and umami flavor. Ann N Y Acad Sci 1998;855:426–437. [PubMed: 9929636]

Rose JE, Behm FM, Westman EC, Mathew RJ, London ED, Hawk TC, Turkington TG, Coleman RE. PET studies of the influences of nicotine on neural systems in cigarette smokers. Am J Psychiatry 2003;160:323–333. [PubMed: 12562580]

Rose JE, Behm FM, Salley AN, Bates JE, Coleman RE, Hawk TC. Regional brain activity correlates of nicotine dependence. Neuropsychopharmacology 2007;32:2441–2452. [PubMed: 17356570]

Rourke SB, Dupont RM, Grant I, Lehr PP, Lamoureux G, Halpern S, Yeung DW. Reduction in cortical IMP-SPET tracer uptake with recent cigarette consumption in a young group of healthy males. San Diego HIV Neurobehavioral Research Center. Eur J Nucl Med 1997;24:422–427. [PubMed: 9096094]

Rowell PP, Carr LA, Garner AC. Stimulation of [^{3}H]dopamine release by nicotine in rat nucleus accumbens. J Neurochem 1987;49:1449–1454. [PubMed: 2889800]

Rusted JM, Caulfield D, King L, Goode A. Moving out of the laboratory: does nicotine improve everyday attention? Behav Pharmacol 2000;11:621–629. [PubMed: 11198133]

Ryan RE, Ross SA, Drago J, Loiacono RE. Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha 4 nicotinic receptor subunit knockout mice. Br J Pharmacol 2001;132:1650–1656. [PubMed: 11309235]

Sakurai Y, Takano Y, Kohjimoto Y, Honda K, Kamiya HO. Enhancement of [^{3}H]dopamine release and its [^{3}H]metabolites in rat striatum by nicotinic drugs. Brain Res 1982;242:99–106. [PubMed: 6179571]

Salokangas RK, Vilkman H, Ilonen T, Taiminen T, Bergman J, Haaparanta M, Solin O, Alanen A, Syvalahti E, Hietala J. High levels of dopamine activity in the basal ganglia of cigarette smokers. Am J Psychiatry 2000;157:632–634. [PubMed: 10739427]

Schilstrom B, Fagerquist MV, Zhang X, Hertel P, Panagis G, Nomikos GG, Svensson TH. Putative role of presynaptic alpha7* nicotinic receptors in nicotine stimulated increases of extracellular levels of glutamate and aspartate in the ventral tegmental area. Synapse 2000;38:375–383. [PubMed: 11044884]

Schuh KJ, Stitzer ML. Desire to smoke during spaced smoking intervals. Psychopharmacology 1995;120:289–295. [PubMed: 8524976]

Sherman SM. Thalamic relay functions. Prog Brain Res 2001;134:51–69. [PubMed: 11702563]

Shiffman S, Paty JA, Gnys M, Elash C, Kassel JD. Nicotine withdrawal in chippers and regular smokers – subjective and cognitive effects. Health Psychol 1995;14:301–309. [PubMed: 7556033]

Shoaib M, Schindler CW, Goldberg SR, Pauly JR. Behavioural and biochemical adaptations to nicotine in rats: influence of MK801, an NMDA receptor antagonist. Psychopharmacology 1997;134:121–130. [PubMed: 9399375]

Shoaib M, Lowe AS, Williams SCR. Imaging localised dynamic changes in the nucleus accumbens following nicotine withdrawal in rats. Neuroimage 2004;22:847–854. [PubMed: 15193614]

Sihver W, Langstrom B, Nordberg A. Ligands for in vivo imaging of nicotinic receptor subtypes in Alzheimer brain. Acta Neurol Scand 2000;102:27–33. [PubMed: 10893059]

Sillito AM, Jones HE. Corticothalamic interactions in the transfer of visual information. Philos Trans R Soc Lond Ser B Biol Sci 2002;357:1739–1752. [PubMed: 12626008]

Smith EE, Jonides J. Neuroscience – Storage and executive processes in the frontal lobes. Science 1999;283:1657–1661. [PubMed: 10073923]

Sommer MA. The role of the thalamus in motor control. Curr Opin Neurobiol 2003;13:663–670. [PubMed: 14662366]

Staley JK, Krishnan-Sarin S, Zoghbi S, Tamagnan G, Fujita M, Seibyl JP, Maciejewski PK, O'Malley S, Innis RB. Sex differences in [^{123}I]beta-CIT SPECT measures of dopamine and serotonin transporter availability in healthy smokers and nonsmokers. Synapse 2001;41:275–284. [PubMed: 11494398]

Staley JK, Krishnan-Sarin S, Cosgrove KP, Krantzler E, Frohlich E, Perry E, Dubin JA, Estok K, Brenner E, Baldwin RM, Tamagnan GD, Seibyl JP, Jatlow P, Picciotto MR, London ED, O'Malley S, van Dyck CH. Human tobacco smokers in early abstinence have higher levels of beta2* nicotinic acetylcholine receptors than nonsmokers. J Neurosci 2006;34:8707–8714. [PubMed: 16928859]

Stapleton JM, Gilson SF, Wong DF, Villemagne VL, Dannals RF, Grayson RF, Henningfield JE, London ED. Intravenous nicotine reduces cerebral glucose metabolism: a preliminary study. Neuropsychopharmacology 2003a;28:765–772. [PubMed: 12655323]

Stapleton JM, Gilson SF, Wong DF, Villemagne VL, Dannals RF, Grayson RF, Henningfield JE, London ED. Intravenous nicotine reduces cerebral glucose metabolism: a preliminary study. Neuropsychopharmacology 2003b;28:765–772. [PubMed: 12655323]

Stein E, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao S, Bandettini PA, Bloom AS. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. Am J Psychiatry 1998;155:1009–1015. [PubMed: 9699686]

Sziraki I, Lipovac MN, Hashim A, Sershen H, Allen D, Cooper T, Czobor P, Lajtha A. Differences in nicotine-induced dopamine release and nicotine pharmacokinetics between Lewis and Fischer 344 rats. Neurochem Res 2001;26:609–617. [PubMed: 11519721]

Terborg C, Birkner T, Schack B, Witte OW. Acute effects of cigarette smoking on cerebral oxygenation and hemodynamics: a combined study with near-infrared spectroscopy and transcranial Doppler sonography. J Neurol Sci 2002;205:71–75. [PubMed: 12409187]

Thompson JC, Wilby G, Stough C. The effects of transdermal nicotine on inspection time. Hum Psychopharmacol 2002;17:157–161. [PubMed: 12404693]

Tsukada H, Miyasato K, Kakiuchi T, Nishiyama S, Harada N, Domino EF. Comparative effects of methamphetamine and nicotine on the striatal [C-11]raclopride binding in unanesthetized monkeys. Synapse 2002;45:207–212. [PubMed: 12125041]

Valette H, Bottlaender M, Dolle F, Guenther I, Coulon C, Hinnen F, Fuseau C, Ottaviani M, Crouzel C. Characterization of the nicotinic ligand 2-[F-18]fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine in vivo. Life Sci 1998;64:L93–L97.

Valette H, Bottlaender M, Dolle F, Guenther I, Fuseau C, Coulon C, Ottaviani M, Crouzel C. Imaging central nicotinic acetylcholine receptors in baboons with [F-18]fluoro-A-85380. J Nucl Med 1999;40:1374–1380. [PubMed: 10450691]

Valette H, Bottlaender M, Dolle F, Coulon C, Ottaviani M, Syrota A. Long-lasting occupancy of central nicotinic acetylcholine receptors after smoking: a PET study in monkeys. J Neurochem 2003;84:105–111. [PubMed: 12485406]

Villemagne V, Horti A, Scheffel U, Ravert H, Finley P, Clough DJ, London E, Wagner H, Dannals RF. Imaging nicotinic acetylcholine receptors with fluorine-18-FPH, an epibatidine analog. J Nucl Med 1997;38:1737–1741. [PubMed: 9374343]

Westfall TC, Grant H, Perry H. Release of dopamine and 5-hydroxytryptamine from rat striatal slices following activation of nicotinic cholinergic receptors. Gen Pharmacol 1983;14:321–325. [PubMed: 6135645]

Wilson SJ, Sayette MA, Fiez JA. Prefrontal responses to drug cues: a neurocognitive analysis. Nat Neurosci 2004;7:211–214. [PubMed: 15001989]

Yamamoto Y, Nishiyama Y, Monden T, Satoh K, Ohkawa M. A study of the acute effect of smoking on cerebral blood flow using 99mTc-ECD SPET. Eur J Nucl Med Mol Imaging 2003;30:612–614. [PubMed: 12589479]

Yates SL, Bencherif M, Fluhler EN, Lippiello PM. Up-regulation of nicotinic acetylcholine receptors following chronic exposure of rats to mainstream cigarette smoke or alpha 4 beta 2 receptors to nicotine. Biochem Pharmacol 1995;50:2001–2008. [PubMed: 8849326]

Yeomans J, Baptista M. Both nicotinic and muscarinic receptors in ventral tegmental area contribute to brain-stimulation. Pharmacol Biochem Behav 1997;57:915–921. [PubMed: 9259024]

Yoshida M, Yokoo H, Tanaka T, Mizoguchi K, Emoto H, Ishii H, Tanaka M. Facilitatory modulation of mesolimbic dopamine neuronal-activity by a mu-opioid agonist and nicotine as examined with in-vivo microdialysis. Brain Res 1993;624:277–280. [PubMed: 8252400]

Zhang X, Tian JY, Svensson AL, Gong ZH, Meyerson B, Nordberg A. Chronic treatments with tacrine and (−)-nicotine induce different changes of nicotinic and muscarinic acetylcholine receptors in the brain of aged rat. J Neural Transm 2002;109:377–392. [PubMed: 11956958]

Zubieta J, Lombardi U, Minoshima S, Guthrie S, Ni L, Ohl LE, Koeppe RA, Domino EF. Regional cerebral blood flow effects of nicotine in overnight abstinent smokers. Biol Psychiatry 2001;49:906–913. [PubMed: 11377408]

Zubieta JK, Heitzeg MM, Xu Y, Koeppe RA, Ni L, Guthrie S, Domino EF. Regional cerebral blood flow responses to smoking in tobacco smokers after overnight abstinence. Am J Psychiatry 2005;162:567–577. [PubMed: 15741475]

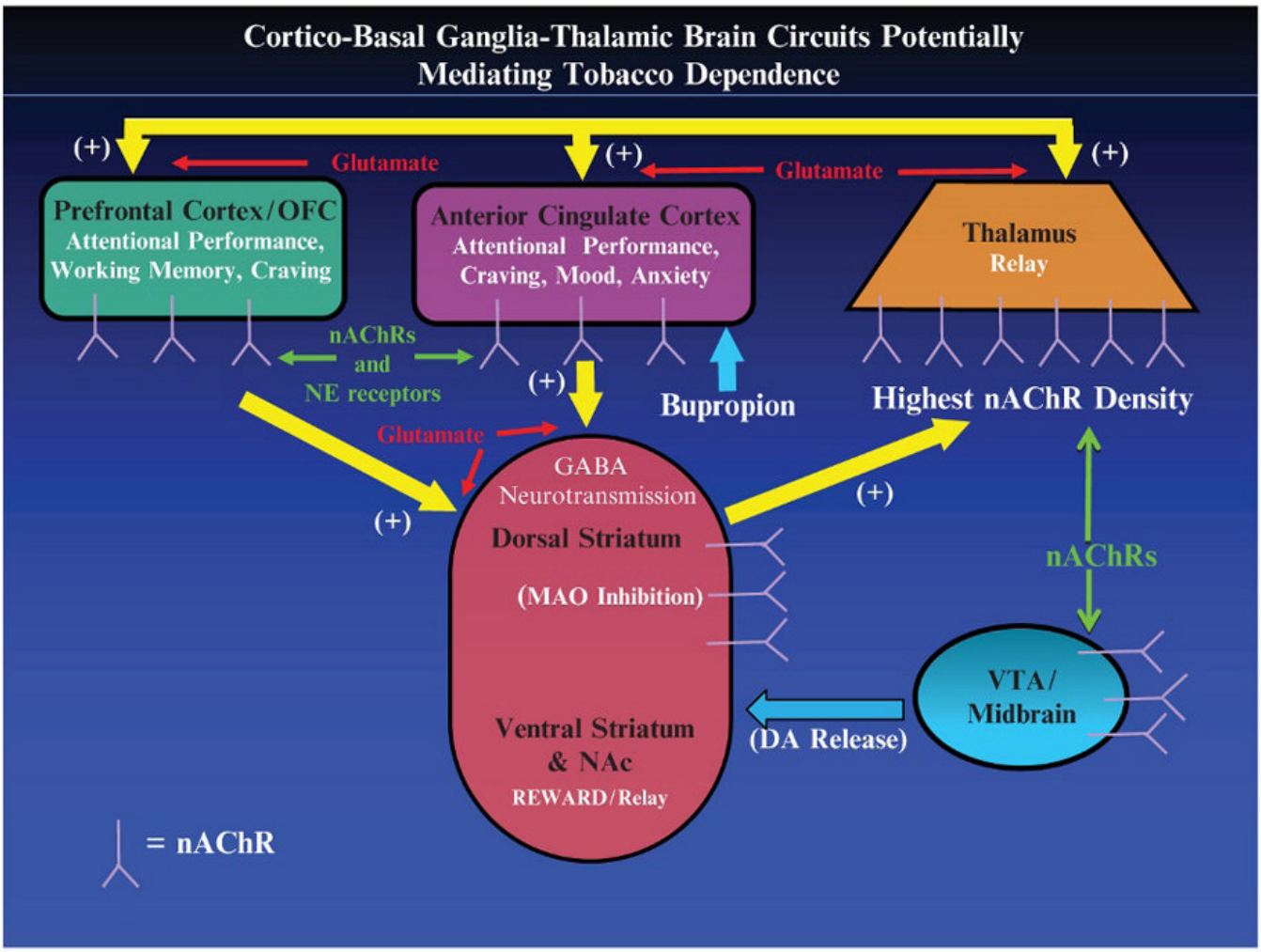

Fig. 1.

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

Table 1

Functional brain imaging studies of nicotine or cigarette administration

Authors	Subjects	Method	Intervention	Results
Animal studies				
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
Human studies				
Rourke et al. (1997)	8 Smokers; 8former smokers; 17 nonsmokers	Iodine-123 iodoamphetamine (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 amyg
Rose et al. (2003)	34 Smokers	^{15}O-PET	Cigarette vs. no nic control conditions	↑ L frontal factor (incl. prefrontal and ACC), ↓ L amyg rCBF
Yamamoto et al. (2003)	10 Smokers	99mTc-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 cingulated, 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, *amyg* amygdala, *FDG* ^{18}F-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

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/photic 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 parietal 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

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 Macada 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